

AMENDED CLINICAL TRIAL PROTOCOL NO. 02

NCT03211858

COMPOUND: SAR341402

Six-month, Randomized, Open-label, Parallel-group Comparison of SAR341402 to NovoLog[®]/NovoRapid[®] in Adult Patients With Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period

STUDY NUMBER: EFC15081

STUDY NAME: GEMELLI 1

CLINICAL STUDY DIRECTOR: [REDACTED]

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CLINICAL TRIAL SUMMARY

COMPOUND: SAR341402	STUDY No.: EFC15081
TITLE	Six-month, Randomized, Open-label, Parallel-group Comparison of SAR341402 to NovoLog®/NovoRapid® in Adult Patients With Diabetes Mellitus Also Using Insulin Glargine, with a 6-month Safety Extension Period
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	Phase 3
STUDY OBJECTIVE(S)	<p>Primary objective:</p> <ul style="list-style-type: none"> To demonstrate non-inferiority of SAR341402 versus NovoLog/NovoRapid in glycated hemoglobin A1c (HbA1c) change from baseline to Week 26 in patients with type 1 or type 2 diabetes mellitus (T1DM or T2DM) also using Lantus®. <p>Secondary objectives:</p> <ul style="list-style-type: none"> To assess the immunogenicity of SAR341402 and NovoLog/NovoRapid in terms of positive/negative status and anti-insulin antibody (AIA) titers during the course of the study. To assess the relationship of anti-insulin antibodies with efficacy and safety. To assess the efficacy of SAR341402 and NovoLog/NovoRapid in terms of proportion of patients reaching HbA1c <7.0% and change in HbA1c, fasting plasma glucose (FPG) and self-measured plasma glucose (SMPG) profiles from baseline to Week 26 and Week 52 (only Week 52 for HbA1c). To assess safety of SAR341402 and NovoLog/NovoRapid.
STUDY DESIGN	<p>Randomized, open-label, active-controlled, 2-arm parallel-group, multicenter trial.</p> <p>The study treatment, SAR341402 and NovoLog/NovoRapid, will be assigned in a 1:1 ratio.</p> <p>Randomization will be stratified by geographical region (Europe, US, Japan), by type of diabetes (T1DM, T2DM [T2DM only for US]), by HbA1c obtained at the screening visit (<8.0%, ≥8.0%), and by prior use of NovoLog/NovoRapid (Yes, No).</p> <p>The study will include a 2-week screening period, a 6-month (26-week) efficacy and safety period and a 6-month (26-week) safety extension period.</p>
STUDY POPULATION Main selection criteria	<p>Inclusion criteria:</p> <ul style="list-style-type: none"> Patients with T1DM or with T2DM (T2DM US only) diagnosed for at least 12 months, who have been treated with a multiple daily injection regimen with <ul style="list-style-type: none"> NovoLog/NovoRapid OR insulin lispro (100 U/mL) in the last 6 months prior to screening visit

	<p>AND</p> <ul style="list-style-type: none"> - insulin glargine (100 U/mL) in the last 6 months prior to screening visit <p>OR</p> <ul style="list-style-type: none"> - insulin detemir (Levemir®) in the last 12 months prior to screening visit. <ul style="list-style-type: none"> • Signed written informed consent obtained. <p>Exclusion criteria:</p> <ul style="list-style-type: none"> • At screening visit, age under legal age of adulthood. • HbA1c <7.0% or >10% at screening. • Patients with incomplete baseline 7-point SMPG profile, defined as patients who do not have 7-point profiles with at least 5 points on at least 2 days in the week before randomization Visit 3. • Less than 1 year on continuous insulin treatment. • Use of insulin pump in the last 3 months before screening visit. • Patients with T1DM: Use of glucose lowering agents other than insulin including use of non-insulin injectable peptides in the last 3 months prior to screening. • Patients with T2DM: <ul style="list-style-type: none"> - Use of glucagon-like peptide-1 (GLP-1) receptor agonists in the last 3 months before screening visit. - Use of oral antidiabetic drugs (OADs) not on stable dose in the last 3 months before screening visit (sulfonylureas will be discontinued at baseline). • At screening visit, body mass index (BMI) ≥ 35 kg/m² in patients with T1DM and ≥ 40 kg/m² in patients with T2DM. • Use of insulin other than <ul style="list-style-type: none"> - insulin glargine 100 U/mL and NovoLog/NovoRapid or insulin lispro 100 U/mL as part of a multiple injection regimen in the last 6 months before screening visit, OR - insulin detemir 100 U/mL in the 12 months before screening visit and NovoLog/NovoRapid or insulin lispro 100 U/mL in the last 6 months before screening visit as part of a multiple injection regimen. • Status post pancreatectomy. • Status post pancreas and/or islet cell transplantation. • Hospitalization for recurrent diabetic ketoacidosis (DKA) in the last 3 months before screening visit. • History of severe hypoglycemia requiring Emergency Room admission or hospitalization in the last 3 months before screening visit. • Unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require treatment (eg, laser, surgical treatment or injectable drugs) during the study period. • Pregnant or breastfeeding women.
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	<ul style="list-style-type: none"> Women of childbearing potential not protected by highly effective method(s) of birth control.
Total expected number of patients	<p>Approximately 580 randomized patients (SAR341402: n = 290; NovoLog/NovoRapid: n = 290).</p> <p>It is planned to randomize approximately 480 patients with T1DM and 100 patients with T2DM (US only). The number of patients with T1DM expected to be randomized in the US versus outside of the US may change owing to the recruitment potential at those regions, however, enrollment will target randomization of approximately 250 patients in countries using EU-approved NovoRapid (including Europe and Japan) and approximately 230 T1DM patients in the US using US-approved NovoLog.</p>
STUDY TREATMENT(s) Investigational medicinal product(s) Formulation: Route(s) of administration:	<p>Tested drug: SAR341402 product</p> <p>SAR341402 will be supplied as 100 U/mL solution in 3 mL pre-filled disposable SoloSTAR® pens.</p> <p>Control drug: NovoLog/NovoRapid</p> <p>NovoLog/NovoRapid will be supplied as 100 U/mL solution in 3 mL pre-filled disposable FlexPen® pens.</p> <p>US-approved NovoLog (hereafter referred to as NovoLog) and EU-approved NovoRapid (hereafter referred to as NovoRapid) comparator will be used at sites depending on the countries, and will be clearly identified.</p> <p>Tested drug: SAR341402 will be self-administered by SC injections.</p> <p>Control drug: NovoLog/NovoRapid will be self-administered by SC injections.</p>
Dose regimen:	<p>SAR341402 and NovoLog/NovoRapid:</p> <p>SAR341402 or NovoLog/NovoRapid will be injected SC immediately (within 5 to 10 minutes) prior to the start of a meal. When necessary, NovoRapid/NovoLog can be given soon after a meal if allowed by the national product label.</p> <p>Changes in the meal related rapid-acting insulin dose will be based on SMPG measurements and the carbohydrate content of the meal (when available).</p> <p>Insulin doses will be self-adjusted/titrated by the patients to achieve a 2-hour postprandial plasma glucose of <10.0 mmol/L (<180 mg/dL) while avoiding hypoglycemia. 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 (1). For the purpose of this protocol, 2 hours postprandial is defined as 2 hours after the start of the meal.</p>
Noninvestigational medicinal product(s) Formulation: Route(s) of administration:	<p>Insulin glargine solution for SC injection 100 U/mL (Lantus) will be used as basal insulin. Lantus will be supplied in 3 mL pre-filled disposable SoloSTAR pens.</p> <p>Mixing of Lantus with other insulin is not allowed.</p> <p>Lantus will be self-administered by SC injections.</p>

Dose regimen:	<p>Lantus will be injected once daily. The time of injection will be fixed at the start of the study and will be maintained during the study. Dose will be self-titrated with site oversight to reach a fasting, prebreakfast SMPG of 4.4 to 7.2 mmol/L (80 to 130 mg/dL).</p> <p>Changes in the Lantus dose are based on fasting (prebreakfast) SMPG measurements.</p>
ENDPOINT(S)	<p>Primary endpoint:</p> <ul style="list-style-type: none"> Change in HbA1c (%) from baseline to Week 26. <p>Secondary endpoints:</p> <p>Immunogenicity</p> <ul style="list-style-type: none"> Anti-SAR341402/NovoLog/NovoRapid antibody positive/negative status, titers and cross-reactivity to human insulin at each sampling visit up to Week 26, and during the extension period up to Week 52. Treatment-induced, treatment-boosted and treatment-emergent anti-insulin antibodies (AIAs) (2) during the main 6-month and the 12-month on-treatment periods. <p>Efficacy</p> <ul style="list-style-type: none"> Change in HbA1c (%) from baseline to Week 52. <p>At Week 26 and Week 52:</p> <ul style="list-style-type: none"> The percentage of patients with HbA1c <7 %. Change from baseline in FPG. Change from baseline in the mean 24-hour plasma glucose concentration, based on the 7-point SMPG profiles. Change from baseline in postprandial plasma glucose excursions (difference between 2-hour postprandial and pre-prandial plasma glucose values at breakfast, lunch and dinner), based on the 7-point SMPG profiles. Change from baseline in 7-point SMPG profiles per time-point. <p>Safety</p> <p>During the main 6-month and the 12-month on-treatment periods:</p> <ul style="list-style-type: none"> Injection site reactions, hypersensitivity reactions. Hypoglycemia (according to ADA Workgroup on Hypoglycemia) (3, 4, 5). Adverse events (AEs), serious adverse events (SAEs). Vital signs. Laboratory data. Body weight.
ASSESSMENT SCHEDULE	<p>Efficacy: see study schedule.</p> <p>Safety: see study schedule.</p>
STATISTICAL CONSIDERATIONS	<p>Randomization:</p> <p>Patients will be randomized to SAR341402 or NovoLog/NovoRapid in a 1:1 ratio. Randomization will be stratified by geographical region (Europe, US, Japan), by type of diabetes (T1DM, T2DM [T2DM only for US]), by HbA1c obtained at the screening visit (<8.0%, ≥8.0%), and by prior use of NovoLog/NovoRapid (Yes, No).</p>

	<p>Sample size determination:</p> <p>The sample size calculations are performed based on the primary endpoint, change in HbA1c from baseline to Week 26 (in %).</p> <p>A sample size of 580 patients (290 patients per treatment group; approximately 480 T1DM patients [230 patients in the US using NovoLog and 250 patients in countries using NovoRapid] and 100 T2DM patients [all in the US using NovoLog]) will ensure that the upper bound of the 2-sided 95% confidence interval (CI) for the adjusted mean difference between SAR341402 and NovoLog/NovoRapid would not exceed a non-inferiority margin of 0.3% HbA1c with at least 95% power. This sample size will also ensure that the lower bound of this 2-sided 95% CI would not be below -0.3% HbA1c with at least 95% power, thus will provide at least 90% power to show both non-inferiority of SAR341402 over NovoLog/NovoRapid (primary analysis) and inverse non-inferiority of NovoLog/NovoRapid over SAR341402 (secondary analysis). These calculations assume a common standard deviation (SD) of 1.0% and a true difference in HbA1c between the treatment groups of zero.</p> <p>An exploratory analysis of the percentage of patients with treatment-emergent AIAs (AIA incidence) will be performed to compare the immunogenicity of SAR341402 versus NovoLog/NovoRapid. The sample size of 580 patients would ensure that the 2-sided 90% CI for the adjusted risk difference between SAR341402 and NovoLog/NovoRapid would be included within the [-10%; 10%] interval with at least 68% power. This calculation assumes a true risk difference between the treatment groups of zero and a maximum AIA incidence of 30% (in previous Sanofi clinical studies performed with rapid-acting insulin analogs, AIA incidence in the range of 15-20% were observed at 6 months). The power calculations are presented in the table below.</p> <p>Power calculation based on the percentage of patients with treatment-emergent AIAs</p> <table><tr><td>Percentage of patients with treatment-emergent AIAs</td><td>10%</td><td>20%</td><td>30%</td></tr><tr><td>Power for N=580 (290/arm)</td><td>97%</td><td>82%</td><td>68%</td></tr></table> <p>Analysis population:</p> <p>The primary efficacy population will be the intent-to-treat (ITT) population, which includes all randomized patients, irrespective of compliance with the study protocol and procedures.</p> <p>Patients will be analyzed for efficacy analyses in the treatment group to which they are randomized.</p> <p>The safety analyses will be conducted on the safety population, defined as all randomized patients who receive at least one dose of investigational medicinal product (IMP) (regardless of the amount of treatment administered). The immunogenicity analyses will be conducted on the AIA population, defined as all patients from the safety population with at least one AIA sample available for analysis during the on-treatment period.</p> <p>For safety and immunogenicity, patients will be analyzed according to the treatment actually received.</p> <p>Analyses will be presented overall (NovoLog/NovoRapid and the corresponding SAR341402 groups) and then for the subgroups defined by region-approved NovoLog/NovoRapid comparing SAR341402 with</p>	Percentage of patients with treatment-emergent AIAs	10%	20%	30%	Power for N=580 (290/arm)	97%	82%	68%
Percentage of patients with treatment-emergent AIAs	10%	20%	30%						
Power for N=580 (290/arm)	97%	82%	68%						

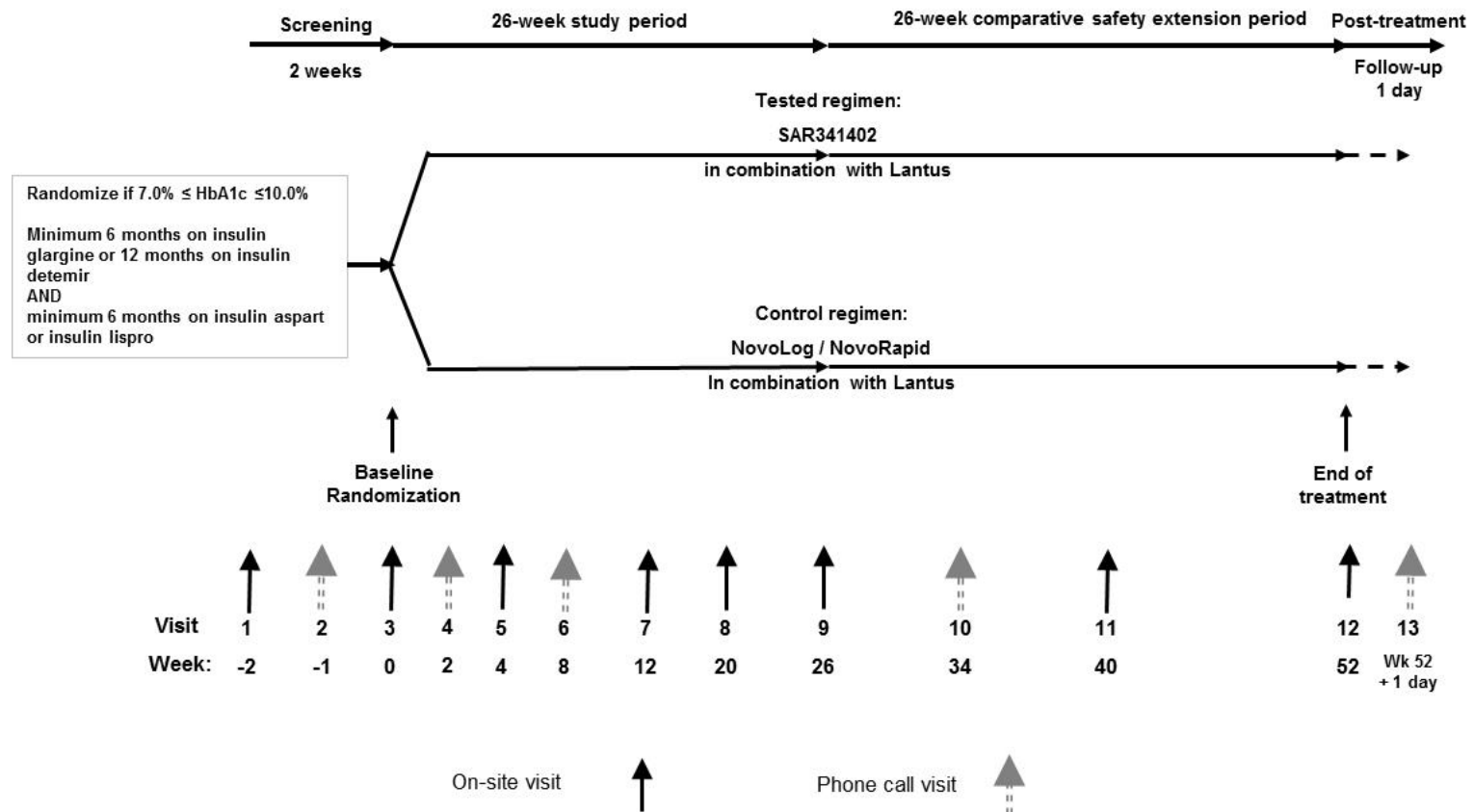
	<p>NovoLog in patients enrolled in the US (approximately 330 patients, 230/330 with T1DM and 100/330 with T2DM) and comparing SAR341402 and NovoRapid in regions using NovoRapid (approximately 250 patients with T1DM). Further subgroup analyses will be defined in the SAP.</p> <p>Primary analysis:</p> <p>The statistical test for the primary efficacy endpoint (change in HbA1c from baseline to Week 26) will be one-sided, with alpha level of 0.025 and using a non-inferiority margin of 0.3% HbA1c.</p> <p>The baseline value is defined as the last available value up to the date of randomization.</p> <p>The primary endpoint will be analyzed on the ITT population using all post-baseline data available during the main 6-month randomized period (ITT estimand).</p> <p>A multiple imputation approach in two parts will be used with missing data imputed separately for patients who did not adhere to IMP and patients who adhered to IMP:</p> <ul style="list-style-type: none"> • Missing data in patients who prematurely discontinued IMP during the main 6-month randomized period will be imputed using a model estimated solely from data observed in other patients who discontinued IMP during the main 6-month randomized period but have the measurement for the primary endpoint at Week 26. • Missing data in patients who completed the main 6-month treatment period will be imputed separately, using a model estimated solely from data observed in other patients who completed the main 6-month treatment period and have the measurement for the primary endpoint at Week 26. <p>Data obtained after the above imputations will be analyzed using an analysis of covariance (ANCOVA) of the change in HbA1c from baseline to Week 26, including the fixed categorical effects of treatment group (SAR341402, NovoLog/NovoRapid), randomization strata, as well as the continuous fixed covariate of baseline value.</p> <p>The adjusted least squares mean (LS mean) of the change in HbA1c from baseline to Week 26 for each treatment group (SAR341402, NovoLog/NovoRapid) will be estimated, as well as the between-group LS mean difference of SAR341402 versus NovoLog/NovoRapid, with the corresponding standard errors and 2-sided 95% CIs.</p> <p>Non-inferiority will be demonstrated if the upper bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid on the ITT population is <0.3%. If non-inferiority of SAR341402 over NovoLog/NovoRapid is demonstrated, using a hierarchical step-down testing procedure, the following additional analysis will be performed (not as primary objective): the inverse non-inferiority (of NovoLog/NovoRapid over SAR341402) will be tested looking at the lower bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid in the ITT population. Non-inferiority of NovoLog/NovoRapid over SAR341402 will be demonstrated if the lower bound is >-0.3%. If SAR341402 is shown to be non-inferior to NovoLog/NovoRapid and NovoLog/NovoRapid non-inferior to SAR341402, similar efficacy (equivalence) of SAR341402 and NovoLog/NovoRapid will be assumed.</p>
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	<p>Analysis of secondary endpoints:</p> <p>Secondary efficacy endpoints will be analyzed in the ITT population, using all post-baseline data available (ITT estimand).</p> <p>A similar multiple imputation approach in two parts, as for the primary efficacy endpoint, will be used for continuous secondary efficacy endpoints (change in HbA1c from baseline to Week 52, and change in FPG, mean 24 hour plasma glucose concentration, and postprandial plasma glucose excursions from baseline to Week 26 and Week 52), followed by a similar ANCOVA model.</p> <p>The categorical secondary efficacy endpoint (HbA1c responders) will be analyzed using a logistic regression model with fixed-effect term for treatment group (SAR341402, NovoLog/NovoRapid) and the randomization strata. Patients without assessment at Week 26 (or Week 52 for the analysis at Week 52) will be considered as failure.</p> <p>Analyses on the secondary efficacy endpoints will be performed for descriptive purpose only (no formal statistical testing).</p> <p>Safety analyses during the main 6-month and the 12-month on-treatment periods will be descriptive, based on the safety population. Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened or became serious during the period from the first administration of study treatment up to 1 day after the last administration.</p> <p>Immunogenicity analyses during the main 6-month and the 12-month on-treatment periods will be descriptive (no formal statistical testing), based on the AIA population. The analysis will focus on the change in AIA response observed following the IMP administration:</p> <ul style="list-style-type: none"> • Patients with treatment-induced AIAs will be defined as patients with AIAs that developed de novo (seroconversion) following the IMP administration. • Patients with treatment-boosted AIAs will be defined as patients with pre-existing AIAs that were boosted to a significant higher titer following the IMP administration (at least 4-fold increase in titer values). • Patients with treatment-emergent AIAs (AIA incidence) will be defined as patients with treatment-induced or treatment-boosted AIAs. <p>For exploratory purposes, the difference between SAR341402 and NovoLog/NovoRapid in the percentage of patients with treatment-emergent AIAs (AIA incidence) will be provided with associated 2-sided 90% CI. Results will be obtained by fitting a binomial regression model with an identity-link function. The model will include fixed categorical effects for treatment, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%), and prior use of NovoLog/NovoRapid (Yes, No). The risks within each treatment group and risk difference will be provided with their 90% CIs using the adjusted LS mean estimates of the treatment effect.</p> <p>Subgroup analyses and/or scatterplots will be conducted as appropriate to assess the relationship between AIA endpoints and efficacy/safety assessments.</p>
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DURATION OF STUDY PERIOD (per patient)	<p>The study will consist of:</p> <ul style="list-style-type: none">• A 2-week screening period.• A 26-week treatment period.• A 26-week comparative safety extension period.• A 1-day follow-up period. <p>In total, the study duration will be 54 weeks per patient (+ 1 day safety follow-up).</p>
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1 FLOW CHARTS






1.1 GRAPHICAL STUDY DESIGN



Note: For patients with T2DM, background as allowed in [Section 7.2.1](#) and [Section 8.8](#) at a stable dose can be continued during the study.

1.2 STUDY FLOW CHART

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1  ^a	Wk 0 (Baseline)	Wk2  ^a	Wk4	Wk8  ^a	Wk12	Wk20	Wk26 ^b (Endpoint)	Wk34  ^a	Wk40	Wk52 ^b (End of treatment)	+1 day ^c  ^a
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Informed consent	X												
Inclusion/Exclusion criteria	X		X										
Demography, medical history, diabetes history	X												
Physical examination	X								X			X	
Vital signs ^d	X		X		X		X	X	X		X	X	
Body weight, height ^e	X		X						X			X	
12-lead ECG	X												
Dispensation of study glucometer and e-diary	X												
Training (glucometer, SMPG profiles, hypoglycemia reporting e-diary)	X		X										
Training or refresher instructions on glucose meter use and routine review of diet and lifestyle counseling along with instructions on dosage self-adjustment including carbohydrate intake ^f	X	X	X	X	X	X	X	X	X	X	X	X	
Dispensation of study medication ^g			X		X		X	X	X		X		
• IMP (SAR341402 or NovoLog/NovoRapid)			X		X		X	X	X		X		
• NIMP (Lantus)			X		X		X	X	X		X		
Counting / collecting used, unused and in use pens					X		X	X	X		X	X	
Compliance check (Review of diary, returned IMP)					X		X	X	X		X	X	
IRT call	X		X		X		X	X	X		X	X	X

Period	Screening		Treatment period (26 weeks)							Comparative Safety Extension period (26 weeks)			Post treatment/Follow-up
Visit:	1	2	3	4	5	6	7	8	9	10	11	12	13
Week:	Wk-2	Wk-1  ^a	Wk 0 (Baseline)	Wk2  ^a	Wk4	Wk8  ^a	Wk12	Wk20	Wk26 ^b (Endpoint)	Wk34  ^a	Wk40	Wk52 ^b (End of treatment)	+1 day ^c  ^a
Day (window [days])	-14	-7 (±3)	1 (±3)	14 (±3)	28 (±3)	56 (±3)	84 (±3)	140 (±3)	182 (±3)	238 (±5)	280 (±5)	364 (±5)	
Visit date confirmation in e-diary web portal		X	X	X	X	X	X	X	X	X	X	X	
Randomization ^h			X										
Patient to come fasting to study site	X		X				X		X		X	X	
Insulin dose collected ⁱ			X		X		X		X		X	X	
7-point SMPG ^j			X				X		X			X	
SMPG to support insulin dose titration ^k		X	X	X	X	X	X	X	X	X	X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X
Central laboratory													
HbA1c	X		X				X		X		X	X	
Fasting plasma glucose			X				X		X		X	X	
C-peptide (fasting)			X										
Anti-insulin antibody ^l			X		X		X		X		X	X	
Safety laboratory													
Hematology ^m , Clinical chemistry ⁿ	X								X			X	
Lipids (fasting) ^o	X								X			X	
Hepatitis serology	X												
Pregnancy test (WOCBP only) ^p	X		X				X		X		X	X	
Serum FSH and estradiol (menopausal women only)	X												
AE / SAE	To be assessed and reported (if any) throughout the study (report SAE to the sponsor within 24 hours)												X
Injection site reactions	To be assessed and reported (if any) throughout the study												X
Hypersensitivity reactions	To be assessed and reported (if any) throughout the study												X
Hypoglycemia recording	To be assessed and reported (if any) throughout the study SMPG to be performed and documented in e-diary / e-CRF in case of symptoms suggesting hypoglycemia												X

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

- a Mandatory telephone visit or optional clinical visit.
- b Or early termination visit. When early termination, refer to the e-CRF completion guidelines.
- c Or 2 to 3 days in the event this visit falls on a weekend or holiday.
- d Heart rate, blood pressure (BP). At screening visit only: determination of reference arm for BP.
- e Height only at Visit 1.
- f Site will provide training at screening visit and baseline visit on the correct handling including regular calibration of the glucose meter provided by the Sponsor; regular refresher instructions will be provided at each on-site visit throughout the study.
- g Patients are trained on the use of IMP and NIMP pens and needles by the study staff and provided with instruction leaflets during the randomization visit.
- h Randomization should be performed only after all baseline evaluations have been done.
- i Mealtime and basal insulin doses are to be documented in the 7 days prior to Baseline (Visit 3) and during the first 7 days after start of IMP, and on 2 days in the weeks prior to Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 26), Visit 11 (Week 40) and Visit 12 (Week 52).
- j 7-point SMPGs (fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) are requested on at least 2 days in the week before Visit 3 (Baseline), Visit 7 (Week 12), Visit 9 (Week 26 [Endpoint]), and Visit 12 (Week 52; End of treatment), measured in a single, 24-hour period; they must be recorded into the e-diary before the visit.
- k SMPG for titration oversight and supporting insulin dosing and carbohydrate intake documentation are recommended daily during the first weeks of study treatment until reaching target ranges for SMPG, and thereafter on at least 3 days each week or more frequently as requested by the Investigator (as specified in titration manual):
 - ➔ To assist titration of the basal insulin (Lantus): fasting (prebreakfast) SMPG.
 - ➔ To assist titration of SAR341402 or NovoLog/NovoRapid: either postprandial or next-meal preprandial (in the case of dinner, bedtime) SMPG will be used, depending on the preference of the Investigator and patient and consistent with standard of care.These SMPGs, supporting optimization of the basal and mealtime insulin dose are recommended to be recorded in the e-diary at least weekly; they will be uploaded in the web portal for review by the site or the Sponsor (titration oversight working group). See titration oversight manual. The results will be discussed between Investigator and patient during on-site and scheduled or unscheduled telephone visits at the discretion of the Investigator. 7-point SMPG can also be used for titration oversight.
For SMPG ≤ 3.9 mmol/L (≤ 70 mg/dL) the hypoglycemia form has to be completed.
- l Eight-hour delay must be respected between the last mealtime insulin dose and antibody sampling.
- m Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets.
- n Clinical chemistry: sodium, potassium, creatinine, eGFR (MDRD), ALT, AST, ALP and total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin).
- o Serum lipids: total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides (in fasting conditions).
- p For women of childbearing potential (WOCBP): Serum pregnancy test for screening; urine pregnancy test for subsequent monitoring.

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2.2 LIST OF FIGURES

Not applicable.

3 LIST OF ABBREVIATIONS

ADA:	American Diabetes Association
AE:	adverse event
AESI:	adverse event of special interest
AIA:	anti-insulin antibody
ALP:	alkaline phosphatase
ALT:	alanine transaminase
ANCOVA:	analysis of covariance
ARAC:	Allergic Reaction Assessment Committee
AST:	aspartate transaminase
BP:	blood pressure
CI:	confidence interval
CPK:	creatine phosphokinase
CSII:	continuous subcutaneous insulin infusion
CSR:	clinical study report
CV:	curriculum vitae
DBP:	diastolic blood pressure
DKA:	diabetic ketoacidosis
DRF:	discrepancy resolution form
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
FPG:	fasting plasma glucose
FSH:	follicle stimulating hormone
GAD:	glutamic acid decarboxylase
GCP:	good clinical practice
GLP-1:	glucagon-like peptide-1
HbA1c:	glycated hemoglobin A1c
HBs-Ag:	Hepatitis B surface antigen
HC-Ab:	Hepatitis C antibody
HDL:	high-density lipoprotein
HLGT:	high level group term
HLT:	high level term
HRT:	hormonal replacement therapy
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
INR:	international normalised ratio
IRB/IEC:	Institutional Review Board / Independent Ethics Committee
IRT:	interactive response technology
ITT:	intent-to-treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system

J-S:	James-Stein
LDL:	low-density lipoprotein
LLT:	lower level term
LS:	least squares
MCMC:	Markov Chain Monte Carlo
MDI:	multiple daily injection
MDRD:	Modification of Diet in Renal Disease
MedDRA:	Medical Dictionary for Regulatory Activities
NGSP:	National Glycohemoglobin Standardization Program
NIMP:	noninvestigational medicinal product
NovoLog:	Novo Nordisk's insulin aspart, US-approved
NovoRapid:	Novo Nordisk's insulin aspart, EU-approved
NYHA:	New York Heart Association
OAD:	oral antidiabetic drug
PCSA:	potentially clinically significant abnormality
PT:	preferred term
PTC:	Product Technical Complaint
rDNA:	recombinant DNA
SAE:	serious adverse event
SBP:	systolic blood pressure
SC:	subcutaneous(ly)
SD:	standard deviation
SMPG:	self-measured plasma glucose
SMQ:	standardized MedDRA query
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T1DM:	type 1 diabetes mellitus
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
TG:	triglycerides
ULN:	upper limit of the normal laboratory range
WOCBP:	woman of child-bearing potential
β-HCG:	β-human chorionic gonadotropin

4 INTRODUCTION AND RATIONALE

Intensive insulin therapy (multiple daily injection [MDI], with 3 or more injections per day of insulin or continuous subcutaneous insulin infusion [CSII], ie, insulin pump therapy) was demonstrated in the Diabetes Control and Complications Trial (6, 7) to result in improved blood glucose control and reduced micro-vascular complications and neuropathy (6). According to the American Diabetes Association (ADA), recommended therapy for type 1 diabetes mellitus (T1DM) (8) consists of: 1) use of multiple-dose insulin injections (three to four injections per day of basal and prandial insulin) or CSII therapy; 2) matching prandial insulin to carbohydrate intake, pre-meal blood glucose, and anticipated activity; and 3) most individuals should use rapid-acting insulin analogs to reduce hypoglycemia risk (1). In patients with type 2 diabetes mellitus (T2DM) who are insufficiently controlled on basal insulin with or without metformin and other non-insulin antihyperglycemic drugs, initiation of rapid acting insulin is recommended. With further progression of the diabetes due to the progressive β -cell failure, insulin replacement using a multiple daily injection regimen (with a standard method for adjusting insulin dose that may include matching prandial insulin to carbohydrate intake) is indicated in patients with T2DM to manage hyperglycemia (9).

SAR341402 is insulin aspart, a rapid-acting human insulin analog of recombinant DNA (rDNA) origin. Insulin aspart (rDNA origin) is the active ingredient of NovoLog/NovoRapid, which has been approved and marketed in many countries worldwide since 1999. Apart from the exchange of proline at position 28 of the B chain for aspartic acid, insulin aspart is structurally identical to human insulin. This modification renders the insulin molecule less prone to self-associate into hexamers and accounts for faster absorption and activity as compared to human insulin given subcutaneously (SC).

Further details on SAR341402 can be found in the Investigator's Brochure SAR341402, latest Edition.

The objectives of Study EFC15081 will be to demonstrate the non-inferiority of SAR341402 versus NovoLog/NovoRapid on glycemic control measured as the glycated hemoglobin A1c (HbA1c) reduction from baseline to Week 26, to assess the immunogenicity of SAR341402 and NovoLog/NovoRapid by measuring anti-insulin antibodies (AIAs) and to determine the safety of SAR341402 and NovoLog/NovoRapid.

Patients with T1DM or with T2DM on insulin treatment for at least one year with a measured HbA1c in the range of 7% to 10% on a multiple daily insulin injection treatment regimen with insulin glargine (100 U/mL) or insulin detemir (100 U/mL, Levemir) and that includes either NovoLog/NovoRapid or insulin lispro 100 U/mL as the rapid-acting insulin are eligible for the study (refer to [Section 7.1](#)). For exclusion criteria, see [Section 7.2](#).

A total of approximately 580 patients will be randomized to one of the two treatment groups, SAR341402 or NovoLog/NovoRapid (1:1). Randomization will be stratified according to geographical region (Europe, US, Japan), type of diabetes (T1DM, T2DM [T2DM only for US]), patients screening HbA1c (<8.0%, \geq 8.0%), and prior use of NovoLog/NovoRapid (Yes, No).

The primary efficacy analysis will test non-inferiority of SAR341402 compared to NovoLog/NovoRapid in terms of HbA1c change from baseline to Week 26. A non-inferiority margin of 0.3 % HbA1c has been defined, which is in line with recommendations by regulatory agencies ([10](#), [11](#)). HbA1c reflects glycemic control over the last 2 to 3 months and has been accepted as measure of overall, long-term blood glucose control in patients with diabetes. HbA1c is an appropriate primary endpoint to support a claim based on glycemic control.

Secondary efficacy analyses will include percentage of patients reaching HbA1c <7%, fasting plasma glucose (FPG; central laboratory) and change in the mean 24-hour glucose concentration and post-prandial plasma glucose excursions from baseline to Week 26 based on self-measured plasma glucose (SMPG) profiles (7-point glucose profiles).

The immunogenic potential will be assessed by determination of antibody formation to SAR341402 or NovoLog/NovoRapid. Antibody titers and cross-reactivity to human insulin will also be determined. Clinically relevant AIA formation in response to exposure to an insulin product may change the pharmacokinetics and pharmacodynamics of the insulin by binding the insulin or even neutralizing the insulin, resulting in an overall unstable glycemic control and increase in HbA1c. This supports further the primary endpoint HbA1c in study EFC15081. In order to assess the clinical relevance of the AIAs, analyses will be conducted to investigate the relationship of AIAs with efficacy and safety endpoints ([12](#), [13](#)).

Safety evaluation will be based on hypersensitivity reactions, injection site reactions, hypoglycemia (classification according to ADA definition [[3](#)]), treatment-emergent adverse events (TEAEs), vital signs, and laboratory data.

Analyses will be presented overall (US-approved NovoLog [hereafter referred to as NovoLog]/EU-approved NovoRapid [hereafter referred to as NovoRapid] and the corresponding SAR341402 groups) and then for the subgroups comparing SAR341402 with NovoLog in patients randomized in the US (approximately 330 patients, 230 with T1DM, 100 with T2DM) and comparing SAR341402 and NovoRapid in regions using NovoRapid (approximately 250 patients with T1DM). Further subgroup analyses will be defined in the SAP.

The study will consist of a 2-week screening period, a 26-week active-controlled treatment period, a 26-week comparative safety extension period and a 1-day follow-up period.

At the end of the screening period, eligible patients will be randomized to SAR341402 or NovoLog/NovoRapid and depending on their prior basal insulin treatment switch to the mandatory basal insulin Lantus (insulin glargine 100 U/mL) or continue to use once daily Lantus (insulin glargine 100 U/mL). Patients will adjust the basal and mealtime insulin throughout the treatment and safety extension period to reach or maintain glucose control. SAR341402 will be administered using the SAR341402 SoloSTAR disposable pen. NovoLog/NovoRapid will be injected using the NovoLog/NovoRapid FlexPen.

Risk Benefit Assessment

NovoLog has been marketed since 2000 and NovoRapid since 1999, and their safety profiles are well documented. No relevant quantitative or qualitative differences in the safety profile are expected for SAR341402. The adverse reactions observed with NovoLog and NovoRapid are known in the pharmacological class of blood glucose-lowering drugs and common to insulin products. A comparable safety profile is expected for SAR341402.

Efficacy of NovoLog and NovoRapid are well described and SAR341402 is expected to have a similar efficacy.

5 STUDY OBJECTIVES

The primary objective will be assessed at the end of the main 6-month period (Week 26), and the result will be presented in the 6-month clinical study report (CSR).

The secondary objectives will be assessed for both the main 6-month (up to Week 26) and 12-month (up to Week 52, including the safety extension) periods, and the results will be presented respectively in the 6-month and 12-month CSR.

5.1 PRIMARY

- To demonstrate non-inferiority of SAR341402 versus NovoLog/NovoRapid in HbA1c change from baseline to Week 26 in patients with T1DM or T2DM also using Lantus.

5.2 SECONDARY

- To assess the immunogenicity of SAR341402 and NovoLog/NovoRapid in terms of positive/negative status and AIA titers during the course of the study.
- To assess the relationship of AIAs with efficacy and safety.
- To assess the efficacy of SAR341402 and NovoLog/NovoRapid in terms of proportion of patients reaching HbA1c <7.0% and change in HbA1c, FPG and SMPG profiles from baseline to Week 26 and Week 52 (only Week 52 for HbA1c).
- To assess safety of SAR341402 and NovoLog/NovoRapid.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

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

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

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

The protocol-mandated background therapy is the insulin glargine (Lantus), which will be continued throughout the study, including the comparative safety extension period.

Approximately 580 patients will be randomized to the rapid-acting insulins SAR341402 or NovoLog/NovoRapid in a 1:1 ratio at the end of the screening period.

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

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

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

Patients with T1DM or T2DM (T2DM US only) on a MDI regimen are eligible for the study. The clinical data that support the diagnosis of T1DM or T2DM are placed into the source documentation prior to randomization. Antibodies such as glutamic acid decarboxylase (GAD) antibodies or C-peptide levels may be supportive but are not alone considered diagnostic of T1DM, and in this trial are not assessed at screening. Patients with late onset T1DM are not excluded from the study. The diagnosis of T2DM will be based on the medical history, including high blood glucose levels caused by a lack of insulin and/or insulin resistance, with an onset most often in middle-aged and older adults. Common co-morbidities include obesity, hypertension, and hyperlipidemia. Insulin is typically initiated when diet and life-style changes, followed by add-on metformin and other oral antihyperglycemic drugs, have failed. The exclusion criteria in this trial based on the pre-trial basal and rapid-acting insulin include: use of an insulin pump in the

3 months before screening visit, use of basal insulin other than insulin glargine in the 6 months before screening visit or insulin detemir in the 12 months before screening visit and use of rapid-acting insulin other than Novolog/NovoRapid or insulin lispro in the 6 months before screening visit.

The dose of SAR341402/NovoLog/NovoRapid will be adjusted at each meal and snack (“meal or snack” will be hereafter referred to as “meal”) by the patient based on the pre-meal SMPG and an assessment of the carbohydrate content of the meal (when available). Changes in activity may also be taken into account.

SAR341402/NovoLog/NovoRapid will be injected SC immediately (within 5 to 10 minutes) before meal intake. Occasional postprandial injection soon after meal intake may be done if deemed necessary and if allowed by the national product label for NovoLog/NovoRapid.

Lantus will be injected SC once daily. The dose of Lantus is to be optimized based on the fasting (prebreakfast) SMPG, and with the titration goal being an SMPG of 4.4 to 7.2 mmol/L (80 to 130 mg/dL), while avoiding hypoglycemia.

At the screening visit, patients will be familiarized with the use of the insulin pens and will be shown how to accurately measure plasma glucose values with the Sponsor glucometer provided in this study. Study patients will be given detailed instruction on use of the electronic diary (e-diary) according to manufacturer’s instructions and how to transfer data from the glucometer to the e-diary. This will include how to assign SMPG and insulin doses that are related to routine “usual habit” daily use and how to assign the 7-point SMPG profiles at pre-specified times that are needed for endpoint analysis. In addition to SMPG measurement per “usual habit”, fasting prebreakfast SMPGs and 3- or 4-point profiles are recommended for site oversight of insulin titration and are not used for endpoint analysis. All data captured in the e-diary including insulin dosing data will be available via the vendor web based portal for review by the Site, Monitoring team and Clinical Study Director.

Detailed instruction will be provided on completion of the hypoglycemic episode diary pages in the e-diary and the importance of avoiding missing data. This training will be repeated at the randomization visit, as needed.

Patients who are unable or unwilling to use the electronic diary during the screening period will be excluded from randomization since there is no alternate paper diary. Patients who have not completed the minimum of 5 out of 7 measurements for either of the 2 required 7-point profiles at baseline are not randomized.

All study patients will receive intensive training at the time of randomization in techniques of using MDI by a trained professional. This may include carbohydrate counting/estimation and dose adjustment for food. When used, supplemental/correction scales for glucose out of goal range and carbohydrate counting ratios will be reviewed and assigned according to insulin sensitivity and previous use, and recorded in source documents at the randomization visit. Review of dosage self-adjustment and re-instruction on MDI will be done at each visit.

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

For each patient, the maximum study duration will be 54 weeks per patient + 1 day safety follow-up.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study in all countries concerned by the trial is reached as soon as the last patient has completed all the scheduled study procedures.

6.3 INTERIM ANALYSIS

No interim analysis is planned for this study. The study will not be terminated early for positive efficacy or safety.

6.4 STUDY COMMITTEES

Allergic Reaction Assessment Committee (ARAC)

As a biological protein, insulin has the potential to be immunogenic. Therefore an Allergic Reaction Assessment Committee (ARAC) independent from the Sponsor and the Investigators will be implemented. The ARAC consists of 4 permanent members who are experts in the field of allergy and at least one of the members will be a diabetologist. The members of the ARAC will be blinded regarding the study treatment.

The mission of the ARAC will be:

- To adjudicate all potential hypersensitivity or hypersensitivity-like events and determine the nature of each event.
- To assess a potential association of the hypersensitivity or hypersensitivity-like event with AIAs (see [Section 9.2.1](#)).
- To recommend a follow up of patients with increase of AIA titers as defined in the ARAC charter and ongoing hypersensitivity or hypersensitivity like events and/or potential indicators of reduced efficacy as defined in the ARAC charter.

The ARAC reviews the reported cases, determines the nature of the events, and based on the information reported by the Investigator confirms whether or not the event is allergic in nature. All ARAC reviews are recorded in addition to the Investigator's assessment. List of allergic reaction codes will be included in the ARAC charter and in the statistical analysis plan (SAP).

Members of the ARAC team will review relevant AIA data and determine if a high titer of AIA correlates with decreased efficacy or an increase in immunological or hypersensitivity reactions. If follow-up of AIA titers by ARAC is recommended, they will be followed up by the Sponsor until return to baseline or until the ARAC decides that no further follow-up is deemed necessary.

A detailed charter describes the ARAC procedures.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

- I 01. Patients with T1DM or with T2DM (T2DM US only) diagnosed for at least 12 months, and have been treated with an MDI regimen with
- NovoLog/NovoRapid
OR
insulin lispro (100 U/mL) in the last 6 months prior to screening visit
- AND
- insulin glargine (100 U/mL) in the last 6 months prior to screening visit
OR
insulin detemir (Levemir) in the last **12 months** prior to screening visit
- I 02. Signed written informed consent obtained.

7.2 EXCLUSION CRITERIA

Patients who have met all the inclusion criteria listed in [Section 7.1](#) will be screened for the following exclusion criteria:

7.2.1 Exclusion criteria related to study methodology

- E 01. At screening visit, age under legal age of adulthood.
- E 02. HbA1c <7% or >10% at screening.
- E 03. Less than 1 year on continuous insulin treatment.
- E 04. Use of insulin pump in the last 3 months before screening visit.
- E 05. Patients with T1DM: Use of glucose-lowering agents other than insulin including use of non-insulin injectable peptides in the last 3 months prior to screening.
- E 06. Patients with T2DM:
- Use of glucagon-like peptide-1 (GLP-1) receptor agonists in the last 3 months before screening visit,
 - Use of oral antidiabetic drugs (OADs) not on stable dose in the last 3 months before screening visit (sulfonylureas will be discontinued at baseline).

- E 07. Use of insulin other than
- insulin glargine 100 U/mL and NovoLog/NovoRapid or insulin lispro 100 U/mL as part of a multiple injection regimen in the last 6 months before screening visit, OR
 - insulin detemir 100 U/mL in the 12 months before screening visit and NovoLog/NovoRapid or insulin lispro 100 U/mL in the last 6 months before screening visit as part of a multiple injection regimen.
- E 08. At screening visit, body mass index (BMI) $\geq 35 \text{ kg/m}^2$ in patients with T1DM and $\geq 40 \text{ kg/m}^2$ in patients with T2DM.
- E 09. Positive serum pregnancy test in women of childbearing potential (WOCBP).
- E 10. Patients who have impaired renal function with estimated glomerular filtration rate (eGFR) (using the Modification of Diet in Renal Disease [MDRD] formula) $< 30 \text{ mL/min/1.73/m}^2$.
- E 11. Liver injury related criteria:
- Alanine transaminase (ALT) or aspartate transaminase (AST): > 3 upper limit of the normal laboratory range (ULN),
 - Total bilirubin > 1.5 ULN (except in case of Gilbert's syndrome).
- E 12. Positive test for Hepatitis B surface antigen (HBs-Ag) and/or Hepatitis C antibody (HC-Ab). In the case of a positive HC-Ab test, negative Hepatitis C RNA test determines absence of active infection and patient is not excluded.
- E 13. Uncontrolled treated/untreated hypertension (systolic blood pressure [SBP] $> 180 \text{ mmHg}$ and/or diastolic blood pressure [DBP] $> 95 \text{ mmHg}$ at screening as the recorded screening blood pressures [BPs], refer to [Section 9.2.3.2.5](#)).
- E 14. Patients with severe or unstable hepatic, gastrointestinal, cardiovascular (including congestive heart failure New York Heart Association [NYHA] III/IV, history of myocardial infarction, stroke or heart failure requiring hospitalization in the last 3 months prior to screening visit), respiratory, neurological, psychiatric, hematological, renal, endocrine, dermatological disease, active malignant tumor, other major systemic disease or patients with short life expectancy or any other medical condition that might interfere with the evaluation of study medication according to Investigator's medical judgment.
- E 15. Any clinically significant abnormality identified on physical examination, laboratory tests or ECG that in the judgment of the Investigator or any subInvestigator would preclude safe completion of the study or constrains efficacy assessment.
- E 16. Known history of drug or alcohol abuse within 6 months prior to the time of screening.
- E 17. Participation or planned participation in another clinical study other than disease registries.
- E 18. Use of investigational drugs or prohibited therapy for this study within 3 months or 5 half-lives, whichever is longer, prior to the screening visit.

E 19. Conditions/situations such as:

- Status post pancreatectomy,
- Status post pancreas and/or islet cell transplantation,
- History of severe hypoglycemia requiring Emergency Room admission or hospitalization in the last 3 months before screening visit,
- Hospitalization for recurrent diabetic ketoacidosis (DKA) in the last 3 months before screening visit,
- Patients with conditions/concomitant diseases making them non evaluable for the primary efficacy endpoint (eg, hemoglobinopathy or hemolytic anemia, receipt of blood products within the last 3 months prior to the screening visit); any anemia with anticipated rapid correction,
- Patients with conditions/concomitant diseases precluding their safe participation in this study (unstable proliferative diabetic retinopathy or any other rapidly progressive diabetic retinopathy or macular edema likely to require treatment [eg, laser, surgical treatment or injectable drugs, etc]) during the study period,
- No latest exam by an ophthalmologist (US/Canada: ophthalmologist or optometrist) within 12 months for patients with retinopathy or within 24 months for those with no evidence of retinopathy (exam during the screening period is acceptable, too),
- Impossibility to meet specific protocol requirements (eg, scheduled visits, patients unable to fully understand patient's study documents and to complete them, etc) including conditions that could make the patient potentially non-compliant to the study procedures,
- Patient is an employee of Sanofi or of sponsor representatives, the Investigator or any SubInvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol,
- Use of systemic glucocorticoids (excluding topical application or inhaled forms) greater than replacement dose for one week or more within 3 months prior to screening visit,
- Likelihood of requiring treatment during the study period with drugs not permitted by the study protocol.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

- E 20. Any contraindication to use of insulin glargine and/or NovoLog/NovoRapid as defined in the national product labels; history of hypersensitivity to insulin glargine and NovoLog/NovoRapid, or to any of the excipients.
- E 21. Pregnant or breast-feeding women.
- E 22. Women of childbearing potential not protected by highly-effective method(s) of birth control and/or who are unwilling or unable to be tested for pregnancy (see contraceptive guidance in [Appendix A](#)). Pregnancy tests may be performed more frequently in some countries due to local legislations related to WOCBP randomized in clinical trials.

7.2.3 Additional exclusion criteria during or at the end of screening before randomization

- E 23. Patients who have incomplete baseline 7-point SMPG profile data, defined as patients who do not have 7-point profiles with at least 5 points on at least 2 days in the week before randomization Visit 3.
- E 24. Patients who have demonstrated during the screening period an unwillingness or inability to use the electronic diary according to Investigator's discretion.
- E 25. Patient who has withdrawn consent before randomization.
- E 26. Any country-related specific regulation that would prevent the subject from entering the study.

A patient should not be randomized more than once. In cases where original screen failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment, the patient can be rescreened one time for this study.

8 STUDY TREATMENTS

Diet and lifestyle counseling is an essential component of this trial. At randomization, a detailed session by a professional competent in treating T1DM or T2DM (as appropriate) will include training in dosage adjustment, consistent with the recommendations of international or local guidelines and practices for T1DM or T2DM patients. This may include patients who perform flexible dosing as well as those who choose to use consistent dosing with more consistent food intake. Compliance with recommendations for insulin dose changes and general information regarding diet and lifestyle recommendations consistent with local practices will be discussed with the patient throughout the study ([Section 1.2](#)), and more specifically in case of insufficient glucose control ([Section 8.1.6](#)).

Investigators and site staff will be required to routinely provide oral instructions, written educational material and training consistent with local practices and individualized for each patient to ensure that the patients understand the importance of routine monitoring and routine dose self-adjustment of their rapid-acting insulin. The goal for all patients must be to attain good glycemic control by titrating to the defined glucose targets without increase of hypoglycemia. Monitoring of the insulin doses and changes in the titration recommendations are made by the Investigators and subInvestigators who are qualified to do so and who are trained in the protocol.

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Name of the investigational medicinal product

SAR341402 product (Sanofi's insulin aspart) (tested drug) and NovoLog/NovoRapid (Novo Nordisk's insulin aspart) (comparator/control drug).

The NovoLog and NovoRapid comparator will be used at sites depending on the countries and will be clearly identified.

8.1.2 Pharmaceutical forms of the investigational medicinal product and injection devices

SAR341402 will be provided as SAR341402 SoloSTAR pen and NovoLog/NovoRapid as NovoLog/NovoRapid FlexPen.

Handling procedures of the pen and needles, administration technique and storage instructions are provided in an instruction leaflet. Patients will be trained by the study staff on the use of the injection devices and needles used in this study in addition to being provided with these instruction materials. No training kits are provided for either investigational medicinal product (IMP).

For the duration of the study, the patients will be required to use the study drug pens and needles supplied by the Sponsor. Different needle lengths supplied may be used interchangeably.

Any defect in the insulin pens must be reported as soon as possible by the Investigator to the monitoring team that will complete a Product Technical Complaint (PTC) 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 adverse event (AE) or serious adverse event (SAE).

Mixing of either SAR341402 or NovoLog/NovoRapid with other insulin is not allowed nor is dilution.

8.1.2.1 SAR341402

The tested drug SAR341402 will be supplied as a 100 U/mL solution for SC injection in 3 mL pre-filled disposable SAR341402 SoloSTAR pens, allowing a maximum dose of SAR341402 per injection of 80 units and minimum dose of 1 unit.

The following commercial pen needles will be provided for use with the SAR341402 SoloSTAR pen:

- BD Ultra-Fine Needles 31 G x 5 mm.
- BD Ultra-Fine Needles 31 G x 8 mm.

In countries where the BD Ultra-Fine needle is not available, the smallest bore BD needle available will be used.

Patients who are randomized to SAR341402 are trained on the use of the study drug pen and needles by the study staff and provided with an instruction leaflet during the randomization visit (Visit 3, Day 1).

8.1.2.2 NovoLog/NovoRapid

The comparator drug, NovoLog/NovoRapid, will be supplied as a 100 U/mL insulin solution for SC injection in the 3 mL NovoLog/NovoRapid FlexPen disposable prefilled pens, allowing a maximum dose of the NovoLog/NovoRapid of 60 units and minimum dose of 1 unit.

The following commercial pen needles will be provided for use with the NovoLog/NovoRapid FlexPen:

- BD Ultra-Fine Needles 31 G x 5 mm.
- BD Ultra-Fine Needles 31 G x 8 mm.

In countries where the BD Ultra-Fine needle is not available, the smallest bore BD needle available will be used.

Patients will be trained on the use of NovoLog/NovoRapid FlexPen and provided with an instruction leaflet during the randomization visit (Visit 3, Day 1).

8.1.3 Route and method of investigational medicinal product administration

SAR341402 or NovoLog/NovoRapid is self-administered by SC injection, in the abdominal wall, thighs, upper arms, or the deltoid or gluteal region. The area of the injections will be consistent with the habits of the individual patient. Injection sites will be rotated within that area. Changes in the area of injection during the study should be avoided as far as possible. The area of injection will be entered into the electronic case report form (e-CRF) at each study visit. The injection areas for IMP and noninvestigational medicinal product (NIMP) should be different so that any injection site reactions can be attributed specifically either to IMP (SAR341402; NovoLog/NovoRapid) or NIMP (Lantus).

8.1.3.1 SAR341402

- Patients randomized to SAR341402 will be supplied with the appropriate number of disposable SAR341402 SoloSTAR pens specifically labeled for the use in the study where required by local regulation along with BD needles. These will be dispensed at all subsequent on site visits up to Visit 11 (Week 40) included. The appropriate number of kits will be dispensed to cover up to the next dispensation visit (please refer to flowchart in [Section 1.2](#)).
- Each SAR341402 SoloSTAR pen contains a cartridge with a total of 300 units of SAR341402. Doses can be set in increments of 1 U up to a maximum single injection of 80 U. If a dose greater than 80 units is required, it will be given as two or more consecutive SC injections at the same time with the dose split in equal or close to equal doses.

8.1.3.2 NovoLog/NovoRapid

Patients randomized to NovoLog/NovoRapid will be supplied with the appropriate number of NovoLog/NovoRapid FlexPen disposable prefilled pens specifically labeled for the use in the study where required by local regulation along with BD needles. These will be dispensed at all subsequent on-site visits up to Visit 11 (Week 40) included. The appropriate number of kits will be dispensed to cover up to the next dispensation visit (please refer to flowchart [Section 1.2](#)).

- Each NovoLog/NovoRapid FlexPen contains a total of 300 units of NovoLog/NovoRapid. Doses can be set in increments of 1 U up to a maximum single injection of 60 U. If a dose greater than 60 units is required, it will be given as two or more consecutive SC injections at the same time with the dose split in equal or close to equal doses.

8.1.4 Timing of investigational medicinal product administration

SAR341402 or NovoLog/NovoRapid is self-administered by SC injection immediately (within 5 to 10 minutes) prior to the start of a meal. When necessary, NovoLog/NovoRapid can be given soon after a meal, if allowed by the national product label.

8.1.5 Dose of investigational medicinal product

8.1.5.1 Starting dose

At baseline, patients will be randomized to SAR341402 or NovoLog/NovoRapid, with a unit to unit conversion from the insulin lispro or NovoLog/NovoRapid dose used prior to the trial or with a dose at the discretion of the Investigator, taking into account the glucose control at the time of randomization. The usual or average total daily dose of insulin lispro or NovoLog/NovoRapid and the average number of daily mealtime injections used in the screening period are recorded once in the clinical database at the time of randomization. The patient's usual supplemental/correction scale if one is used is recorded in source.

8.1.5.2 Dose adjustment

Changes in the SAR341402 or NovoLog/NovoRapid dose will be based on SMPG measurements and the carbohydrate content of the meal (when available).

Doses will be self-titrated by the patients to achieve a 2-hour postprandial plasma glucose of <10.0 mmol/L (<180 mg/dL) while avoiding hypoglycemia. 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 (1). 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 patients, if deemed necessary, eg, due to age, comorbid conditions, and individual patient considerations. The individual targets will be recorded in source documents. Insulin doses may be reduced or modified at any time for hypoglycemia.

Patients who experienced mild to moderate hypoglycemia as a result of a missed meal, unusual exercise or alcohol use will be counseled on the correction of those behaviors and will not have their insulin dose decreased.

Regular plasma glucose monitoring is important to achieve these plasma glucose targets. Efforts should be made to reach the target range for fasting, prebreakfast plasma glucose and 2-hour postprandial or premeal plasma glucose in the first 12 weeks of the study.

The doses of the mealtime insulin should be reviewed when the basal insulin dose is increased, as they may have to be reduced to avoid daytime hypoglycemia.

On specified days (refer to [Section 9.2.2.2.3](#), [Section 9.3.2](#) and titration manual), patients must record all of the SAR341402 or NovoLog/NovoRapid doses, and the Lantus dose in their e-diary. SMPG and insulin doses are used to adjust doses of both basal and rapid-acting insulin and monitor trends in use of insulin. Insulin doses related to specified days are transferred to the clinical database.

8.1.6 Evaluation of patients not meeting glycemic goals

In addition to the scheduled SMPG done by patients, central laboratory alerts on FPG and on HbA1c are set up to ensure that glycemic parameters remain below predefined threshold values. There is no specified rescue treatment. The thresholds values are defined as follows:

- From Visit 7 (Week 12) onwards and inclusive to Visit 9 (Week 26): FPG >11 mmol/L (>200 mg/dL) or HbA1c >8.5%.
- In case of FPG or HbA1c above the target values and/or SMPG are not improving as expected in spite of successive insulin dose titration, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:
 - Plasma glucose was actually measured in fasting condition (ie, after at least 8 hours fasting),
 - Rebound hyperglycemia is excluded,
 - IMP dose is properly adjusted,
 - NIMP dose is properly adjusted,
 - Correction doses for pre-prandial glucose values above goal are used by patient,
 - 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 carbohydrate content of the meal and SMPG.
- If any of the above can reasonably explain the insufficient glycemic control, the Investigator should undertake appropriate action, ie:
 - Titrate the mealtime insulin dose of IMP,
 - Set up adequate investigation and treatment of inter-current disease (to be reported in AE/SAE/concomitant medication parts of the e-CRF),
 - 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,
 - 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 carbohydrate content of the meal and covering all snacks with a dose of rapid-acting insulin,
 - Schedule a FPG / HbA1c assessment at the next visit.

8.1.7 Reasons for treatment discontinuation

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time. List of criteria for permanent treatment discontinuation are found in [Section 10.3.3](#). Handling of patients after permanent treatment discontinuation is described in [Section 10.3.4](#).

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

Insulin glargine (Lantus), which is to be used as the mandatory background basal insulin therapy throughout the study, is considered NIMP.

At randomization, all patients will be supplied with the appropriate number of disposable Lantus SoloSTAR pens specifically labeled for the use in the study when required by local regulations and needles (BD Ultra-Fine Needles 31 G x 5 mm; BD Ultra-Fine Needles 31 G x 8 mm). These will be dispensed at all subsequent on-site visits up to Visit 11 (Week 40) included. Patients will be trained by the study staff at the site on the use of the injection devices and needles, administration techniques and storage conditions used in this study in addition to being provided with instruction materials.

Similar to IMP, for the duration of the study, the patients will be required to use the NIMP study drug pens and needles supplied by the Sponsor. Different needle lengths supplied may be used interchangeably. In countries where the BD Ultra-Fine needle is not available, the smallest bore BD needle available will be used.

Each Lantus SoloSTAR pen contains 3 mL of solution with a total of 300 units of insulin glargine. Doses can be set in increments of 1 U up to a maximum single injection of 80 U. If a dose greater than 80 units is required, it will be given as two or more consecutive SC injections at the same time with the daily dose split in equal or close to equal doses.

Lantus will be injected once daily SC consistent with the local label. The time of injection (hh:mm) will be fixed at randomization (Visit 3, Baseline) according to patient and site preference.

The area for the injection sites for Lantus injection should be different from that of the IMP so that any injection site reactions can be attributed specifically to the IMP or NIMP. The injection area is recorded in the e-CRF at each study visit.

Mixing of Lantus with other insulin is not allowed, and nor is dilution.

8.2.1 Starting dose of noninvestigational medicinal product (Lantus)

Starting dose of Lantus at randomization will be the same as the last dose of insulin glargine 100 U/mL or insulin detemir prior to baseline visit or at the discretion of the Investigator, taking into consideration the actual glycemic control and usual doses of basal insulin needed to manage diabetes mellitus.

8.2.2 Dose adjustment of noninvestigational medicinal product (Lantus)

Doses of Lantus will be adjusted to achieve glycemic targets without hypoglycemia. Changes in the Lantus dose are based on fasting prebreakfast SMPG measurements using the glucometer provided for this study. Pre-prandial SMPG measurements will be taken into account also.

The recommended target range for fasting, pre-prandial plasma glucose SMPG is 4.4 to 7.2 mmol/L (80 to 130 mg/dL). This target range may be adapted for individual patients, if deemed necessary, (eg, due to age, comorbid conditions, individual patient considerations) so that an individual target range may be appropriate for individual patients. The individual targets for fasting SMPG will be recorded in source documents.

The Lantus dose can be increased, if the median of fasting, pre-prandial plasma glucose over the previous 3 to 4 days is greater than the recommended target range of 4.4 to 7.2 mmol/L (80 to 130 mg/dL), or the individual pre-specified individual fasting SMPG target as recorded in source, and there has been no evidence of relevant hypoglycemia. The increase of the Lantus dose should not exceed 10% of the daily dose of Lantus (8). The Investigator may choose to change rapid-acting insulin doses instead and a change in basal insulin is not required by the protocol. Whenever the basal insulin dose is changed, the rapid-acting insulin doses need to be reviewed to avoid hypoglycemia.

Doses of Lantus may be reduced or modified at any time for hypoglycemia. Patients who experienced mild to moderate hypoglycemia as a result of a missed meal, unusual exercise or alcohol use will be counseled on the correction of those behaviors and will not have their insulin dose decreased.

Glycemic excursions related to inter-current illness should be primarily treated with rapid-acting insulin.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

SAR341402 in the SAR341402 SoloSTAR pen and the control drug, NovoLog/NovoRapid in the NovoLog/NovoRapid FlexPen are distinguishable and so this study is an open-label design. Administration of SAR341402/NovoLog/NovoRapid throughout the trial is to be open-label. Potential bias will be reduced by the following steps:

- The specific treatment to be taken by a participant will be assigned using an interactive response technology (IRT) system.
- HbA1c, FPG, and AIAs are determined in central laboratories blinded to the treatment received.
- The study team will review data including the primary efficacy parameter in descriptive statistics without treatment assignment during data review meetings.
- Members of the study team may review compliance with dosing and titration blinded to treatment; monitoring team is not blinded when reviewing.

- Measures will be undertaken to minimize that the treatment arm is not disclosed to the operational study team.
- At Sponsor level, the unblinded treatment group allocation variable will be included in the clinical study database only at the time of 6-month database lock, to perform the corresponding analyses; summary results by treatment arm will therefore not be available to anyone before the last participant end of main 6-month period and corresponding database lock.
- Medical monitor for insulin oversight will remain blinded to treatment arm.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number list and NIMP kit number list are generated centrally by Sanofi. The IMPs and NIMPs are packaged in accordance with these lists.

The Trial Supply Operation Manager provides the treatment kit number list and the Study Biostatistician provides the randomization scheme (including stratification, see [Section 6.1](#)) to the centralized treatment allocation (IRT) system. Then, the IRT generates the patient randomization list according to which it allocates treatment arms to the patients.

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

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

Randomization ratio is 1:1, stratification will be done by geographical region (Europe, US, Japan), by type of diabetes mellitus (T1DM, T2DM [T2DM only for US]), by HbA1c obtained at the screening visit ($<8.0\%$, $\geq 8.0\%$), and by prior use of NovoLog/NovoRapid (Yes, No).

On Visit 3 (Day 1, Randomization), after all the baseline evaluations have been performed, the Investigator or designee has to call the IRT for the first treatment kit(s) allocation (randomization). Afterwards the IRT is called again each time a new treatment kit(s) allocation is necessary.

A randomized patient is a patient who has been assigned to a randomized treatment arm by the IRT regardless whether the treatment kit was used or not. A patient cannot be randomized more than once in the study. Patients who need to be moved to another site will keep their number.

8.5 PACKAGING AND LABELING

The respective number of the study treatment will be packaged under the responsibility of Sanofi according to good manufacturing practice and local regulatory requirement.

SAR341402, the active IMP, will be supplied in disposable SAR341402 SoloSTAR pens. The content of the labeling will be in accordance with the local regulatory specifications and requirements.

Commercially available comparator NovoLog/NovoRapid and NIMP (Lantus) will be repackaged in study specific kits and relabeled with study specific labels in accordance with local regulatory specifications and regulations.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements for both IMP and NIMP.

8.6 STORAGE CONDITIONS AND SHELF LIFE

Investigators or Pharmacists are responsible for storing throughout the trial both the IMP (not in use SAR341402 or NovoLog/NovoRapid) and also NIMP (not in use Lantus) in a securely locked and safe place in accordance with local regulations and labeling specifications (eg, refrigerated storage), policies, and procedures.

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

In-use pens of investigational medicinal product NovoLog/NovoRapid for use as mealtime insulin for this study and the mandatory basal insulin NIMP Lantus are to be stored by the patients in accordance with the storage conditions indicated on the label of each product. SAR341402 will be stored in accordance with the label for NovoLog/NovoRapid.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP and NIMP will be responsible for ensuring that the IMP and NIMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMP will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP and NIMP issued and returned is maintained.

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

A potential defect in the quality of IMP and 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 IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP or NIMP to a third party and allow the IMP or NIMP to be used other than as directed by this Clinical Trial Protocol or dispose of IMP or NIMP in any other manner.

Investigators in this open-label study are reminded of the need to strictly follow dispensing guidelines using the IRT system in order to perform correct allocation of IMP at each dispensation.

At each on-site visit after baseline as well as at the end of the treatment period, participants will take study drug with them to the site. It is important that sites:

- Instruct patients to take with them all used, unused and in-use IMP/NIMP for each on-site visit.
- Collect from patients all used, unused and in-use study treatments starting from Visit 5 (Week 4) which is the first on site visit after randomization.
- Be available to discuss the patient's progress, dose regimens, and data from the study (hypoglycemic events, HbA1c) with future caregivers as needed.
- Review patients' prior regimens and give a reminder about follow-up care, no later than the visit prior to the end-of-treatment visit.
- At end of treatment period: remind patients to arrange for follow-up care and supply of insulin from their physician, before the end of treatment visit.

8.7.1 Treatment accountability and compliance

At each visit, the Investigator or his/her delegate asks the patient about administered doses of IMP (SAR341402 or NovoLog/NovoRapid) and NIMP (Lantus).

An adequate supply of labeled IMP and NIMP treatment kits with shelf life adequate to reach the next in-person visit will be provided at each on site visit starting with Visit 3 (Day1, baseline).

Treatment kits (used, unused and in-use) are returned by the patient at each on-site visit. The Investigator or delegate has to inspect IMP and NIMP remaining in the returned kits are consistent with dose used. Discrepancies will be addressed to the patient for clarification of real treatment administration.

The Investigator or delegate fills the Product Accountability Form per patient based on the used/unused IMP and NIMP kits returned.

The monitor in charge of the study then checks the data entered on the IMPs administration page by comparing them with the IMPs that has been retrieved and the Product Accountability Form per patient.

Similar to use of IMP, patients have to record the administration of their mandatory background NIMP, Lantus, in the electronic patient diary.

8.7.2 Return and/or destruction of treatments

Investigational medicinal product and NIMP reconciliation must be performed at the site by the Investigator (or the Pharmacist) and the monitoring team using the Product Accountability Forms (at site level and patient level) countersigned by the Investigator (or the Pharmacist) 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.

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

A potential defect in the quality of IMP or 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.

In case of a clear relationship of a SAE to NIMP, the batch number of the NIMP administered during the occurrence of the event has to be documented in the patient source.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to IMP treatment.

Short term therapy (less than 10 days maximum) with either basal insulin or short acting insulin not specified in this study protocol such as may occur due to acute illness or surgery is allowed.

8.8.1 Prohibited concomitant therapy

The following drugs are not permitted during the screening period and the randomized open-label treatment periods:

- Any glucose-lowering agents including injectable non-insulin peptides such as Symlin[®] and GLP-1 receptor agonists other than the IMP, authorized insulin analog SAR341402 or NovoLog / NovoRapid and the background basal anti-diabetic therapy (Lantus). Patients on insulin lispro 100 U/mL are permitted to continue their mealtime insulins during the screening period until randomization.
- Systemic glucocorticoids at doses greater than replacement for more than 10 days (topical or inhaled applications are allowed).
- Insulin pump therapy.
- Initiation of body weight loss drugs.
- Any other investigational product (ie, participation in another clinical trial).

Patients with T2DM using OADs prior to the study may continue using them on stable dose except sulfonylureas, which must be discontinued at baseline and cannot be used during the study.

There is no rescue therapy defined for this study.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

All biological efficacy and safety analysis will be performed by a Central Laboratory. Secondary assessments with SMPG will include analysis of 7-point SMPG profiles, including post meal excursions. Detailed information on samples drawing, management, and analysis will be provided in a specific manual.

9.1 PRIMARY ENDPOINT

The primary endpoint is change in HbA1c (%) from baseline to Week 26.

For assessment methods refer to [Section 9.2.2.2.1](#).

9.2 SECONDARY ENDPOINTS

9.2.1 Immunogenicity endpoints

- Anti-SAR341402/NovoLog/NovoRapid antibody positive/negative status, titers and cross-reactivity to human insulin at each sampling visit up to Week 26, and during the extension period up to Week 52.
- Treatment-induced, treatment-boosted and treatment-emergent (treatment induced plus treatment boosted) AIAs (2) during the main 6-month and the 12-month on-treatment periods (refer to [Section 9.2.1.1](#) for definition of on-treatment periods).

9.2.1.1 *Observation period of immunogenicity variables*

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

9.2.1.2 *Immunogenicity assessments*

For the assessment of immunogenicity the anti-SAR341402 / anti-NovoLog/NovoRapid antibody status (positive or negative), anti-SAR341402 / NovoLog/NovoRapid antibody titer at baseline and during the course of the clinical study as well as the cross-reactivity to human insulin will be evaluated.

Blood samples for AIAs will be taken at 6 visits: Visit 3 (Day 1, baseline), Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 26, Endpoint), Visit 11 (Week 40) and Visit 12 (Week 52, end of treatment) (see flowchart, [Section 1.2](#)). They will be determined in a blinded fashion at a centralized laboratory using a validated AIA binding assay.

In subjects who present with elevated AIA titers above baseline at endpoint and in whom the ARAC assesses AIA-mediated hypersensitivity reaction or effects on efficacy or safety, the increased AIA titers will be followed until return to baseline or until the ARAC decides that no further follow-up is deemed necessary.

Detailed procedures for sample preparation, storage and shipment as well as exact AIA sampling times in relation to the last injection of mealtime insulin will be described in the specific laboratory manual.

9.2.1.3 Immunogenicity variables definition

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

- Patients with treatment-induced AIAs will be defined as patients with AIAs that developed de novo (seroconversion) following the IMP administration (ie, patients with at least one positive AIA sample at any time during the on-treatment period, in those patients without pre-existing AIA or with missing sample at baseline).
- Patients with treatment-boosted AIAs will be defined as patients AIA positive at baseline that were boosted to a significant higher titer following the IMP administration (ie, patients with at least one AIA sample with at least a 4-fold increase in titers compared to baseline value at any time during the on-treatment period, in those patients with preexisting AIA).

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

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

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

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

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

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

9.2.2 Secondary efficacy endpoints

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

At Week 26 and Week 52:

- The percentage of patients with HbA1c <7% (HbA1c responders; Yes/No variable). Patients without assessment will be considered as failure.
- Change from baseline in FPG.
- Change from baseline in the mean 24-hour plasma glucose concentration, based on the 7-point SMPG profiles.
- Change from baseline in postprandial plasma glucose excursions (difference between 2-hour postprandial and pre-prandial plasma glucose values at breakfast, lunch and dinner), based on the 7-point SMPG profiles.
- Change from baseline in 7-point SMPG profiles per time-point.

9.2.2.1 Observation period of efficacy variables

- The 6-month randomized period is defined as the time from randomization up to Week 26 (Visit 9).
- The 12-month randomized period is defined as the time from randomization up to Week 52 (Visit 12).

9.2.2.2 Efficacy assessment methods

9.2.2.2.1 Hemoglobin A1c

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified Level I “National Glycohemoglobin Standardization Program” central laboratory according to [Section 1.2](#).

9.2.2.2.2 Fasting plasma glucose

Blood samples for FPG measurement are taken and measured at central laboratory according to [Section 1.2](#).

9.2.2.2.3 *Self-measured plasma glucose profiles and plasma glucose during symptomatic hypoglycemia*

At Visit 1 (Week -2, screening), the Investigator or a member of the investigational staff will provide patients with glucometer provided by the Sponsor including the corresponding supplies (needles, control solutions, test strips etc). Intensive training on the correct handling (including checks with the control solution of the glucose meter provided by the Sponsor) will be provided at the screening visit (Visit 1, Week -2) and baseline visit (Visit 3, Day 1). Regular refresher instructions will be provided at each visit throughout the study.

All plasma glucose values collected in the study, including during the screening period to document compliance and including 7-point profiles for endpoint analysis and fasting prebreakfast SMPGs and 3- or 4-point profiles that are used for self-adjustment of the insulin dose, have to be measured by the patient using the sponsor-provided glucometer. Patients will be provided with an electronic diary in order to record their SMPG and complete the 3-4 point or 7-point SMPG profiles, insulin doses, and hypoglycemic events including symptoms of hypoglycemia.

The patients will be instructed to bring the glucometers provided by the Sponsor to each on-site visit. The glucometers should be calibrated according to manufacturer's instructions and the investigational site should also check regularly the glucometers using the provided control solutions for data validity.

The electronic diary needs to be brought to each visit. Detailed information regarding the Web based portal and other software support is provided at the screening visit.

To ensure safety when there are technical problems with the glucometer provided by the Sponsor, patients are to contact the site and the e-diary helpdesk immediately and should use an alternative meter until resolved.

All SMPG values will be used by the Investigator to monitor glycemic control, for dosage adjustment of meal related rapid-acting insulin (SAR341402/NovoLog/NovoRapid) and for titration of basal insulin (Lantus) throughout the trial.

SMPG measurements are scheduled as follows:

- **7-point SMPGs** (fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime): on at least 2 days in the week before Visit 3 (Baseline), Visit 7 (Week 12), Visit 9 (Week 26 ([Endpoint])), and Visit 12 (Week 52; End of treatment), measured in a single, 24-hour period; they must be recorded into the e-diary before the visit, reviewed by the Investigator and transferred into the clinical database.
- **SMPG to assist insulin titration/dosing** (to include minimum 3- or 4-point SMPG to be recorded into the e-diary along with insulin dose and carbohydrate intake) is recommended daily during the first weeks of study treatment until reaching target ranges for SMPG, and thereafter on at least 3 days each week or more frequently as requested by the Investigator as specified in titration manual:
 - To assist titration of the basal insulin (Lantus): fasting (prebreakfast) SMPG,

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

These SMPGs, supporting optimization of the basal and mealtime insulin dose are recommended to be recorded in the e-diary at least weekly; they will be uploaded in the e-diary web portal and for review by the site or the Sponsor (titration oversight working group) (see titration oversight manual). The results will be discussed between Investigator and patient during on site and unscheduled telephone visits at the discretion of the Investigator.

For SMPG ≤ 3.9 mmol/L (≤ 70 mg/dL) transferred to the e-diary, the patient will be prompted to the hypoglycemic episode diary after the SMPG are transferred regardless if symptoms of hypoglycemia were present or not.

7-point SMPG can also be used for titration oversight.

- **SMPG during episodes of symptoms of hypoglycemia:** whenever the patients feel hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible.

For details please refer to [Section 9.2.3.2.1.1](#).

9.2.3 Safety endpoints

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

- Hypoglycemia (according to ADA Workgroup on Hypoglycemia) (3, 4, 5).
- AEs, SAEs.
- Laboratory data:
 - Hematology: erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets,
 - Clinical chemistry: electrolytes including sodium and potassium, renal function including creatinine and eGFR (MDRD), and liver function including ALT, AST, alkaline phosphatase (ALP) and total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin),
 - Serum lipids: total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG) (in fasting condition).
- Injection site reactions, hypersensitivity reactions.
- Vital signs: heart rate, and SBP and DBP.
- Body weight.

9.2.3.1 *Observation period for safety variables*

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

9.2.3.2 *Safety assessment methods*

9.2.3.2.1 *Hypoglycemia*

Hypoglycemia will be analyzed as incidence of patients (%) with at least one hypoglycemia event and number of hypoglycemia event per patient year of exposure.

Hypoglycemia events will be categorized (3, 4, 5) as follows:

- **Severe hypoglycemia:** Severe hypoglycemia is an event requiring 3rd party 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 patients at risk for injury to themselves or others. Note that “requires 3rd party assistance” means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident.

Severe hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. All 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 of (≤ 3.9 mmol/L (≤ 70 mg/dL) (3). 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 without a test of plasma glucose.
- **Relative hypoglycemia:** (recently termed “pseudo-hypoglycemia” [4]) 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).

Hypoglycemia events will be evaluated regardless the time of onset.

In addition to the threshold of plasma glucose of less than or equal to 3.9 mmol/L (70 mg/dL), documented hypoglycemia with a measured plasma glucose concentration less than 3.0 mmol/L (54 mg/dL) will also be analyzed (5).

9.2.3.2.1.1 Self-measured plasma glucose during symptomatic hypoglycemia

Whenever the patients feel hypoglycemic symptoms, plasma glucose should be measured by the patient (or others, if applicable), if possible. Patients 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, plasma glucose may be recorded with other devices.

Patients will then complete the hypoglycemic episode diary in their e-diary. Site will receive alerts from e-diary for all severe hypoglycemic events and will review for decision on any necessary measures to be taken such as dose reduction of IMP or NIMP.

All hypoglycemia episodes will be documented by the patient on the hypoglycemic episode diary page of the e-diary as soon after the event as possible, so that this information can be reviewed in the web based portal by the site. This requires that the SMPG values related to hypoglycemia (measured with the glucometer and transferred to the e-diary) are linked to the appropriate hypoglycemic symptoms directly entered into the e-diary.

9.2.3.2.2 Adverse events, serious adverse events

All reported AEs and SAEs will be collected from the time of signed informed consent until the end of the study (defined as patient's last visit planned per protocol or the resolution/stabilization of all SAE and AEs with pre-specified monitoring). All events will be managed and reported in compliance with all applicable regulations, and included in the final CSR.

All AEs and SAEs will be coded to a Lower Level Term (LLT), Preferred Term (PT), High Level Term (HLT), High Level Group Term (HLGT) and associated primary System Organ Class (SOC) using the version of MedDRA (Medical Dictionary for Regulatory Activities) currently in effect at the sponsor at the time of database lock. The occurrence of AEs and SAEs is recorded from the time of signed informed consent until the end of the study.

For further details on AEs refer to [Section 10.4](#).

9.2.3.2.2.1 Adverse event observation periods

If an AE/SAE is ongoing and not resolved by the end of the study observation period and leads to subsequent death of the patient, it will have to be reported.

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

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

9.2.3.2.2.2 Death observation periods

The death observations are per the observation periods defined above. In addition, after the post-treatment period, death related to IMP as well as death resulting from TEAE must be reported to the Sponsor.

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

9.2.3.2.3 Laboratory safety variables

The clinical laboratory data collected consist of blood analysis (including hematology, clinical chemistry and fasting lipids). Clinical laboratory values will be analyzed after conversion into standard international units. International units will be used in all listings and tables.

Blood for assessment of laboratory safety variables in central laboratory will be collected at screening (Visit 1), Visit 9 (Week 26), and Visit 12 (Week 52).

The following safety laboratory endpoints will be assessed:

- Hematology at Visit 1 (Week -2), Visit 9 (Week 26), Visit 12 (Week 52): erythrocytes, hemoglobin, hematocrit, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets.

- Clinical chemistry at Visit 1 (Week -2), Visit 9 (Week 26), Visit 12 (Week 52):
 - Electrolytes including sodium, potassium,
 - Renal function including creatinine and eGFR (MDRD),
 - Liver function including ALT, AST, alkaline phosphatase (ALP) and total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin).
- Serum lipids at Visit 1 (Week -2), Visit 9 (Week 26), Visit 12 (Week 52): total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG) (in fasting condition).

The following additional safety laboratory assessments will be done:

- Hepatitis serology to include HBs-Ag, HC-Ab at screening visit (Visit 1, Week -2).
- Serum pregnancy test in WOCBP at screening and urine pregnancy test at most of the subsequent on-site visits will be performed. In the event of a positive urine pregnancy test, a confirmatory serum pregnancy test should be performed. Urine pregnancy tests can be performed more often if required by local law.
- Serum follicle stimulating hormone (FSH) and estradiol (only in females requiring confirmation of postmenopausal status) at screening visit (Visit 1, Week -2).

Note: Any abnormal laboratory value estimated as clinically significant by the Investigator should be immediately rechecked (whenever possible using the central laboratory) for confirmation before making a decision of permanent discontinuation of IMP for the concerned patient. Any confirmed laboratory abnormality estimated as clinically significant by the Investigator must be reported as an AE/SAE as applicable.

9.2.3.2.4 *Injection site reactions and hypersensitivity reactions*

If the Investigator or the patient recognizes any signs related to local reactions at the study drug injection site or potential hypersensitivity reactions, the event should be recorded in the e-CRF (for details refer to [Section 10.6.2](#) and [Section 10.6.3](#)).

If a patient reports an injection site or 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, so that the event can be properly assessed and reported (see also [Section 10.6.3](#)).

9.2.3.2.5 *Vital signs*

Vital signs parameters are heart rate, and SBP and DBP in sitting position.

Determination of the screening BP and reference arm for BP measurements: At Visit 1, after the patient has rested comfortably for at least 10 minutes, BP is measured on both of the patient's arms while the patient is in sitting position and then again after two minutes on both arms. The arm with the highest SBP will be determined at this visit, identifying the reference arm for future

measurement throughout the study. The highest value will be recorded in the e-CRF (all BP values are to be recorded in the source data) as the BP to determine the reference arm. Additional measurements may be made to determine the screening SBP and DBP. Blood pressure measurements which are not the defined screening BP are not exclusionary.

Blood pressure at all subsequent on-site visits should be measured when the patient is quiet and seated and with their determined reference arm outstretched in line with mid-sternum and supported. Measurement at all subsequent visits should be taken under standardized conditions, approximately at the same time of the day, on the reference arm, with the same device (after the patient has rested comfortably for at least five minutes), and the values are to be recorded in the e-CRF. Both SBP and DBP should be recorded. Devices for BP measurement should be regularly recalibrated according to manufacturers' instructions.

Heart rate will be measured at the time of the BP measurement in sitting position and recorded in the e-CRF.

9.2.3.2.6 *Height and body weight*

Height will be measured at screening visit (Visit 1, Week -2) when the patient's shoes are off, feet together, and arms by the sides. Heels, buttocks and upper back should also be in contact with the wall when the measurement is made.

Body weight should be obtained at 4 visits, screening visit (Visit 1, Week -2), Visit 3 (Day 1), Visit 9 (Week 26), and End of treatment Visit 12 (Week 52 and, if applicable, early treatment discontinuation) with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer. The weight is read and recorded in the e-CRF and Source Data. Self-reported weights are not acceptable and patients must not read the scales themselves.

9.2.3.2.7 *Electrocardiogram*

A 12-lead ECG record will be performed locally at Visit 1 (Screening visit) and thereafter only when justified by the occurrence of an AE (see flowchart, [Section 1.2](#)).

The 12-lead ECG should be performed after at least 10 minutes in supine position. The Investigator has to review the ECG and document his interpretation and sign and date on the ECG printout. In case of subsequent ECGs, each ECG trace is analyzed in comparison with the screening recorded trace. All original traces are kept as source data.

In the e-CRF the assessment "normal" or "abnormal"/ "clinically significant" or "clinically not significant", as determined by the Investigator, is collected and the ECG is kept in source.

Note: Any abnormal ECG parameter should be immediately rechecked for confirmation before making a decision of permanent discontinuation of treatment with IMPs. If the abnormality is confirmed, the finding must be reported as an AE/SAE as applicable.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

Pharmacokinetic assessment is not planned.

9.3.2 Insulin dose

All mealtime insulin doses and the basal insulin dose will be integrated into e-CRF from the e-diary record as follows:

- For the 7 days prior to Baseline (Visit 3) and during the first 7 days after start of IMP.
- For 2 days in the weeks prior to Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 26), Visit 11 (Week 40) and Visit 12 (Week 52).

9.4 FUTURE USE OF SAMPLES

Not applicable.

9.5 APPROPRIATENESS OF MEASUREMENTS

The primary efficacy analysis will test non-inferiority of SAR341402 compared to NovoLog/NovoRapid in terms of change of HbA1c from baseline to Week 26. The 26-week duration of study treatment is considered to be sufficient for achieving steady state conditions of the MDI insulin regimen with SAR341402 or NovoLog/NovoRapid in combination with Lantus after randomization, enabling an adequate assessment of time-dependent changes in HbA1c and the concomitant risk of hypoglycemia. HbA1c reflects the average glycemia over several months and has strong predictive value for diabetes complications. For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I “National Glycohemoglobin Standardization Program” (NGSP) central laboratory.

HbA1c is accepted by regulatory agencies as primary endpoint to support a claim based on glycemic control (10, 11).

Parameters defining secondary efficacy endpoints including percentage of patients reaching HbA1c targets, change in FPG, and change in mean 24-hour and postprandial glucose levels are all assessments of glycemic control that are recognized and accepted by regulatory agencies. Change in mean 24-hour and postprandial glucose levels are collected at Week 12, the end of the critical titration period, and at the endpoints at Week 26 and at Week 52. SMPG-related data are not collected at Week 40 during the comparative safety extension period.

As a biological protein, insulin has the potential to be immunogenic. Therefore, immunogenicity will be assessed by evaluating anti-SAR341402/NovoLog/NovoRapid antibody positive/negative status and titers, as well as cross-reactivity to human insulin at various time points throughout the study. A single immunogenicity assay based on SAR341402 will be used to test samples from both SAR341402 and NovoLog/NovoRapid treated subjects. The immunoassay will detect all immunoglobulin isotypes and will be validated in accordance with recent recommendations (2, 12, 13).

All potential hypersensitivity or hypersensitivity-like events will be adjudicated by the members of an ARAC, who are blinded to the treatment and will also assess a potential association of the hypersensitivity or hypersensitivity-like event with treatment induced or treatment boosted AIAs. The ARAC members will further recommend a follow up of patients with increase of AIA titers above baseline at the end of the study. All the ARAC assessments will further strengthen the robustness of the clinical assessment of the immunogenicity of SAR341402 in comparison with NovoLog/NovoRapid.

Safety will be evaluated by standard clinical and laboratory measurements, including safety parameters of special interest for an insulin product such as hypoglycemia, injection site reactions and potential hypersensitivity reactions.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments listed in the “Study Flow Chart” ([Section 1.2](#)) are not repeated in this section. The aim of this section is to provide details on how some of the procedures/assessments have to be performed.

This is an outpatient study and consists of 8 on-site visits and 5 phone-call visits. Additional, optional phone call visits to monitor and support the progress of insulin titration should be scheduled whenever considered necessary by the Investigator.

All on-site visits should take place in the morning. The patients must be fasting for Visit 1 (Week -2, screening), Visit 3 (Day 1, baseline), Visit 7 (Week 12), Visit 9 (Week 26, Endpoint), Visit 11 (Week 40), and at end of treatment assessment Visit 12 (Week 52) or at early discontinuation from IMP. Patient is required to come to the visit after a fasting period of at least 8 hours: during this time, only water or tea without sugar or sweetener and without milk is allowed. No coffee, no other beverages; no injection of rapid-acting insulin at home are allowed. Patients do not need to come to other on-site titration visits fasting.

Eight-hour delay must be respected between the last mealtime insulin dose and AIA sampling time for Visit 3 (Day 1, baseline), Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 26 Endpoint), Visit 11 (Week 40) and at end of treatment assessment Visit 12 (Week 52) or at early discontinuation from IMP.

Visit window: Visit 2 should take place 7 days \pm 3 days after Visit 1 (screening). Visit 3 should occur 14 days \pm 3 days after Visit 1 (screening). From Visit 4 (Week 2) until the primary efficacy endpoint visit (Visit 9, Week 26), visits should occur within \pm 3 days, taking the baseline (Visit 3) visit day as a reference. Visits in the extension period, phone visit (Visit 10, Week 34), and on site visits (Visit 11, Week 40) to end of treatment (Visit 12, Week 52) may occur within \pm 5 days. Post treatment follow-up visit, (Visit 13, Week 52+1 day) may occur at +2 to 3 days in the event this visit falls on a weekend or holiday.

If one visit date is changed, the next visit should occur according to the original schedule.

For a complete list of procedures scheduled for each study visit please refer to the Study flowchart ([Section 1.2](#)). The aim of the sections of the “Visit schedule” in [Section 1.2](#) as well as “Assessment methods” in ([Section 9.2.1.1](#), [Section 9.2.2.2](#) and [Section 9.2.3.2](#)) is to detail procedures to be performed.

All data obtained during the trial visits are reviewed by the Investigator and SubInvestigators who are qualified in treatment of T1DM or T2DM (as appropriate) with MDI therapy and who are familiar with the study.

10.1.1 Screening period

The duration of the screening period is 2 weeks from Visit 1 (Week -2) to Visit 3 (Week 0) and must be long enough to establish inclusion/exclusion criteria.

Patients will be screened at Visit 1 after signature of the informed consent form. All laboratory tests measured at central laboratory needed for checking the exclusion criteria of the patients will be performed at Visit 1. Patients will be called at Visit 2 (Week -1), and patients who meet the inclusion criteria and have no exclusion criteria as noted in [Section 7.1](#) and [Section 7.2](#) will be randomized at Visit 3 (Day 1).

If any of the laboratory parameters are not available upon the end of the screening period (eg, sample material damaged during transport etc) a retest can be performed. Retesting done by the Central Laboratory for quality purposes by the reference lab for HbA1c cannot be used for screening purposes.

Patients can be re-screened one time before randomization in case of non-evaluable exclusion criteria (eg, not evaluable screening laboratory findings) or in case of a HbA1c out of the included range when there is an acute disease at the initial screening visit (Visit 1, Week-2) that is expected to affect the HbA1c.

The IRT will be contacted at Visit 1 for notification of screening and for patient number allocation, before study related measures are performed.

10.1.1.1 On-site Visit 1 (Week -2) screening visit

The following procedures/assessments will be performed at the Visit 1 (Week -2):

- Obtaining the informed consent:
 - The patient will receive verbal information concerning the aims and methods of the study, its constraints and risks and the study duration. Written information will be provided to the patient. Written informed consent must be signed by the patient and Investigator prior to any study-specific investigations.
- IRT notified (allocation of patient number, registration of screening, collection of demographic information):
 - The patient number is composed of a 12-digit number containing the 3-digit country code, the 4-digit center code and the 5-digit patient chronological number (which is 00001 for the first patient screened in a center, 00002 for the second patient screened in the same center etc).
- Assessment of inclusion/exclusion criteria.
- Demographics (age, gender, and ethnic origin).
- Patient's medical (including detailed cardiovascular) and surgical history as well as family history of diabetes in the immediate family.

- History of T1DM or T2DM treatment including documentation for diagnosis, of insulin treatment (including start date of first insulin treatment), documentation of current treatment and treatment in the last 6 months with insulin glargine (in the last 12 month with insulin detemir) and insulin lispro or NovoLog/NovoRapid (including start dates), duration, and of microvascular complications (eye, kidney) and their treatments, all of which must be in the source documentation prior to randomization.
- History of T1DM or T2DM, supporting documentation for diagnosis, must be in source documentation prior to randomization.
- Concomitant medication history.
- Habits: alcohol habits and smoking status (during the last 12 months).
- Physical examination.
- Body height and weight, vital signs (determination of reference arm for BP; SBP, DBP, heart rate).
- 12-lead ECG.
- Laboratory testing by central laboratory:
 - HbA1c,
 - Safety laboratory test for hematology, clinical chemistry (please refer to [Section 9.2.3.2.3](#)),
 - Serum lipids (please refer to [Section 9.2.3.2.3](#)),
 - Hepatitis serology (HBs-Ag, HC-Ab),
 - Serum pregnancy test (β -human chorionic gonadotropin [β -HCG]) in WOCBP only,
 - FSH and estradiol in postmenopausal women only.
- Report AE/SAE, hypersensitivity reactions and hypoglycemia if any.
- E-diary and Sponsor provided glucometer dispensation:
 - Creation of the patient number provided by IRT in the e-diary web portal and in the allocated e-diary,
 - Dispensation of Sponsor provided glucometer, training materials and supplies,
 - Pairing of the e-diary with the glucometer,
 - Dispensation of e-diary, instruction on use and software support information,
 - Completion of the training session by the patient on the e-diary.
- Routine review of diet and lifestyle counseling along with instructions on dosage self-adjustment including carbohydrate intake (when available) and review of correction scales.

A time will be selected for the telephone Visit 2 (Week -1) in the screening period.

10.1.1.2 Screening telephone visit: Visit 2 (Week-1) +/- 3 days

Patient is called by the Investigator or qualified designee at a scheduled time. If the call has been completed by site staff other than the Investigator, the Investigator has to be consulted if AE/SAE is suspected. This visit is a mandatory telephone visit, but can optionally be performed as clinical visit.

- During the phone call, ask the patient:
 - Did you experience any new medical event, disease or symptom since the last visit? (Please pay attention to any possible hypoglycemic event or symptom, possible allergic or injection site reactions).
 - Did you experience any change in a pre-existing medical event or disease or symptom since the last visit?
 - Did you change or add any concomitant medication since the last visit?
 - Do you feel comfortable using the e-diary and glucometer or do you need more training?
- Review patient diary through the e-diary web portal (StudyWorks):
 - Basal insulin (glargine or detemir) and mealtime NovoLog/NovoRapid or insulin lispro doses,
 - SMPG values,
 - Hypoglycemia if any.
- Review any potential questions related to screening and inclusion/exclusion criteria.
- Refresher instructions for use of glucometer, and routine review of diet and lifestyle counseling along with instructions on dosage self-adjustment including carbohydrate intake (when available) are provided.
- Patients are reminded to record in their e-diary when they return for randomization:
 - On at least 2 days in the week before the baseline Visit 3: 7-point plasma glucose profile (7 values: fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) measured in a single, 24-hour period,
 - Any SMPG related to hypoglycemia, symptoms of hypoglycemia,
 - All doses of NovoLog/NovoRapid or insulin lispro injected either prior to meal intake or immediately after meal intake, any corrective dose related to the SMPG on each day of the week preceding the baseline visit,
 - Daily dose of insulin glargine or insulin detemir 100 U/mL on each day of the week preceding the baseline visit.
- An appointment is made at telephone Visit 2 for the randomization visit (Day 1). Patients are reminded to bring their glucometer and their e-diary to their visit and come to their randomization visit fasting. Eight-hour delay between injection of SAR341402 or NovoLog/NovoRapid and AIA sampling must be respected.

- Visit 2 must be confirmed in the e-diary web portal and Visit 3 date should be corrected if the scheduled appointment is different from the planned per protocol (Visit 1 + 14 days).

10.1.2 Open-label randomized treatment period and comparative safety extension period (Week 0 to Week 52)

The 26-week open-label randomized treatment period will last from Visit 3 (Week 0, Day 1, baseline) to Visit 9 (Week 26, primary endpoint).

After completion of the 26-week open-label active-controlled treatment period and measurement of the primary efficacy endpoint at Visit 9 (Week 26), patients will enter the 26-week active controlled safety extension period.

Patients meeting all inclusion criteria and no exclusion criteria during the screening period undergo assessment Visit 3 (Day 1) as described in the flowchart ([Section 1.2](#)).

After these assessments the patients will be 1:1 randomized through the IRT in one of the two following treatment arms using the HbA1c from the screening visit:

- SAR341402 (SAR341402 SoloSTAR) + Lantus once daily.
- NovoLog/NovoRapid (NovoLog/NovoRapid FlexPen) + Lantus once daily.

After randomization, patients will enter the 26-week open-label active-controlled treatment period, and receive their assigned treatment of SAR341402 (SAR341402 SoloSTAR) or NovoLog/NovoRapid (NovoLog/NovoRapid FlexPen) in addition to their once daily mandatory Lantus background therapy.

During the treatment period, patients are to continue their SMPG with routine dosage adjustment of rapid-acting/prandial insulin at all meals.

Self-measured plasma glucose and insulin doses are to be transferred to the clinical database or entered into the e-CRF during the treatment period Visit 3 to Visit 12 and will include:

- On at least 2 days in the week before on-site visits (Visit 3, Visit 7, Visit 9, and Visit 12): 7-point plasma glucose profile (7 values: fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) measured in a single, 24-hour period.
- Any SMPG related to hypoglycemia, symptoms of hypoglycemia.
- All mealtime insulin doses and the basal insulin dose
 - for the 7 days prior to Baseline (Visit 3) and during the first 7 days after start of IMP,
 - for the 2 days in the weeks prior to Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 26), Visit 11 (Week 40) and Visit 12 (Week 52).
- In case of hypoglycemia: hypoglycemic episode diary completed in e-diary or on the hypoglycemic event information (e-diary) page in the e-CRF.

- In case of severe hypoglycemia: hypoglycemic episode diary completed in e-diary to include symptoms AND transfer of data to web portal ensuring automatic notification of the Investigator from the e-diary web portal so that the event can be properly assessed and reported and insulin dose be adjusted if needed.

Self-measured plasma glucose and insulin doses are available in the web based portal.

In case of permanent study treatment discontinuation before Visit 12 (Week 52), please refer to [Section 10.3.2](#). In case of patients not meeting glycemic goals, please refer to [Section 8.1.6](#). Patients are encouraged to continue IMP at least to Week 26, primary efficacy endpoint. Even if patients stop IMP, they are continued in the trial on their insulin regimen without IMP until at least Week 26.

10.1.2.1 Baseline visit (Visit 3, Week 0/Day 1)

Patients meeting all inclusion criteria and with no exclusion criteria at the end of the screening period (based on data collected at the screening Visit 1 [Week -2], at Visit 2 [Week -1] [if applicable] and Visit 3 [Week 0]) are eligible to be randomized and can participate in the study. Patients must have demonstrated the ability and willingness to use the e-diary during the screening period.

For the complete list of procedures scheduled for this visit, please refer to the study flowchart ([Section 1.2](#)) and for detailed description of assessments ([Section 9.2.2.2](#), [Section 9.2.3.2](#)).

At this visit, the patient must return to the investigation site in the morning after an overnight fast (no less than 8 hours fasting) and not having injected their mealtime insulin at home. Eight-hour delay between injection of insulin lispro or insulin aspart and AIA sampling must be respected.

Patients will come with the sponsor provided glucometer and the e-diary.

Key procedures and assessments during the visit:

- Body weight, vital signs (SBP and DBP, heart rate).
- Laboratory testing done by central laboratory:
 - HbA1c,
 - FPG,
 - AIA,
 - C-peptide.
- Urine pregnancy test in WOCBP.
- Concomitant medications are reviewed.

- Patient e-diary is verified to ensure that no pending data are stored in the e-diary and if so, data should be transmitted. The e-diary data is reviewed in the vendor web portal by the Investigator or SubInvestigator who are qualified and familiar with the study and the following is validated in the clinical database:
 - On at least 2 days in the week before the baseline visit (Visit 3): 7-point plasma glucose profile (fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) measured in a single, 24-hour period,
 - All doses of NovoLog/NovoRapid or insulin lispro injected either prior to meal intake or immediately after meal intake, including any corrective dose related to the SMPG on each day of the week prior to the baseline visit,
 - Doses of insulin glargine or insulin detemir 100 U/mL on each day of the week prior to the baseline visit,
 - Any SMPG related to hypoglycemia and symptoms of hypoglycemia.
- Patients will be reminded to record daily dose of IMP and NIMP, including any corrective dose related to the SMPG on each day of the week after the baseline visit.
- Additional SMPG, insulin dosage adjustment, and carbohydrate intake (when available) to assist the patient with insulin dosage self-adjustment is reviewed.
- Training is repeated for use of glucometer, insulin pens and completion of the electronic diary as needed; instruction on the importance of timely completion of SMPG monitoring using the sponsor provided glucometer is provided.
- AE/SAEs are collected and injection site reactions, hypersensitivity reactions, and hypoglycemic events are to be assessed and reported in the clinical database.
- Review of inclusion/exclusion criteria.
- IRT is called to randomize the patient if they still meet inclusion/exclusion criteria and after all baseline evaluations have been performed.
- Visit occurrence is confirmed in the e-diary web portal.
- Diet and lifestyle counseling is provided including assessment of food intake and how to adjust meal related rapid-acting insulin for changes in food intake.
- Patients will be provided with kits containing pens for administration of IMP along with the instruction leaflet and corresponding supplies (needles, control solution, test strips etc.). A patient card, including emergency contact details and treatment arm will be provided to every patient who participates in the study.
- Patients will be instructed by the study staff how to properly use the study drug pens; (NovoLog/NovoRapid FlexPen, SAR341402 SoloSTAR).
- IMP administration will be explained to patients including communication of the starting IMP dose and dose self-adjustment requirements. Study medications until the next on-site visit are dispensed (NIMP [Lantus SoloSTAR] and IMP [NovoLog/NovoRapid FlexPen or SAR341402 SoloSTAR]).

- Investigators and their study staff are required to offer adequate training, thus enabling patients to successfully adjust their meal related boluses of IMP. The goal for all patients is to attain good glycemic control (recommended target 2 hour postprandial glucose value of <10 mmol/L (<180 mg/dL) while avoiding hypoglycemia or to a pre-prandial glucose target range of 4.4 to 7.2 mmol/L (80 to 130 mg/dL), for all of their meals [1]).
- The target for titration of basal insulin is a FPG (fasting plasma glucose) is 4.4 to 7.2 mmol/L (80 to 130 mg/dL).
- Glycemic targets may be adapted for individual patients, if deemed necessary, eg, due to age, comorbid conditions, and individual patient considerations. The individual target will be documented in the source documents. Arrangements are made for contact between the Investigator or medically qualified designee and the patient is provided an appointment in 4 weeks (Visit 5, Week 4) to monitor insulin doses for both Lantus and IMP (NovoLog/NovoRapid FlexPen or SAR341402 SoloSTAR).
- Patients are instructed to return to the site for Visit 5 (Week 4) four weeks later, in the morning, and to bring used and in-use Lantus SoloSTAR and IMP (NovoLog/NovoRapid FlexPen or SAR341402 SoloSTAR), as well as the sponsor provided glucometer and the e-diary.

10.1.2.2 On-site visits: Visit 5 (Week 4), Visit 8 (Week 20) +/- 3 days

Key procedures and assessments during the visit:

- Vital signs (SBP and DBP, heart rate).
- Laboratory testing done by central laboratory Visit 5 (Week 4) only:
 - AIA (8-hour delay between injection of IMP and AIA sampling must be respected).
- Concomitant medications are reviewed.
- Diet and lifestyle counseling is provided including assessment of food intake and how to adjust meal related rapid-acting insulin for changes in food intake.
- Patient data from the web based portal is reviewed and the following is transferred into the clinical database :
 - Any SMPG related to hypoglycemia and symptoms of hypoglycemia,
 - For Visit 5 (Week 4) only – on at least 2 days during the week before the visit:
 - a) All doses of SAR341402/NovoLog/NovoRapid injected either prior to meal intake or immediately after meal intake, including any corrective dose related to the SMPG,
 - b) Daily Lantus dose.
- SMPG data are reviewed and patients instructed in adjustment of insulin doses; instruction on the importance of timely completion of SMPG monitoring using the sponsor provided glucometer is provided.
- Compliance is checked with review of diary and web based portal.
- Used and unused pens are counted and collected.

- Main area of injection for IMP and NIMP since last on-site visit is documented.
- AE/SAEs are collected and injection site reactions, hypersensitivity reactions, and hypoglycemic events assessed and reported into the clinical database. Special attention has to be paid on severe hypoglycemia.
- IRT is called.
- Visit occurrence is confirmed in the e-diary web portal.
- Doses of SAR341402/NovoLog/NovoRapid titration and dose self-adjustment requirements will be reviewed.
- Study medications until the next on-site visit are dispensed (NIMP [Lantus SoloSTAR] and IMP [NovoLog/NovoRapid FlexPen or SAR341402 SoloSTAR]).
- Patients are also instructed to return to the next on-site visit and to bring used and in-use Lantus SoloSTAR and IMP (NovoLog/NovoRapid FlexPen prefilled disposable pens or SAR341402 SoloSTAR), as well as the glucose meter and the diary.
- At Visit 8, patients are reminded to come to their next visit fasting and to complete two 7-point profiles the week prior Visit 9.

10.1.2.3 On-site visits: Visit 7 (Week 12) +/- 3 days and Visit 11 (Week 40) +/- 5 days

Key procedures and assessments during the visit:

- Vital signs (SBP and DBP, heart rate).
- Laboratory testing done by central laboratory:
 - HbA1c,
 - FPG,
 - AIA (8-hour delay between injection of IMP and AIA sampling must be respected).
- Urine pregnancy test done in WOCBP.
- Diet and lifestyle counseling is provided including assessment of food intake and how to adjust meal related rapid-acting insulin for changes in food intake.
- Concomitant medications are reviewed.
- Patient diary is reviewed and the following is validated in the clinical database:
 - Visit 7:
 - a) On at least 2 days in the week before the visit: 7-point plasma glucose profile (7 values: fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) measured in a single, 24-hour period,
 - b) All doses of SAR341402/NovoLog/NovoRapid injected either prior to meal intake or immediately after meal intake, including any corrective dose related to the SMPG on the two 7-point profile days.

- c) Daily Lantus dose on the two 7-point profile days.
- d) Any SMPG related to hypoglycemia and symptoms of hypoglycemia.
- Visit 11:
 - a) All doses of SAR341402/NovoLog/NovoRapid injected either prior to meal intake or immediately after meal intake, including any corrective dose related to the SMPG on 2 days during the week prior to the visit,
 - b) Daily Lantus dose on 2 days during the week prior to the visit,
 - c) Any SMPG related to hypoglycemia and symptoms of hypoglycemia.
- Additional SMPG, insulin dosage adjustment, and any carbohydrate counts (when available) are reviewed; instruction on the importance of timely completion of SMPG monitoring using the sponsor provided glucometer is provided.
- Compliance is checked with review of diary and unused IMP.
- Used and unused pens are collected.
- Main area of injection for IMP and NIMP since last on-site visit is documented.
- AE/SAEs are collected and injection site reactions, hypersensitivity reactions, and hypoglycemic events are to be assessed and reported in the clinical database. Special attention has to be paid on severe hypoglycemia.
- IRT is called.
- Visit occurrence is confirmed in the e-diary web portal.
- Study medications until the next on-site visit are dispensed (NIMP (Lantus SoloSTAR) and IMP (NovoLog/NovoRapid FlexPen or SAR341402 SoloSTAR).
- Arrangements are made for contact between the Investigator or medically qualified designee and the patient in 8 weeks at Visit 8 (Week 20) for Visit 7 or in 12 weeks at Visit 12 (Week 52) for Visit 11 to monitor doses for both Lantus and IMP (NovoLog/NovoRapid FlexPen or SAR341402 SoloSTAR).
- Patients are also instructed to return to the next on site visit-and to bring used and in-use as well as not used that may include expired Lantus SoloSTAR and IMP (NovoLog/NovoRapid FlexPen prefilled disposable pens or SAR341402 SoloSTAR), in addition to the sponsor provided glucose meter and the e-diary. At Visit 11, patients must be instructed to:
 - Return fasting. Eight-hour delay between injection of SAR341402 or NovoLog/NovoRapid and AIA sampling must be respected,
 - Complete two 7-point SMPG profiles the week prior to Visit 12.

10.1.2.4 Visit 9 (Week 26, primary efficacy endpoint) +/- 3 days

Key procedures and assessments during the visit:

- Laboratory testing done by central laboratory:
 - HbA1c,
 - FPG,
 - Safety laboratory test for hematology, clinical chemistry (please refer to [Section 9.2.3.2.3](#)),
 - Serum lipids (please refer to [Section 9.2.3.2.3](#)),
 - AIA (8-hour delay between injection of IMP and AIA sampling must be respected).
- Urine pregnancy test in WOCBP.
- Physical examination, vital signs and body weight are measured.
- Concomitant medications are reviewed.
- Diet and lifestyle counseling is provided including assessment of food intake and how to adjust meal related rapid-acting insulin for changes in food intake.
- Patient diary is reviewed using the vendor web based portal and the following is validated in the clinical database:
 - On at least 2 days in the week before the Visit 9: 7-point plasma glucose profile (7 values: fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) measured in a single, 24-hour period,
 - All doses of SAR341402/NovoLog/NovoRapid injected either prior to meal intake or immediately after meal intake, including any corrective dose related to the SMPG on the two 7-point profile days,
 - Daily Lantus dose on the two 7-point profile days,
 - Any SMPG related to hypoglycemia and symptoms of hypoglycemia.
- Additional SMPG, dosage adjustment, and any carbohydrate counts (when available) are reviewed; instruction on the importance of timely completion of SMPG monitoring using the sponsor provided glucometer is provided.
- Compliance is checked with review of e-diary and unused IMP.
- Used and unused pens are counted and collected.
- Main area of injection for IMP and NIMP since last on-site visit is documented.
- AE/SAEs are collected. Injection site reactions, hypersensitivity reactions, and hypoglycemia recording are to be assessed and reported. Special attention has to be paid on severe hypoglycemia.
- IRT is called.
- Visit occurrence is confirmed in the e-diary web portal.

- Study medications until the next on-site visit are dispensed (NIMP (Lantus SoloSTAR) and IMP (NovoLog/NovoRapid FlexPen or SAR341402 SoloSTAR).
- Patients are instructed to schedule the Visit 10 phone visit and to schedule a return on-site visit, Visit 11, in the morning and to bring in all used and in-use, as well as not used pens that may include expired Lantus SoloSTAR and IMP (NovoLog/NovoRapid FlexPen prefilled disposable pens or SAR341402 SoloSTAR), in addition to the sponsor provided glucose meter and the e-diary.

10.1.2.5 Telephone visits: Visit 4 (Week 2) +/-3 days, Visit 6 (Week 8) +/-3 days, Visit 10 (Week 34) +/- 5 days; unscheduled telephone/fax/email visits

Only at scheduled visits (Visit 4 [Week 2], Visit 6 [Week 8], and Visit 10 [Week 34]):

- Patient diary is reviewed using the vendor web based portal and the following is validated in the clinical database:
 - Any SMPG related to hypoglycemia and symptoms of hypoglycemia,
 - Only at Visit 4: All doses of NovoLog/NovoRapid or SAR341402 injected either prior to meal intake or immediately after meal intake, any corrective dose related to the SMPG on each day of the week following the baseline visit,
 - Only at Visit 4: Daily dose of Lantus on each day of the week following the baseline visit,
 - Visit occurrence is confirmed in the e-diary web portal.
- Patients are reminded that for their return (Visits 5, 7 and 9), 8-hour delay between injection of SAR341402 or NovoLog/NovoRapid and AIA sampling must be respected.
- At Visit 6, patients are reminded to complete two 7-point profiles the week prior Visit 7.
- At Visit 6 and 10, patients are reminded to come to their next visit fasting.

During the phone call, ask the patient:

- Did you experience any new medical event, disease or symptom since the last visit? (Please pay attention to any possible hypoglycemic event or symptom, possible allergic or injection site reactions).
- Did you experience any change in a pre-existing medical event or disease or symptom since the last visit?
- Did you change or add any concomitant medication since the last visit?
- Did you have any technical difficulties with use of the e-diary or glucometer?

Review with the patient:

- Diet and lifestyle counseling.
- Dosage self-adjustment for food and glucose out of goal range.
- Correction/supplemental scales.

Instruct patients by:

- Providing information on how to adjust dose according to their SMPG values.
- Encourage patients to continue to measure required SMPG in the sponsor provided glucometer and complete the insulin doses and hypoglycemic form for all hypoglycemic events into the e-diary.

Record in the clinical database:

- Any changes to concomitant medication.
- AE/SAE, injection site reaction, hypersensitivity, and hypoglycemia if any. Special attention has to be paid on severe hypoglycemia.

Patient is called by the Investigator or qualified designee at a scheduled time. Patient may at the discretion of the Investigator, communicate SMPG and AE/SAE via email and fax, which are then placed into the source documents.

10.1.2.6 End of treatment visit: Visit 12 (Week 52) +/- 5 days

Key procedures and assessments during the visit:

- Laboratory done via central laboratory:
 - HbA1c,
 - FPG,
 - Safety laboratory test for hematology, clinical chemistry (please refer to [Section 9.2.3.2.3](#)),
 - Serum lipids (please refer to [Section 9.2.3.2.3](#)),
 - AIA (8-hour delay between injection of IMP and AIA sampling must be respected).
- Urine pregnancy test in WOCBP.
- Physical examination, vital signs and body weight are measured.
- Patient diary is reviewed by the site Investigator for concomitant medications.
- Patient diary is reviewed using the vendor web based portal and the following is entered into the clinical database:
 - On at least 2 days in the week before the Visit 12: 7-point plasma glucose profile (7 values: fasting prebreakfast, 2 hours postbreakfast, pre- and 2 hours after lunch, pre- and 2 hours after dinner, and at bedtime) measured in a single, 24-hour period,
 - All doses of SAR341402/NovoLog/NovoRapid injected either prior to meal intake or immediately after meal intake, including any corrective dose related to the SMPG on the two 7-point profile days,
 - Daily Lantus dose on the two 7-point profile days,
 - Any SMPG related to hypoglycemia and symptoms of hypoglycemia.
- Additional SMPG, insulin dosage adjustment, and any carbohydrate counts if available are reviewed by the site in the vendor web based portal.
- Compliance is checked with review of diary/vendor web based portal and unused IMP.

- Counting/collecting used and unused pens.
- Main area of injection for IMP and NIMP since last on-site visit is documented.
- AE/SAEs, injection site reactions, hypersensitivity reactions, and hypoglycemic events are assessed and reported into the clinical database. Special attention has to be paid on severe hypoglycemia.
- IRT is called to register end of treatment.
- Visit occurrence is confirmed in the e-diary web portal, and the end of treatment information is entered.

10.1.3 Post-treatment follow-up

A post-treatment safety follow-up period will be performed 1 day after permanent discontinuation of the IMP.

10.1.3.1 Post-treatment follow-up telephone visit: Visit 13 (Week 52 + 1 day)

Following the last administration of IMP (SAR341402 or NovoLog/NovoRapid) either as scheduled at Visit 12 (Week 52) or prematurely with early end of IMP but with the assessments of Visit 12 (Week 52) the patient will be followed until at least Week 26, and a post-treatment follow-up should be scheduled. This is scheduled for all the patients 1 day after Visit 12 (or 2 to 3 days in the event this visit falls on a weekend or holiday) for patients who complete the trial or 1 day after premature end of treatment visit (or 2 to 3 days in the event this visit falls on a weekend or holiday) for those who had premature end of treatment. This visit can be a phone call visit or an on-site visit in case of ongoing or new AE during the post-treatment period, if necessary. The patient is called by the Investigator or qualified designee at scheduled time.

Concomitant medications, AE/SAEs, local reactions such as injection site reactions, hypersensitivity reactions, and hypoglycemia are reviewed by the site and reported in the clinical database at Visit 13. This will include the basal and mealtime insulins used post-trial including dose.

IRT has to be called in order to register end of study.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in patient's file

Evaluations recorded in the e-CRF must be supported by appropriately signed source documentation related but not limited to the following:

- Agreement and signature of informed consent form with the study identification.
- Study identification (name).

- Patient number, confirmation of randomization, Treatment batch number (treatment arm), dates and doses of study medication administration.
- Medical, surgical, diabetes history, including information on:
 - Demography, inclusion and exclusion criteria,
 - Last participation in a clinical trial,
 - Contraception method for WOCBP,
 - Previous and concomitant medication.
- Dates and times of visits and assessments including examination results.
- Vital signs, height, body weight, Laboratory reports, Investigation results (eg, ECG traces, imaging reports).
- Adverse events and follow-up:
 - In case of SAE, the site should file in the source documents at least copies of the hospitalization reports and any relevant examination reports documenting the follow-up of the SAE.
- Date of premature study discontinuation (if any) and reason.
- Nursing notes.
- Dietician's notes.
- Physician's notes, to include
 - Initial insulin doses for basal insulin, meal related insulin which may include carbohydrate ratio and individualized goal ranges for glucose control.
- Patient SMPG, insulin doses, and hypoglycemia event data will be stored on the vendor web based portal as electronic source available for the site.
- For patients who are identified as outliers for severe hypoglycemia, patient and site retraining will be kept in source as well as any supporting clinical information as to underlying causes of the increased severe hypoglycemia.

10.2.2 Source data verification requirements for screen failures

For screen failure patients, the following source data must be verified: patient's identification details, the informed consent signed by the patient, the study identification (name), dates of study visits and the main reasons for screen failure. Data related to the AEs for screen failure patients will be checked against source documents.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs, see decision tree in [Section 17](#). Reinitiating treatment 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 in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met ([Section 7.1](#), [Section 7.2](#)).

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

During any temporary treatment discontinuation, doses of alternative treatment used for plasma glucose control should be recorded by the Investigator in the concomitant medication page.

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 e-CRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

The following reasons lead to permanent discontinuation:

- At the patient's own request, ie, withdrawal of consent for treatment.
- If, in the Investigator's opinion, continuation with the administration of the study treatment would be detrimental to the patient's well-being.
- Inter-current condition that requires permanent discontinuation of the study treatment (eg, laboratory abnormalities according to the decision tree in [Section 17](#), [Appendix B](#)) as long as the abnormality persists and if the casual relationship of the concerned event and the IMP is possible according to the Investigator's best medical judgment).
- Pregnancy.
- Specific request of the sponsor.

Any abnormal laboratory value or ECG will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

The assessments planned at end of treatment visit ([Section 10.1.2.4](#) and [Section 1.2](#)) will be performed as soon as possible after the permanent discontinuation of treatment.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed. Reason for discontinuation will be clearly specified and the newly prescribed rapid-acting insulin analogue will be recorded.

After this end of treatment visit, the follow-up safety phone call will be performed 1 day (or 2 to 3 days in the event this visit falls on a weekend or holiday) after end of treatment visit.

Afterwards, patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, to a minimum of Visit 9 (Week 26) (14) or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Refer to e-CRF completion guidelines for description of how reasons for missing data are collected.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason without any effect on their care. However, if patients no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. If possible, the patients are assessed using the procedure normally planned for the end-of-treatment visit (see [Section 10.1.2.4](#) and [Section 1.2](#)).

Patients who withdraw should be explicitly asked about the contribution of possible AEs to their decision to withdraw consent, and any AE information elicited should be documented.

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

Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

For patients who fail to return to the site, unless the patient withdraws the consent for follow-up, the Investigator should make the best effort to re-contact the patient (eg, contact patient's family or private physician, review available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

The statistical analysis plan will specify how these patients lost to follow-up for their primary endpoints will be considered.

Patients who have withdrawn from the study cannot be re-randomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **AE** is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

An **SAE** is any untoward medical occurrence that at any dose:

- Results in death, or,
- Is life-threatening, or,

Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient 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.

- Requires inpatient hospitalization or prolongation of existing hospitalization, or,
- Results in persistent or significant disability/incapacity, or,
- Is a congenital anomaly/birth defect,
- Is a medically important event,
Medical and scientific judgment should be exercised in deciding whether expedited 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 patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
 - Allergic bronchospasm,
 - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),

- Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse.
- ALT >3 x ULN + total bilirubin >2 x ULN or asymptomatic ALT increase >10 x ULN.
- Suicide attempt or any event suggestive of suicidality.
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling).
- Bullous cutaneous eruptions.
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies).
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor may be appropriate. 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.

The AESI for this study:

- ALT increase (refer to related flowchart and protocol appendices).
- 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:
 - Pregnancy occurring in a female patient included in the clinical trial or in a female partner of a male subject entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see [Section 10.4.1.2](#)),
 - 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.
- Symptomatic overdose 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 patient and resulting in clinical symptoms and/or signs and considered a "significant overdose" by the Investigator. It will be recorded in the e-CRF as an AESI with immediate notification "Symptomatic OVERDOSE (accidental or intentional)" in all cases and will be qualified as an SAE only if it fulfills the SAE criteria.
- Of note, asymptomatic overdose (accidental or intentional) with the IMP/NIMP is defined as any "significant" overdose, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient (not based on accountability

assessment). It will be recorded as an AESI “Asymptomatic OVERDOSE (accidental or intentional)” that does not require immediate notification.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

There are no waivers from expedited reporting of serious events to health authorities in this trial.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) included in the e-CRF.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP.
- In this study, the required use of the mandatory background basal Lantus (NIMP) and use of IMP (SAR341402 or NovoLog/NovoRapid) may make it difficult to assess the causal relationship to the specific insulin, particularly for hypoglycemia. Global Safety Officer with input from other appropriate study team members will determine the causal relationship when it is not clearly provided by the Investigator.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor.
- When treatment is prematurely discontinued, the patient’s observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
 - Symptomatic and/or,
 - Requiring either corrective treatment or consultation, and/or,
 - Leading to IMP discontinuation or modification of dosing, and/or,
 - Fulfilling a seriousness criterion, and/or,
 - Defined as an AESI.

Instructions for AE reporting are summarized in [Table 1](#).

10.4.4 Instructions for reporting serious adverse events

- In the case of occurrence of an SAE, the Investigator or any designees must immediately:
 - ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the

- monitoring team after approval of the Investigator within the e-CRF or after a standard delay,
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the Clinical Trial Protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges,
 - All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc.) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification,
 - A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.
- Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for reporting adverse events of special interest

For AESIs, the Sponsor must be informed immediately (ie, within 24 hours), as per SAE notification guidelines described in [Section 10.4.4](#), even if not fulfilling a seriousness criterion, using the corresponding pages of the CRF (to be sent) or screens in the e-CRF.

10.4.5.1 Reporting of adverse events of special interest with immediate notification

For AESIs with immediate notification, the Sponsor will be informed immediately (ie, within 24 hours), as per the SAE notification instructions described in [Section 10.4.4](#), even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

10.4.5.2 Reporting of adverse events of special interest without immediate notification

Asymptomatic overdose (accidental or intentional) with the IMP/NIMP is defined as any “significant” overdose, without clinical symptoms and/or signs, either suspected by the Investigator or spontaneously notified by the patient (not based on accountability assessment). It will be recorded as an AE “Asymptomatic OVERDOSE (accidental or intentional)”.

10.4.6 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in [Appendix B](#).

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices:

- Neutropenia.
- Thrombocytopenia.
- Increase in ALT.
- Acute renal insufficiency.
- Suspicion of rhabdomyolysis.

Table 1 - Summary of adverse event reporting instructions

Event category	Reporting timeframe	Specific events in this category	Case Report Form completion		
			AE form	Safety Complementary Form	Other specific forms
Adverse event (non-SAE, non-AESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
Adverse event	Routine	Allergic or allergic-like	Yes	No	Yes
Serious adverse event (non-AESI or AESI)	Expedited (within 24 hours)	Any AE meeting seriousness criterion per Section 10.4.1.2	Yes	Yes	No
Adverse event of special interest	Expedited (within 24 hours)	Pregnancy	Yes	No	Yes
		Symptomatic overdose with IMP/NIMP	Yes	Yes	No
		ALT ≥ 3 x ULN or ALT > 2 x baseline if baseline ALT \geq ULN	Yes	Yes	Yes

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are both expected and at least reasonably related to the IMPs to the health authorities, according to local regulations.
- The following AESIs to the Health Authorities
 - Pregnancy,
 - Symptomatic overdose with IMP/NIMP,
 - ALT > 3 x ULN or ALT > 2 x baseline if baseline ALT \geq ULN.

Adverse events that are considered expected will be specified by the reference safety information (Investigator's Brochure).

As this is an open label study, no un-blinding of SUSARs is necessary.

The Sponsor will report all safety observations made during the conduct of the trial in the CSR.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypoglycemia

Severe symptomatic hypoglycemia

- Severe symptomatic 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 patients at risk for injury to themselves or others.
- Note that “requires assistance” means that the patient could not help himself or herself. Assisting a patient out of kindness, when assistance is not required, should not be considered a “requires assistance” incident.
- Severe symptomatic hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria. All events of seizure, unconsciousness or coma must be reported as SAEs.
- If a participant reports a severe hypoglycemia between the on-site visits or during a phone call visit, the Investigator should ask him/her to come to the study site on the same or the next day, so that the event can be properly assessed and reported.

For description of all other hypoglycemia event types and discussion of endpoints related to hypoglycemia, see [Section 9.2.3.2.1](#).

10.6.2 Injection site reactions

In case the Investigator or the patient recognizes any sign related to local non-allergic reactions at the study drug injection site ([Section 9.2.3.2.4](#)), this should be recorded on the AE page in the e-CRF.

10.6.3 Hypersensitivity reactions

In case a patient 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 e-CRF on the AE page; additional information is collected on the specific allergic reaction complementary forms. Allergic reaction or possible allergic reaction will be adjudicated by the ARAC ([Section 6.4](#)).

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 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 Allergic Reaction Complementary Form.

10.6.4 SMPG

Safety instructions are provided for SMPG in [Section 9.2.2.2.3](#) and [Section 9.2.3.2.1.1](#).

10.6.5 Follow-up of laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities are provided in [Section 17](#), [Appendix B](#). Assessment of General Safety Laboratory data is provided in [Section 9.2.3.2.3](#).

In subjects in whom the ARAC assesses AIA-mediated hypersensitivity reaction or insulin resistance, the increased AIA titers will be followed until return to baseline or until ARAC decides that no further follow-up is deemed necessary.

10.6.6 Other

Assessment of vital signs is noted in [Section 9.2.3.2.5](#) and of ECG in [Section 9.2.3.2.7](#).

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final CSR.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

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

A sample size of 580 patients (290 patients per arm; approximately 480 T1DM patients [230 patients in the US using NovoLog and 250 patients in countries using NovoRapid] and 100 T2DM patients [all in the US using NovoLog]) will ensure that the upper bound of the 2-sided 95% confidence interval (CI) for the adjusted mean difference between SAR341402 and NovoLog/NovoRapid would not exceed a non-inferiority margin of 0.3% HbA1c with at least 95% power. This sample size will also ensure that the lower bound of this 2-sided 95% CI would not be below -0.3% HbA1c with at least 95% power, thus will provide at least 90% power to show both non-inferiority of SAR341402 over NovoLog/NovoRapid (primary analysis) and inverse non-inferiority of NovoLog/NovoRapid over SAR341402 (secondary analysis). These calculations assume a common standard deviation (SD) of 1.0% and a true difference in HbA1c between the treatment groups of zero.

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

Table 2 - Power calculation based on the percentage of patients with treatment-emergent AIAs

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

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

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented.

- Screened: all patients who have originally met inclusion criteria and have signed the informed consent.

- Screen failure patients and reason for screen failure.
- Randomized: all screened patients with a treatment arm allocated and recorded in the IRT database, regardless of whether the treatment was used or not.
- Safety population ([Section 11.3.2](#)), presented as treated.
- Treated but not randomized patients.
- Randomized but not treated patient.
- The intent-to-treat (ITT) population ([Section 11.3.1.1](#)), analyzed as randomized.
- The per protocol population ([Section 11.3.1.2](#)), analyzed as randomized.
- The randomization strata (geographical region [Europe, US, Japan], type of diabetes [T1DM, T2DM], screening HbA1c categories [$<8\%$, $\geq 8\%$], and prior use of NovoLog/NovoRapid [Yes, No]) assigned by IRT will be summarized. The discrepancy between the stratum assigned by IRT and the information reported on CRF will be listed for all randomized patients.
- Disposition for the main 6-month period:
 - Patients who completed the main 6-month treatment period (patients who have performed Visit 9 [Week 26] and who did not permanently discontinue treatment before Visit 9 [Week 26]),
 - Patients who permanently discontinued the IMP during the main 6-month treatment period, and the reasons for permanent treatment discontinuation,
 - Patient's decision for treatment discontinuation during the main 6-month period,
 - Patients who completed the main 6-month study period (patients who have performed Visit 9 [Week 26]),
 - Patients who prematurely discontinued the study during the main 6-month period, and the reasons for premature study discontinuation,
 - Status at last study contact of patients who prematurely discontinued the treatment during the main 6-month period.
- Disposition for the 12-month period:
 - Patients who completed the 12-month treatment period including 6-month extension (patients who have performed Visit 12 [Week 52] and who did not permanently discontinue treatment before Visit 12 [Week 52]),
 - Patients who permanently discontinued the IMP during the 12-month treatment period, and the reasons for permanent treatment discontinuation,
 - Patient's decision for treatment discontinuation during the 12-month period,
 - Patients who completed the main 12-month study period (patients who have performed Visit 12 [Week 52]),
 - Patients who prematurely discontinued the study during the 12-month period, and the reasons for premature study discontinuation,
 - Status at last study contact.

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

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

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

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

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

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

11.3.1.1 Intent-to-treat population

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

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

11.3.1.2 Per protocol population

The Per Protocol population is a subset of the ITT population, which includes all randomized and exposed patients, who do not permanently discontinue IMP allocated by randomization during the main 6-month period, who perform Week 26 and who do not present major or critical protocol deviations that could impact the analysis during the main 6-month period. The major and critical protocol deviations will be detailed in the SAP.

11.3.2 Safety population

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

Patients will not be considered exposed if there is documented evidence that patients have not taken the IMP:

- If a patient is dispensed IMP and is lost to follow-up without any documented evidence whether or not the patient took IMP, the patient will be considered exposed and included in the safety population.

- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

In addition:

- Non-randomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- For patients receiving more than one study treatment during the trial, the patient will be analyzed in the treatment group in which he/she was treated longer.

11.3.3 Anti-insulin antibody population

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

11.4 STATISTICAL METHODS

Unless specified otherwise, all analyses will be presented pooling NovoLog and NovoRapid in the comparator group. Specific subgroup analyses will be performed by type of comparator used (NovoLog in the US, NovoRapid in other countries).

11.4.1 Extent of study treatment exposure

The extent of study treatment exposure will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of the open-label IMP exposure.

The duration of exposure during the study will be the total number of days of administration of IMP, ignoring temporary drug discontinuation.

The duration of exposure to the open-label IMP during the study is defined as:

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

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

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

- Up to 4 weeks,

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

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

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

In addition, the cumulative duration of exposure is also described using the same time periods.

11.4.1.2 Daily insulin doses

The daily insulin doses (basal, mealtime, total) will be described at each visit, as well as the changes from baseline (in U and U/kg).

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoint(s)

11.4.2.1.1 Primary efficacy analysis

First step analysis:

The statistical test for non-inferiority assessment of SAR341402 versus NovoLog/NovoRapid on the primary efficacy endpoint (change in HbA1c from baseline to Week 26 as defined in the [Section 9.1](#)) will be one-sided, with alpha level of 0.025 and using a non-inferiority margin of 0.3% HbA1c.

The baseline value is defined as the last available value up to the date of randomization.

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

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

A multiple imputation approach will be used where missing data from patients who do not adhere to IMP will be represented by the data from those patients in the same treatment group who also do not adhere to IMP but have the measurement for the primary endpoint. Details of the proposed multiple imputation analysis in two parallel parts (according the status of the patients), are provided below:

1. Missing data in patients who prematurely discontinued IMP during the main 6-month randomized period will be imputed using a model estimated solely from data observed in other patients who discontinued IMP during the main 6-month randomized period but have the measurement for the primary endpoint at Week 26. Due to the anticipated small number of these latter patients, a basic imputation model will be built, including only the randomized treatment group as predictor. Missing data will be imputed using the regression method.
2. Missing data in patients who completed the main 6-month treatment period will be imputed separately, using a model estimated solely from data observed in other patients who completed the main 6-month treatment period and have the measurement for the primary endpoint at Week 26. Since in general, the missing pattern will not be monotone, a two-step approach will be used:
 - Step 1: the Markov Chain Monte Carlo (MCMC) method will be used in conjunction with the IMPUTE=MONOTONE option to create an imputed data set with a monotone missing pattern. The imputation model will include the continuous fixed covariates of the baseline HbA1c value as well as the changes from baseline in HbA1c at Week 12 and Week 26.
 - Step 2: using the monotone data set from step 1, missing data will be imputed using the regression method. The imputation model will include the fixed categorical effects of the treatment group, the randomization strata geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, ≥8%) (except when analyzing the change in HbA1c) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariates of the baseline HbA1c value and the changes from baseline in HbA1c at Week 12 and Week 26.

Missing values will be imputed 10 000 times. Completed datasets from the two parts detailed above will be combined into a single dataset. Each completed dataset will be analyzed using an analysis of covariance (ANCOVA) of the change in HbA1c from baseline to Week 26, including the fixed categorical effects of treatment group (SAR341402, NovoLog/NovoRapid), the randomization strata geographical region and type of diabetes (Europe T1DM, US T1DM,

US T2DM, Japan T1DM), screening HbA1c ($<8\%$, $\geq 8\%$) (except when analyzing the change in HbA1c) and prior use of NovoLog/NovoRapid (Yes, No), as well as the continuous fixed covariate of baseline value. Results from the 10 000 analyses will be combined using Rubin's formula.

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

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

Second step analysis:

If non-inferiority of SAR341402 over NovoLog/NovoRapid is demonstrated, using a hierarchical step-down testing procedure, the following additional analysis will be performed (not as primary objective): the inverse non-inferiority (of NovoLog/NovoRapid over SAR341402) will be tested looking at the lower bound of the 2-sided 95% CI of the difference between SAR341402 and NovoLog/NovoRapid in the ITT population. Non-inferiority of NovoLog/NovoRapid over SAR341402 will be demonstrated if the lower bound is $>-0.3\%$.

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

11.4.2.1.2 Sensitivity analysis

Sensitivity analyses will be conducted to describe the missing data frequency and pattern and assess the robustness of primary efficacy analysis with regard to missing data.

11.4.2.1.3 Supportive analysis

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

11.4.2.1.4 Additional analysis

Analyses on the primary efficacy endpoint will be presented for the subgroups comparing SAR341402 with NovoLog in patients randomized in the US (approximately 330 patients, 230 with T1DM and 100 with T2DM) and comparing SAR341402 and NovoRapid in regions using NovoRapid (approximately 250 patients with T1DM). The analysis will be performed using a similar multiple imputation approach in two parts, as for the primary efficacy endpoint, followed by a similar ANCOVA model (as described in [Section 11.4.2.1.1](#)) adding the corresponding subgroup factor and subgroup factor-by-treatment interaction. The randomization strata of geographical region (Europe, Japan, US) and Type of diabetes (T1DM, T2DM) will not be included in the model.

Least square means difference of SAR341402 versus NovoLog and SAR341402 versus NovoRapid at Week 26 will be provided, as well as the corresponding SEs and 95% CI, within each subgroup. The significance level of the treatment-by-subgroup factor interaction term will also be provided for descriptive purpose. Forest plots will be provided.

Additionally, the James-Stein (J-S) shrinkage estimator may be used to evaluate the treatment effect in each subgroup defined by type of comparator, with a different approach (15). This estimate is derived from the overall and subgroup treatment effect estimates in order to use all study information (including information collected in the other subgroup). Details will be provided in the statistical analysis plan.

Explorative analyses will be performed on the primary endpoint to summarize the treatment effects across subgroups defined by baseline and screening factors, such as: category of age (<65, [65 to 75] and ≥ 75 years of age), baseline BMI (<30 and ≥ 30 kg/m²), randomization strata (geographical region [Europe, US, Japan], type of diabetes [T1DM, T2DM], screening HbA1c categories [<8%, $\geq 8\%$] and prior use of NovoLog/NovoRapid [Yes, No]) and type of comparator (NovoLog and NovoRapid). Subgroup analyses will be detailed in the SAP.

11.4.2.2 Analyses of secondary efficacy endpoints

All secondary efficacy endpoints (as defined in [Section 9.2.2](#)) will be analyzed in the ITT population, for descriptive purpose only (no formal statistical testing). Separate analyses will be performed for the main 6-month and the 12-month periods.

All continuous secondary efficacy endpoints will be analyzed using a similar multiple imputation approach in two parts, as for the primary efficacy endpoint, followed by a similar ANCOVA model (as described in [Section 11.4.2.1](#)).

The categorical secondary endpoint (HbA1c responders) will be analyzed using a logistic regression model adjusted on the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c (<8%, $\geq 8\%$), and prior use of NovoLog/NovoRapid (Yes, No). Patients without assessment at Week 26 (or Week 52 for the analysis at Week 52) will be considered as failure.

11.4.2.3 Multiplicity considerations

11.4.2.3.1 Primary Endpoint

A hierarchical step-down testing procedure is applied to test the non-inferiority of NovoLog/NovoRapid over SAR341402 only if the non-inferiority of SAR341402 over NovoLog/NovoRapid is demonstrated (primary comparison).

11.4.2.3.2 Secondary Endpoints

No multiplicity adjustment will be made as no formal statistical testing will be done on secondary endpoints.

11.4.3 Analyses of safety data

Safety analyses will be presented by treatment group for the main 6-month and the 12-month on-treatment periods on safety endpoints (defined in [Section 9.2.3](#)).

All safety analyses will be descriptive and performed on the Safety population using the following common rules:

- The baseline value is defined as the last available value prior to the first injection of IMP.

The following definitions will be applied to laboratory parameters and vital signs:

- The Potentially Clinically Significant Abnormality (PCSA) values are defined as abnormal values considered medically important by the sponsor according to predefined criteria/thresholds based on literature review and defined by the sponsor for clinical laboratory tests, and vital signs.
- PCSA criteria will determine which patients had at least one PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including non-scheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.3.1 Hypoglycemia

Proportions of patients with at least one hypoglycemia event will be presented for any hypoglycemia and by type of event (see [Section 9.2.3.2.1](#)) for each treatment group on the safety population.

Incidences of hypoglycemia per patient year will be computed as: $365.25 \times (\text{number of episodes of hypoglycemia}) / (\text{number of days exposed})$ and summarized for any hypoglycemia and by type of event for each treatment group.

For exploratory purpose, odds-ratios and rate ratios of hypoglycemia event may be provided for SAR341402 versus NovoLog/NovoRapid, overall and for some categories of hypoglycemia. Details will be provided in the SAP.

Exploratory analyses will be performed by subgroups defined by baseline and screening factors, such as: category of age (<65, [65 to 75] and ≥ 75 years of age), baseline BMI (<30 and ≥ 30 kg/m²), randomization strata and type of comparator (NovoLog and NovoRapid). Further subgroup analyses may be performed if deemed necessary for interpretation of results.

Further analyses over time or by time of the day may be performed if appropriate.

11.4.3.2 Injection site reactions and hypersensitivity reactions

Injection site and hypersensitivity reactions will be identified by MedDRA search (list of MedDRA terms will be specified in the SAP).

Number (n) and proportion (%) of patients with related event will be summarized by treatment group as appropriate. Events adjudicated as possible hypersensitivity reactions by ARAC will also be described.

11.4.3.3 Adverse events

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

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 permanent treatment discontinuation and all TEAEs leading to death.

Death

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

- Number (n) and proportion (%) of patients who died by study period (TEAE, on-study, post-study) and reasons for death.
- A listing of all deaths.

11.4.3.4 Analyses of laboratory variables

Descriptive statistics will be used to summarize results of laboratory parameters, including the summary of incidence of PCSAs at any time during the main 6-month and 12-month on-treatment periods.

11.4.3.5 Analyses of vital sign variables

Descriptive statistics will be used to summarize results of vital signs, including the summary of incidence of PCSAs at any time during the main 6-month and 12-month on-treatment periods by treatment group.

11.4.3.6 Drug-induced liver injury

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

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

The incidence of liver related TEAEs will be summarized by treatment group. The selection of PTs will be based on standardized MedDRA query (SMQ) Hepatic disorder.

11.4.4 Analysis of immunogenicity data

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

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

On the group of patients with anti-SAR341402/NovoLog/NovoRapid antibody positive sample at a given visit, anti-SAR341402/NovoLog/NovoRapid antibody titers will be summarized using quantitative descriptive statistics, and the number and percentage of patients with cross-reactivity to human insulin will be provided.

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

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

For exploratory purposes, the difference between SAR341402 and NovoLog/NovoRapid in the percentage of patients with treatment-emergent AIAs (AIA incidence) will be provided with associated 2-sided 90% CI. Results will be obtained by fitting a binomial regression model with an identity-link function. The model will include fixed categorical effects for treatment, the randomization strata of geographical region and type of diabetes (Europe T1DM, US T1DM, US T2DM, Japan T1DM), screening HbA1c ($<8\%$, $\geq 8\%$), and prior use of NovoLog/NovoRapid (Yes, No). The risks within each treatment group and risk difference will be provided with their 90% CIs using the adjusted LS mean estimates of the treatment effect.

For patients with treatment-induced and treatment-boosted AIAs, the kinetics of AIA response (transient, persistent, or indeterminate AIA response as defined in [Section 9.2.1.3](#)) will be further summarized using number and percentage of patients, and the peak titer will be described using median, Q1 and Q3.

Exploratory analyses will be performed by subgroups defined by baseline and screening factors, such as: category of age (<65, [65 to 75] and ≥ 75 years of age), baseline BMI (<30 and ≥ 30 kg/m²), randomization strata (geographical region [Europe, US, Japan], type of diabetes [T1DM, T2DM], screening HbA1c categories [$<8\%$, $\geq 8\%$] and prior use of NovoLog/NovoRapid [Yes, No]) and type of comparator (NovoLog and NovoRapid). Further subgroup analyses may be performed if deemed necessary for interpretation of results. Details will be provided in the SAP.

Subgroup analyses and/or scatterplots will be conducted to assess the relationship between immunogenicity endpoints and efficacy/safety assessments. Listings will be provided for patients with high AIA titers (AIA outliers). Change in HbA1c from baseline to Week 26 and Week 52, hypoglycemia, injection site reactions, hypersensitivity reactions, TEAE and SAEs will be summarized by treatment-emergent AIA (Yes, No) and treatment-emergent AIA at last on-treatment value (Yes, No). The relationship between the AIA titer and the efficacy and safety will be explored using scatter plot of maximal titer during the main 6-month and the 12-month on-treatment periods versus change in HbA1c from baseline to Week 26 and Week 52, total insulin dose, hypoglycemia, injection site reactions and hypersensitivity reactions.

Further analyses may be performed if appropriate.

11.4.5 Analyses of pharmacokinetic and pharmacodynamic variables

Not applicable.

11.5 INTERIM ANALYSIS

No interim analysis is planned.

This controlled open-label study will not to be early terminated with a positive claim for efficacy or safety. The primary analysis of the efficacy and safety will be performed on the data collected during the main 6-month comparative efficacy and safety period. The timing of this analysis is when the last randomized patient has completed the Week 26 (Visit 9) visit. The results of the primary analysis will not be used to change the conduct of the ongoing study in any aspect.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, and delegated Investigator staff and SubInvestigator, in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the International Council for Harmonisation (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the clinical trial including the written information giving approval/favorable opinion by the Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the written informed consent form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient.

The informed consent form used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

If the race/ethnic origin of the patients will be collected in the clinical trial, the scientific justification should be specified.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this Clinical Trial Protocol to the health authorities (competent regulatory authority) and the appropriate Ethics Committee (IRB/IEC), and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with Ethics Committee (IRB/IEC) composition.

The clinical trial (study number, Clinical Trial Protocol title and version number), the documents reviewed (Clinical Trial Protocol, informed consent form, Investigator's Brochure with any addenda, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

The IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the Clinical Trial Protocol should be submitted to the health authorities (competent regulatory authority), as required by local regulation, in addition to the Ethics Committee (IRB/IEC) before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the health authorities (competent regulatory authority) and the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the Ethics Committee (IRB/IEC) and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the Ethics Committee (IRB/IEC) at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the Clinical Trial Protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the Clinical Trial Protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as SubInvestigators to assist in the conduct of the clinical trial in accordance with the Clinical Trial Protocol. All SubInvestigators shall be appointed and listed in a timely manner. The SubInvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the Clinical Trial Protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, Clinical Trial Protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with Clinical Trial Protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor's duly authorized

personnel, the ethics committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate e-CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All e-CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

In this trial, SMPG data from the glucometer and insulin dose and hypoglycemic events entered into the e-diary will be available on a vendor web based portal for review. Data for endpoint analysis will be captured in the clinical database. At the end of trial, data in the web based portal will be stored and then will later be destroyed according to local regulation.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the CV describing the experience, qualification and training of each Investigator and SubInvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the Clinical Trial Protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this Clinical Trial Protocol and other necessary documentation to the ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The SubInvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the SubInvestigators of the confidential nature of the clinical trial.

The Investigator and the SubInvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /SubInvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the SubInvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations.
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor's databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Not Reported, Unknown) or ethnicity (Hispanic or Latino, Not Hispanic or Latino, Not Reported, Unknown) will be collected in this study because these data are required by several health authorities (eg, on African American population for FDA, on Asian population for the PMDA in Japan or S-FDA in China).

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the Clinical Trial Protocol, GCP, and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Patient enrollment is unsatisfactory.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon.

- Noncompliance of the Investigator or SubInvestigator, delegated staff with any provision of the Clinical Trial Protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The total number of patients are included earlier than expected.

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a CSR and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway, or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this Clinical Trial Protocol.

The Investigator should not implement any deviation from, or changes to the Clinical Trial Protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC and/or notification/approval of health authorities (competent regulatory authority) of an amendment, as required by local regulation, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this Clinical Trial Protocol.

Any amendment to the Clinical Trial Protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In case of substantial amendment to the Clinical Trial Protocol, approval from the health authorities (competent regulatory authority) will be sought before implementation.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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17 APPENDICES

Appendix A Guidance on contraceptive methods and collection of pregnancy information

DEFINITIONS

Nonreproductive potential

1. Premenopausal female with 1 of the following:
 - Documented hysterectomy,
 - Documented bilateral salpingectomy,
 - Documented bilateral oophorectomy.
3. Postmenopausal
 - A postmenopausal state is defined as no menses for 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 hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use 1 of the 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 enrolment.

Reproductive potential (WOCBP)

A woman is considered of reproductive potential (WOCBP), ie, fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

CONTRACEPTIVE GUIDANCE

Male subjects

- Male subjects with heterosexual partners of reproductive potential (WOCBP) are eligible to participate if they agree to use the following during the protocol defined timeline:
 - Refrain from donating sperm,

and

 - At least 1 of the following conditions applies:
 - Are and agree to remain abstinent from penile-vaginal intercourse on a long term and persistent basis, when this is their preferred and usual lifestyle.

or

 - Agree to use a male condom plus an additional contraceptive method with a failure rate of < 1% per year (see table for female subjects).
- Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom for the time defined in the protocol.

<p>Highly Effective Contraceptive Methods That Are User Dependent</p> <p><i>Failure rate of <1% per year when used consistently and correctly^a</i></p> <ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – Oral, – Intravaginal, – Transdermal. • Progestogen-only hormone contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – Oral, – Injectable.
<p>Highly Effective Methods That Are User Independent</p> <ul style="list-style-type: none"> • Implantable progestogen-only hormone contraception associated with inhibition of ovulation^b. • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion. • Vasectomized partner. <p><i>(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)</i></p> <ul style="list-style-type: none"> • Sexual abstinence. <p><i>(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 drug. 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 subject.)</i></p>
<p>NOTES:</p> <p>^a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.</p> <p>^b Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 3 months after the last injection of study medication, covering more than 5 times the terminal half-life of the IMP after the last dose of study treatment.</p>

Female subjects:

<p>Highly Effective Contraceptive Methods That Are User Dependent</p> <p><i>Failure rate of <1% per year when used consistently and correctly^a</i></p> <ul style="list-style-type: none"> • Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation^b <ul style="list-style-type: none"> – Oral, – Intravaginal, – Transdermal. • Progestogen-only hormone contraception associated with inhibition of ovulation^b: <ul style="list-style-type: none"> – Oral, – Injectable.
<p>Highly Effective Methods That Are User Independent</p> <ul style="list-style-type: none"> • Implantable progestogen-only hormone contraception associated with inhibition of ovulation^b. • Intrauterine device (IUD). • Intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion. • Vasectomized partner. <p><i>(Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method(s) of contraception should be used. Spermatogenesis cycle is approximately 90 days.)</i></p> <ul style="list-style-type: none"> • Sexual abstinence. <p><i>(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 drug. 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 subject.)</i></p>
<p>NOTES:</p> <p>^a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for subjects participating in clinical studies.</p> <p>^b Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraceptive method. In this case TWO highly effective methods of contraception should be used during the treatment period and for at least 3 months after the last injection of study medication, covering more than 5 times the terminal half-life of the IMP after the last dose of study treatment.</p>

COLLECTION OF PREGNANCY INFORMATION

Male subjects with partners of reproductive potential who become pregnant

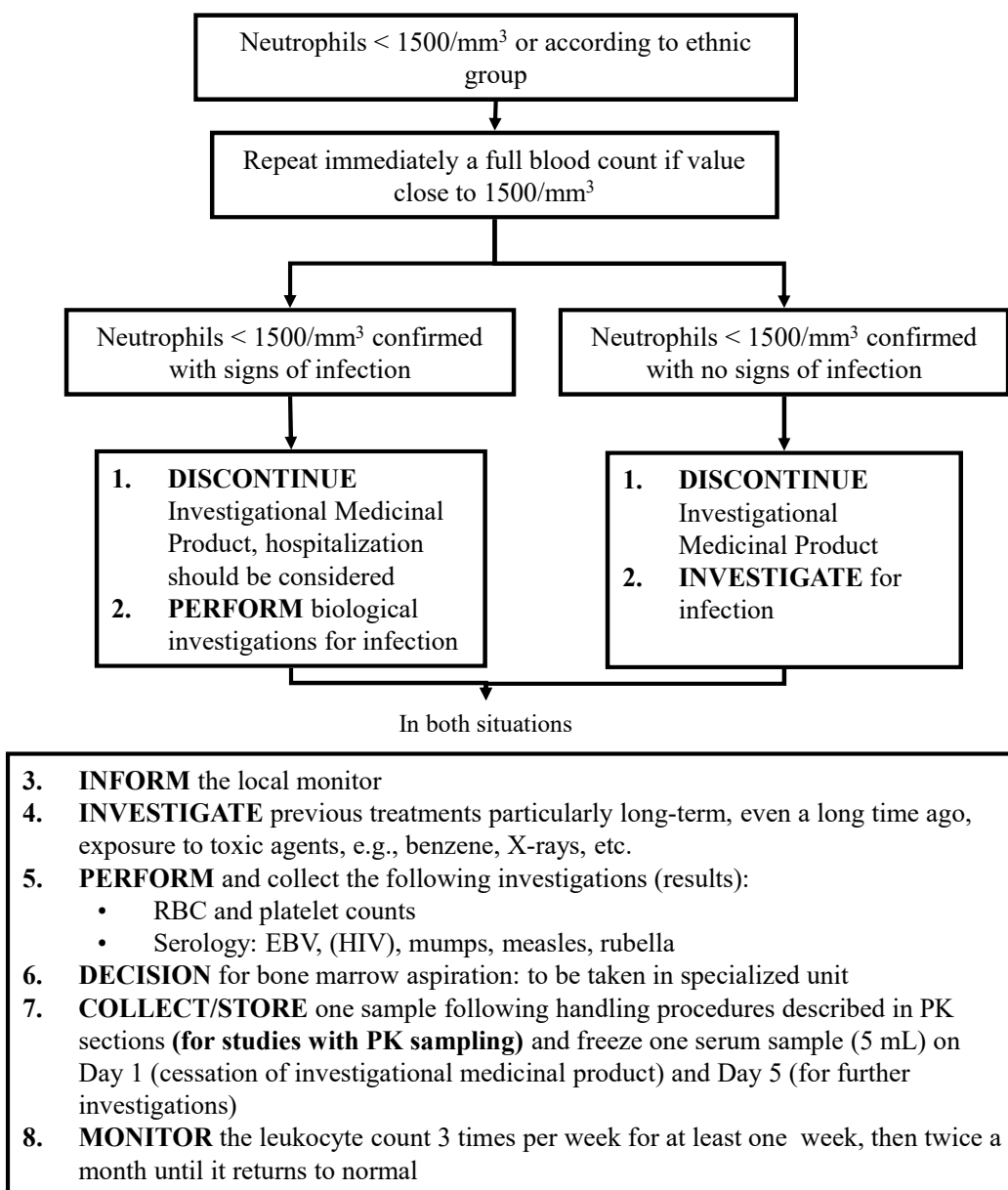
- The Investigator will attempt to collect pregnancy information on any female partner of a male study subject who becomes pregnant while participating in this study. This applies only to subjects who receive study treatment.
- After obtaining the necessary signed informed consent from the pregnant female 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.
- 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, 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 procedure.

Female subjects who become pregnant

- The Investigator will collect pregnancy information on any female subject, 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.
- Participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on participant and neonate, which 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 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 SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the Investigator, will be reported to the Sponsor as described in [Section 10.4.4](#). While the Investigator is not obligated to actively seek this information in former study subjects, he or she may learn of an SAE through spontaneous reporting.

Appendix B General guidance for the follow-up of laboratory abnormalities by Sanofi

NEUTROPENIA

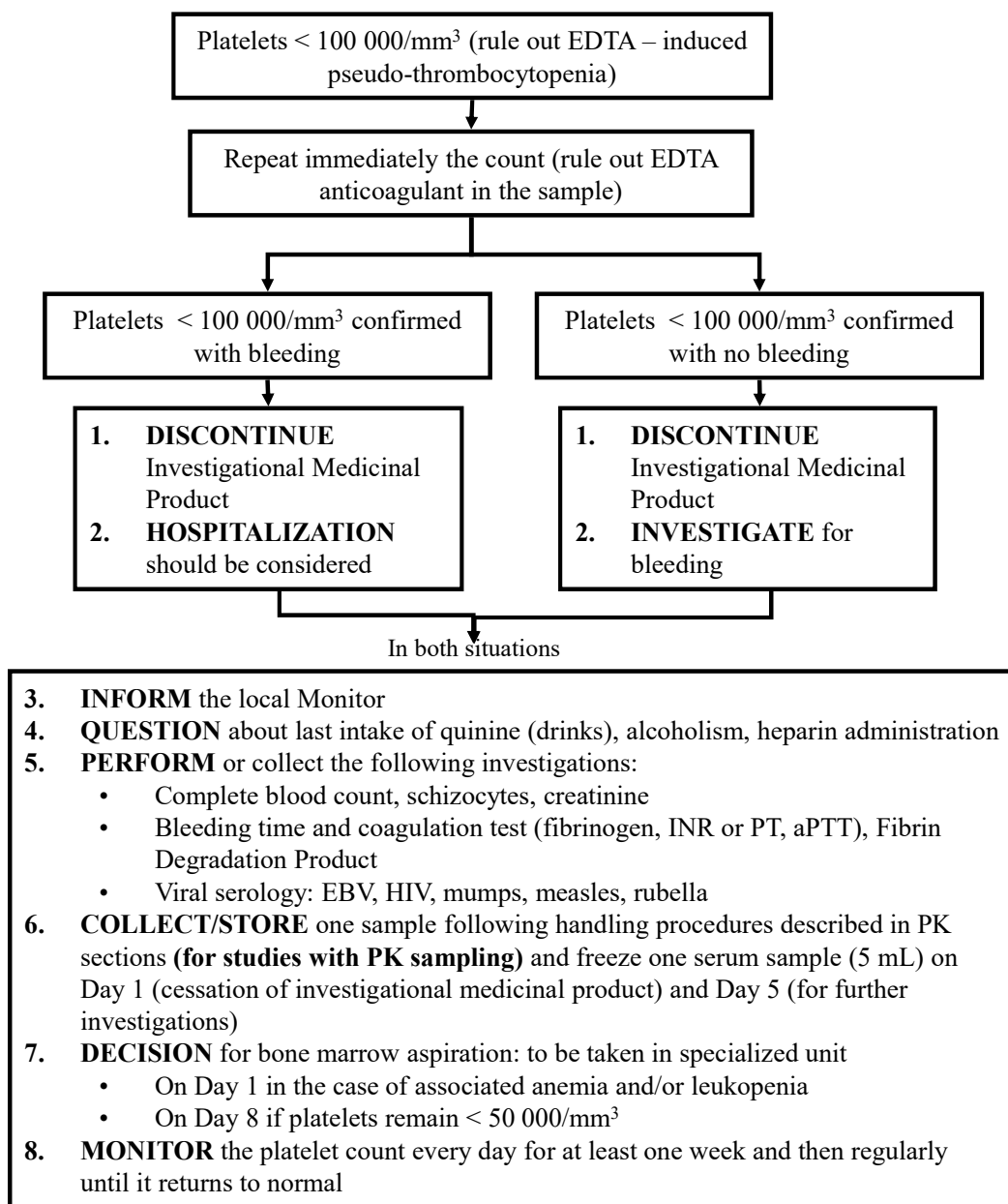


Note:

- The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
- For individuals of African descent, the relevant value of concern is $<1000/\text{mm}^3$

Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in [Section 10.4.3](#) is met.

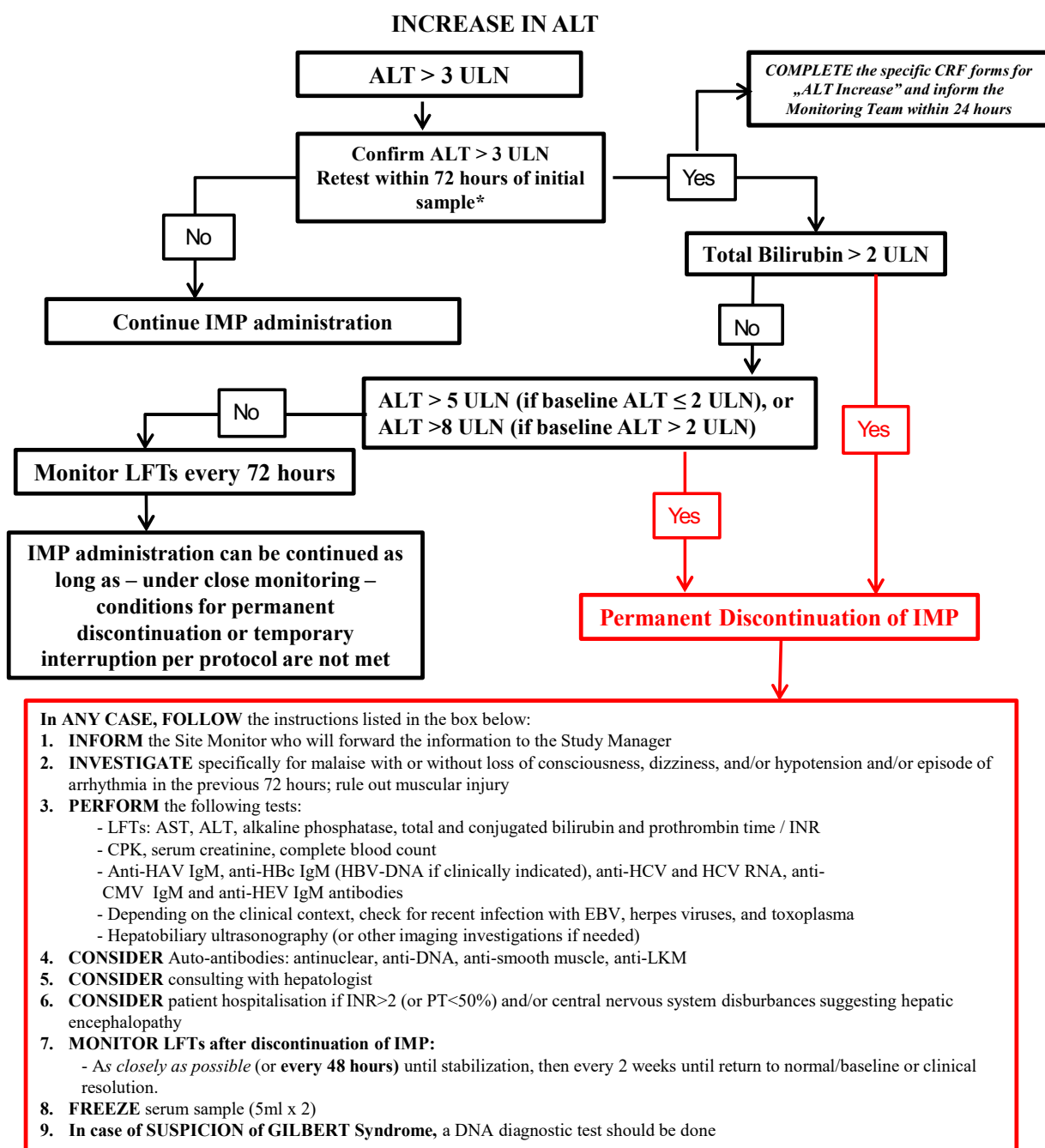
THROMBOCYTOPENIA



Note:

The procedures above flowchart are to be discussed with the patient only in case described in the the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in [Section 10.4.3](#) is met.

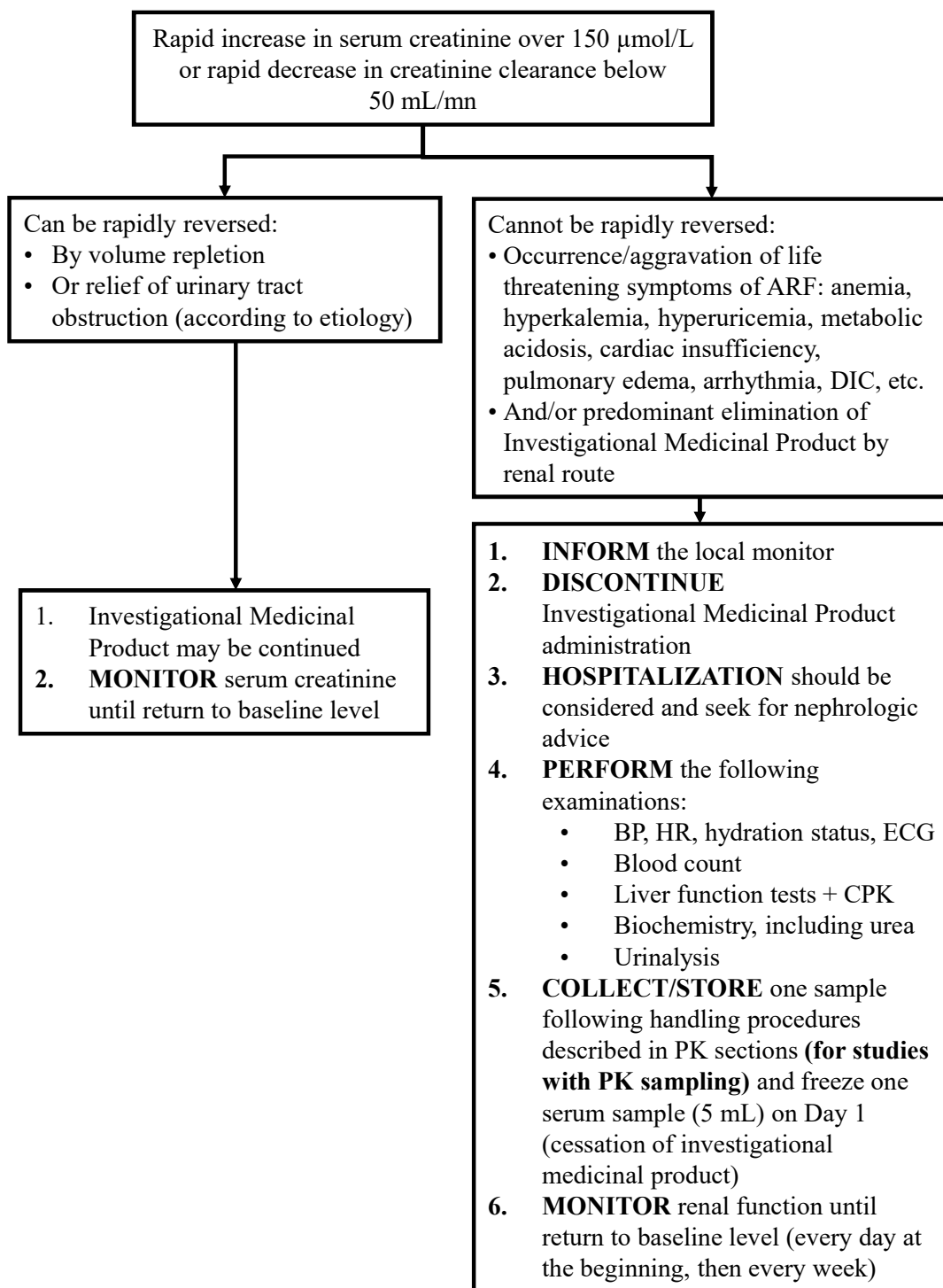


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

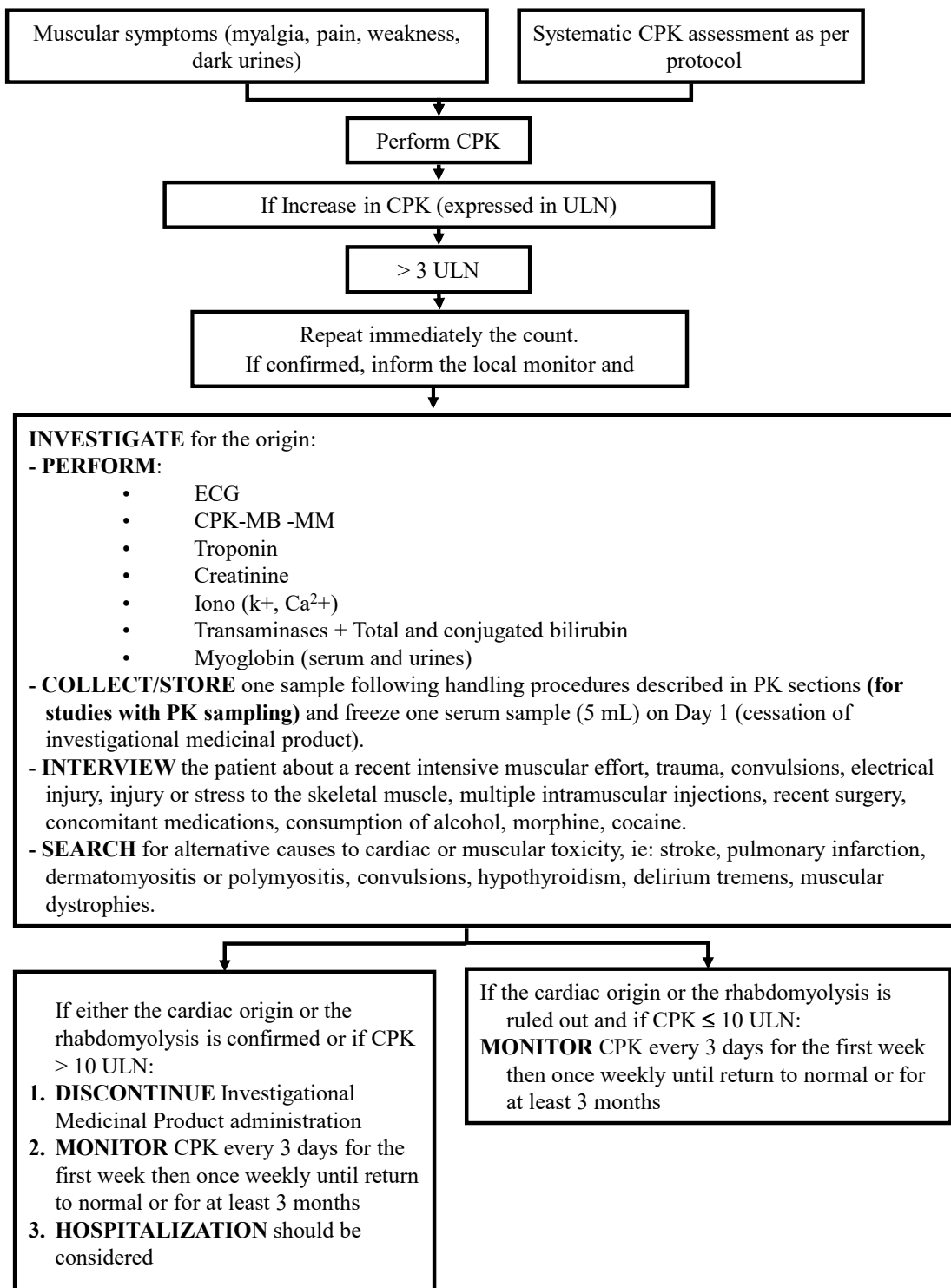
- “Baseline” refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See in [Section 10.4](#) for guidance on safety reporting.
- Normalization is defined as ≤ULN or baseline value, if baseline value is >ULN.

ACUTE RENAL FAILURE



Acute renal failure is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in [Section 10.4.3](#) is met.

SUSPICION OF RHABDOMYOLYSIS



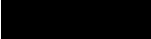
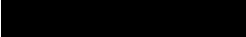
Suspicion of rhabdomyolysis is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting AEs in [Section 10.4.3](#) is met.

Appendix C Country specific requirements

Not applicable.

EFC15081 Amended Protocol 02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
	Clinical Approval	19-Dec-2017 11:01 GMT+0100
	Clinical Approval	19-Dec-2017 14:05 GMT+0100