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AMENDED CLINICAL TRIAL PROTOCOL NO. 01

COMPOUND: SAR425899

A 26-week Randomized, Double-blind, Placebo-controlled, Dose-ranging Phase 2 Study to Assess the Safety and Efficacy of SAR425899 in Patients with Type 2 Diabetes Mellitus

STUDY NUMBER: DRI13940

VERSION DATE / STATUS: Approval date (23-Jan-2017) / Approved

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: SAR425899	**STUDY No.: DRI13940**
TITLE	A 26-week Randomized, Double-blind, Placebo-controlled, Dose-ranging Phase 2 Study to Assess the Safety and Efficacy of SAR425899 in Patients with Type 2 Diabetes Mellitus
INVESTIGATOR/TRIAL LOCATION	Multinational
PHASE OF DEVELOPMENT	Phase 2
STUDY OBJECTIVE(S)	**Primary objective:** The primary objective of this study is to assess the dose-response relationship of SAR425899 versus placebo in terms of glycemic control as measured by the change in glycosylated hemoglobin (HbA_{1c}) from baseline to Week 26. **Secondary objectives:** • To assess the effect of once daily dosing of SAR425899 on body weight over 26 weeks. • To assess the safety and immunogenicity profile of SAR425899 when administered as daily subcutaneous (SC) injections over 26 weeks, including assessment of the heart rate (HR) change from baseline to Week 26 by electrocardiogram (ECG) and Holter monitor. • To assess the proportion of patients achieving predefined HbA1c targets of <7% and <6.5% as well as the proportion of patients achieving ≥5% and ≥10% body weight loss at Week 26. • To assess the effect of once daily dosing of SAR425899 on additional parameters of glycemic control and lipid metabolism. • To assess the effect of once daily dosing of SAR425899 on additional pharmacodynamic (PD) biomarkers. • To assess the pharmacokinetic (PK) profile and parameters of SAR425899, inter-individual and inter-occasion variability in PK parameters using a population PK approach. **Exploratory objectives:** • To assess and compare the safety and efficacy of SAR425899 versus open-label liraglutide from baseline to Week 26. • To explore SAR425899 PK/PD relationships for glycemic parameters, body weight loss and heart rate. • To assess the treatment effects in each group on patient-reported outcomes. • To assess the treatment effects in each group on nonalcoholic steatohepatitis (NASH) and cardiovascular biomarkers.

STUDY DESIGN	This is a randomized, placebo-controlled, parallel-group study which is double-blind for SAR425899 versus placebo and open-label for the active control liraglutide. The volume of investigational medicinal product (IMP; ie, dose of SAR425899 or matching placebo) is not blinded. Patients will be assigned to 1 of the 7 treatment arms: 3 SAR425899 treatment arms with 3 different dose levels (60 patients per arm), 3 matching SAR425899 placebo treatment arms (10 patients per arm), and 1 liraglutide arm (active comparator arm with 60 patients). For the biostatistical analyses, data from the 3 SAR425899 placebo arms will be pooled into 1 placebo group (30 patients total). The randomization will be stratified by screening visit HbA_{1c} (<8.0% versus ≥8.0%) and Visit 4 (Day 1) body mass index (BMI; <35.0 kg/m^2 versus ≥35.0 kg/m^2). Up to 50% of patients will perform additional assessments: meal test and Holter monitor. Full PK will be performed in a subset of 40 patients. The study will include a 3-week screening period, a 26-week treatment period, and a 3-day post treatment follow-up period. In case of fasting plasma glucose (FPG) or HbA_{1c} (assessed by central laboratory) above predefined thresholds and if no reasons can be found for insufficient glucose control, it is recommended to add rescue therapy. The choice of rescue therapy is at the Investigator's discretion with the exception of using glucagon-like petide-1 (GLP-1) receptor agonists or dipeptidyl peptidase 4 (DPP4) inhibitors. Thresholds: • FPG >270 mg/dL (15.0 mmol/L) from baseline Visit 4 (Week 0) to Visit 9 (Week 8, including value at Visit 9). • FPG >240 mg/dL (13.3 mmol/L) from Visit 9 (Week 8) to Visit 10 (Week 14). • FPG >200 mg/dL (11.1 mmol/L) or HbA1C >8% from Visit 10 (Week 14) to Visit 12 (Week 26). All assessments planned in Visit 12 are to be performed before initiating rescue therapy. After these assessments are completed and rescue therapy initiated, the patient will remain in the study and continue to administer the study treatment (including background therapy). The planned visits and assessments should be performed until the last scheduled visit.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** • Patients with type-2 diabetes mellitus (T2DM) for at least 3 months before the screening visit. • On diet/exercise and/or treatment with metformin (stable dose of ≥1500 mg/day or maximal tolerated dose) for at least 3 months prior to screening. • Signed informed consent. **Exclusion criteria:** • At screening, patient's age < legal age of adulthood or >80 years. • HbA1c at screening visit <7.0% or >10.0%.

	• BMI <25 kg/m^2 or >45.0 kg/m^2. • Pregnant or lactating women. • Women of childbearing potential (WOCBP) 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). • Diagnosis of type-1 diabetes mellitus. • FPG >15 mmol/L (270 mg/dL) measured by the central laboratory at screening (Visit 1), and confirmed (>15 mmol/L [270 mg/dL]) by a repeat test before randomization. • Treatment with glucose-lowering agents(s) other than metformin, currently or within the 3 months prior to screening. • Previous insulin use, except for episode(s) of short-term treatment (≤15 consecutive days) for intercurrent illness or pregnancy, or use of insulin within the last 6 months. • Contraindication(s) to metformin use. • Contraindication(s) to liraglutide use. • Significant change in body weight in the 3 months before screening. • Poorly controlled hypertension (a resting systolic blood pressure [SBP] >160 mm Hg and/or diastolic blood pressure [DBP] >95 mm Hg at screening). • History of long QT syndrome and/or QTc more than 450 ms at screening visit. • History of pancreatitis or pancreatectomy. • History of weight loss surgery. • Personal or immediate family history of medullary thyroid cancer (MTC) or genetic conditions that predispose to MTC. • Any prior exposure to drugs belonging to the class of GLP-1 receptor agonists or GLP-1 analogs. • Contraindications or known hypersensitivity reaction to glucagon.
Total expected number of patients	Approximately 270 randomized patients. Approximately 70 sites anticipated.
STUDY TREATMENT(s) **Investigational medicinal product(s)** **Formulation:** **Route(s) of administration:**	 1. SAR425899 or its placebo (injection solution). 2. Liraglutide as open-label comparator (injection solution). 1. Cartridges containing 3 mL solution for injection, at a concentration of 0.5 mg/mL SAR425899 or matching placebo. 2. Pens prefilled with a 3-mL solution of 6 mg/ml liraglutide. Tactipen® injector will be used to deliver SC doses of SAR425899 and matching placebo. Three (3) SAR425899 dose levels are planned. Prefilled, multidose pen will be used to deliver SC doses for liraglutide.

Dose regimen:	Doses of SAR425899, placebo, and liraglutide should be injected in the morning at the same time every day except on clinic visit days. On clinic visit days, SAR425899, placebo and liraglutide injection time should be after blood tests/ECG measurement time in the morning and be coordinated with the meal test/PK sampling time. SAR425899 and matching placebo treatment regimens plan to include a 1 to 3-week dose increase period before the maintenance dose, as follows: • Low dose regimen: 1 dose increase step of 1 week (if no significant tolerability issues [for example, nausea and vomiting] are observed): 0.06 mg ie, 12U – 0.12 mg ie, 24U (0.12mg ie, 24U for 25 weeks). • Mid dose regimen: 2 dose increase steps of 1 week each (if no significant tolerability issues [for example, nausea and vomiting] are observed): 0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U (0.16 mg ie, 32U for 24 weeks). • High dose regimen: 3 dose increase steps of 1 week each (if no significant tolerability issues [for example, nausea and vomiting] are observed): 0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U – 0.20 mg ie, 40U (0.20 mg ie, 40U for 23 weeks) Liraglutide: 1.8 mg daily after dose increase (0.6 mg daily for 7 days followed by 1.2 mg daily for 7 days followed by 1.8 mg daily for 24 weeks).
Noninvestigational medicinal product(s) **Formulation:** **Route(s) of administration:** **Dose regimen:**	Metformin background treatment: previous metformin treatment should be continued and kept stable for the duration of the study. Coated tablets or powder depending on formulation available in each country. oral ≥1500 mg daily stable dose or maximal tolerated dose.
ENDPOINT(S)	**Primary endpoint:** • Change in HbA1c from baseline to Week 26. **Secondary endpoints:** • Secondary efficacy endpoints: - Change in body weight from baseline to Week 26, - Percentage of patients achieving predefined HbA1c targets of <7% and <6.5% at Week 26, - Percentage of patients achieving ≥5% and ≥10% body weight loss at Week 26, - Change in FPG from baseline to Week 26, - Change in 7-point self-measured plasma glucose (SMPG) profile from baseline to Week 26 (each time point and mean daily value), - Change in postprandial plasma glucose (PPG) in response to a standardized meal test in up to 50% subset of all patients from baseline to Week 26 at time points premeal, 10min, 20min, 0.5h, 1h, 1.5h, 2h, 3h, 4h post meal, and associated glucose excursion values at these time points, - Percentage of patients requiring rescue therapy during 26-week treatment period,

	- Change in fasting insulin, proinsulin, and C-peptide from baseline to Week 26, change in postprandial insulin, proinsulin and C-peptide in response to a standardized meal test in up to 50% subset of all patients from baseline to Week 26 at time points premeal, 10min, 20min, 0.5h, 1h, 1.5h, 2h, 3h, 4h post meal, and associated excursion values for each of the above parameters values at these time points, - Change in β-cell function assessed by HOMA-β from baseline to Week 26, - Change in insulin resistance assessed by HOMA-IR from baseline to Week 26, - Change in fasting lipid profile (total cholesterol, triglycerides, LDL-C, and HDL-C), free fatty acids, and ketone bodies from baseline to Week 26, - Change in PD biomarkers (including waist circumference, hip circumference, waist to hip ratio, VAS for appetite/satiety score related to meal test, and to assess fasting levels of adiponectin) from baseline to Week 26. • Safety: - Adverse events (AEs), serious adverse events (SAEs) and adverse events of special interest (AESIs), hypoglycemia (severe, documented, asymptomatic, probable, relative), vital signs, ECG changes, and safety laboratory values, - Change of heart rate from baseline to Week 26 by ECG, - Change of heart rate from baseline to Week 26 by Holter monitor in up to 50% subset of all patients, - Antibody assessments: anti-SAR425899 antibodies samples will be collected in all patients (except patients on Liraglutide) at baseline, Week 2, Week 4, Week 14, and Week 26 before dosing. Patients will be asked to provide sample for anti-SAR425899 antibodies assessments 3 months after the end of the study if needed. • Pharmacokinetics: - Basic PK parameters include CL/F, Vz/F and $t_{1/2}$, and variability in PK (inter- individual and inter-occasion) will be assessed using population PK approach. For that purpose, blood samples for plasma SAR425899 determination will be collected at 2 different occasions after the end of the dose increase phase in 40 patients in total of SAR425899/placebo arm according to the following schedule: - Predose, 2h, 4h, 6h, 8h, 12h and 24h postdose on 2 different occasions, Week 14 and Week 26, - In addition to the full PK sampling scheduled, sparse PK sampling will be done in the remaining subset of patients in each SAR425899/placebo arm conducted also at Weeks 14 and 26. Sparse sampling schedule is predose and 6h postdose.

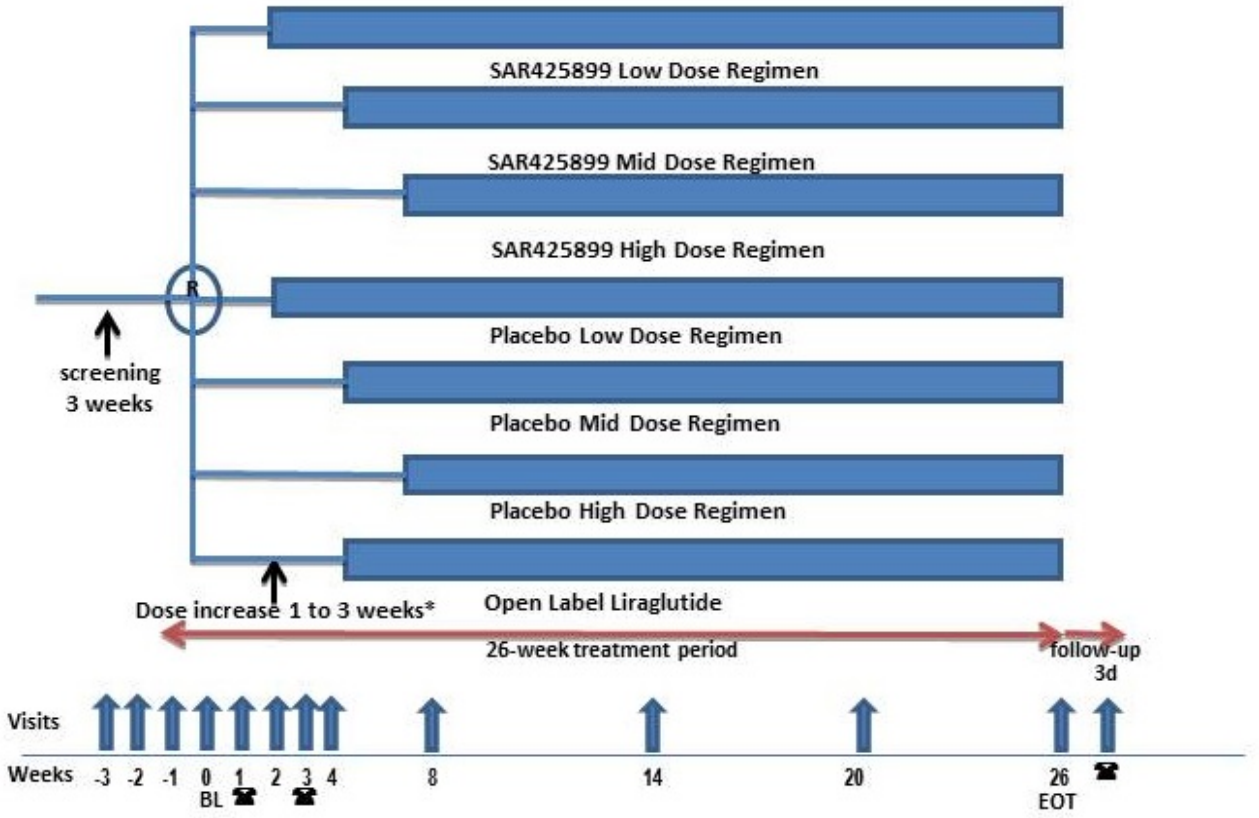
	Exploratory endpoints: • Change in NASH biomarkers and cardiovascular biomarkers from baseline to Week 26. • Exploratory PK/PD analysis will be performed in SAR425899 and matching placebo patients using glycemic parameters (HbA1c, FPG, PPG) excursion in response to a standardized meal test, body weight, and heart rate. • Patient-reported outcome endpoints: - Change from baseline at Week 26 in: - Weight-Related Symptoms Measure (WRSM), - Ability to Perform Physical Activities of Daily Living (APPADL), - Impact of Weight on self-perception (IW-SP), - Patient's qualitative self-assessment of treatment.
ASSESSMENT SCHEDULE	The schedule of study-related procedures/assessments is detailed in the Study Flowchart.
STATISTICAL CONSIDERATIONS	**Sample size determination:** For the primary endpoint of change in HbA_{1c} from baseline to Week 26, a sample size of 60 patients per arm of SAR425899 and 30 patients in the placebo group (pool of the 3 placebo arms) will provide 80% power to detect a difference of 0.7% in the HbA_{1c} change from baseline to Week 26 between a dose group of SAR425899 and placebo (standard deviation [SD] 1.1%; 5% significance level 2-sided). The total sample size will be 270 patients to be randomized over 7 arms (3 SAR425899 dose arms of 60 patients each, 3 matching placebo arms with a total of 30 patients [10 patients per arm], and 1 active comparator arm of liraglutide 1.8 mg of 60 patients). **Analysis population:** The primary efficacy population will be the intent-to-treat (ITT) population, which includes all randomized patients. Patients will be analyzed in efficacy analyses by the treatment group to which they are randomized by Interactive Response Technology (IRT) (as randomized). Safety analyses will be based on the safety population, defined as all randomized patients who receive at least 1 dose of IMP. Patients will be analyzed for safety analyses according to the treatment actually received. For a patient randomized to a SAR425899 treatment arm, the patient will be analyzed in the treatment he/she receives starting Week 8 visit (inclusive) when no adjustment of dose level is allowed. However, for a patient randomized to a SAR425899 treatment arm and discontinues the IMP before Week 8 visit, the patient will be analyzed in the SAR425899 treatment arm the patient is randomized to. If a patient is exposed to more than one dose level of SAR425899 since Week 8 visit or later, then the patient will be analyzed in the lowest dose level that the patient is exposed from Week 8 visit or later. If a patient is treated with both placebo and SAR425899 any time during the study, the patient will be analyzed in the SAR425899 treatment arm. Liraglutide patients will be included in the Liraglutide treatment arm regardless of dose amount patients receive.

	Primary endpoint analysis: The primary efficacy endpoint of change in HbA1c from baseline to Week 26 will be analyzed with missing values imputed by Control-based multiple imputation method under the missing not at random frame work. • For placebo group patients, missing data will be imputed based on the placebo group data. • For patients in the SAR425899 groups, missing data will be imputed as if the patients were on placebo group throughout the study. Each of the complete dataset will be analyzed by the Analysis of Covariance (ANCOVA) model with treatment groups (SAR425899 0.12 mg, SAR425899 0.16 mg, SAR425899 0.20 mg, placebo and liraglutide), randomization strata of screening HbA1c value (<8, ≥8 %), randomization strata of Visit 4 (Day 1) BMI (<35.0 kg/m^2, ≥35.0 kg/m^2), and country as fixed effects, and baseline HbA1c value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from baseline to Week 26 for each treatment group, as well as the between-group difference (comparing each SAR425899 dose group versus placebo) and the 95% confidence interval (CI) for the difference. HbA1c values at baseline and Week 26 (observed or imputed) regardless of treatment discontinuation or initiation of rescue therapy will be used. **Analysis of secondary endpoints:** Analysis of secondary efficacy endpoints: All continuous secondary efficacy endpoints at Week 26 will be analyzed using the same ANCOVA model with missing values imputed by Control-based multiple imputation method. Means and adjusted means of each treatment group will be provided, as well as adjusted mean and associated two-sided 95% CI of the differences between each SAR425899 dose group and placebo group. The analyses include values at baseline and Week 26 (observed or imputed) regardless of treatment discontinuation or initiation of rescue therapy. All categorical secondary efficacy endpoints will be analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata. The proportion in each treatment group will be provided, as well as the difference of proportions between each SAR425899 dose group and placebo with associated 2-sided 95% CI. For HbA1c and body weight responders, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no measurement at Week 26 will be treated as non-responders. For percentage of patients requiring rescue therapy, patients who have received rescue therapy during the 26-week treatment period will be summarized.

	Safety analysis Safety analyses for the 26-week treatment period will be descriptive, based on the safety population (randomized and exposed). Treatment-emergent adverse events (TEAEs) are defined as AEs that developed or worsened or became serious during the period from the administration of first dose of the study treatments up to 3 days after the last administration. **Interim analysis** An interim analysis for body weight will be conducted when 108 patients (about 24 patients per dose arm of SAR425899 and liraglutide and 12 patients from the SAR425899 placebo arm) have been randomized and completed 14 weeks of treatment. Descriptive statistics will be used to summarize the body weight results and the changes from baseline by visit for each treatment group. Potentially an interim analysis for PK/PD will be conducted when 60% of patients have completed the end of treatment visit. An internal sponsor team, independent of the study team, will perform the analysis, which is for internal project planning purposes. It will not lead to changes in the conduct of this protocol. Only those necessary for the analysis and project planning will have the access to the interim analysis results before study completion. Study team and investigational sites will continue to be blinded to individual randomization codes except for the open-label liraglutide until after study completion and database lock.
DURATION OF STUDY PERIOD (per patient)	The study duration is approximately 30 weeks (3-week screening period, 26-week treatment period, 3-day post treatment follow-up period).

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



* depending on the SAR425899/placebo dose regimen
SAR425899 and matching placebo: low dose regimen = 0.06 (1 week) – 0.12 mg (25 weeks)
mid dose regimen = 0.06 (1 week) – 0.12 (1 week) – 0.16 mg (24 weeks)
and high dose regimen = 0.06 (1 week) – 0.12 (1 week) – 0.16 mg (1 week) – 0.20 mg (23 weeks)
Liraglutide: 0.6 mg (1 week) – 1.2 mg (1 week) – 1.8 mg (24 weeks)

1.2 STUDY FLOW CHART

	Screening period			Treatment period									Follow-up period
				Dose increase phase depending on IMP dose regimen			Maintenance Dose Phase						
VISIT	**1**	**2**	**3**	**4 BL**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 EOT[a]**	**13**
WEEK	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**20**	**26**	**3 day FU**
Phone visit					☎		☎						☎
Start of maintenance dose					**Low dose**	**Mid dose**	**High dose**						
Informed consent	X												
Inclusion criteria	X												
Sub-study informed consent	X												
Exclusion criteria	X	X	X	X									
Patient demography	X												
Medical/surgical history	X												
Alcohol and smoking history	X												
Medication history	X												
Vital signs (blood pressure [sitting], heart rate [supine])	X		X	X		X		X	X	X	X	X	
Height without shoes	X												
Body weight[b]	X			X		X		X	X	X	X	X	
Physical examination	X			X					X[c]	X		X	
Injection training/instruction (to be repeated as needed throughout the study)	X	X	X	X		X		X	X	X	X		
Diary training and dispense[d]			X										
Glucometer training and dispense			X										
Check SMPG technique (training as needed throughout the study)		X	X	X		X		X	X	X	X		
Diet and lifestyle counseling			X[e]	X						X			
Randomization				X									
Interactive Response Technology (IRT) contact	X			X		X		X	X	X	X	X	X
Dispense of Tactipen [f]				X									

	Screening period			Treatment period									Follow-up period
				Dose increase phase depending on IMP dose regimen			Maintenance Dose Phase						
VISIT	**1**	**2**	**3**	**4 BL**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 EOT[a]**	**13**
WEEK	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**20**	**26**	**3 day FU**
Phone visit					☎		☎						☎
Start of maintenance dose					**Low dose**	**Mid dose**	**High dose**						
Dispense IMP				X		X		X	X	X	X		
IMP administration				X[g]	X	X	X	X	X	X	X	X	
Compliance: count returned IMPs						X		X	X	X	X	X	
Concomitant medication	X		X	X	X	X	X	X	X	X	X	X	X
7-point glucose profile (SMPG)				X[h]						X[h]		X[h]	
12-lead ECG	X			X				X		X		X	
Holter monitor[i]			X							X		X	
Waist and hip measurements				X						X		X	
Standardized meal test with Visual Analog Scale for Appetite/Satiety (VAS)[j]			X									X	
Laboratory testing (central lab)													
24h urine free-cortisol and creatinine[k]				X								X	
HbA_{1c}	X			X		X		X	X	X	X	X	
Fasting Plasma Glucose	X			X		X		X	X	X	X	X	
Fasting insulin for calculation of HOMA-β, HOMA-IR				X						X		X	
Women only : Estradiol and FSH test (if necessary to confirm postmenopausal status)	X												
Women only : pregnancy test[l]	X			X						X		X	
Viral Serology (hepatitis)	X												
Hematology[m]	X			X				X		X		X	
Liver function test[n]	X			X				X		X		X	
Renal function test[o]	X			X				X		X		X	
Blood electrolytes[p]	X			X				X		X		X	

	Screening period			Treatment period									Follow-up period
				Dose increase phase depending on IMP dose regimen			Maintenance Dose Phase						
VISIT	**1**	**2**	**3**	**4 BL**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 EOT[a]**	**13**
WEEK	**-3**	**-2**	**-1**	**0**	**1**	**2**	**3**	**4**	**8**	**14**	**20**	**26**	**3 day FU**
Phone visit					☎		☎						☎
Start of maintenance dose					**Low dose**	**Mid dose**	**High dose**						
Lipid panel (including free fatty acid)	X			X						X		X	
Ketone bodies				X				X	X	X	X	X	
Fasting level of adiponectin				X						X		X	
Amylase/lipase	X			X				X	X	X	X	X	
Calcitonin	X			X				X		X		X	
Thyroid-stimulating hormone (TSH) /Total triiodothyronine (T3) /Free Thyroxine (FT4)				X								X	
Urinalysis[q]	X			X						X		X	
Urine albumin/creatinine ratio assessment (to be done on first morning urine sample)			X										
Anti-SAR425899 antibodies[r]				X		X		X		X		X	
PK sampling[s]										X		X	
Exploratory biomarkers				X								X	
PRO questionnaires (WRSM, APPADL, IW-SP)				X								X	
PRO qualitative questions[t]												X	
AE/SAE reporting	To be assessed and reported throughout the study												
Hypoglycemia reporting	To be assessed and reported throughout the study												

a In case of rescue therapy, all assessments planned in V12 should be performed before starting rescue therapy, patients then continue the study treatment (including metformin), and all visits and assessments should be performed as scheduled. In case of premature permanent IMP discontinuation, patients should have a visit as soon as possible with the assessments normally planned in V12 (the standardized meal test and PK collections are performed only if the patient receives the IMP the day of the visit, note that otherwise predose PK sample can be taken if the patient receives the IMP the day before). Afterward, the patients should continue in the study up to the scheduled date of study completion. They should be followed up according to the study procedures as specified in the protocol (except for the 3 day safety post-treatment and PK assessment). If the patient drops out from the study at the time of IMP discontinuation regardless if the patient receives the IMP or not on the day of the meal test, the meal test should be performed. However, PK collections are performed only if the patient receives the IMP the day of the visit, otherwise predose PK sample can be taken if the patient receives the IMP the day before.

b Weight will be recorded to the nearest 0.1 kg and should be measured using calibrated scales. The same pair of scales should preferably be used throughout the trial. Weight should be measured in the fasting state in the morning at approximately the same time with an empty bladder, without shoes and only wearing undergarments or light clothing. Weight measured at screening Visit 1 will be used only for calculation of screening BMI for eligibility criteria whereas weight measured at Visit 4 will be used as baseline for assessment of change in body weight and for calculation of baseline BMI which will be the BMI value used for stratification.

c At Visit 9, abbreviated/targeted physical examination only.
d Diary will be reviewed at each on site visit.
e Counseling will be provided at screening Visit 3 or Visit 4.
f Only for patients in SAR425899 or Placebo arms.
g First dose of IMP will be done on-site .IMP administration every day along the 26-weeks, but at each visit on site, the IMP administration will be done on site by the patient himself.
h 7-point profile to be conducted over a single 24-hour period in the week before Visit 4, Visit 10 and Visit 12.
i 24 hour Holter monitoring to be performed in a subset of patients.
j Standardized meal test to be performed in a subset of patient.
k Containers will be provided at V3 and V11, the patient should collect his/her urine for the 24 hours prior to V4 and V12 and brig the container to the visit
l Serum pregnancy test should be done at screening and Week 26; serum or urine pregnancy test may be used at other timepoints. A positive urine pregnancy test should be confirmed with a serum test.
m Blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets.
n Total bilirubin (and, in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT).
o Creatinine, Cystatin C, uric acid.
p Sodium, potassium, calcium, phosphorus.
q By central lab to include pH, glucose, ketones, leukocytes, blood, protein, nitrite, urobilinogen, bilirubin.
r Not for patients in the liraglutide arm.
s Full PK sampling in 40 patients in total in SAR425899/placebo cohort conducted at Weeks 14 and 26. Sampling schedule as follows: Predose, 2h, 4h, 6h, 8h, 12h and 24h postdose. Patients who will have full sampling will need to return the next day for the 24 hour timepoint. Sparse PK sampling to be done in the remaining subset of subjects in each SAR425899/placebo cohort conducted also at weeks 14 and 26. Sparse sampling schedule is pre-dose and 6h post-dose.
t Patient's qualitative self-assessment of the treatment.

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3 LIST OF ABBREVIATIONS

AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine transaminase
ANCOVA:	analysis of covariance
APPADL:	ability to perform physical activities of daily living
AST:	aspartate aminotransferase
BMI:	body mass index
BNP:	brain natriuretic peptide
CAC:	Cardiovascular events Adjudication Committee
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
CRF:	case report form
DBP:	diastolic blood pressure
DMC:	Data Monitoring Committee
DRF:	discrepancy resolution form
ECG:	electrocardiogram
eCRF:	electronic case report form
EE:	energy expenditure
eGFR:	estimated glomerular filtration rate
FPG:	fasting plasma glucose
GGT:	gamma-glutamyl transpeptidase
GLP-1:	glucagon-like peptide-1
HbA_{1c}:	glycosylated hemoglobin
HLGT:	high-level group term
HLT:	high level term
HR:	heart rate
hs-CRP:	high-sensitivity C-reactive protein
IEC:	independent ethics committee
IMP:	investigational medicinal product
IRB:	institutional review board
IRT:	Interactive Response Technology
ITT:	intent-to-treat
IW-SP:	Impact of Weight on self-perception
LC-MS/MS:	liquid chromatography with tandem mass spectrometry
LLOQ:	lower limit of quantification
MDRD:	modification of diet in renal disease
MedDRA:	Medical Dictionary for Regulatory Activities
NASH:	nonalcoholic steatohepatitis
NIMP:	noninvestigational medicinal product
OC:	observed case

OXM:	oxyntomodulin
PCSA:	potentially clinically significant abnormality
PD:	pharmacodynamic
PK:	pharmacokinetic
PPG:	postprandial plasma glucose
PRO:	patient-reported outcome
PSAC:	Pancreatic Safety Assessment Committee
PT:	preferred term
PTC:	product technical complaint
SAE:	serious adverse event
SBP:	systolic blood pressure
SC:	subcutaneous
SMPG:	self-measured plasma glucose
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T2DM:	type-2 diabetes mellitus
TEAE:	treatment-emergent adverse event
ULN:	upper limit of the normal laboratory range
WRSM:	weight-related symptoms measure

4 INTRODUCTION AND RATIONALE

Glucagon-like peptide-1 (GLP-1) is an endogenous enteroendocrine hormone secreted by L-cells of the distal intestine in response to oral nutrient ingestion. Glucagon-like peptide-1 has multiple physiologic effects that contribute to ameliorating hyperglycemia in the treatment of type-2 diabetes mellitus (T2DM). These effects include enhancing insulin secretion from pancreatic β-cells in a glucose dependent manner, suppressing glucagon secretion, and slowing gastric emptying (1). Glucagon-like peptide-1 also enhances satiety with subsequent reduction in food intake thereby promoting weight loss. About 80% of patients with T2DM are overweight or obese. Many of the available classes of treatment options for T2DM (eg, sulfonylureas, glinides, thiazolidenediones, and insulin) are actually associated with promoting weight gain, a distressing side effect for patients already struggling with excess body weight and one that may adversely impact adherence to therapy (2). In recent years, a new class of pharmacotherapy for T2DM has emerged in the form of GLP-1 receptor agonists, which are notable for promoting modest weight loss in addition to having insulinotropic actions and glycemic efficacy.

Another enteroendocrine hormone that has gained interest as a potential therapeutic option for the treatment of obesity/T2DM is oxyntomodulin (OXM). Like GLP-1, OXM is secreted by L-cells of the distal gut and is also derived from the same precursor peptide proglucagon. Oxyntomodulin is a dual agonist at both the GLP-1 receptor and the glucagon receptor. Like GLP-1, glucagon also has an anorectic effect and suppresses food intake (3). However, glucagon has additionally been shown to increase energy expenditure (EE) (4). Therefore, it has been hypothesized that activation of both GLP-1 and glucagon receptors leading to a dual effect of reduced food intake along with enhanced energy expenditure could be expected to produce greater weight loss than simply decreasing food intake alone (as in the case with pure GLP-1 receptor agonist). Studies conducted in obese mice treated with OXM versus a selective GLP-1-receptor agonist that did not exert any significant glucagon receptor activity support this hypothesis as OXM administration led to superior weight loss with similar glucose lowering activity compared to the GLP-1 receptor agonist group (5). Additional work conducted in GLP-1 receptor knockout mice which received OXM and a glucagon receptor antagonist also yielded results that implicate activation of the glucagon receptor as a component to driving the weight loss observed with OXM (6). Finally, OXM has also been suggested as a potential contributing factor in the metabolic improvements associated with bariatric surgery when it was observed that OXM concentrations rise markedly in response to oral glucose in morbidly obese women with T2DM who had undergone recent gastric bypass surgery (6).

Although activation of the glucagon receptor increases blood glucose levels, simultaneous activation of the GLP-1 receptor could potentially counterbalance this (via a GLP-1 stimulated increase in insulin release with subsequent inhibition of gluconeogenesis) and prevent undesirable hyperglycemia. This concept was supported by a rodent study which showed that OXM administration ameliorated glucose intolerance in mice fed a high-fat diet (7). Other preclinical studies with synthetic dual agonists of the GLP-1 and glucagon receptors in rodent models have demonstrated similarly promising results in terms of weight loss as well as improvements in additional metabolic parameters, including antihyperglycemic effects (8, 9). Likewise, a study of coinfusion of GLP-1 and glucagon in overweight/obese humans demonstrated an increase in EE

and an amelioration of the hyperglycemia observed with infusion of glucagon alone (10). Yet another study of coadministration of GLP-1 and glucagon conducted in overweight humans also resulted in an increase in EE and reduction in food intake and showed that the addition of GLP-1 protected against glucagon-induced hyperglycemia (11).

Oxyntomodulin administration has also been studied in humans and has been shown to produce effects on body weight reduction, suppression of food intake, and increase in EE (12, 13). Furthermore, OXM administered as a single dose to males with T2DM was shown to blunt glucose excursions during a continuous glucose infusion to an extent that was comparable to liraglutide administration in the same study (14). Based on this finding, the authors hypothesize that OXM, a dual agonist of the GLP-1 and glucagon receptors, may exert glucoregulatory effects that are independent of weight loss. Thus, the concept of dual activation of the GLP-1 and glucagon receptors merits further investigation as a potential means of promoting significant weight loss coupled with improvement in glucose control.

SAR425899 is a dual agonist of the GLP-1 and glucagon receptors, and is being developed for the treatment of patients with T2DM who are overweight/obese. Preclinical studies conducted in several animal models (rats, DIO mice, db/db mice, and monkeys) have demonstrated reductions in blood glucose and body weight as well as increase in EE (shown in mice) with SAR425899 administration or its tool molecule surrogate. Nonclinical pharmacology data and available preclinical toxicology results for SAR425899 are provided in the Investigator's Brochure. Recently, the phase 1 study (TDR13700) conducted in both healthy volunteers and patients with T2DM was completed. The effect of SAR425899 on glucose lowering and weight reduction was observed in the study. There are no safety concerns from these completed studies to preclude the planning of the DRI study.

Study DRI13940 is a 26-week randomized, double-blind, placebo-controlled, dose ranging Phase 2 study to assess the safety and efficacy of SAR425899 in overweight to obese patients with T2DM. The study will consist of a 3-week screening period, a 26-week treatment period, and a 3-day follow-up period. The primary objective of study DRI13940 is to assess the dose response relationship of SAR425899 versus placebo in terms of glycemic control as measured by change in glycosylated hemoglobin (HbA_{1c}) from baseline to Week 26. The main secondary objectives are to assess safety of SAR425899 as well as its effect on body weight. The inclusion of an active comparator arm with liraglutide (Victoza®) is intended to help bestow further clinical perspective on the safety and efficacy of SAR425899 in this study.

5 STUDY OBJECTIVES

5.1 PRIMARY

The primary objective of this study is to assess the dose-response relationship of SAR425899 versus placebo in terms of glycemic control as measured by the change in glycosylated hemoglobin (HbA_{1c}) from baseline to Week 26.

5.2 SECONDARY

Main secondary objectives:

- To assess the effect of once daily dosing of SAR425899 on body weight over 26 weeks.
- To assess the safety and immunogenicity profile of SAR425899 when administered as daily subcutaneous (SC) injections over 26 weeks, including assessment of the heart rate (HR) change from baseline to Week 26 by electrocardiogram (ECG) and Holter monitor.

Additional secondary objectives:

- To assess the proportion of patients achieving predefined HbA1c targets of <7% and <6.5% as well as the proportion of patients achieving ≥5% and ≥10% body weight loss at Week 26.
- To assess the effect of once daily dosing of SAR425899 on additional parameters of glycemic control and lipid metabolism.
- To assess the effect of once daily dosing of SAR425899 on additional pharmacodynamic (PD) biomarkers.
- To assess the pharmacokinetic (PK) profile and parameters of SAR425899, inter-individual and inter-occasion variability in PK parameters using a population PK approach.

5.3 EXPLORATORY OBJECTIVE

- To assess and compare the safety and efficacy of SAR425899 versus open-label liraglutide from baseline to Week 26.
- To explore SAR425899 PK/PD relationships for glycemic parameters, body weight loss and heart rate.
- To assess the treatment effects in each group on patient-reported outcomes.
- To assess the treatment effects in each group on nonalcoholic steatohepatitis (NASH) and cardiovascular biomarkers.

6 STUDY DESIGN

6.1 DESCRIPTION OF THE STUDY

This is a multicenter, multinational, randomized, placebo-controlled, 7-arm parallel-group Phase 2 study. The study is double-blind with regard to SAR425899 and placebo treatments. It is open-label with regard to liraglutide comparative treatment. The volume of investigational medicinal product (IMP; ie, dose of SAR425899 or matching placebo) is not blinded.

Patients will be randomized into 1 of the 7 treatment arms:

- 3 SAR425899 treatment arms receiving 3 dose levels (60 patients per arm).
- 3 corresponding SAR425899 placebo treatment arms receiving 3 dose levels (10 patients per arm, 30 patients total).
- 1 active comparator arm receiving 1.8 mg liraglutide (60 patients).

For the biostatistical analyses, data from the 3 SAR425899 placebo arms will be pooled into 1 placebo group.

Patients will be stratified by screening visit HbA_{1c} (<8 % versus ≥8 %) and Visit 4 (Day 1) body mass index (BMI: <35.0 kg/m^2 versus ≥35.0 kg/m^2).

Treatment doses and dose increase process are described in Section 8.1.

In case of fasting plasma glucose (FPG) or HbA_{1c} (assessed by central laboratory) above predefined thresholds and if no reasons can be found for insufficient glucose control, it is recommended to add a rescue therapy (please see rescue therapy in Section 8.8.2).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The study comprises 3 periods as described below (please see the graphical study design and study flowchart in Section 1.1 and Section 1.2, respectively):

- A 3-week screening period,
- A 26- week treatment period,
- And a 3-day post treatment follow-up period.

The total duration of the study will be approximately 30 weeks for each patient.

A detailed description of the assessments performed in each study period is provided in Section 10.1.

6.2.2 Determination of end of clinical trial (all patients)

The end of the study is defined as the last patient last visit planned per protocol, including the follow-up visit.

6.3 INTERIM ANALYSIS

An interim analysis for body weight will be conducted when 108 patients (about 24 patients per dose arm of SAR425899 and liraglutide and 12 patients from the SAR425899 placebo arm) have been randomized and completed 14 weeks of treatment. Potentially an interim analysis for PK/PD will be conducted when 60% of patients have completed the end of treatment visit. For details, see Section 11.5.

6.4 STUDY COMMITTEES

6.4.1 Pancreatic Safety Assessment Committee

Potential safety signals for acute pancreatitis have been identified in the postmarketing experience of GLP-1 receptor agonists. Specific monitoring for pancreatic events is planned in this study (see Section 10.6.4) and a Pancreatic Safety Assessment Committee (PSAC) has been set up. This is a committee of experts in the field of pancreatitis and pancreatic neoplasm, independent from the Sponsor and the Investigators, implemented to assess pancreatic events that may occur during the study. The PSAC will review pancreatic events, including pancreatitis, pancreatic neoplasms and abnormal levels of amylase or lipase. This review will be conducted in a blinded manner with regard to study treatment. A detailed charter describes the PSAC procedures.

6.4.2 Cardiovascular adjudication committee

An independent Cardiovascular events Adjudication Committee (CAC) will be set up. The CAC is a committee of experts in the field of cardiovascular or cerebrovascular diseases, independent from the Sponsor and the Investigators, implemented to adjudicate major cardiovascular events that may occur during the study. The CAC reviews the cases in a blinded manner with regard to study treatment. A detailed charter describes the CAC procedures.

6.4.3 Data monitoring committee

A Data Monitoring Committee (DMC) with members independent from the Sponsor and the Investigators is implemented in order to make appropriate recommendations on the conduct of the study for ensuring the protection and the safety of the enrolled patients. The DMC will assess the adverse outcomes and if necessary, the risk/benefit ratio in DRI13940 through periodic review of the accumulated unblinded safety data. A detailed charter outlines the activities of the DMC.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Patients with T2DM, diagnosed at least 3 months before the screening visit, inadequately controlled on diet/exercise and/or metformin therapy (stable dose of at least 1.5 g/day or maximal tolerated dose) for at least 3 months prior to the screening visit.

I 02. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 3 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. At screening, patient's age < legal age of adulthood or >80 years.

E 02. Screening HbA_{1c} <7.0% or >10.0%.

E 03. FPG >15 mmol/L (270 mg/dL) measured by the central laboratory at screening (Visit 1), and confirmed (>15 mmol/L [270 mg/dL]) by a repeat test before randomization.

E 04. Type 1 diabetes mellitus.

E 05. BMI <25 kg/m^2 or >45 kg/m^2.

E 06. Treatment with glucose-lowering agent(s) other than metformin currently or within the 3 months prior to screening.

E 07. Previous insulin use, except for episode(s) of short-term treatment (≤15 consecutive days) for intercurrent illness or pregnancy or use of insulin within the last 6 months.

E 08. History of acute metabolic complication, such as metabolic acidosis, including diabetic ketoacidosis, or hyperosmolar hyperglycemic state within 3 months prior to screening Visit 1.

E 09. Hypoglycemic unawareness as judged by the Investigator.

E 10. Untreated or uncontrolled hypothyroidism/hyperthyroidism.

E 11. Use of systemic glucocorticoids for one week or more within the last 3 months, or anticipated need for systemic glucocorticoids during the study.

E 12. Current or history of treatment with medications within the 3 months prior to screening Visit 1, that may cause significant weight gain: including systemic glucocorticoids (except for <7 days), tricyclic antidepressants, atypical antipsychotic and mood stabilizers (eg, imipramine, amitryptiline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium) and weight loss (including but not limited to: orlistat, lorcaserin, pramlintide, metreleptin, topiramate and phentermine either alone or in combination, zonisamide and burproprion, either alone or in combination).

E 13. Current participation in an organized diet reduction program or clinical trial of weight control (within the last 3 months prior to screening).

E 14. History of prior surgical treatment for obesity or intent to pursue surgical treatment for obesity during the study period.

E 15. Weight loss attempt, plans for major changes in physical activities or significant change in body weight in the 3 months prior to screening (Significant change in body weight is defined as ≥5 kg self-reported change during the previous 3 months).

E 16. Any technical/administrative reason (eg, patient homeless) that makes it impossible to randomize the patient in the study.

E 17. Patient who has previously participated in any clinical trial of SAR425899.

E 18. Previous treatment with GLP-1 receptor agonists or GLP-1 analogs.

E 19. Patients who are night shift workers.

E 20. Current drug or alcohol abuse or known history of drug or alcohol abuse within 6 months prior screening Visit 1.

E 21. Patient who has taken other investigational drugs or prohibited therapy for this study within 3 months or 5 half-lives from screening or randomization, whichever is longer

E 22. Any clinically significant abnormality identified on physical examination, laboratory tests, ECG or vital signs at the time of screening that in the judgment of the Investigator or qualified Subinvestigator would make implementation of the protocol or interpretation of the study results difficult or would preclude the safe participation of the subject in this protocol (example: heart rate >100 bpm at screening).

E 23. Laboratory findings at the time of screening (central laboratory):

- Amylase and/or lipase >2 times the upper limit of the normal laboratory range (ULN).
- Alanine aminotransferase (ALT) >3 ULN.
- Total bilirubin >1.5 ULN (except in case of Gilbert's syndrome).
- Calcitonin ≥20 pg/mL (5.9 pmol/L).

- Serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females], or estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, by modification of diet in renal disease (MDRD) measurement.
- Fasting serum triglyceride >400 mg/dL.
- Clinical criteria of severe anemia as per investigator judgment.
- Neutrophils <1500/mm^3 (or according to ethnic group) and/or platelets <100 000/mm^3.
- Positive test for Hepatitis B surface antigen and/or Hepatitis C antibody.

E 24. Conditions/situations such as:

- Patients with a short life expectancy.
- Patients with conditions/concomitant diseases making them non-evaluable for the primary efficacy endpoint (eg, hemoglobinopathy or hemolytic anemia, receipt of blood or plasma products within 3 months prior to screening Visit 1, or plan to receive transfusion during the screening period).
- Patients with conditions/concomitant diseases precluding their safe participation in this study (eg, active malignant tumor, sever or unstable major systemic diseases).
- 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.
- Subjects with unstable heart condition, defined as any one of the following within 6 months prior to screening:
  a) Current heart failure (class III or IV),
  b) A myocardial infarction, coronary artery bypass graft surgery, or angioplasty,
  c) Diagnosis of unstable angina requiring medication,
  d) Transient ischemic attack, cerebral infarct, or cerebral hemorrhage.
- Planned coronary, carotid or peripheral artery revascularization procedures.
- Poorly controlled hypertension (a resting systolic blood pressure [BP] >160 mm Hg and/or diastolic BP >95 mm Hg at screening).
- History of long QT syndrome and/or QTc more than 450 ms at screening visit.
- History of pancreatitis or pancreatectomy.
- Clinically relevant evidence or history of gastrointestinal disease associated with prolonged nausea and vomiting, including, but not limited to: gastroparesis or uncontrolled (ie, associated with prolonged nausea and vomiting) gastroesophageal reflux or chronic diarrhea in the past 6 months.
- History of gastric emptying abnormality, malabsorption syndrome, irritable bowel syndrome, or inflammatory bowel disease.
- History of major depressive disorder or suicide attempt or other major psychiatric disorder (eg, schizophrenia, bipolar disorder, etc.).
- Obesity induced by other endocrinologic disorders (eg, Cushing Syndrome/Disease).
- History of glucagonoma, insulinoma or pheochromocytoma.

- Impossibility to meet specific protocol requirements (eg, scheduled visits, patients unable to fully understand patient's study documents and complete them, patients unable to fully understand the nature, scope, and possible consequences of the study, etc.).
- Patient is uncooperative or has a condition that could lead to non-compliance with study procedures (eg, patient unable or unwilling to do self-injection or blood glucose monitoring using the sponsor-provided blood glucometer at home, etc.).
- Patient is the Investigator or any Sub-investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol.
- Patient not suitable for participation, whatever the reason, as judged by the Investigator, including medical, psychological, social or clinical conditions, or patients potentially at risk of noncompliance to the study procedures.

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

E 25. All contraindications to the use of the open label comparator liraglutide or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling that was used for defining these exclusion criteria.

E 26. Known hypersensitivity to liraglutide.

E 27. All contraindications to the use of the protocol background therapy metformin or warning/precaution of use (when appropriate) as displayed in the respective National Product Labeling that was used for defining these exclusion criteria.

E 28. Known hypersensitivity to metformin.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 29. Pregnant or lactating women.

E 30. Women of childbearing potential (WOCBP) not protected by highly-effective method(s) of birth control as listed below and/or who are unwilling or unable to be tested for pregnancy (for more details see contraceptive guidance in Appendix A).

E 31. Male participant with a female partner of childbearing potential not protected by highly-effective method(s) of birth control as listed below for the duration of the study and up to 3 months after last dosing (for more details see contraceptive guidance in Appendix A).

Hormonal contraception may be susceptible to interaction with the study drug, which may reduce the efficacy of the contraception method. In this case TWO highly effective methods of contraception should be used during the treatment periods and for at least 33 days, [corresponding to time needed to eliminate study treatment plus 30 days for study treatments with genotoxic potential] after the last dose of study treatment.

- Highly Effective Contraceptive Methods
  - Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal).
  - Progestogen-only hormone contraception associated with inhibition of ovulation (oral, injectable).
  - Implantable progestogen-only hormone contraception associated with inhibition of ovulation
  - Intrauterine device (IUD)
  - Intrauterine hormone-releasing system (IUS)
  - Bilateral tubal occlusion
  - Vasectomized partner
  - Sexual abstinence

E 32. Male participant who is unwilling to refrain from donating sperm for the duration of the study and up to 3 months after last dosing.

E 33. Personal or immediate family history of medullary thyroid cancer (MTC) or genetic conditions that predispose to MTC (eg, multiple endocrine neoplasia syndromes).

E 34. Known hypersensitivity to glucagon or contraindications to glucagon use.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCTS

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, IMPs may be supplied from the site to the patient via a Sponsor-approved courier company which was allowed by local regulations and approved by the subject.

8.1.1 SAR425899 or matching placebo (solution for injection)

- Pharmaceutical form: SAR425899 solution for injection or matching placebo are supplied as cartridges containing 3 mL solutions for injection containing:
  - For SAR425899: SAR425899 at a concentration of 0.5 mg/mL in sodium dihydrogen phosphate dihydrate, di-sodium hydrogen phosphate dodecahydrate, sodium chloride, m-cresol, HCL/NaOH and water for injection,
  - For SAR425899 placebo: sodium dihydrogen phosphate dihydrate, disodium hydrogen phosphate dodecahydrate, sodium chloride, m-cresol, HCL/NaOH and water for injection.
- Route and method of administration: SC injection using the pen-type injector (Tactipen®).
- Dose of IMP per administration:
  - For SAR425899 and matching placebo, patients will be randomized to following dose regimen :
    - Low dose: 1 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed): 0.06 mg ie, 12U – 0.12 mg ie, 24U (0.12mg ie, 24U for 25 weeks).
    - Mid dose: 2 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed): 0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U (0.16 mg ie, 32U for 24 weeks).
    - High dose: 3 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed): 0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U – 0.20 mg ie, 40U (0.20 mg ie, 40U for 23 weeks).
- Timing: doses of SAR425899 and placebo should be injected in the morning at the same time every day except on clinic visit days.
- On clinic visit days, SAR425899 and placebo injection time should be after blood tests/ECG measurement time in the morning and be coordinated with the meal test/PK sampling time.

If the target dose is not tolerated, the study treatment can be decreased. Another attempt for dose increase may take place within 4 weeks and before Week 8 of treatment. Then, if the patient cannot reach or tolerate the target dose, he/she remains at the lower dose. If he/she cannot tolerate the lower dose, end of treatment assessments are done. Then, the patient will be discontinued from IMP but continues in the study and is followed up according to the study procedures as specified in this protocol (except for the post-treatment follow-up), up to the scheduled date of study completion. After Week 8, if the dose is no longer tolerated, final on-treatment visit assessments are done and the patient is discontinued from the IMP.

Reasons and handling of patient temporary or permanent treatment discontinuation are provided in Section 10.3.

8.1.2 Liraglutide

- Pharmaceutical form: liraglutide is supplied as 1 prefilled pen of Victoza® containing 18 mg liraglutide in a 3 ml solution for injection (6 mg/mL, 3 mL). Victoza marketed in USA will be used for USA, Victoza marketed in Canada will be used for Canada, and Victoza marketed in Germany will be used for the rest of the world.
- Route of administration: prefilled, multidose pen will be used to deliver SC doses of 0.6 mg, 1.2 mg, or 1.8 mg.
- Dose of IMP per administration: liraglutide 1.8 mg daily after dose increase (0.6 mg daily for 7 days followed by 1.2 mg daily for 7 days followed by 1.8 mg daily for 24 weeks).
- Timing: doses of liraglutide should be injected in the morning at the same time every day except on clinic visit days.
- On clinic visit days, liraglutide injection time should be after blood tests/ECG measurement time in the morning and be coordinated with the meal test time.

Reasons and handling of patient temporary or permanent treatment discontinuation are provided in Section 10.3.

8.1.3 Injection device and training

Tactipen injector (specifically labelled for the use of the study) with needles will be provided to each patient separately from the cartridges kits. Cartridges will have to be assembled in the Tactipen by the patient. Handling procedure, detailed storage instructions of the pen-type injector and SC injection technique will be provided in a specific manual.

For both Tactipen and liraglutide pen, before starting the first dosing and repeat as often as required, the patients will be trained on site by the study staff to use the injector pens and to perform the SC injection (see the flow chart Section 1.2). Pen-device or related issues (malfunctions) should be reported to the Sponsor by the means of a procedure on product technical complaint (PTC) forms, which will be described in a separate manual.

Training on self-measured plasma glucose (SMPG) technique will be performed and repeated as needed throughout the study.

Liraglutide is a marketed product, it will be administrated as per local labelling (such as SmPC in the European Union or PI in the US), except for the time of injection in order to be consistent with the study request. The first administration will be done under clinical staff supervision and it will have to follow the PTC process.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCTS

8.2.1 Background treatment

Patients included in the study should either be following a diet and exercise therapy and/or be taking metformin for at least 3 months prior to screening.

8.2.1.1 Metformin

Background treatment with metformin is considered as a noninvestigational medicinal product (NIMP).

Metformin should be administered orally according to the local product labeling. Metformin should be used at a stable dose of at least 1500 mg/day or at the maximal tolerated dose for at least 3 months prior to screening (Visit 1).

The doses of metformin (if applicable) should be continued and should remain stable throughout the study unless there is a specific safety issue related to this treatment.

The background treatment is to be reported in the electronic case report form (eCRF).

The cost of the background treatment (metformin), if not covered by health insurance, can be reimbursed where permitted by local regulations.

8.2.1.2 Diet and exercise

Lifestyle and diet therapy followed before the time of screening is to be continued during the study. Counseling will be provided by a healthcare professional at screening Visit 3 or Visit 4, and Visit 10, and should be consistent with international or local guidelines for patients with T2DM (with regard to the distribution of calories among carbohydrates, proteins, and fats, exercise, etc.).

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

For SAR425899, a double-blind design has been set up. The cartridges, containing either SAR425899 or matching placebo solution for injection, are indistinguishable to preserve the double-blind. The dose level is not blinded as the volume to be injected and the number of kits dispensed is different between the doses.

Each cartridges treatment kit for SAR425899 or placebo is labeled with a treatment kit number, which is generated by a computer program from the Sponsor. In accordance with the double-blind design, Investigators will remain blinded to study treatment on SAR425899/placebo (dose level not blinded) and will not have access to the randomization (treatment codes) except under exceptional medical circumstances described in Section 8.3.2. Consequently, the double blinded will be maintained on SAR425899/placebo (dose level not blinded).

Liraglutide (Victoza®) kits are under open-label design.

The Investigator and the Sponsor will not have access to the data of the primary efficacy endpoint (ie, HbA1c) nor to FPG, or the data of the meal test endpoints (postprandial plasma glucose [PPG], and blood glucose excursion, insulin, proinsulin, and C peptide and associated excursion values) obtained after baseline visit until V12 (Week 26), or until End of Treatment visit in case of premature treatment discontinuation. In case the central laboratory detects a FPG or HbA1c above the rescue threshold the investigator will receive an alert by the central laboratory. CAC members will review and adjudicate major cardiovascular events in a blinded manner (please refer to Section 6.4.2). PSAC members will review and adjudicate pancreatic events in a blinded manner (please refer to Section 6.4.1). The DMC will receive unblinded, closed reports from an independent statistical group for review (see Section 6.4.3). These reports will have to be handled strictly confidentially. None of these reports may be delivered to unauthorized persons.

However, the study team may review the data for the primary efficacy parameter in descriptive statistics for the overall treatment during data review meetings. An independent programmer will generate the descriptive statistics for HbA1c, FPG and meal test related parameters.

Refer to Section 10.5 for suspected unexpected serious adverse drug reaction unblinding by the Sponsor.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the Interactive Response Technology (IRT) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking.

If the code is broken, the patient must withdraw from IMP administration.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

The randomized treatment kit number list is generated centrally by Sanofi.

The IMPs are packaged in accordance with this list.

The randomization and treatment allocation are performed centrally by an Interactive Response Technology (IRT):

- The study biostatistician provides the randomization scheme and the IRT generates the patient randomization list (including stratification) according to which it allocates treatment groups to the patients and the corresponding treatment kits.
- Patients will be randomized to 1 of the following treatment arms during the 26-weeks according to a randomization ratio of 6:6:6:1:1:1:6:
  - SAR425899 0.12 mg,
  - SAR425899 0.16 mg,
  - SAR425899 0.20 mg,
  - Placebo 0.12 mg,
  - Placebo 0.16 mg,
  - Placebo 0.20 mg,
  - Liraglutide 1.8 mg.

The randomization is stratified by screening HbA_{1c} value (<8.0% versus ≥8.0%) and Visit 4 (Day 1) BMI (<35.0 kg/m^2 versus ≥35.0 kg/m^2).

At screening visit, the Investigator or designee has to contact the IRT center to receive the Patient number. The patient identification (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).

On V4 (Day 1), assessment results are reviewed and baseline assessments are completed. After confirming that the patient is eligible for randomization, the IRT is called, the investigator or designee has to provide some information (such as patient number provided by the IRT at screening visit, date of birth/dummy date of birth, etc.). The first treatment kit(s) are then allocated by the IRT. Afterwards the IRT is called again each time a new treatment kit(s) allocation is necessary, ie, at V6 (Week 2), V8 (Week 4) and V9 (Week 8), V10 (Week 14), and V11 (Week 20).

The IRT will allocate sufficient treatment kits numbers until the next on-site visit. In some specific circumstances, eg, damaged kit, the Investigator can perform a “replacement call” to the IRT to obtain an additional treatment kit.

A randomized patient is defined as a patient who is allocated a treatment kit number by the IRT , and recorded in the IRT database, regardless of whether the treatment kit was used or not.

A patient cannot be randomized more than once in the study. In cases where original screen failure is due to reasons expected to change (except for HbA1c) at rescreening and based upon the Investigator’s clinical judgment, the patient can be rescreened one time for this study.

8.5 PACKAGING AND LABELING

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

The appropriate number of kits will be dispensed to cover up to the next dispensing visit (please refer to Section 1.2).

Table 1 - List of treatment kits

Kit name	Packaging details
SAR425899 and placebo treatment kits	1 double blind label kit contains 2 pre-filled cartridges 0,5mg/mL or placebo labelled in randomized conditions
Tactipen® kit	1 open-label kit contains 1 empty Tactipen label
Liraglutide/Victoza® kit	1 open-label kit contains 2 pens prefilled with a solution of 6 mg/mL liraglutide labelled in sequential conditions

8.6 STORAGE CONDITIONS AND SHELF LIFE

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

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

The expiry date is mentioned on the IMP labels, and storage conditions are written on the IMP labels and in the instruction leaflet.

8.6.1 SAR425899 0.5 mg/ml or placebo

Prior to first use, the cartridges have to be stored between +2°C and +8°C (36°F to 46°F), protected from light, and must not be frozen.

Once in use, the cartridges have to be stored below +30°C (86°F) (do not refrigerate).

Once in use, the cartridge has to be replaced if not completely used within 31 days.

8.6.2 Liraglutide (Victoza)

Prior to first use, liraglutide should be stored in a refrigerator between 2°C to 8°C (36°F to 46°F).

After first use, liraglutide pen can be kept in a controlled room (15°C to 30°C; 59°F to 86°F) or in a refrigerator (2°C to 8°C; 36°F to 46°F).

Liraglutide should be protected from light, must not be frozen, and must not be used if it has been frozen. The pen should be replaced if not completely used within 30 days.

8.7 RESPONSIBILITIES

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

All IMPs 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 issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (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 may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

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

8.7.1 Treatment accountability and compliance

Measures taken to ensure and document treatment compliance and IMPs accountability include:

- Proper recording of treatment kit number or packaging number as required on appropriate eCRF page for accounting purposes.
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned.
- The Investigator or his/her delegate tracks treatment accountability/compliance comparing the treatment number recorded on the patient diary with the treatment number of returned treatment kits (whether empty or unused) and fills in the patient treatment log.
- 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 patient treatment log form.
- For the NIMP not provided by the Sponsor, tracking and reconciliation will be documented in patient’s source documents and reported in appropriate eCRF pages.

8.7.2 Return and/or destruction of treatments

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. The Investigator will not destroy the used and unused IMP unless the Sponsor provides written authorization.

For NIMP reimbursed by the Sponsor, tracking and reconciliation will be achieved by the Investigator (or the pharmacist, if appropriate) according to the system proposed by the Sponsor.

8.8 CONCOMITANT MEDICATION

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

8.8.1 Prohibited medications

Use of the following medications will not be permitted during the study:

- Weight control treatment, including any medication with a labelled reference to weight loss or weight gain.
- Systemic glucocorticoid use for more than 7 days.
- Any antidiabetic treatment other than IMP, authorized background antidiabetic therapy and rescue therapy, if necessary.
- GLP-1 receptor agonists or dipeptidyl peptidase 4 (DPP4) inhibitors.
- Drugs that affect gastrointestinal motility (eg, chronic use of anticholinergics, antispasmodics, 5HT3 antagonists, opiates).
- Medications that may cause significant weight gain such as antipsychotic medications, tricyclic antidepressants, and mood stabilizers (eg, imipramine, amitryptiline, mirtazapine, paroxetine, phenelzine, chlorpromazine, thioridazine, clozapine, olanzapine, valproic acid and its derivatives, and lithium), and growth hormone.
- Cannabis, even if prescribed for medical reasons.

8.8.2 Rescue therapy

In case of FPG or HbA1c above pre-defined thresholds and if no reasons can be found for insufficient glucose control, it is recommended to add rescue therapy.

Central laboratory alerts on FPG and HbA1c are set up to ensure that glycemic parameters remain under predefined threshold values (see hereinafter).

The threshold values are defined as follows, depending on study period:

From baseline Visit 4 (Week 0) to Visit 9 (Week 8, including value at Visit 9): FPG >270 mg/dL (15.0 mmol/L).

From Visit 9 (Week 8) to Visit 10 (Week 14): FPG > 240 mg/dL (13.3 mmol/L).

From Visit 10 (Week 14) to Visit 12 (Week 26): FPG>200 mg/dL (11.1 mmol/L) or HbA1c>8%.

In case of FPG / HbA1c above the threshold values, 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 hrs fast).
- Investigational product is given at planned dose.

- There is no intercurrent disease, which may jeopardize glycemic control (eg, infectious disease).
- Compliance with treatment is appropriate.
- Compliance with diet and lifestyle is appropriate.

If any of the above can reasonably explain the insufficient glycemic control, the investigator should undertake appropriate action, ie,

- Dose increase of investigational product according to protocol (if tolerance allows).
- Set up adequate investigation and treatment of intercurrent disease (to be reported in AE/concomitant medication parts of the eCRF).
- Stress on the absolute need to be compliant with treatment.
- Organize a specific interview with a Registered Dietician or other qualified nutrition professional and stress on the absolute need to be compliant to diet and lifestyle recommendations, and check a FPG / HbA1c assessment at the next visit.

If none from the above-mentioned reasons can be found, or if appropriate action fails to decrease FPG / HbA1c under the threshold values, rescue medication may be introduced.

The choice of rescue therapy is at the investigator's discretion with the exception of using GLP-1 receptor agonists or DPP4 inhibitors.

All assessments planned in Visit 12 are to be performed before initiating rescue therapy. After these assessments are completed and rescue therapy initiated, the patient will remain in the study and continue to administer the study treatment (including background therapy). The planned visits and assessments should be performed until the last scheduled visit.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

All biological efficacy and safety assessments will be performed by a central laboratory. Detailed information on samples drawing, management, and analysis will be provided in a specific manual.

9.1.1 Primary efficacy endpoint

- Change in HbA1c from baseline to Week 26.

9.1.1.1 Observation period of the primary efficacy endpoint

All scheduled measurements collected during the study will be used in the analysis, including those obtained after IMP discontinuation or rescue medication use.

The baseline value for efficacy endpoints is the last available value prior to the first injection of IMP or the last available value on or before the date of randomization if not treated with IMP.

9.1.1.2 Assessment method

For the eligibility and efficacy assessments of the study, HbA1c is measured by a certified level I National Glycohemoglobin Standardization Program (NGSP) central laboratory at time points according to the flow chart in Section 1.2.

9.2 SECONDARY ENDPOINTS

9.2.1 Secondary efficacy endpoints

- Change in body weight from baseline to Week 26.
- Percentage of patients achieving predefined HbA1c targets of <7% and <6.5% at Week 26.
- Percentage of patients achieving ≥5% and ≥10% body weight loss at Week 26.
- Change in FPG from baseline to Week 26.
- Change in 7-point SMPG profile from baseline to Week 26 (each time point and mean daily value).
- Change in PPG in response to a standardized meal test in up to 50% subset of all patients from baseline to Week 26 at time points premeal, 10mn, 20mn, 0.5h, 1h, 1.5h, 2h, 3h, 4h post meal, and associated glucose excursion values at these time points.
- Percentage of patients requiring rescue therapy during 26-week treatment period.
- Change in fasting insulin, pro-insulin, and C-peptide from baseline to Week 26, change in postprandial insulin, proinsulin and C-peptide in response to a standardized meal test in up to 50% subset of all patients from baseline to Week 26 at time points premeal, 10mn, 20mn, 0.5h, 1h, 1.5h, 2h, 3h, 4h post meal, and associated excursion values for each of the above parameters at these time points

- Change in β-cell function assessed by HOMA-β from baseline to Week 26.
- Change in insulin resistance assessed by HOMA-IR from baseline to Week 26.
- Change in fasting lipid profile (total cholesterol, triglycerides, LDL-C, and HDL-C), free fatty acids, and ketone bodies from baseline to Week 26.
- Changes in PD biomarkers assessments from baseline to Week 26 will be performed on the following variables:
  - Waist circumference, hip circumference, waist to hip ratio,
  - VAS for appetite/satiety score,
  - Fasting levels of adiponectin.

9.2.1.1 Observation period of secondary efficacy endpoints

All scheduled measurements collected during the study will be used in the analysis, including those obtained after IMP discontinuation or rescue medication use.

The baseline value for the efficacy endpoints is the last available value prior to the first injection of IMP or the last available value on or before the date of randomization if not treated with IMP.

9.2.1.2 Assessment methods

9.2.1.2.1 Fasting plasma glucose

Blood samples for FPG measurements will be assessed at the central laboratory for the time points referenced according to the flow chart in Section 1.2.

9.2.1.2.2 Standardized meal test definition and change in postprandial glucose

Patients will undergo a standardized meal challenge to assess PPG, insulin, proinsulin, C-peptide as well as excursion values for above parameters at Visit 3 (Week -1) and at the end of treatment (Visit 12, Week 26) (Table 2).

A standardized meal will be served 2 hours after morning dose (at T2H) on Visit 12 (Week 26), and at the corresponding time on Visit 3 (Week -1). The standardized meal for all patients should be consumed within a 10-minute period.

The standardized meal contains approximately 600 kcal and is composed of 50 to 55% carbohydrates, 15 to 20% proteins, and 25 to 30% fat. The composition and quantity of standardized meal must be identical throughout the study.

The start of the standardized meal is defined as a reference timepoint for further blood sample collection.

Blood samples for determination of plasma glucose, and insulin, proinsulin, C-peptide, in response to meal test will be collected at (premeal, 10 min, 20min, 0.5h, 1h, 1.5h, 2h, 3h, 4h postmeal) on Weeks -1 and 26. The excursions values for plasma glucose, and insulin, proinsulin, C-peptide will be calculated by subtracting the premeal values from the values collected for each respected timepoints at 10min, 20min, 0.5h, 1h, 1.5h, 2h, 3h and 4h. The AUC values for the above meal test parameters may be calculated as necessary.

Meal test ingestion time should be recorded in the eCRF.

Meal test will be proposed to all the population, and will be limited to the first up to 50% of patient who agree.

If the patient needs to receive a rescue antidiabetic medication, the standardized meal test should be performed before the introduction of the rescue medication and at the end of the study.

In case of permanent discontinuation of the treatment with IMP, the standardized meal test should be performed only if the patient receives the IMP on the day of the visit. The meal test should also be performed at the end of study as planned.

Table 2 - Sampling schedule for glucose, insulin, proinsulin and C peptide in response to a standardized meal test in up to 50% subset of all patients

Blood sampling time (hh:mm)		Blood sampling
Morning study treatment injection	00:00	
Pre meal		X
Standardized meal	02:00	
2h10 after morning injection	02:10	X
2h20 after morning injection	02:20	X
2h 30 after morning injection	02:30	X
3h00 after morning injection	03:00	X
3h30 after morning injection	03:30	X
4h00 after morning injection	04:00	X
5h00 after morning injection	05:00	X
6h00 after morning injection	06:00	X

9.2.1.2.3 Self-monitored plasma glucose profiles

The 7-point SMPG profile should be measured at the following 7 points: preprandial and 2 hours postprandial for breakfast, lunch, dinner and at bedtime. Two hours postprandial (breakfast, lunch and dinner) is defined as 2 hours after the start of the meal.

The patients are requested to perform 7-point SMPG profile measurement over a single 24-hour period in the week before Visit 4 (Week 0), Visit 10 (Week 14), and Visit 12 (Week 26, end of treatment assessment visit). All SMPG values measured on these days will be recorded with a glucometer provided by the Sponsor.

9.2.1.2.4 Body weight

Body weight should be obtained with the patient wearing undergarments or very light clothing and no shoes, and with an empty bladder in fasting conditions, in the morning before breakfast. The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer. The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at zero and the balance bar aligned. The patient should stand in the center of the platform as standing off-center may affect measurement. The weights are moved until the beam balances (the arrows are aligned). The weight is read and recorded in the eCRF and source data. Self-reported weights are not acceptable; patients must not read the scales themselves.

Body weight will be measured on days indicated in the flow chart (see Section 1.2). Weight should be measured in the fasting state in the morning at approximately the same time with an empty bladder, without shoes and only wearing undergarments or light clothing. Weight measured at screening Visit 1 will be used only for calculation of screening BMI for eligibility criteria whereas weight measured at Visit 4 will be used as baseline for assessment of change in body weight and for calculation of baseline BMI which will be the BMI value used for stratification.

9.2.1.2.5 Blood glucose, insulin, and C-peptide

Glucose, C-peptide, and insulin samples collected for the determination of the PD effects (including calculation of HOMA-β and HOMA-IR) will be analyzed by a central laboratory using standardized and validated methods on days indicated in the flow chart (see Section 1.2).

9.2.1.2.6 Change in lipid panel

Change in fasting lipid profile (total cholesterol, triglycerides, LDL-C, and HDL-C), free fatty acids will be analyzed by a central laboratory at screening (Week -3), baseline (Week 0), Visit 10 (Week 14), and Visit 12 (Week 26).

Fasting ketone bodies will be analyzed by a central laboratory at baseline (Week 0), Visit 8 (Week 4), Visit 9 (Week 8), Visit 10 (Week 14), Visit 11 (Week 20), and Visit 12 (Week 26).

9.2.1.2.7 Change in pharmacodynamics (PD) biomarkers

Waist and hip measurement method

Waist and hip circumference will be measured on days indicated in the flow chart (Section 1.2).

Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest, using a stretch-resistant tape that provides a constant 100 g tension. Hip circumference should be measured around the widest portion of the buttocks, with the tape parallel to the floor.

For both measurements, the subject should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing. The subject should be relaxed, and the measurements should be taken at the end of a normal expiration. Each measurement should be repeated twice; if the measurements are within 1 cm of one another, the average should be calculated. If the difference between the two measurements exceeds 1 cm, the 2 measurements should be repeated, final measurement will be recorded in the eCRF.

Visual analog scale (VAS) for appetite /satiety score

To be conducted in conjunction with the meal test, completed by the patients twice: before the meal and 4 hours post meal.

The VAS consists of 100-mm lines with words anchored at each end, describing Hunger, Satiety, Fullness, Prospective food consumption , Desire to eat something fatty, Desire to eat something salty, Desire to eat something sweet, Desire to eat something savory.

Patients will be asked to make a vertical mark across the line corresponding to their feelings. Quantification will be performed by measuring the distance from the left end of the line to the mark.

Fasting levels of adiponectin

Fasting levels of adiponectin will be analyzed at central laboratory using standardized and validated methods at baseline Visit 4 (Week 0), Visit 10 (Week 14) and Visit 12 (Week 26).

9.2.2 Safety endpoints

The following safety parameters will be analyzed:

- AEs, serious adverse events (SAEs) and adverse events of special interests (AESIs).
- Hypoglycemia (severe, documented, asymptomatic, probable, relative).
- Safety laboratory values.
- Vital signs and physical examination.
- Electrocardiogram (ECG) changes.
- Change of heart rate from baseline to Week 26 by ECG.
- Change of heart rate from baseline to Week 26 by Holter monitor in up to 50% subset of all patients.
- Immunogenicity (anti-SAR425899 antibodies).

9.2.2.1 Observation period of safety endpoints

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

- The pretreatment period is defined as the time between the date of the informed consent and the first injection of IMP.
- The on-treatment period is defined as the time from the first injection of IMP up to 3 days (1 day for hypoglycemia) after the last injection of IMP, regardless of the introduction of rescue therapy. The 3-day interval is chosen based on the half-life of the IMP (approximately 5 times the half-life of SAR425899).
- The post treatment period is defined as the time starting 4 days after last injection of IMP (after the on-treatment period).

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

9.2.2.2 Adverse events

All AEs/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 Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at the sponsor at the time of database lock. MedDRA terms for hypersensitivity and injection site reactions will be included. The occurrence of AE/SAEs is recorded from the time of signed informed consent until the end of the study.

Refer to Section 10.4 to Section 10.7 for details.

9.2.2.3 Hypoglycemia

Hypoglycemia will be classified in categories according to the ADA Workgroup on hypoglycemia (severe, documented, asymptomatic, probable and relative) and assessed (15).

Please refer to Section 10.6 for additional details.

9.2.2.4 Laboratory safety variables

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

The following laboratory safety variables will be analyzed:

- Hematology: blood count (erythrocytes, hemoglobin, hematocrit, leukocytes), differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils) and platelets.
- Clinical chemistry: total bilirubin (and, in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), gamma-glutamyl transpeptidase (GGT), creatinine, Cystatin C, uric acid, sodium, potassium, calcium, phosphorus.

- Thyroid-stimulating hormone (TSH), Total Triiodothyronine (T3) and Free Thyroxine (FT4).
- Serum amylase and lipase.
- Serum calcitonin.
- Urine albumin/creatinine ratio assessment (to be done on first morning urine sample).

In addition, the following laboratory data will also be collected at screening visit, baseline visit, and at on-site visits depending on the item (see the study flow chart in Section 1.2):

- Serology tests: hepatitis B antigen, hepatitis C antibodies.
- Serum pregnancy test in females of childbearing potential (serum pregnancy test should be done at screening and Week 26; serum or urine pregnancy test may be used at other timepoints. A positive urine pregnancy test should be confirmed with a serum test).
- Serum follicle stimulating hormone (FSH) and estradiol (only in females requiring confirmation of postmenopausal status, and only at screening).

Collection of 24h urine sample: On the day before the visit, patient urinates into the toilet when he/she gets up in the morning. Afterwards, all urine should be collected in the special container for the next 24 hours. On the day of the visit, the patient urinates into the container when he/she gets up in the morning. The patient should cap the container and keep it in the refrigerator or a cool place during the collection period.

9.2.2.5 Vital signs and physical examination

Clinical safety will be assessed by:

- Physical examination
- Vital signs (systolic and diastolic blood pressure, heart rate).
  - Blood pressure (mmHg) should be measured in sitting position,
  - Heart rate (bpm) will be measured in supine position at the time of the measurement of blood pressure (predose on Weeks -3, -1, 0, 2, 4, 8, 14, 20 and 26),
  - Height without shoes only at screening.

9.2.2.6 Electrocardiogram variables

9.2.2.6.1 Twelve-lead electrocardiogram

Electrocardiogram data will be assessed by the Investigator based on the automatic device reading in the morning before the IMP intake.

Standard 12-lead ECGs are recorded after at least 10 minutes in supine position (10-second recording at 25 mm/s, 10 mm/mV) at Week -3, 0, 4, 14, and 26. The electrodes will be positioned at the same place for each ECG recording throughout the study.

Each ECG will consist of a 10-second recording of the 12 leads simultaneously, leading to:

A single 12-lead ECG (25 mm/s, 10 mm/mV) printout with heart rate, PR, QRS, QT, QTc automatic correction evaluation (by the ECG device), including date, time, initials, and number of the subject, signature of the research physician.

The Investigator's medical opinion and automatic values will be recorded in the eCRF. This printout and/or digital storage will be retained at the site.

Please also refer to Section 10.3 and the "General Guidelines for reporting AEs" in Section 10.4.3.

9.2.2.6.2 Holter monitoring

Holter ECG will be collected over approximately 24 hours, starting on Visit 3 (Week -1), on Visit 10 (Week 14), and on Visit 12 (Week 26). The electrodes will be positioned at the same place for each Holter recording throughout the study (attachment sites of the leads will be marked with an indelible pen).

The Holter monitor will be proposed to all the population, and will be limited to the first up to 50% of patient who agree. Twenty–four hour average and night time average heart rate will be derived based on the holter monitoring. Twenty-four hour interval is defined to be from the time of dosing until 24 hours post dose. Night time is defined to be the interval from 12 hours post dose until 24 hours post dose. For Visit 3, time of dosing is expected time of dosing on Day 1.

Storage and shipment

Holter recordings will be sent to an ECG reading center for further analysis.

If the Holter memory cards will be downloaded to CDs/DVDs at the investigational site and the CDs/DVDs are then shipped to the reading center, the investigational site will keep a copy of the CDs/DVDs and will not erase the memory cards until being notified by the reading center to do so (when Holter recordings will be correctly downloaded into the reading center system). Paper copies of all notifications will be kept as source documents on the investigational site.

The digital recording, data storage, and transmission need to comply with all applicable regulatory requirements (eg, FDA 21 CFR Part 11).

9.2.2.7 Anti-SAR425899 antibody assessment

Anti-SAR425899 antibody samples will be collected in all patients (not for patients in the liraglutide arm) at baseline, Week 2, Week 4, Week 14, and Week 26 before dosing. Patients will be asked to provide sample for anti-SAR425899 antibodies assessments 3 months after the end of the study if needed. As immunogenicity might contribute to patient safety, it is important for an ADA-assay intended to be used for clinical trials to achieve the highest sensitivity. Therefore, a 3-tiered approach will be employed to evaluate immunogenicity of SAR425899 in a clinical setting. In the first tier, all samples will be screened in order to distinguish putative positive

samples from negative samples. Identified putative positive samples will be re-tested in the confirmatory assay in tier 2 where specific ADAs are identified. All confirmed anti-SAR425899 positive samples from tier 2 will be further characterized in tier 3. These samples will be titrated and ADAs cross-reacting with endogenous human Glucagon and GLP1 will be identified. In order to assess the neutralizing capacity of confirmed anti-SAR425899 positive ADA samples, dedicated anti-SAR425899 neutralizing assays will be employed.

9.3 OTHER ENDPOINTS

9.3.1 Pharmacokinetics

9.3.1.1 Sampling time

Blood samples for determination of SAR425899 concentration in plasma will be collected at predose, 2h, 4h, 6h, 8h, 12h and 24h postdose on 2 different occasions, ie, Week 14, Week 26, in 40 patients in total under SAR425899 or placebo (Table 3). In addition to this full PK sampling scheduled, sparse PK sampling will be done in the remaining subset of patients in each SAR425899/placebo cohort conducted also at Weeks 14 and 26 (Table 4). Sparse sampling schedule is predose and 6h postdose.

The patients involved in the full PK analyses may also participate to the meal test substudy as well as the Holter monitor substudy. This subanalysis will be proposed to a population of specific sites, and will be limited to the first 40 patients who agree.

If the patient needs to receive a rescue antidiabetic medication, The PK samples should be collected before the introduction of the rescue medication and at the end of the study.

In case of permanent discontinuation of the treatment with IMP, the PK samples should be collected only if the patient receives the IMP on the day of the visit. Note that otherwise predose PK sample can be taken if the patient receives the IMP the day before.

Table 3 - Sampling schedule for Full PK in 40 patients in total under SAR425899 or placebo

Blood sampling time (hh:mm)		Blood sampling
breakfast[a]		
Pre dose		X
Morning study treatment injection	00:00	
2h 00 after morning injection	02:00	X
4h00 after morning injection	04:00	X
6h00 after morning injection	06:00	X
8h00 after morning injection	08:00	X
12h00 after morning injection	12:00	X
24h00 after morning injection	24:00	X

a Breakfast will not be taken for patients who will perform the meal test on the same day of the PK assessment.

Table 4 - Sampling schedule for Sparse PK in patients under SAR425899 or placebo not involved in the Full PK sampling

Blood sampling time (hh:mm)		Blood sampling
breakfast[a]		
Pre dose		X
Morning study treatment injection	00:00	
6h00 after morning injection	06:00	X

a Breakfast will not be taken for patients who will perform the meal test on the same day of the PK assessment.

9.3.1.2 Pharmacokinetics handling procedure

Table 5 - Pharmacokinetics handling for SAR425899

Sample type	SAR425899
Matrix	plasma
Blood sample volume	2 mL
Anticoagulant	K2 EDTA
Blood handling procedures	Described in Laboratory manual
Storage conditions	-20°C

9.3.1.3 Bioanalytical method

Plasma samples will be analyzed for determination of SAR425899 concentration using a liquid chromatography with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.0 ng/mL.

9.3.1.4 Pharmacokinetics parameters

Due to sparse sampling approach, PK analysis will be done using population PK modeling approach in order to estimate population PK parameters (CL/F, Vz/F, $t_{1/2}$) and their variability.

9.3.2 Pharmacogenetic assessment

No pharmacogenetic assessments will be performed.

9.3.3 Exploratory variables

9.3.3.1 Change in NASH and cardiovascular biomarkers

- Change in NASH biomarkers from baseline to Week 26: α2-macroglobulin, apolipoprotein A1, haptoglobin, CK18, GGT, ALT and AST.

  α2-macroglobulin, apolipoprotein A1, haptoglobin, GGT, ALT and AST will be analyzed from blood samples by a centralized laboratory using standardized and validated method.

  CK18 will be analyzed using validated method.
- Change in Cardiovascular biomarkers from baseline to Week 26: high-sensitivity C-reactive protein (hs-CRP), brain natriuretic peptide (BNP).

9.3.3.2 Exploratory pharmacokinetic/pharmacodynamic analysis

Exploratory PK/PD analysis will be performed using glycemic parameters (HbA_{1c}, FPG, PPG) excursion in response to a standardized meal test, body weight loss, and heart rate.

9.3.4 Quality of life/health economic variables/other endpoints

The patient-reported outcome (PRO) questionnaires in this study are the Weight-Related Symptoms Measure (WRSM), the Ability to Perform Physical Activities of Daily Living (APPADL, initially called the Impact of Weight on Activities of Daily Living) and the Impact of Weight on self-perception (IW-SP). The questionnaires are attached in the Appendices (16).

The 3 PRO questionnaires will be administered at baseline and Week 26. The patients will be requested to complete the questionnaires by themselves during selected clinical visits in specific booklets, independently from investigator, site staff and any help from friends or relatives. For validity purposes, patients will be asked to answer all the questions of the questionnaires at the start of the visit in a quiet place, before any procedures/tests and before discussing with the investigator, and while on site to return the completed questionnaires to the investigator or his/her designee on the same day.

In case of early IMP discontinuation, the questionnaires will be administered at the visit planned for the last dosing day with IMP and afterwards as normally planned.

The WRSM is a validated PRO questionnaire to measure the presence and bothersomeness of obesity symptoms (16). It was developed with and for obese and overweight adults. It includes 20 items on shortness of breath, tiredness, sleep problems, sensitivity to cold, increased thirst, increased irritability, back pain, frequent urination, pain in the joints, water retention, foot

problems, sensitivity to heat, snoring, increased appetite, leakage of urine, lightheadedness, increased sweating, loss of sexual desire, decreased physical stamina, and skin irritation. The presence of each symptom is first asked to patient (Yes/No) and then the bothersomeness of symptom is evaluated on a 7-point Likert scale (from 0 [not at all] to 6 [a very great deal bothersomeness]). A total score is calculated by summing the bothersomeness for each symptom, ranging from 0 to 120, with lower scores corresponding to less bothersomeness. The completion time of the WRSM is less than 5 minutes. It demonstrated robust psychometric properties in obese and overweight people including its responsiveness to weight decrease.

The APPADL, previously named the Impact of Weight on Activities of Daily Living (IW-ADL) is a validated PRO questionnaire to measure the ability of moderately obese individuals with T2DM to perform daily physical activities (17). It was developed with T2DM individuals with BMI between 25 and 40 kg/m². It includes 7 items on flexibility, mobility, and activity level, evaluated on a 5-point Likert scale (from 1 [unable to do] to 5 [not at all difficult]). A total score is calculated by summing the 7 items and dividing by the number of items, it ranges from 1 to 5, with higher scores corresponding to greater ability to do physical daily activities. The completion time of the APPADL is estimated to be less than 5 minutes. It demonstrated robust psychometric properties in patients with T2DM and BMI >30 kg/m² and was able to discriminate patients who achieved at least 5% weight loss from others who did not (18).

The IW-SP is a validated questionnaire to assess an individual's self-perception related to his or her weight. It was developed with moderately obese individuals with T2DM (BMI 25 to 40 kg/m²) (19). It includes 3 items on unhappiness with appearance, self-consciousness in social situations, and overall self-perception, evaluated on a 5-point Likert scale (from 1 [always] to 5 [never]). A total score is calculated by summing the 3 items and dividing by the number of items, it ranges from 1 to 5, with higher scores corresponding to better self-perception. The completion time of the IW-SP is estimated to be less than 2 minutes. It demonstrated robust psychometric properties in patients with T2DM and BMI >30 kg/m² and was able to discriminate patients who achieved at least 5% weight loss from others who did not.

In addition of the 3 PRO questionnaires, patients will be asked to answer questions at the end of the treatment period (Week 26). This patient qualitative assessment of treatment aims to better understand patients' views on benefits and disadvantages of the treatment they experienced during the trial. The two first questions will ask patients to describe in free text the benefits and disadvantages of the drug they experienced during the trial. A third question will ask patients if they would be willing to pursue the treatment they had during the trial (yes/no) and to describe the reasons in free text. Finally, patients will be asked to give their perception of the drug benefit-risk on 7-point Likert scale ranging from -3 (disadvantages significantly outweigh the benefits) to 3 (Benefits significantly outweigh the disadvantages) and where 0 corresponds to 'Equal benefits and disadvantages'. This patient qualitative assessment should take between 10 and 20 minutes. Patients' answers to the 3 first questions will be analyzed qualitatively. Due to the availability of this questionnaire only in English, it will be limited to English speakers in United States and Canada only.

9.4 FUTURE USE OF SAMPLES

Samples for PK will be stored until final clinical study report is issued. Thereafter they will be discarded. Samples for immunogenicity will be stored for longer time period if necessary dependent on whether issues related to immunogenicity occurs in the study. The timeframe will be defined after the availability of immunogenicity results.

9.5 APPROPRIATENESS OF MEASUREMENTS

SAR425899 is a dual agonist of the GLP-1 and glucagon receptors, and is being developed for the treatment of patients with T2DM who are overweight/obese. Preclinical studies have demonstrated reductions in blood glucose and body weight as well as increase in energy expenditure with SAR425899 administration.

The primary objective of this study is the change in HbA1c from baseline to Week 26.

Several studies have documented a reduced risk for the development and progression of complications of type 2 diabetes, when HbA1c values are lowered. HbA1c is the benchmark for the overall glycemic control and is strongly correlated with FPG and PPG levels. Therefore, diabetes management strategies recommend strict glycemic control with an HbA1c <7% according to the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD), and a more stringent goal of <6.5% for appropriate patients. The duration of study treatment is considered to be sufficient for achieving stable conditions with IMP and for enabling an adequate assessment of time-dependent changes in HbA1c.

The problem of weight gain in type 2 diabetes is widely recognized. More than 80% of individuals with type 2 diabetes are overweight, many at the time of diagnosis. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycemic control. Recently, the phase 1 study (TDR13700) conducted in both healthy volunteers and patients with T2DM was completed. The effect of SAR425899 on glucose lowering and weight reduction was observed in the study.

A number of biomarkers will be integrated into the trial, as these markers may serve to better understand the mechanism of action (MoA) of dual agonism and confirm that target receptors were hit. For glucagon effects on lipid metabolism and lipolysis have been described.

Increased heart rate has been linked to cardiovascular diseases. BNP and hs-CRP are added as biomarkers to evaluate the risk of cardiovascular diseases (20).

The therapeutic potential of GLP-1 analog in the treatment of NASH has been suggested recently. The change of NASH biomarkers will be evaluated in the study (21).

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The visit schedule and procedures/assessments listed in the study flow chart in 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.

The study consists of 10 on-site visits and 3 phone-call visits.

The patient has to be fasting for all on-site visits. For all these visits, the patient should be seen in the morning, at approximately the same time, as far as possible.

The fasting condition is defined as an overnight fast no less than 8 hours that consisted of no food or liquid intake, other than water. The IMP and other glucose-lowering agents (ie, metformin) should be administered after the fasting blood sample is drawn for all laboratory tests on the study site.

Note: If the patient is not fasting at the visits specified above, the blood sample will not be collected and a new appointment should be given to the patient for the following day if possible, with instruction to be fasted.

Visit window: during the screening period and for randomization visit a visit window of ±3 days is acceptable. During the treatment period a visit window of ±3 days is acceptable between Visit 4 (Week 0) and Visit 9 (Week 8), and a visit window of ±5days is acceptable from Visit 10 (Week 14) to Visit 12 (Week 26). A visit window of -1 days or +3 days for the post-treatment follow up visit (V13) is acceptable using the day of V12 as reference. If one visit date is changed, the next visit should occur according to the original schedule.

10.1.1 Screening Period (Week -3 to Week 0)

The duration of the screening period is 3 weeks from Visit 1 (Week -3) to Visit 4 (Week 0) which has a window of 21 ±3 days.

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 during the screening period. Patients who meet the inclusion criteria and who have no exclusion criteria, as noted in Section 7.1 and Section 7.2, will be randomized at Visit 4 (Week 0). The IRT will be contacted at Visit 1 for notification of screening and for patient number allocation.

10.1.1.1 On-site Visit 1 (Week -3, screening visit)

For the complete list and contents of procedures/assessments scheduled for the screening period, please refer to the "Study Flow Chart" in Section 1.2 and for detailed description of assessments Section 9 and Section 10.6.

The following procedures/assessments will be performed at Visit 1 (Week -3):

- 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 investigations. For patients included in PK, Holter monitor or meal test substudy, a specific inform consent must be signed by the patients and investigator prior to any investigations,
  - IRT will be 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.
- Collection of demographic data (age, gender, race and ethnic origin).
- Patient's medical (including detailed cardiovascular) and surgical history.
- History of T2DM treatment including documentation of treatment regimen, and microvascular complications (eye, kidney) and their treatments.
- Concomitant medication history.
- Habits: alcohol habits (during the last 12 months), smoking status.
- Prior medication history, particularly as it relates to diabetes and weight loss medications.
- Physical examination including vital signs (systolic blood pressure [SBP] and diastolic blood pressure [DBP] in sitting position, heart rate in supine position).
- Height without shoes.
- Body weight measurement.

Injection training and training on performing SMPG measurement (see Section 8.1.3): Patients randomized will be instructed by the staff how to properly use the injector pen as well as how to store it. Instructions on self-injection technique are also given.

- Laboratory assessments performed by the central laboratory:
  - HbA1c,
  - FPG.

Safety laboratory assessments for hematology and chemistry (please refer to Section 9.2.2.4):

- Lipid panel,
- Amylase/lipase,
- Calcitonin,
- Urinalysis,
- Hepatitis serology (HBsAg, HCAb),
- Serum pregnancy test (β-HCG) in women of childbearing potential, only,
- Estradiol and FSH test for postmenopausal women only,

- 12-lead ECG.
- Provide patient with a urine container and instruct them how to collect at home in the morning of their first urine and to bring the urine sample to the site at planned visit for the urine /creatinine ratio assessment.

10.1.1.2 On site Visit 2 (Week -2, screening visit)

- Assessment exclusion criteria.

Injection training and training on performing SMPG measurement (see Section 8.1.3): Patients randomized will be instructed by the staff how to properly use the injector pen as well as how to store it. Instructions on self-injection technique are also given.

- Recording of AEs.
- Recording of hypoglycemic events (if any).

10.1.1.3 On site Visit 3 (Week -1, screening visit)

- Assessment exclusion criteria.
- Vital signs (SBP and DBP in sitting position and heart rate in supine position).
- Diary and glucometer dispense.
- Injection training and training on performing SMPG measurement (see Section 8.1.3): Patients randomized will be instructed by the staff how to properly use the injector pen as well as how to store it. Instructions on self-injection technique are also given.
- Diet and lifestyle counseling please see Section 8.2.1.2.
- Concomitant medication.
- Holter monitor if applicable (subset of patients).
- Standardized meal test with VAS for appetite/satiety if applicable (subset of patient) (see Section 9.2.1.2.2 and Section 9.2.1.2.7).
- Urine albumin/creatinine ratio assessment (to be done on first morning urine sample).
- Recording of AEs.
- Recording of hypoglycemic events (if any).
- Provide patient with a urine container and additional appropriate materials and instruct them how to collect at home his/her urine for the 24 hours prior to Visit 4 and to bring the urine sample to the site at visit 4 for the urinary free-cortisol and creatinine measurement.

For safety and practical reasons, approximately 45 minutes before start of blood sampling on days with meal test an indwelling catheter may be inserted in a peripheral vein of the forearm in order to obtain blood samples. Between samplings, the catheter will be locked with a mandrel.

10.1.2 Twenty-six-week double-blind treatment period

Primary efficacy assessment takes place at the end of this randomized, double-blind, placebo-controlled main treatment period. This period lasts from baseline (Visit 4, Week 0) to end of main double-blind period (Visit 12, Week 26).

For SAR425899 and matching placebo, patients will be randomized to following dose regimen:

- Low dose: 1 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed).

  0.06 mg ie, 12U – 0.12 mg ie, 24U (0.12mg ie, 24U for 25 weeks).
- Mid dose: 2 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed).

  0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U (0.16 mg ie, 32U for 24 weeks).
- High dose: 3 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed).

  0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U – 0.20 mg ie, 40U (0.20 mg ie, 40U for 23 weeks).

For liraglutide arm, dose of IMP per administration is liraglutide 1.8 mg daily after dose increase (0.6 mg daily for 7 days followed by 1.2 mg daily for 7 days followed by 1.8 mg daily for 24 weeks).

For safety and practical reasons, approximately 45 minutes before start of blood sampling on days with a full PK and/or meal test an indwelling catheter may be inserted in a peripheral vein of the forearm in order to obtain blood samples. Between samplings, the catheter will be locked with a mandrel.

10.1.2.1.1 Baseline Visit 4 (Week 0)

At this visit, the patient must return to the investigation site in the morning after 8 hours fasting not having background therapy (metformin) at home.

IRT contact

After the baseline assessments are completed and eligibility confirmed, the Investigator contacts IRT for randomization to the study.

The visit includes:

- Check of exclusion criteria.
- Vital signs and physical examination.

- Body weight.
- Injection training and check SMPG technique (training as needed throughout the study).
- Diet and life style counseling if not performed at V3.
- Tactipen® dispense.
- Dispensation of IMP.
- Concomitant medication.
- IMP administration:
  - The investigator must explain to the patient the treatment regimen the patient was assigned to (ie, SAR425899/matching placebo or liraglutide),
  - The dose of IMP will be done on site.
- 7-point glucose profile to be conducted on the day prior to randomization beginning in the morning.
- 12-lead ECG.
- Waist and hip measurements.
- Laboratory assessments performed by the central laboratory:
  - HbA1c,
  - FPG,
  - Fasting insulin for calculation of HOMA- β, HOMA-IR,
  - Pregnancy test,
  - Clinical chemistry and hematology,
  - Lipid panel,
  - Ketone bodies,
  - Fasting level of adiponectin,
  - Amylase/lipase,
  - TSH/T3/FT4
  - Calcitonin,
  - Urinalysis,
  - Anti-SAR425899 antibodies,
  - Exploratory biomarkers,
  - Urinary free-cortisol and creatinine measured in 24h urines.
- The PRO questionnaires will be provided and completed by the patients.
- Recording of AEs.
- Recording of hypoglycemic events (if any).

An appointment for 1 week later is given to the patient for the phone call visit.

10.1.2.1.2 Phone call Visit 5 (Week 1)

The 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 and informed in case AE/SAE occurred. In case of an AE the patient may be asked to come to the investigational site, as appropriate. A phone call visit can optionally be performed as a clinical visit in case of AE (example, nausea and vomiting), or other reasons.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any hypoglycemic events or symptoms?
- Did you experience any possible allergic symptoms, or skin reactions?
- Do you feel comfortable in handling the diary, glucometer and IMP injection device or do you need any more explanation?
- What is the daily dose you are using?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you miss, change, take or add any new medications (including OAD if appropriate) since the last visit?

If the safety and tolerability are acceptable to the investigator, the study treatment dose should be increased to a maintenance dose for low doses patient and to subsequent dose for mid and high doses

The patient is instructed to repeat the same dose daily up to next visit.

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

An appointment for 1 week later is given to the patient.

10.1.2.1.3 Visit 6 (Week 2)

The patient should return to the investigational site in the morning in fasting condition (at least 8 hours fasting) with the study medication box containing used and unused cartridges, pen device, glucometer and the e-diary.

This visit includes:

- IMP dispense.
- IMP administration.
- Injection training/instruction (if needed).
- IRT contact.
- Recording of AEs.

- Recording of hypoglycemic events (if any).
- Recording of the use or change of any concomitant medications.
- Review of the patient's diary, compliance with study medication and use of the glucometer.
- Recording of the dose of study medication.
- Vital signs.
- Body weight.
- Laboratory assessments performed by the central laboratory:
  - HbA1c,
  - FPG,
  - Anti-SAR425899 antibodies.

If the safety and tolerability are acceptable to the investigator, the study treatment dose should be increased to the maintenance dose for mid dose arms and increased to the subsequent dose for high dose.

The low dose patients are already in maintenance dose

The patient is instructed to repeat the same dose daily up to next visit.

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

An appointment for 1 week later is given to the patient.

10.1.2.1.4 Visit 7 (Week 3)

The 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 and informed in case AE/SAE occurred. In case of an AE the patient may be asked to come to the investigational site, as appropriate. A phone call visit can optionally be performed as a clinical visit in case of AE (example, nausea and vomiting), or other reasons.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any hypoglycemic events or symptoms?
- Did you experience any possible allergic symptoms, or skin reactions?
- Do you feel comfortable in handling the diary, glucometer and IMP injection device or do you need any more explanation?
- What is the daily dose you are using?

- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you miss, change, take or add any new medications (including OAD if appropriate) since the last visit?

If the safety and tolerability are acceptable to the investigator, the study treatment dose should be increased to a maintenance dose for high doses.

Low and mid doses patients are already in maintenance dose.

The patient is instructed to repeat the same dose daily up to next visit.

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

An appointment for 1 week later is given to the patient.

10.1.2.1.5 Visit 8 (Week 4)

The patient should return to the investigational site in the morning in fasting condition (at least 8 hours fasting) with the study medication box containing used and unused cartridges, pen device, glucometer and the diary.

This visit includes:

- IMP dispense.
- IMP administration: The patient is instructed to repeat the same dose daily.
- IRT contact.
- Recording of AEs.
- Recording of hypoglycemic events (if any).
- Recording of the use or change of any concomitant medications.
- Review of the patient's diary, compliance with study medication and use of the glucometer.
- Injection training /instruction as needed.
- Vital signs
- Body weight.
- 12 lead ECG.
- Laboratory assessments performed by the central laboratory:
  - HbA1c,
  - FPG,
  - Clinical chemistry and hematology,

- Ketone bodies,
- Amylase/lipase,
- Calcitonin,
- Anti-SAR425899 antibodies.

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

10.1.2.1.6 Visits 9 and 11 (Weeks 8 and 20)

The patient should return to the investigational site in the morning in fasting condition (at least 8 h fasting) with the study medication box containing used and unused cartridges, pen device, glucometer and the diary.

This visit includes:

- IMP dispense.
- IRT contact.
- IMP administration: The patient is instructed to repeat the same dose daily.
- Recording of AEs.
- Recording of hypoglycemic events (if any).
- Recording of the use or change of any concomitant medications.
- Review of the patient's diary, compliance with study medication and use of the glucometer.
- Vital signs.
- Body weight.
- Physical examination (only for Visit 9 [Week 8] abbreviated/targeted physical examination).
- Injection training/instruction of needed.
- Laboratory assessments performed by the central laboratory:
  - HbA1c,
  - FPG,
  - Amylase/lipase,
  - Ketone bodies at Visit 9 (Week 8), and Visit 11(Week 20).
- At Visit 11, provide patient with a urine container and additional appropriate materials to collect at home his/her urine for the 24 hours prior to Visit 12 and to bring the urine sample to the site at visit 12 for the urinary free-cortisol and creatinine measurement

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

10.1.2.1.7 Visit 10 (Week 14)

The patient should return to the investigational site in the morning in fasting condition (at least 8 hours fasting) with the study medication box containing used and unused cartridges, pen device, glucometer and the diary.

The visit includes:

- IMP dispense.
- IMP administration: The patient is instructed to repeat the same dose daily.
- Recording of AEs.
- Recording of hypoglycemic events (if any).
- Recording of the use or change of any concomitant medications.
- Review of the patient's diary, compliance with study medication and use of the glucometer.
- Injection training/instruction if needed.
- Vital signs.
- Body weight.
- Diet and life style counseling.
- Physical examination.
- IRT contact.
- 7-point glucose profile to be conducted one day on the week prior to visit beginning in the morning.
- 12-lead ECG.
- Holter monitor if applicable (subset of patients).
- Waist and hip measurements.
- Laboratory assessments performed by the central laboratory:
  - HbA1c,
  - FPG,
  - Fasting insulin for calculation of HOMA-β, HOMA-IR,
  - Pregnancy test,
  - Clinical chemistry and hematology,
  - Lipid panel,
  - Ketone bodies,
  - Fasting level of adiponectin,
  - Amylase/lipase,

- Calcitonin,
- Urinalysis,
- Anti-SAR425899 antibodies.

PK sampling will be collected (sparse or full if applicable) (Section 9.3.1.1).

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

An appointment for the next visit is given to the patient.

10.1.2.1.8 End of treatment Visit 12 (Week 26)

The patient should return to the investigational site in the morning in fasting condition (at least 8 hours fasting) with the study medication box containing used and unused cartridges, pen device, glucometer and the diary.

The visit includes:

- Recording of AEs.
- Recording of hypoglycemic events (if any).
- IRT contact.
- Recording of the use or change of any concomitant medications.
- Review of the patient's diary, compliance with study medication and use of the glucometer.
- Vital signs.
- Body weight.
- Physical examination.
- 7-point glucose profile to be conducted on the day prior to visit beginning in the morning.
- 12-lead ECG.
- Holter monitor if applicable (subset of patients).
- Standardized meal test with VAS for appetite/satiety in a subset of patients (see Section 9.2.1.2.2 and Section 9.2.1.2.7).
- Waist and hip measurements.
- Laboratory assessments performed by the central laboratory:
  - HbA1c,
  - FPG,
  - Fasting insulin for calculation of HOMA-β, HOMA-IR,
  - Pregnancy test,
  - Clinical chemistry and hematology,
  - Lipid panel,

- Ketone bodies,
- Fasting level of adiponectin,
- Amylase/lipase,
- Calcitonin,
- TSH/T3/FT4
- Urinalysis,
- Anti-SAR425899 antibodies,
- Urinary free-cortisol and creatinine measured in 24 hours urines.

PK sampling will be collected (sparse or full if applicable) (Section 9.3.1.1).

PRO questionnaires and PRO qualitative questions will be completed by the patient.

Exploratory biomarkers.

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

10.1.2.2 Follow up period phone call Visit 13 (3 days FU)

During the phone call, the following questions should be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- 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?

All reports of any AEs are recorded. In case of an AE the patient may be asked to come to the investigational site, as appropriate,

All reports of hypoglycemic events (if any) are recorded, in case of a hypoglycemia the patient may be asked to come to the investigational site, as appropriate,

The use or change of any concomitant medications is reported (including rescue therapy).

Note: This visit should not be performed in case of premature treatment discontinuation.

IRT is contacted for notification of the end of study.

10.1.3 Unscheduled visits

If the target dose is not tolerated, the study treatment can be decreased. Another attempt for dose increase may take place within 4 weeks and before week 8 of treatment.

If the safety and tolerability are acceptable to the investigator, the study treatment dose should be increased in 1, 2 or 3 weeks depending on the decreased dose

- Low dose: 1 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed); 0.06 mg ie, 12U – 0.12 mg ie, 24U (0.12mg ie, 24U for 25 weeks).
- Mid dose: 2 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed); 0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U (0.16 mg ie, 32U for 24 weeks).
- High dose: 3 step weekly dose increase (if no significant tolerability issues [example, nausea and vomiting] are observed); 0.06 mg ie, 12U – 0.12 mg ie, 24U – 0.16 mg ie, 32U – 0.20 mg ie, 40U (0.20 mg ie, 40U for 23 weeks).

The visits for dose increase could be done by phone (additional phone call visit) or at the site if it is corresponding to regular visit.

During the phone call, the following questions are to be asked:

- Did you experience any new medical event, disease or symptom since the last visit?
- Did you experience any hypoglycemic events or symptoms?
- Did you experience any possible allergic symptoms, or skin reactions?
- Do you feel comfortable in handling the diary, glucometer and IMP injection device or do you need any more explanation?
- What is the daily dose you are using?
- Did you experience any changes in a pre-existing medical condition, disease or symptom since the last visit?
- Did you miss, change, take or add any new medications (including OAD if appropriate) since the last visit?

The patient is instructed to repeat the same dose daily up to next visit.

The patient is instructed, in case of occurrence of AE, to contact /return to the site as deemed appropriate.

A phone call visit can optionally be performed as a clinical visit in case of AE (example, nausea and vomiting), or other reasons.

If the visit is at the investigator site, the assessments are those planned in the corresponding visit.

10.2 DEFINITION OF SOURCE DATA

10.2.1 Source data to be found in the patient's file

Evaluations that are reported in the eCRF must be supported by appropriately signed identified source documentation related but not limited to the following:

- Agreement and signature of informed consent form with the study identification and any privacy forms.
- Study identification (name).
- Treatment kit number, dates of administration and doses of SAR42899/placebo administration (0.06 mg, 0.12 mg, 0.16 mg, or 0.20 mg) or liraglutide doses of administration (0.6 mg, 1.2 mg, 1.8 mg).
- Patient number, confirmation of randomization.
- Medical, surgical, diabetes history, including information on:
- Demography, inclusion and exclusion criteria.
- Comorbidities.
- Last participation in a clinical trial.
- Contraception method for women of child bearing potential.
- Previous and concomitant medication. (including background metformin and rescue therapy).
- Dates and times of visits and assessments including examination results.
- Vital signs, height, body weight, laboratory reports.
- Adverse events and follow-up.
- In case of an 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.

Source documentation may be found in the following:

- Patient's identity.
- Medical history.
- Nursing notes.
- Dietician's notes.
- Physician's notes.
- Patient's diaries.
- Glucometer.

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.

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 eCRF. In any case, the patient should remain in the study as long as possible.

Pregnancy will lead to definitive treatment discontinuation in all cases.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of 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(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

Temporary treatment discontinuation decided by the Investigator corresponds to more than 1 dose not administered to the patient.

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 reason(s) for treatment discontinuation and this should be documented in the eCRF.

Patients may withdraw from treatment with IMP in case of the following reasons:

- At patient's own request, ie, withdraw of consent for treatment.
- If, in the investigator's opinion, continuation with the administration of IMP would be detrimental to the patient's well-being.
- At the specific request of the sponsor.

A patient must withdraw from treatment with IMP in case of the following:

- Intercurent condition that requires discontinuation of IMP: eg, laboratory abnormalities (see decision tree and general guidance for the follow up of laboratory abnormalities in Appendix C), diagnosis of acute pancreatitis confirmed by gastroenterologic evaluation and imaging (see Section 10.6.4), calcitonin value ≥ 50pg/ml (see Section 10.6.6).
- Pregnancy.
- Systemic hypersensitivity reaction.

Any code-breaking requested by the Investigator will lead to permanent treatment discontinuation.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (eg after 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned patient.

Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the permanent discontinuation of treatment, the patients will be assessed using the procedure normally planned for the last dosing day with the IMP including a pharmacokinetics sample if already scheduled.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

10.3.4 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. 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 records check.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a pharmacokinetics sample if already scheduled.

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. The site should document and sign the reason for the patient's failure to withdraw consent in writing.

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

For patients who fail to return to the site, unless the patient withdraws consent for follow-up, the Investigator should make the best effort to recontact 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 rerandomized (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.
- Chronic neurodegenerative diseases (newly diagnosed).
- Suspected transmission of an infectious agent.

10.4.1.3 Adverse event of special interest

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

- Pregnancy of a female patient 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 will be recorded as an AESI with immediate notification in all cases,
  - 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 (serious or nonserious) with IMP/NIMP: An overdose (accidental or intentional) with the IMP/NIMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pen count) and defined as:
  - For SAR 425899 and matching placebo: any dose greater than the planned dose administered per day during this clinical trial,
  - For Liraglutide: any dose greater than the planned dose administred per day during this clinical trial,

- For metformin: any dose greater than the recommended dose administered per day during this clinical trial.

- Of note, asymptomatic overdose has to be reported as a standard AE.
- Increase in ALT >3 x ULN (refer to related decision chart in Appendix C).
- Other project specific AESIs:
  - In the event of prolongation of QTc interval (automatic measurement) ≥500 ms, confirmed by a manual reading by the Investigator or a physician delegated by the Investigator using the Fridericia formula for correcting QT, the subject should be placed under supervision in a specialized setting. Investigational medicinal product administration must be stopped and appropriate blood samples collected. Subsequent ECG monitoring of the subject should then be performed on a regular and clinically responsible basis until the QTc interval returns to a safe value as determined by the Investigator in agreement with the Sponsor,
  - Persistence of sinus tachycardia (defined as confirmed sinus tachycardia [heart rate >100 bpm] in supine position reported at more than 2 visits) and associated with a concomitant increase, from baseline, in heart rate of ≥15 beats per minute
  - Severe allergic or allergic-like reaction (except local reactions at site of injection),
  - Calcitonin ≥20 pg/mL after immediate retest (See Section 10.6.6),
  - Amylase or lipase > 2 x ULN after immediate retest (refer to Section 10.6.4.1 and Section 10.6.4.2),
  - Metabolic acidosis: In the event of metabolic acidosis, patients taking metformin should discontinue metformin until event resolution.

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

Not applicable.

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) of the eCRF.
- 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 or by the study procedure(s).
- 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 6.

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 eCRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the eCRF 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 eCRF 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 case report form [CRF] process) is available and should be used when the eCRF 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 eCRF. Instructions for AE reporting are summarized in Table 6.

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 C.

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

- Neutropenia.
- Thrombocytopenia.
- ALT increase.
- Acute renal insufficiency.
- Suspicion of rhabdomyolysis.

Table 6 - 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 (nonSAE, nonAESI)	Routine	Any AE that is not SAE or AESI	Yes	No	No
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	Yes	Yes
		Symptomatic overdose	Yes	Yes	Yes
		Increase in alanine transaminase (ALT)	Yes	Yes	Yes
		Prolongation of QTc interval (automatic measurement) ≥500 ms	Yes	Yes	No
		Persistence of sinus tachycardia per definition in Section 10.4.1.3 and associated with a concomitant increase, from baseline, in heart rate of ≥15 beats per minute	Yes	Yes	No
		Severe allergic or allergic-like reaction (except local reactions at site of injection)	Yes	Yes	Yes
		Calcitonin ≥20 pg/mL	Yes	Yes	Yes
		Amylase/lipase>2xULN	Yes	Yes	Yes
		Metabolic acidosis	Yes	Yes	No

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 (SUSAR), to the regulatory authorities, independent ethics committee (IECs)/institutional review boards (IRBs) as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

Adverse events that are considered expected will be specified by the reference safety information.

For safety reason, the treatment code will be unblinded for reporting to the health authorities of any suspected unexpected serious adverse reaction (SUSAR), ie, any SAE that is both unexpected (per the investigator's brochure) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

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

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypoglycemia

Hypoglycemic events will be categorized as follows:

- Severe hypoglycemia: Severe hypoglycemia is an event requiring third 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 third 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 a 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 ≤70 mg/dL (3.9 mmol/L). Clinical symptoms that are considered to result from a hypoglycemic episode include: 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 70 mg/dL (3.9 mmol/L).
- 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 70 mg/dL (3.9 mmol/L); symptoms treated with oral carbohydrate without a test of plasma glucose.
- Relative hypoglycemia: Relative hypoglycemia recently termed "pseudo-hypoglycemia" is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (3.9 mmol/L), but approaching this level.

Patients will be instructed to measure finger stick plasma glucose levels prior to the administration of carbohydrates whenever symptomatic hypoglycemia is suspected, unless safety considerations necessitate immediate glucose rescue prior to confirmation, and then a glucose measurement should be performed as soon as safe, with appropriate diary documentation. Details on hypoglycemia episodes will be captured in the patient diaries, and patients will contact the sites as soon as possible following severe events to review the details and decide on any necessary measures to be taken.

Symptomatic hypoglycemia episodes will be documented on the dedicated hypoglycemia event page in the eCRF. Symptomatic hypoglycemia events fulfilling the criteria of a SAE will also be documented on AE and SAE forms form in the eCRF.

10.6.2 Local tolerability at injection site

In case the Investigator or the patient recognizes any signs of local intolerability at injection site, this should be recorded on the standard AE page in the eCRF.

10.6.3 Allergic or allergic-like reaction

In case a patient experiences an allergic reaction or an allergic-like reaction, this has to be reported as an AE and recorded in the eCRF on the specific AE form for suspected allergic event.

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 Monitoring of patients with increased lipase and/or amylase >2 ULN

Potential safety signals for acute pancreatitis had been identified in the postmarketing experience of other GLP-1 receptor agonists. Therefore, patients enrolled in this study should be followed for any suspected pancreatitis, eg, with symptoms and/or signs of acute abdominal distress or abnormal levels of pancreatic enzymes. Serum amylase and lipase concentrations are monitored routinely at screening, baseline, and periodically during the study treatment period.

In the presence of clinical signs and/or symptoms evocative of pancreatitis, eg, persistent abdominal pain, which can radiate to the back, often with characteristic positional features, with possible occurrence of nausea, vomiting, fever and leucocytosis, further measurement of amylase and lipase should be performed. The clinical signs and/or symptoms should be documented in the source data.

10.6.4.1 Elevation of amylase and/or lipase >2 ULN without clinical signs and/or symptoms

In any case where amylase and/or lipase are >2 ULN, a retest (centrally assessed as far as possible) must be performed as follows:

- An immediate retest have to be performed before reporting it as an AESI.
- If value(s) is/are >2 to 3 ULN: retest within 7 days.
- If value(s) is/are >3 ULN: retest within 48 hours.
- If the value(s) remain(s) >2 ULN upon retesting: amylase and/or lipase levels should be retested weekly until values are <2 ULN.

In case a retest is >2 ULN a gastroenterological evaluation and imaging (ultrasound and/or CT or MRI with contrast, as appropriate) must be performed. Please document in the source data the absence of clinical signs and/or symptoms (if clinical signs and/or symptoms develop, please see Section 10.6.4.2 below).

Best clinical judgment is to be used when interpreting elevated serum amylase and lipase levels in asymptomatic patients. Temporary discontinuation of the IMP may be considered in these cases if deemed necessary by the Investigator.

10.6.4.2 Elevation of amylase and/or lipase >2 ULN with clinical signs and/or symptoms

In the presence of clinical signs and/or symptoms evocative of pancreatitis (as described above) associated with elevated amylase and/or lipase, treatment with the IMP should be promptly and at least temporarily discontinued pending further clinical evaluation and diagnosis confirmation.

Clinical signs and/or symptoms are to be documented in the source data. A laboratory determination of amylase and lipase has to be obtained at the time of the event and again within 48 hours or earlier as clinically indicated. If the value(s) remain(s) >2 ULN, then amylase and/or lipase levels should be retested as described in Section 10.6.4.1 above, or more often if clinically indicated.

A gastroenterologic evaluation and imaging (ultrasound and/or CT or MRI with contrast, as appropriate) must be performed. If a diagnosis of pancreatitis is confirmed, IMP should not be restarted and should be permanently discontinued.

In both cases as described above in Section 10.6.4.1 and Section 10.6.4.2, all laboratory or clinical documentations are to be collected. If the retest confirms lipase and/or amylase values are >2 ULN, the event must be reported in the eCRF and on the specific AE form for increased lipase and/or amylase >2 ULN", using the appropriate verbatim: eg, "increased amylase and/or lipase" in case of isolated enzyme elevation, "suspected pancreatitis" in the presence of clinical signs evocative of pancreatitis if the diagnosis is suspected but cannot be confirmed or excluded, and "pancreatitis" if the diagnosis has been confirmed.

The PSAC will review selected pancreatic events, including pancreatitis, pancreatic neoplasms and abnormal levels of amylase or lipase.

10.6.5 Major Cardiovascular events

In case a patient experiences a major cardiovascular event, the Investigator, in addition to AE reporting on specific AE forms for cardiovascular events, has to collect more detailed information on specific complementary forms. Major cardiovascular events will be adjudicated by the CAC in a blinded manner at the latest before the database lock.

Please also refer to Section 6.4.2.

10.6.6 Management of patients with increased calcitonin values

During the course of the study, if calcitonin value is found ≥20 pg/mL (5.9 pmol/L), an immediate retest have to be performed before reporting it as an AESI:

- A retest should be performed by the central laboratory within 7 days. In addition, blood should be collected and sent to the central laboratory for measurement of: calcium, phosphorus, gastrin, thyroid stimulating hormone (TSH), and antithyroid peroxidase (anti-TPO) antibodies.
- The clinical and laboratory documentations listed below are to be collected and recorded in source documents as soon as possible:
  - Potential false positive circumstances: smoking status, proton-pump inhibitor treatments (eg, omeprazole), autoimmune thyroid diseases (Hashimoto's thyroiditis or Grave's disease), differentiated thyroid cancer, hypercalcemia, hypergastrinemia, chronic renal insufficiency (not on dialysis), other neuroendocrine tumors (lung small cell cancer, intestinal carcinoid), acute pulmonary inflammatory conditions, or sepsis,
  - Specific personal and/or familial medical history in relation to thyroid or other endocrine diseases,
  - Specific physical examination (neck, thyroid gland).

If the retest confirms that the calcitonin value is ≥20 pg/mL:

- The event must be reported as an AESI in the eCRF and on the specific AE form and specific complementary form for "increased calcitonin ≥20 pg/mL" with all appropriate clinical and laboratory documentation.
- An ultrasound scan of the thyroid should be performed and the patient may be referred to a thyroid specialist if judged necessary.
- The patient should continue to be followed according to protocol schedule (including planned calcitonin measurements). The specific AE form "increased calcitonin ≥20 pg/mL (5.9 pmol/L)" should be updated with any new information collected during the follow up.

If at any time during further follow up a calcitonin value ≥50 pg/mL (14.75 pmol/L) is found, the patient should be permanently discontinued from IMP (see Section 10.3.3) and referred to a specialist. As far as possible, blood should be collected 1 to 2 weeks after IMP discontinuation and sent to the central laboratory for calcitonin measurement.

If at any time during follow-up a calcitonin value ≥20 pg/mL increases by 20 % or more between 2 assessments (while remaining below50 pg/mL), a repeated measurement should be performed earlier than scheduled in the protocol, ie, 1 month later. Once results are available, discussion with Sponsor should be initiated without delay for further guidance.

10.6.7 Monitoring of renal function in case of prolonged and severe nausea and vomiting

In case of prolonged or severe nausea and vomiting, if clinically indicated, serum creatinine measurement has to be centrally performed. If there is an acute increase of serum creatinine, metformin has to be discontinued until resolution of renal dysfunction.

10.6.8 Follow-up of laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities are provided in Appendix C.

10.7 ADVERSE EVENTS MONITORING

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

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

For the primary endpoint of change in HbA_{1c} from baseline to Week 26, a sample size of 60 patients per arm of SAR425899 and 30 patients in the placebo group (pool of the 3 placebo arms) will provide 80% power to detect a difference of 0.7% in the HbA_{1c} change from baseline to Week 26 between a dose group of SAR425899 and placebo (SD 1.1%; 5% significance level 2-sided).

The total sample size will be 270 patients to be randomized over 7 arms: 3 SAR425899 treatment arms with 3 different dose levels (60 patients per arm), 3 matching SAR425899 placebo treatment arms (10 patients per arm; 30 patients total), and 1 liraglutide arm (active comparator arm with 60 patients).

For the biostatistical analyses, data from the 3 SAR425899 placebo arms will be pooled into 1 placebo group (30 patients total).

11.2 DISPOSITION OF PATIENTS

The total number of patients for each of the following categories will be presented in the clinical study report:

- Screened patients: patients who signed the informed consent.
- Randomized patients: patients with a treatment kit number allocated and recorded in IRT database, regardless of whether the treatment kit was used or not.
- Safety population: randomized and treated patients.
- Intent-to-treat (ITT) population: as defined in Section 11.3.1.1 and analyzed as randomized.
- PK population: as defined in Section 11.3.3.
- The randomization strata screening HbA1c value (<8%, ≥8%) and Visit 4 (Day 1) BMI (<35.0 kg/m^2, ≥35.0 kg/m^2) assigned by IRT will be summarized. The discrepancy between the strata assigned by IRT and the information reported on the eCRF will be listed for all randomized patients.
- Patients who have completed the 26-week treatment period.
- Patients who discontinued the IMP during the 26-week treatment period, and the reasons for treatment discontinuation.

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

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

Patients treated but not randomized, patients randomized but not treated and patients randomized but not treated as randomized will be identified and described in separate listings. A Patient of the second category (randomized but not treated) will be part of efficacy analyses if the patient has both a baseline assessment and at least 1 post baseline assessment of efficacy. Patients of the third category (randomized and not treated as randomized) will be part of efficacy and safety analyses.

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

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

Efficacy analyses will be based on the treatment group allocated by the IRT according to the randomization schedule at randomization visit (as randomized), irrespective of the treatment actually received.

11.3.1.1 Intent-to-treat population

Efficacy analyses will be based on the ITT population, defined as all randomized patients.

11.3.2 Safety population

Safety analyses will be based on the safety population, defined as all randomized patients who receive at least 1 dose of IMP. Patients will be analyzed for safety analyses according to the treatment actually received. For a patient randomized to a SAR425899 treatment arm, the patient will be analyzed in the treatment he/she receives starting Week 8 visit (inclusive) when no adjustment of dose level is allowed. However, for a patient randomized to a SAR425899 treatment arm and discontinues the IMP before Week 8 visit, the patient will be analyzed in the SAR425899 treatment arm the patient is randomized to. If a patient is exposed to more than one dose level of SAR425899 since Week 8 visit or later, then the patient will be analyzed in the lowest dose level that the patient is exposed from Week 8 visit or later. If a patient is treated with both placebo and SAR425899 any time during the study, the patient will be analyzed in the SAR425899 treatment arm. Liraglutide patients will be included in the Liraglutide treatment arm regardless of dose amount patients receive.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.
- Patients will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that patients have not taken the study medication.

11.3.3 Pharmacokinetic population

For PK analyses, the PK population is defined as all randomized and treated patients who contribute with at least 1 valid plasma concentration of SAR425899.

11.3.4 Patient-reported outcome population

The analysis of PROs will be conducted on the ITT population.

11.4 STATISTICAL METHODS

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

Categorical data will be summarized by treatment group using count and percentage.

In general, descriptive statistics of quantitative efficacy and safety parameters (result and change from baseline) by scheduled visits will be provided on observed cases (OCs), ie, inclusion of only patients having nonmissing assessments at a specific visit.

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance 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 study treatment exposure will be assessed by the duration of treatment exposure during the study.

The duration of treatment exposure will be the total number of days of administration of the IMP, regardless of unplanned intermittent discontinuations. The duration of IMP exposure will be calculated as:

(Date of the last IMP injection – Date of the first IMP injection) + 1

The number (%) of patients randomized and exposed to the IMP will be presented by specific time periods for each treatment group in the safety population. The time periods of interest are grouped as follows:

- 1 to 14 days.
- 15 to 28 days.
- 29 to 56 days.
- 57 to 98 days.
- 99 to 182 days.
- >182 days.

Descriptive statistics of duration of treatment exposure (number, mean, SD, minimum, median, and maximum) and cumulative exposure in patient-year will also be presented by treatment group in the safety population.

11.4.1.2 Compliance

Overall treatment compliance is defined as the actual number of days with IMP injection compared to the planned number of days with IMP injection during the treatment period up to treatment discontinuation. It is calculated according to the following formula:

$$\text{Compliance rate (\%)} = \left[\frac{\text{Total number of days with IMP injection}}{\text{Planned number of days with IMP injection}} \right] \times 100$$

Treatment compliance will be summarized by treatment group using mean, SD, median, and range for the safety population. In addition, the percentage of patients who have <60%, ≥60 to <80%, ≥80 to ≤100%, and >100% compliance will be summarized by treatment group.

11.4.2 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population.

The statistical test will be two-sided tests at the 5% significance level.

11.4.2.1 Analysis of primary efficacy endpoint(s)

11.4.2.1.1 Primary analysis

The primary efficacy endpoint of change in HbA1c from baseline to Week 26 will be analyzed with missing values imputed by Control-based multiple imputation method under the missing not at random frame work.

- For placebo group patients, missing data will be imputed based on the placebo group data.
- For patients in the SAR425899 groups, missing data will be imputed as if the patients were on placebo group throughout the study.

Each of the complete dataset will be analyzed by the Analysis of Covariance (ANCOVA) model with treatment groups (SAR425899 0.12 mg, SAR425899 0.16 mg, SAR425899 0.20 mg, placebo and liraglutide), randomization strata of screening HbA1c value (<8, ≥8 %), randomization strata of Visit 4 (Day 1) BMI (<35.0 kg/m^2, ≥35.0 kg/m^2), and country as fixed effects, and baseline HbA1c value as a covariate. Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from baseline to Week 26 for each treatment group, as well as the between-group difference (comparing each SAR425899 dose group versus placebo) and the 95% CI for the difference. The overall Type 1 error for multiple comparisons of the primary efficacy endpoint will be controlled by a step-down testing procedure as detailed in Section 11.4.2.3.

The ANCOVA model will be implemented using statistical analysis system (SAS®) (Version 9.4 or higher) MIXED procedure (PROC MIXED).

HbA1c values at baseline and Week 26 (observed or imputed) regardless of treatment discontinuation or initiation of rescue therapy will be used.

11.4.2.1.2 Sensitivity analyses

For the primary efficacy endpoint, sensitivity analyses will be conducted by differently handling missing data under the Missing Not at Random (MNAR) assumption.

11.4.2.1.3 Summary statistics at scheduled visits

Summary statistics (for screening value, baseline value, observed values, and observed changes from baseline) at scheduled visits (using OC) will be provided for each treatment group. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE) at each of the scheduled visits (using OC).

11.4.2.2 Analyses of secondary efficacy endpoints

Descriptive statistics (number, mean, standard deviation, median, minimum, and maximum) will be provided by treatment for all continuous secondary variables at the scheduled visits.

All continuous secondary efficacy endpoints at Week 26 defined in Section 9.2.1 will be analyzed using the same ANCOVA model with missing values imputed by Control-based multiple imputation method as described in Section 11.4.2.1 to compare each SAR425899 dose group with placebo. This model will include fixed effect terms of treatment groups (SAR425899 0.12 mg, SAR425899 0.16 mg, SAR425899 0.20 mg, placebo and liraglutide), randomization strata of screening HbA1c value (<8, ≥8 %), randomization strata of Visit 4 (Day 1) BMI (<35.0 kg/m^2, ≥35.0 kg/m^2), and country, and the covariate of baseline value. Means and adjusted means of each treatment group will be provided, as well as adjusted mean and associated two-sided 95% CI of the differences between each SAR425899 dose group and placebo. The analyses include values at baseline and Week 26 (observed or imputed) regardless of treatment discontinuation or initiation of rescue therapy.

All categorical secondary efficacy endpoints defined in Section 9.2.1 will be analyzed using a Cochran-Mantel-Haenszel (CMH) method stratified on randomization strata of screening HbA1c value (<8, ≥8 %) and randomization strata of Visit 4 (Day 1) BMI(<35.0 kg/m^2, ≥35.0 kg/m^2). The proportion in each treatment group will be provided, as well as the difference of proportions between each SAR425899 dose group and placebo with associated 2-sided 95% CI. For HbA1c (<6.5%, <7% respectively at Week 26) and body weight (≥5%, ≥10% body weight loss respectively from baseline at Week 26) responders, all values at Week 26 will be used to determine whether a patient is a responder or not, even if they are measured after IMP discontinuation or rescue medication use. Patients who have no measurement at Week 26 will be treated as non-responders.

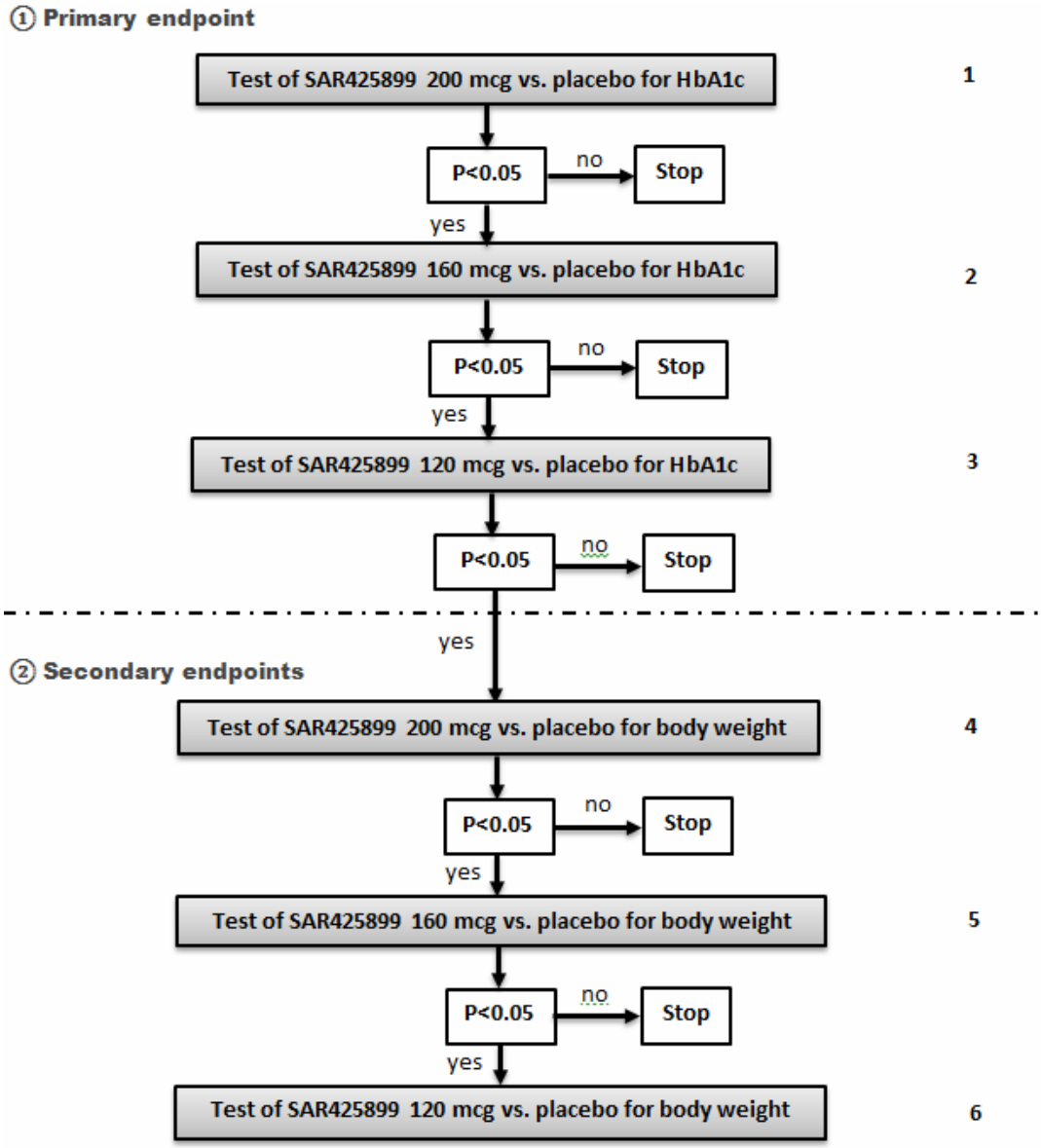
For percentage of patients requiring rescue therapy, patients who have received rescue therapy during the 26-week treatment period will be summarized.

For HbA1c and body weight responders, a sensitivity analysis will be performed treating patients as non-responders if they receive rescue therapy, or have no measurement at Week 26. The sensitivity analysis includes measurement at Week 26, regardless of treatment discontinuation.

11.4.2.3 Multiplicity considerations

To control the type I error, a step-down testing procedure will be applied. The testing procedure will be performed to test the primary and secondary efficacy variables (HbA1c and body weight) by the following prioritized order. The test stop as soon as an endpoint is found not statistically significant at α=0.05 (2-sided).

Figure 1 - The step-down testing procedure



No multiplicity adjustment will be made on other secondary efficacy variables other than body weight.

11.4.3 Analyses of safety data

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

All safety analyses will be performed on the safety population as defined in Section 11.3.2 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, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values for clinical laboratory tests,vital signs and ECG are defined as abnormal values considered medically important by the Sponsor's Global Pharmacovigilance and Epidemiology department and in effect at the time of the final statistical analysis plan approval. Potentially clinically significant abnormality criteria for parameters not cited in the protocol as safety parameters will not be analyzed.
- Potentially clinically significant abnormality criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

The "observation period" defined in Section 9.2.2 are applicable for classification of AEs, determination of on-treatment PCSA values and the last on-treatment value for the laboratory, vital sign and ECG parameters.

11.4.3.1 Analyses of hypoglycemia

The number (%) of patients and rate in patient years (2 types: the number of patients with events or the total number of events per 100 patient-year) of each type of hypoglycemia (severe, documented, asymptomatic, probable and relative hypoglycemia) will be summarized by treatment group. The pattern of symptomatic hypoglycemia occurrence over time will also be assessed, as appropriate. An overall hypoglycemia (includes severe, documented, asymptomatic, probable and relative) table will also be provided.

11.4.3.2 Analyses of adverse events

Pretreatment AEs are AEs that developed or worsened or became serious during the pretreatment period.

Treatment-emergent AEs (TEAEs) are AEs that developed or worsened (according to the Investigator's opinion) or became serious during the on-treatment period.

Posttreatment AEs are AEs that developed or worsened or became serious during the posttreatment period.

The primary focus of AE reporting in the clinical study report will be on TEAEs. Pre- and posttreatment AEs will be described separately.

All adverse events

AE 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.

Summaries of all TEAEs in each treatment group will include:

- The overview of AEs, summarizing number (%) of patients with any
  - TEAE,
  - serious TEAE,
  - TEAE leading to death,
  - TEAE leading to permanent treatment discontinuation.
- The number (n) and percentage (%) of patients with at least 1 TEAE by primary SOC, HLGT, HLT and PT.
- Summary of TEAEs by maximal severity (severe, moderate, mild), presented by primary SOC and PT.
- Summary of TEAEs possibly related to IMP, presented by primary SOC, HLGT, HLT and PT.

A detailed listing of TEAE summaries will be provided in the statistical analysis plan.

Death and serious adverse events

Death and treatment-emergent SAEs will be summarized and presented as number and percent of patients in each treatment group.

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) summarized on the safety population by treatment received.
- Death in nonrandomized patients or randomized and not treated patients.
- TEAE leading to death (death as an outcome on the AE eCRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Adverse events leading to permanent treatment discontinuation

Treatment-emergent AEs leading to permanent treatment discontinuation will be summarized and presented as number and percent of patients in each treatment group.

Local tolerability at injection site

Adverse events related to local intolerability at the injection site will be identified by searching the term "injection site" in the PTs coded from the Investigator reported terms. The number (%) of patients with related events will be summarized by treatment group.

Allergic reactions

The number (%) of patients with events reported by the investigator on the AE forms for suspected allergic event will be summarized by treatment group. All the allergic events reported by the Investigators on the AE form for suspected allergic event and its associated complementary forms will be listed.

Increased pancreatic enzymes and pancreatic events

- Increased pancreatic enzymes >2 x ULN:
  - The number (%) of patients with events reported on the AE form for increased lipase and/or amylase >2 x ULN and its associated complementary forms will be summarized by PTs for each treatment group.
- Pancreatic events
  - The following will be summarized for each treatment group: Number (%) of patients with events adjudicated by the PSAC as: 1) acute pancreatitis, 2) chronic pancreatitis, 3) acute exacerbation of chronic pancreatitis, 4) unknown pancreatitis.
  - Number (%) of patients with pancreatic neoplasms adjudicated by the PSAC as: 1) related to the IMP, 2) possibly related to the IMP, 3) unlikely related to the IMP, 4) not related to the IMP.

All the events sent to PSAC for adjudication will be listed along with the adjudication outcome.

Major cardiovascular events

The number (%) of patients with events adjudicated as major cardiovascular events by CAC will be summarized by treatment group. All events reported by the Investigators on the AE forms for cardiovascular events and the associated complementary forms (confirmed or not confirmed by CAC) will be listed along with the adjudication outcome.

Increased calcitonin values

The number (%) of patients with events reported on the AE form for increased calcitonin $\geq$ 20 pg/mL and its associated complementary forms will be summarized by PTs for each treatment group.

ALT increase

The number (%) of patients with events reported on the AE form for ALT increase and its associated complementary forms will be summarized by PT for each treatment group.

11.4.3.3 Analyses of laboratory variables

The number and percentage of patients with a PCSA at any evaluation during the on-treatment period will be summarized for each clinical laboratory test within each treatment group. The summaries will include patients in the safety population who have at least one laboratory test performed during the on-treatment period and, when required by the definition of the abnormality, with an available baseline value and available laboratory normal ranges.

Descriptive statistics will be used to summarize the laboratory results and the changes from baseline by visit and for the last on-treatment value within each treatment group.

Shift tables and other tabular and graphical methods may be used to present the results for laboratory tests of interest.

Listings will be provided with flags indicating the out of laboratory range values as well as the PCSA values.

Drug-induced liver injury

The liver function tests, namely AST, ALT, ALP and total bilirubin are used to assess possible drug induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any post baseline visit will also be displayed by duration of exposure for each treatment group only if a tabulation summary is necessary.

A listing will be provided of possible Hy's Law cases identified by treatment group (eg, patients with any elevated ALT >3 x ULN, and associated with an increase in total bilirubin >2 x ULN) with liver-related TEAEs, ALT, AST, ALP, total bilirubin and the following complementary parameters, if available: conjugated bilirubin and prothrombin time / International Normalized Ratio (INR) ,creatine phosphokinase, serum creatinine, complete blood count, immunoglobin M (IgM) antibodies to hepatitis A virus, IgM antibodies to hepatitis B core antigen, antibodies to hepatitis C Virus, and hepatitis C ribonucleic acid, IgM antibodies to cytomegalovirus, and IgM antibodies to hepatitis E virus, auto-antibodies: antinuclear, antideoxyribonucleic acid, anti-smooth muscle, Epstein-Barr virus, herpes viruses and antiliver/kidney microsomes.

11.4.3.4 Analyses of vital sign variables

The number and percentage of patients with a PCSA at any evaluation during the on-treatment period will be summarized for each vital sign parameter within each treatment group. The summaries will include patients in the safety population who have at least one parameter to be analyzed during the on-treatment period. When the PCSA definition involves the change from the baseline value, patients need also to have a baseline value to be included in the summaries.

Descriptive statistics will be used to summarize the results and the changes from baseline by visit and for the last on-treatment value within each treatment group.

Tabular and graphical methods may be used to present the results for parameters of interest.

Listings will be provided with flags indicating the PCSA values.

11.4.3.5 Analyses of 12 lead electrocardiogram status

ECG (12-lead ECG)

For HR, PR-, QRS- and QT-intervals and corrected QT (QTc), number and percentage of patients with a PCSA at any evaluation during the on-treatment period will be summarized by treatment group. The summaries will include patients in the safety population who have at least one parameter to be analyzed during the on-treatment period. When the PCSA definition involves the change from the baseline value, patients need also to have a baseline value to be included in the summaries.

Descriptive statistics will be used to summarize the results and the changes from baseline by visit and for the last on-treatment value within each treatment group.

Tabular and graphical methods may be used to present the results for parameters of interest.

Listings will be provided with flags indicating the PCSA values.

A listing of subjects with at least one abnormality in qualitative assessment (ie, abnormal ECG) during the on-treatment period will be also provided.

24-hours Holter ECG

For 24-hour average and night time average heart rate, descriptive statistics will be used to summarize the results and the changes from baseline by visit and for the last on-treatment value within each treatment group.

Tabular and graphical methods may be used to present the results for parameters of interest.

11.4.3.6 Analyses of antidrug antibody variables

Analyses of antibody variables will be performed on the safety population (only in patients from SAR treatment arms).

The number and percentage of patients by antibody status will be listed and summarized by treatment group and visit, as well as the percentage of conversion from negative to positive status from baseline to Week 26.

Antibody levels (titer or concentration) will be listed and summarized by treatment group and visit using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum and maximum.

11.4.4 Analyses of pharmacokinetic and pharmacodynamic variables

11.4.4.1 Analyses of pharmacokinetic variables

SAR425899 plasma concentrations of patients in the SAR425899 groups will be listed and summarized by visit and time window and by antibody status in the PK population, using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum and maximum.

Population PK modeling will be performed.

11.4.4.2 Analysis of the pharmacodynamics variables

Analysis of the pharmacodynamics biomarkers

The analysis of pharmacodynamics biomarkers will be conducted on the ITT population.

Descriptive statistics will be used to summarize the results and the changes from baseline by visit within each treatment group.

11.4.5 Analyses of patient reported outcomes (health-related quality of life/health economics variables)

11.4.5.1 Analysis of PRO questionnaires (WRSM, APPADL and IW-SP)

Change from baseline at Week26 will be provided for the WRSM, APPADL and IW-SP total scores, and will be analyzed using ANCOVA with missing values imputed by Control-based multiple imputation method as described in Section 11.4.2.1 to compare each SAR425899 dose group with placebo. This model will include treatment group, randomization strata of screening HbA1c value (<8, ≥8 %), randomization strata of Visit 4 (Day 1) BMI (<35.0 kg/m^2, ≥35.0 kg/m^2), and country as fixed effects, and a covariate using the corresponding baseline value. Mean and adjusted means of each treatment group will be provided, as well as adjusted mean and associated two-sided 95% CI of the difference between each SAR425899 dose group and placebo. The values at Week 26 regardless of treatment discontinuation or initiation of rescue therapy will be used in these analyses.

11.4.5.2 Analysis of the patient qualitative assessment of the treatment

Patients' answers to the 3 open-ended questions will be analyzed qualitatively using a qualitative data analysis software. This qualitative thematic analysis of patients answers will be based on grounded theory methods and involve creating codes corresponding to concepts and sub-concepts identified in the text. A global synthesis will establish the most relevant concepts reported by the patients (benefits, disadvantages and reasons to continue or not the drug). Additional descriptive statistics will be provided on the closed-ended questions. The analyses method for this exploratory analysis will be provided in a separate SAP and the analyses results will be documented in a separate report.

11.5 INTERIM ANALYSIS

An interim analysis for body weight will be conducted when 108 patients (about 24 patients per dose arm of SAR425899 and liraglutide and 12 patients from the SAR425899 placebo arm) have been randomized and completed 14 weeks of treatment. Descriptive statistics will be used to summarize the body weight results and the changes from baseline by visit for each treatment group. Potentially an interim analysis for PK/PD will be conducted when 60% of patients have completed the end of treatment visit.

An internal Sponsor team, independent of the study team, will perform the analysis, which is for internal project planning purposes. It will not lead to changes in the conduct of this protocol. Only those necessary for the analysis and project planning will have the access to the interim analysis results before study completion. Study team and investigational sites will continue to be blinded to individual randomization codes except for the open-label liraglutide until after study completion and database lock.

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 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.

Prior to collection of blood for the optional PK and PD assessments, the optional substudy informed consent forms (written) should be signed, name filled in, and personally dated by the patient or by the subject’s legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The informed consent form the optional substudy informed consent forms 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.

12.3 HEALTH AUTHORITIES AND INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE

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 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 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, 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 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. They 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 IRB/IEC and to health authorities (competent regulatory authority), as required by local regulation.

A progress report is sent to the 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 eCRF, 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 eCRFs. 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

According to the ICH GCP, the monitoring team must check the eCRF entries against the source documents, except for the pre-identified source data directly recorded in the eCRF. 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 eCRFs (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).

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs (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 eCRFs 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 eCRF 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 eCRF.

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 eCRF.

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 curriculum vitae 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 eCRFs, 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 or ethnicity (“American Indian or Alaska Native” / “Asian” / “African American” / “Native Hawaiian or Other Pacific Islander” / “White”) will be collected in this study because these data are required by several regulatory authorities.

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, good clinical practice, 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.

14.8.3 Clinical trial results

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

14.9 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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