AMENDED CLINICAL TRIAL PROTOCOL 02

NCT03496298

Protocol title:	**A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk**
Protocol number:	**EFC14828**
Amendment number:	**02**
Compound number (Trademark/INN):	**SAR439977/efpeglenatide**
Short title:	**Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O)**
Sponsor name:	
Legal registered address:	

Regulatory agency identifying number(s):

EudraCT number:	2017-002954-35
IND number:	112780
UTN number:	U1111-1182-1806

Approval Date: 30 July 2018 Total number of pages: 90

Sponsor signatory:

Please refer to the last page of this document for electronic signatures including date and time.

Monitoring Team's Representative Name and Contact Information:

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document	Country impacted by amendment	Date, version
Amended protocol 02	All	30 July 2018, version 1 (electronic 2.0)
Amended protocol 01	All	28 May 2018, version 1 (electronic 1.0)
Original Protocol		15 January 2018, version 1 (electronic 2.0)

Amended protocol 02 (30 July 2018)

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

OVERALL RATIONALE FOR THE AMENDMENT

The protocol is being amended to add an electrocardiogram (ECG) assessment at Week 12, when steady state has been achieved, to allow Investigators to assess the effects of efpeglenatide on the heart earlier in the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SOA)	An additional ECG assessment will be performed at the on-site visit at Week 12	Efpeglenatide is titrated in 2 mg steps every 4 weeks, so that the 4 mg dose will be achieved after 4 weeks and the 6 mg dose after 8 weeks of treatment. Therefore, the steady state level of the 6 mg dose will be reached around Week 12
Section 1.1 Synopsis, Section 3 Objectives and Endpoints, and Section 9.4.3 Other analyses	Change of anti-drug antibody (ADA) objective/endpoint from secondary objective/endpoint to tertiary/exploratory objective/endpoint	To harmonize the ADA endpoint with the other efpeglenatide Phase 3 clinical protocols
	Removal of Table 9 describing the statistical analysis of ADA	Section 9.4.3 describes statistical analysis of secondary endpoints and the ADA endpoint has been moved to tertiary/exploratory endpoint

Section 5.1 Inclusion Criteria	Clarification of the documentation criteria for symptomatic myocardial infarction by adding a prior discharge hospital diagnosis and removal of cardiac enzymes	To clarify the documentation needed for history of symptomatic myocardial infarction
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A Randomized, Double-blind, Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Effect of Efpeglenatide on Cardiovascular Outcomes in Type 2 Diabetes Patients at High Cardiovascular Risk

Short title: Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O)

Rationale:

The Food and Drug Administration (FDA) requires new therapies for Type 2 Diabetes Mellitus (T2DM) to demonstrate that they do not result in an unacceptable increase in cardiovascular (CV) risk. The European Medicines Agency (EMA) reflection paper on assessment of CV safety of medical products recommends assessment of CV risk by either a meta-analysis of Phase 3 studies or a dedicated cardiovascular outcome trial (CVOT). The present study is a CVOT that has been designed to demonstrate the CV safety of efpeglenatide by assessing the noninferiority (NI) of efpeglenatide over placebo on 3-point major adverse cardiac events (MACE). If NI is established, superiority will also be tested.

Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate that efpeglenatide 4 and 6 mg is noninferior to placebo on 3-point MACE in T2DM patients with high CV Risk	• Time to the first occurrence of any of the following clinical events, positively adjudicated by the Clinical Endpoint Committee (CEC): - CV death - Non-fatal myocardial infarction (MI) - Non-fatal stroke
Secondary	
• To demonstrate that efpeglenatide 4 and 6 mg is superior to placebo on 3-point MACE in T2DM patients with high CV risk	• Time to the first occurrence of any of the following clinical events, positively adjudicated by the CEC: - CV death - Non-fatal MI - Non-fatal stroke

Objectives	Endpoints
• To demonstrate that efpeglenatide 4 and 6 mg is superior to placebo on the expanded CV outcome in T2DM patients with high CV risk	• Time to the first occurrence of any of the following clinical events, positively adjudicated by the CEC: - CV death - Non-fatal MI - Non-fatal stroke - Coronary revascularization - Hospitalization for unstable angina
• To demonstrate that efpeglenatide 4 and 6 mg is superior to placebo on the composite outcome of new or worsening nephropathy in T2DM patients with high CV risk	• Time to the first occurrence of any of the following clinical events: - New onset or progression to macro albuminuria (>300 mg/g) accompanied by an albumin-to-creatinine ratio (UACR) value increase of ≥30% from Baseline - Sustained ≥40% decrease in estimated glomerular filtration rate (eGFR) from Baseline (for ≥30 days) - Chronic dialysis (for ≥90 days) - Renal transplant - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
• To assess the safety of efpeglenatide 4 and 6 mg once per week (QW), both added to standard of care in T2DM patients with high CV risk	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation, AEs of special interest (AESI), AEs requiring specific monitoring • Safety laboratory values • Vital signs • 12-lead electrocardiogram (ECG)

Overall design:

This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in approximately 4000 T2DM patients at High CV Risk.

To be eligible for the study, patients must have T2DM with high CV risk and a glycated hemoglobin A1c (HbA1c) >7% at screening, and the antihyperglycemic treatment must have been stable for 12 weeks prior to randomization, in the opinion of the Investigator.

Prior to randomization, the Investigator will be asked to pre-specify which therapeutic approach will be implemented should intensification of the background antihyperglycemic treatment be considered necessary during the study.

Patients who meet all eligibility criteria will come back for the randomization visit (Visit 3) and, if they are still eligible for the study, they will be randomized 1:1:1 to efpeglenatide 4 mg, efpeglenatide 6 mg or placebo. Randomization will be stratified by the current or potential future use of a sodium-glucose linked transporter-2 (SGLT2) inhibitor (Current use, Potential future use, Neither current nor potential future use).

Any antihyperglycemic treatment is allowed as background therapy (with the exception of glucagon-like peptide-1 [GLP-1] receptor agonists [RAs] and dipeptidyl peptidase-4 [DPP4] antagonists). For participants with HbA1c <7.5% at time of Screening, and who are treated with either insulin, glinide, or sulfonylurea, the doses of the glucose-lowering medications may be decreased at Randomization in order to prevent possible hypoglycemia. Antihyperglycemic therapy must not be modified for the first 12 weeks after randomization (other than for medical necessity). After the first 12 weeks post randomization and during the remaining double-blind treatment period, the management of glycemia will be left to the Investigator's and/or treating provider's judgment, informed by clinical guidelines and local/regional standards of care. Investigators will monitor the glycemic status and potassium levels of participants throughout the study. If treatment intensification is still considered necessary after dose increase of the background antihyperglycemic treatment, the Investigator can prescribe any other antihyperglycemic medication (according to its labeling), with the exception of a GLP-1 RA or a DPP4 inhibitor, that must not be used during the study.

Participants with a suspected renal event (reduction of eGFR) should have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained.

If a participant discontinues treatment with investigational medicinal product (IMP) prematurely, the participant will undergo a premature End-of-Treatment (pEOT) Visit, but every effort will be made to have the participants return to the site at the time corresponding to their scheduled visits, until the end of study. There must be at least 6 weeks of post-treatment safety follow-up between the last IMP administration and the Study Closeout Visit for participants who discontinue IMP prematurely.

Participants will continue taking IMP after a CV or renal outcome has occurred. If the participant does not agree to continue taking IMP or to attend site visits, they will be contacted by telephone to inquire about safety status (including outcomes).

The study is event driven and will continue until 330 participants have at least one primary event (3-point MACE) positively adjudicated by the CEC. At that point all randomized patients have to be scheduled to return to the site for a Study Closeout Visit (timing and window will be communicated to the sites).

All randomized participants, including those who prematurely discontinued from IMP, will be followed from Randomization until the Study Closeout Visit or death, whichever comes first. A

post-treatment safety follow-up visit 6 weeks after the last dose of IMP will be implemented for patients still on study treatment at the Study Closeout Visit.

An independent Data Monitoring Committee (DMC) will review clinical study safety data and an independent CEC will review, assess and/or adjudicate all events of deaths, selected CV events (non-fatal MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), pancreatic events, and other selected AEs. An independent ophthalmologist expert will review in a treatment-blinded manner all reported AEs suspected to be diabetic retinopathy to assess the presence of retinopathy and the relationship of reported AE to IMP. See Appendix 1 (Section 10.1) for further details of study committees.

Number of participants:

Approximately 4000 patients will be randomly assigned to study intervention to end up with an estimated total of 330 participants with at least one positively adjudicated 3-point MACE event.

All randomized participants will be evaluable. See Section 9.2 for details.

Intervention groups and duration:

The study will consist of 3 periods:

- A 2- to 3-week screening period
- A double-blind, placebo-controlled, multiple dose treatment period, including up to 8 weeks for dose titration
  - If, at any time during the study, a participant does not tolerate the study treatment, the IMP may be temporarily discontinued or if medically necessary, permanently discontinued.
  - If a maximum of 2 (two) consecutive doses are missed, the IMP can be restarted with the latest dose given; if 3 or more consecutive doses are missed, the IMP will be restarted using a new titration kit.
  - All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol.
- A follow-up period of 6 weeks after the last dose of IMP

The estimated study treatment duration will be approximately 24 to 36 months, assuming approximately 12 months of recruitment, and approximately 24 months of treatment and follow-up after the last randomized participant.

Study interventions

Investigational medicinal products

Efpeglenatide

- Formulation: 0.5 mL of a sterile, non-pyrogenic, clear, colorless solution in a 1 mL disposable prefilled syringe (PFS). The two doses tested will be injected as 4 mg/0.5 mL

or 6 mg/0.5 mL. A third dose, 2 mg/0.5 mL will be used as the initial dose during the first 4 weeks of the titration phase

- Route of administration: Subcutaneous (SC) injection administered to the abdomen. Within this region, the site of injection should be changed (rotated) at each time to prevent skin reactions
- Dose regimen: once weekly on the same week day (eg, each Monday) at any time of the day
  - Dose will be titrated during Weeks 0 to 8 as shown in Table 1.

Placebo

- Formulation: matching placebo (sterile, non-pyrogenic, clear, colorless solution in a 1 mL disposable PFS)
- Route of administration: SC injection administered to the abdomen. Within this region, the site of injection should be changed (rotated) at each time to prevent skin reactions
- Dose regimen: once weekly on the same week day (eg, each Monday) at any time of the day

Table 1 – IMP dose schedule

	Dose 1	Doses 2-4	Doses 5-8	Doses 9 onward
	Day 1	Weeks 1-3	Weeks 4-7	As of Week 8
Efpeglenatide 4 mg	2 mg	2 mg	4 mg	4 mg
Efpeglenatide 6 mg	2 mg	2 mg	4 mg	6 mg
Placebo	Placebo	Placebo	Placebo	Placebo

No posttrial access to study medication is foreseen.

Statistical considerations:

- **Analysis of primary objective:**

The primary analysis population will be the intent-to-treat (ITT) population that includes all randomized participants irrespective of compliance with the study protocol and procedures. Participants will be analyzed in the treatment group to which they are randomized.

The time to the first occurrence of the primary composite CV endpoint event (CV death, non-fatal MI, or non-fatal stroke) will be analyzed using Cox proportional hazards model with treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo), region, and randomization strata of current or potential future use of a SGLT2 inhibitor (Current use, Potential future use, Neither current nor potential future use) as the covariates. Participants who receive either 4 mg or 6 mg of efpeglenatide will be combined as one efpeglenatide treatment group when making comparisons using the appropriate contrast for the purposes of the primary analysis. The hazard ratio between

pooled efpeglenatide and placebo will be estimated along with the associated two-sided 95% confidence interval (CI).

The NI with the 1.8 and 1.3 margin will be demonstrated on the primary endpoint if the upper bound (UB) of the two-sided 95% CI is <1.8 and <1.3, respectively.

Kaplan-Meier curves of the cumulative incidence rate will also be provided by treatment groups.

All participants will be followed up to the Study Closeout Visit or death, whichever comes first. The primary analysis will be based on the ITT approach that includes events occurring from randomization to the end of study, even after the participant has discontinued the study treatment. In the ITT approach, all randomized participants will be included and analyzed as randomized.

The analysis will be based on the positively-adjudicated CV endpoint events. Participants who have not experienced any of these primary CV outcomes as positively adjudicated by the CEC during the study will be censored at the last date with available information on the CV outcomes on or before the study end date for the participant.

- **Analysis of secondary objectives:**

If the NI with the 1.8 and 1.3 margin is demonstrated on the primary endpoint, the superiority of pooled efpeglenatide group (4 and 6 mg) vs placebo for the 3-point MACE will be tested in a hierarchical fashion.

The two other secondary efficacy endpoints will be analyzed using the same Cox proportional hazards model used for the analysis of primary endpoint with treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo), region, and randomization strata as the covariates.

The safety analysis will be conducted on the safety population that includes all randomized participants who have received at least 1 dose of double-blind treatment, regardless of the amount of treatment administered. Participants will be analyzed for safety analyses according to the treatment actually received.

All safety summaries will be descriptive; no statistical significance tests will be performed on safety data. These analyses will be based on the Safety Population. Treatment-emergent adverse events (TEAEs) are defined as AEs that developed or worsened or became serious during the period from the administration of first double-blind IMP dose treatments up to 30 days after the last administration.

Each of the two efpeglenatide treatment groups will be compared with the placebo group.

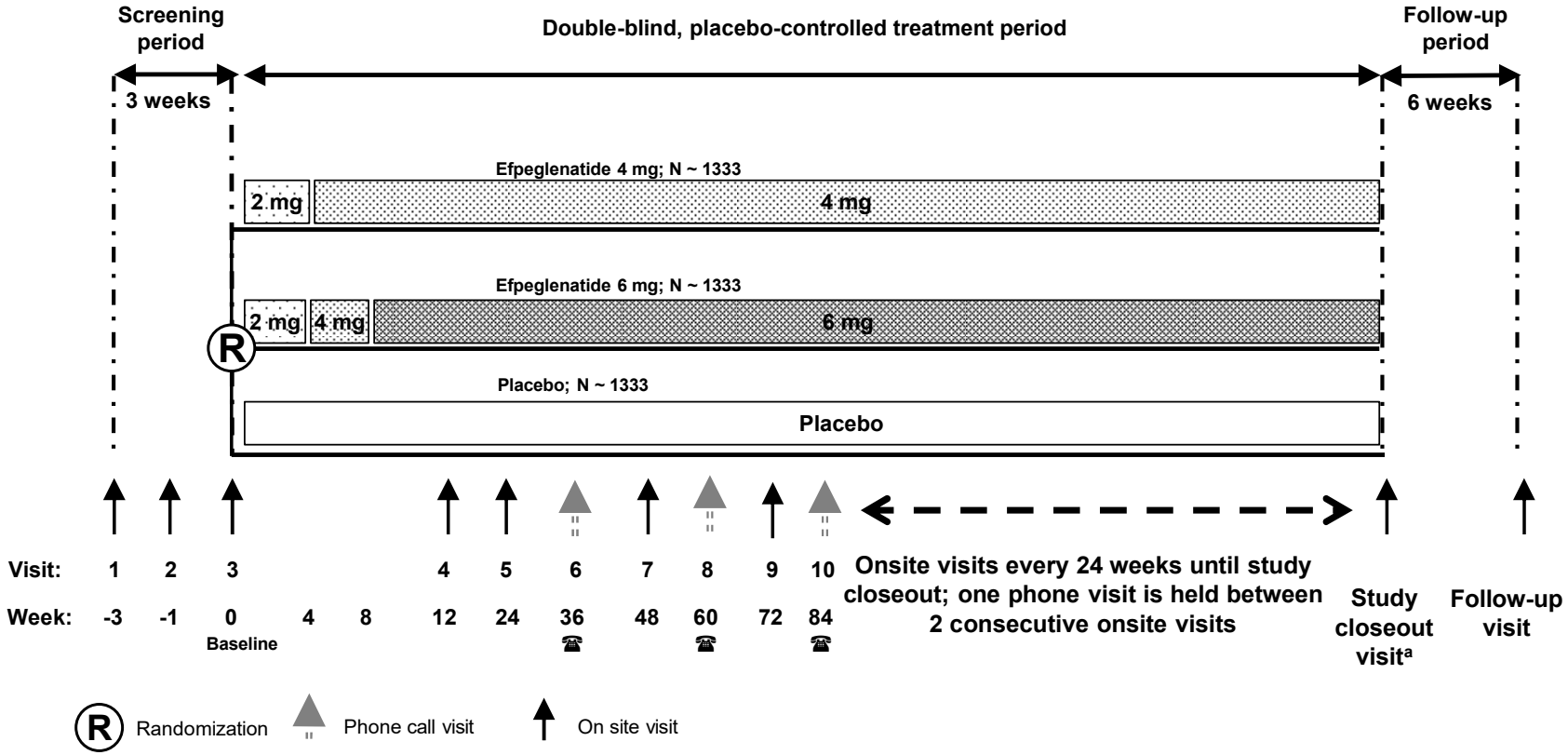
A pre-specified safety analysis will be performed in the subsets of participants on the background therapy of metformin + SGLT2, and on metformin + sulfonylurea. Safety summaries will be provided by treatment group for each of the subsets, including the summaries for AEs, SAEs, deaths, hypoglycemia, AESIs, and AEs requiring specific monitoring.

Data Monitoring Committee: Yes

See Appendix 1 (Section 10.1) for further details on Steering Committee, DMC, CEC, and Independent Expert.

1.2 SCHEMA

Figure 1 – Graphical study design



1:1:1 randomization, stratified by the current or potential future use of SGLT2 inhibitor (Current use, Potential future use, Neither current nor potential future use).

[a] All randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 330 participants have at least one primary event (3-point MACE) positively adjudicated by the CEC

R: randomization; CEC: Clinical Endpoint Committee; SGLT2: sodium-glucose linked transporter-2

1.3 SCHEDULE OF ACTIVITIES (SOA)

	Screening		Intervention Period[b]							Participants who prematurely discontinued IMP		Participants who did not prematurely discontinue IMP		Notes
Month			**0**	**3**	**6**	**9**	**12/ 24/ …**	**15/21/ 27/ …**	**18/30/ …**					
Week	**-3**	**-1**	**0**	**12**	**24**	**36**	**48/96/ …**	**60/84/ 108/…**	**72/120/ …**					
Visit	1	2	3 R	4	5	6 ☎	7/11/…	8/10/12/… ☎	9/13/…	pEOT *c*	Study closeout[d]	Study closeout[d]	Follow-up	
Acceptable range (days)	+7[a]	± 3[a]		± 7	± 7	± 7	± 7	± 7	± 7				Closeout + 6 weeks	
Informed consent	X													
Inclusion and exclusion criteria	X		X											
Demography	X													
Physical examination	X		X				X			X		X		
Medical/surgical history	X													
Vital signs	X	X	X	X	X		X		X	X	X	X		
Height	X									X		X		
Body weight	X		X	X	X		X		X	X	X	X		
Ophthalmologic exam with fundoscopy	X[e]													

	Screening		Intervention Period[b]							Participants who prematurely discontinued IMP		Participants who did not prematurely discontinue IMP		Notes
Month			**0**	**3**	**6**	**9**	**12/ 24/ …**	**15/21/ 27/ …**	**18/30/ …**					
Week	**-3**	**-1**	**0**	**12**	**24**	**36**	**48/96/ …**	**60/84/ 108/…**	**72/120/ …**					
Visit	1	2	3 R	4	5	6 ☎	7/11/…	8/10/12/… ☎	9/13/…	pEOT [c]	Study closeout[d]	Study closeout[d]	Follow-up	
Acceptable range (days)	+7[a]	± 3[a]		± 7	± 7	± 7	± 7	± 7	± 7				Closeout + 6 weeks	
12-lead ECG			X	X						X		X		Recording at Week 0 (Visit 3) should be obtained prior to first dose of double-blind IMP
Randomization			X											
Interactive response technology (IRT) contact	X	X	X	X	X		X		X	X	X	X	X	
Injection training/retraining and self-injection at site		X												
IMP dispensed			X	X	X		X		X					
IMP accounting				X	X		X		X	X		X		
IMP compliance				X	X	X	X	X	X	X		X		
Concomitant medication review	X	X	X	X	X	X	X	X	X	X	X	X		
AE and SAE review	←==========													==========→

	Screening		Intervention Period[b]							Participants who prematurely discontinued IMP		Participants who did not prematurely discontinue IMP		Notes
Month			**0**	**3**	**6**	**9**	**12/ 24/ …**	**15/21/ 27/ …**	**18/30/ …**					
Week	**-3**	**-1**	**0**	**12**	**24**	**36**	**48/96/ …**	**60/84/ 108/…**	**72/120/ …**					
Visit	1	2	3 R	4	5	6 ☎	7/11/…	8/10/12/… ☎	9/13/…	pEOT [c]	Study closeout[d]	Study closeout[d]	Follow-up	
Acceptable range (days)	+7[a]	± 3[a]		± 7	± 7	± 7	± 7	± 7	± 7				Closeout + 6 weeks	
Laboratory assessments														Laboratory assessments performed at Week 0 (Visit 3) should occur prior to first dose of double-blind IMP
HbA1c	X			X	X		X		X	X		X		
HBsAg and HCAb	X													
Hematology[f]	X		X	X	X		X		X	X	X	X	X	
Clinical chemistry[g]	X		X	X	X		X		X	X	X	X	X	
Lipid profile[h]	X			X			X			X		X		
Amylase, lipase, and calcitonin	X		X	X	X		X		X	X	X	X	X	
Urinalysis	X													Urine analysis: pH, glucose, ketones, leucocytes, blood/hemoglobin, protein.
Urinalysis (spot)	X		X	X	X		X		X	X		X		Urinary albumin-to-creatinine ratio (UACR) performed by spot urine
Pregnancy test (WOCBP only)[i]	X		X	X	X		X		X	X		X	X	

	Screening		Intervention Period[b]							Participants who prematurely discontinued IMP		Participants who did not prematurely discontinue IMP		Notes
Month			**0**	**3**	**6**	**9**	**12/ 24/ …**	**15/21/ 27/ …**	**18/30/ …**					
Week	**-3**	**-1**	**0**	**12**	**24**	**36**	**48/96/ …**	**60/84/ 108/…**	**72/120/ …**					
Visit	1	2	3 R	4	5	6 ☎	7/11/…	8/10/12/… ☎	9/13/…	pEOT [c]	Study closeout[d]	Study closeout[d]	Follow-up	
Acceptable range (days)	+7[a]	± 3[a]		± 7	± 7	± 7	± 7	± 7	± 7				Closeout + 6 weeks	
Anti-efpeglenatide antibody sampling			X	X	X		X			X		X[j]		Samples will be drawn before the IMP dosing at the site

a There must be not more than 3 weeks + 3 days between screening visit and randomization. In some cases, Visit 2 might be combined with Visit 3 (Randomization), as per Investigator's judgement, according to the patient's medical profile.

b Additionally, in between each on site visit, starting after Visit 5, participants will be contacted by phone to collect endpoint events, IMP administration information, and safety data.

c If a participant prematurely permanently discontinues treatment with IMP, the participant will undergo a pEOT Visit as soon as possible. Participants will then continue in the study with all study procedures/visits except those associated with IMP administration. Participants will continue to be followed after a CV or renal endpoint occurs irrespective of their treatment status. If the participant does not agree to site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and endpoints).

d All randomized participants will be asked to return to the study site for a Study Closeout Visit when primary 3-point MACE are positively adjudicated in approximately 330 participants. The timing and window of this visit will be communicated to sites. For participants who previously prematurely permanently discontinued IMP, there must be at least 6 weeks between the last IMP administration and the Study Closeout Visit, the Study Closeout Visit will be the final study visit, and no further visits are planned.

e Examination to be done unless exam has been performed within the last 6 months prior to randomization or within 3 months in patients with severe non proliferative diabetic retinopathy (NPDR)/ proliferative diabetic retinopathy (PDR)/Diabetic Macular Edema (DME) and documented. The ophthalmologic exam, whether completed within the last 6 months prior to randomization or at screening, will serve as the baseline assessment.

f Hemoglobin, hematocrit, red blood cell (RBC) count with indices, white blood cell (WBC) count with differential, and platelets.

g Total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), non-fasting plasma glucose, creatinine, estimated creatinine clearance, uric acid, sodium, potassium.

h Non-fasting triglyceride, total cholesterol, high density lipoprotein (HDL) and low density lipoprotein (LDL); will be done once a year for the duration of the study after Week 24.

i FSH and estradiol may be checked in case the status of post-menopausal cannot be decided. Serum beta-human chorionic gonadotropin (β-HCG) test at screening; urine pregnancy test for subsequent monitoring; if the urine test is positive, serum β-HCG should be tested for confirmation of the pregnancy. A monthly home urine pregnancy test should be performed by the patient between visits.

j Participants with positive anti-drug antibody (ADA) at the end of study, and who experienced severe injection site or hypersensitivity reaction at whatever time during the study, will be asked to provide sample for anti-efpeglenatide antibodies assessments 4 and 6 months after the end of the treatment.

AE: adverse event; DME: diabetic macular edema; ECG: electrocardiogram; IMP: investigational medicinal product; HbA1c: glycated hemoglobin; HBsAg: hepatitis B surface antigen; HCAb: hepatitis C antibody; IRT: interactive response technology; NPDR: non proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy; pEOT: premature end of treatment; R: randomization; RBC: red blood cells; SAE: serious adverse event; WBC: white blood cells; WOCBP: woman of childbearing potential

2 INTRODUCTION

Efpeglenatide (LAPS-exendin-4, SAR439977, previous code HM11260C), a glucagon-like peptide-1 receptor agonist, is a novel long-acting form of CA exendin-4 (an exendin-4 analogue) that is being developed for the treatment of adults with T2DM.

2.1 STUDY RATIONALE

In 2008, the FDA issued a guidance requiring new therapies for T2DM to demonstrate that they do not result in an unacceptable increase in CV risk (1). The 2016 EMA reflection paper on assessment of CV safety of medical products recommends assessment of CV risk by either a meta-analysis of Phase 3 studies or a dedicated CVOT (2). In this CVOT, CV safety of efpeglenatide will be assessed by demonstrating NI of efpeglenatide over placebo on 3-point MACE (CV death, non-fatal MI, or non-fatal stroke) at the 1.8 and 1.3 NI margins (UB of the 2-sided 95% CI) as specified by the 2008 FDA Guidance discussed above. If NI is established, superiority will also be tested.

2.2 BACKGROUND

In recent years, the GLP-1 RA class of pharmacotherapy for T2DM has evolved as an effective treatment option from multiple daily injections to daily and then to weekly injections. Glucagon-like peptide-1 is an endogenous enteroendocrine hormone secreted by L-cells of the distal intestine in response to oral nutrient ingestion, and it has multiple physiologic effects that contribute to ameliorating hyperglycemia. These effects include enhancing insulin secretion from pancreatic β-cells in a glucose dependent manner, suppressing glucagon secretion, and slowing gastric emptying. Due to its glucose-dependent mechanism of action, GLP-1 RAs are generally associated with a low risk of hypoglycemia.

Glucagon-like peptide-1 RAs exhibit multiple effects across several organ systems, including the gastrointestinal (GI), CV, renal and central nervous systems that could decrease the CV risk of patients with diabetes. Cardioprotective mechanisms of GLP-1 RAs include weight loss, improvement of glucose metabolism, blood pressure (BP) reduction, antiatherogenic properties and lipid lowering effects. Glucagon-like peptide-1 RAs are associated with clinically relevant weight loss, perhaps via early satiety and delayed gastric emptying, resulting in decreased food intake and appetite, without an increase in energy expenditure (3, 4). The adipocyte releases regulators of BP and vascular tone, which may influence vasculature, and also myocardial ischemia, infarction and contractility. With an injured heart, metabolism shifts toward greater oxidation of glucose, rather than free fatty acids (normally 60-90%), due to less oxygen consumption. Glucagon-like peptide-1 RAs may increase glucose uptake and facilitate this metabolic shift (5).

Glucagon-like peptide-1 RAs decrease both systolic and diastolic blood pressure (SBP and DBP) perhaps via a natriuretic/diuretic effect on the kidney, vasodilation and/or decreased sympathetic nervous system activity. Glucagon-like peptide-1 receptors are expressed in endothelial cells

vascular smooth muscle cells, monocytes, macrophages and lymphocytes, and therefore, may directly affect atherosclerosis, inflammation and may reduce vascular endothelial dysfunction (which precedes atherosclerosis) (3, 4). Finally, GLP-1 RAs can lower total cholesterol, LDL, fatty acid and triglyceride levels (5).

2.3 BENEFIT/RISK ASSESSMENT

Efpeglenatide is a long-acting GLP-1 RA; it is being developed as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

In 2 Phase 1 and 5 Phase 2 studies, efpeglenatide at doses ranging from 1 to 6 mg weekly and 8 to 16 mg monthly has been shown to lower blood glucose in participants with T2DM in comparison with placebo. A Phase 2 study in obese subjects without diabetes (HM-EXC-205) provided evidence for a benefit of efpeglenatide in combination with a hypocaloric diet in terms of body weight loss.

HM-EXC-203 and HM-EXC-204, both Phase 2 studies, showed administration of efpeglenatide to patients (n=254 and n=209, respectively) with T2DM improved several metabolic parameters including HbA1c levels, proportion of patients who had a goal HbA1c level of <7%, LS mean changes from baseline in the levels of certain 7-point blood glucose profile parameters, glycated albumin levels, and LDL C levels. In addition, decreases from baseline in body weight were statistically significantly greater (at least $p<0.049$ for both) compared to placebo.

Study HM-EXC-205 was conducted in 295 overweight/obese patients without T2DM. The primary objective of this study was to evaluate the efficacy of efpeglenatide in reducing body weight. In this study, 6 mg efpeglenatide administered once weekly for 20 weeks resulted in slightly greater weight reduction than what was observed for the 4 mg weekly dose (LS mean change from baseline of -7.32 kg [SE 0.63] versus -6.63 kg (SE 0.62), for the 6 and 4 mg weekly dose groups, respectively).

The non-clinical toxicological data and the safety data from clinical studies with efpeglenatide to date suggest a safety profile consistent with the known AE profile of currently marketed GLP-1 RAs, with the exception of potential liver toxicity. Below is a summary of safety findings in all Phase I and 2 studies with a data lock date of 22 June 2017.

- No major safety concerns were found in the Phase 1 and 2 program of efpeglenatide.
- Gastrointestinal AEs, in particular, nausea, were the most common. The trend over time for nausea and vomiting events appeared dose related with an increase after the first injection, and generally decreasing thereafter. In studies where a titration phase (ie, where a schedule of gradual dose escalation up to the randomized dose) occurred, the effect was less pronounced during the titration phase. The percent of TEAEs, discontinuations and nausea and vomiting appeared to be dose dependent.
- There were no reports of pancreatitis.

- TEAEs leading to discontinuation in the GI disorders system organ class (SOC) for efpeglenatide in Studies HM-EXC-203, HM-EXC-204 and HM-EXC-205 (the large Phase 2 studies) were 2.2%, 8.3% and 9.8%, respectively.
- There was one case of medullary thyroid cancer and one case of pancreatic cancer reported in the Phase 1 and 2 programs. They were considered by the investigators to be unrelated or unlikely related to efpeglenatide respectively.
- No serious or severe immunogenicity events (eg, allergic reactions or immune complex disease and injection site reactions) were reported.
- No severe hypoglycemia was reported.
- No fetal toxicity was reported.
- Elevated ALT levels ≥3 x upper limit of normal (ULN) post-baseline were seen in 15 of 754 subjects in the large Phase 2 studies (HM-EXC-203 and HM-EXC-204 in patients with T2DM and HM-EXC-205 in obese subjects); 2 of 147 subjects on placebo, 12 of 571 subjects on efpeglenatide, and 1 of 36 subjects on liraglutide. There were several confounding factors such as acetaminophen (paracetamol) used and elevated levels at either baseline or screening. None of these subject experienced increased bilirubin >2 x ULN. Four of the 15 subjects discontinued study medication due to abnormal liver function tests. There were no cases of ALT increase ≥3 x ULN in the Phase 1 studies (HM-EXC-101 and HM-EXC-102) and the Phase 2 studies (HM-EXC-201 and HM-EXC-202).
- Diabetic retinopathy complications have been reported for one of GLP-1 RAs (as of 05 December 2017). No case has been reported for efpeglenatide.
- The 24-hour ECG performed in Study HM-EXC-102 showed that the increase of heart rate (HR) seen with 6 mg efpeglenatide was in the range of liraglutide 1.8 mg.
- There were no deaths in the studies.
- The SAEs considered related to efpeglenatide included severe dehydration and renal failure, in a single subject (6 days after starting efpeglenatide 6 mg QW), possibly caused by GI complications (vomiting); and constipation in another patient.

Overall, the potential benefits of efpeglenatide therapy for patients with T2DM, including improvement in glycemic control and reduction in body weight, outweigh the potential risks. The favorable benefit-risk assessment to date supports the further development.

The risks to the study participants will be minimized by careful participant selection according to appropriate inclusion and exclusion criteria based on existing nonclinical and clinical data. During the study participants will be closely monitored at the regular visits, including physical examinations and laboratory tests to early detect eventual adverse reactions.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of efpeglenatide may be found in the Investigator's Brochure (IB) (6).

3 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

Objectives	Endpoints
Primary	
• To demonstrate that efpeglenatide 4 and 6 mg is noninferior to placebo on 3-point MACE in T2DM patients with high CV Risk	• Time to the first occurrence of any of the following clinical events, positively adjudicated by the Clinical Endpoint Committee (CEC): - CV death - Non-fatal myocardial infarction (MI) - Non-fatal stroke
Secondary	
• To demonstrate that efpeglenatide 4 and 6 mg is superior to placebo on 3-point MACE in T2DM patients with high CV risk	• Time to the first occurrence of any of the following clinical events, positively adjudicated by the CEC: - CV death - Non-fatal MI - Non-fatal stroke
• To demonstrate that efpeglenatide 4 and 6 mg is superior to placebo on the expanded CV outcome in T2DM patients with high CV risk	• Time to the first occurrence of any of the following clinical events, positively adjudicated by the CEC: - CV death - Non-fatal MI - Non-fatal stroke - Coronary revascularization - Hospitalization for unstable angina
• To demonstrate that efpeglenatide 4 and 6 mg is superior to placebo on the composite outcome of new or worsening nephropathy in T2DM patients with high CV risk	• Time to the first occurrence of any of the following clinical events: - New onset or progression to macro albuminuria (>300 mg/g) accompanied by an albumin-to-creatinine ratio (UACR) value increase of ≥30% from Baseline - Sustained ≥40% decrease in estimated glomerular filtration rate (eGFR) from Baseline (for ≥30 days) - Chronic dialysis (for ≥90 days) - Renal transplant - Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)
• To assess the safety of efpeglenatide 4 and 6 mg once per week (QW), both added to standard of care in T2DM patients with high CV risk	• Adverse events (AEs), serious adverse events (SAEs), AEs leading to treatment discontinuation, AEs of special interest (AESI), AEs requiring specific monitoring • Safety laboratory values • Vital signs

Objectives	Endpoints
	• 12-lead electrocardiogram (ECG)
Tertiary/exploratory	
• To compare efpeglenatide versus placebo on the occurrence of the following events in T2DM patients with high CV Risk : - CV death - Stroke (fatal and non-fatal) - MI (fatal and non-fatal) - All cause death - Hospitalization for unstable angina - Hospitalization for Heart Failure (HHF) - Coronary revascularization procedures (percutaneous coronary intervention [PCI] or coronary artery bypass graft [CABG]	• Time to CV death • Time to first occurrence of Stroke (fatal and non-fatal) • Time to first occurrence of MI (fatal and non-fatal • Time to all cause death • Time to first occurrence of hospitalization for unstable angina • Time to first occurrence of HHF • Time to first occurrence of coronary revascularization procedures (PCI or CABG)
• To compare efpeglenatide versus placebo on the following endpoints: - Change in HbA1c - Change in body weight - Change in BP - Change in Urinary Albumin-Creatinine Ratio (UACR)	• Change in HbA1c • Change in body weight • Change in BP • Change in UACR
• To compare efpeglenatide versus placebo on immunogenicity	• Anti-drug (efpeglenatide) antibody (ADA): - Number of participants by ADA status (positive/negative) at baseline - Number of participants with treatment boosted ADAs - Number of participants with treatment induced ADAs - Number of participants by ADAs cross-reactivity to endogenous GLP-1 - Number of participants by ADAs cross-reactivity to endogenous Glucagon - Number of participants with ADAs directed against the PEG linker of Efpeglenatide

3.1 APPROPRIATENESS OF MEASUREMENTS

As explained in Section 2, the first primary endpoint of 3-point MACE is in concordance with appropriate guidance from the Health Authorities (1, 2). If NI of efpeglenatide on 3-point MACE is met, superiority will also be assessed.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in approximately 4000 T2DM patients at High CV Risk. The study will consist of 3 periods:

- A 2- to 3-week screening period
- A double-blind, placebo-controlled, multiple dose treatment period, including up to 8 weeks for dose titration
  - If, at any time during the study, a participant does not tolerate the study treatment, the IMP may be temporarily discontinued or if medically necessary, permanently discontinued.
  - If a maximum of 2 (two) consecutive doses are missed, the IMP can be restarted with the latest dose given; if 3 or more consecutive doses are missed, the IMP will be restarted using a new titration kit.
  - All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol.
- A follow-up period of 6 weeks after the last dose of IMP

The study is event driven and will continue until 330 participants have at least one primary event (3-point MACE) positively adjudicated by the CEC.

To be eligible for the study, patients must have T2DM with high CV risk and an HbA1c >7% at screening, and the antihyperglycemic treatment must have been stable for 12 weeks prior to randomization, in the opinion of the investigator.

Prior to randomization, the Investigator will be asked to pre-specify which therapeutic approach will be implemented should intensification of the background antihyperglycemic treatment be considered necessary during the study.

Patients who meet all eligibility criteria will come back for the randomization visit (Visit 3) and, if they are still eligible for the study, they will be randomized 1:1:1 to efpeglenatide 4 mg, efpeglenatide 6 mg or placebo. Randomization will be stratified by the current or potential future use of an SGLT2 inhibitor:

- Current use
- Potential future use
- Neither current nor potential future use

Any antihyperglycemic treatment is allowed as background therapy with the exception of GLP-1 agonists and DPP4 inhibitors. For participants with HbA1c <7.5% at time of Screening, and who

are treated with either insulin, glinide, or sulfonylurea, the doses of the glucose-lowering medications may be decreased at Randomization in order to prevent possible hypoglycemia. Antihyperglycemic therapy must not be modified for the first 12 weeks after randomization (other than for medical necessity). After the first 12 weeks post randomization and during the remaining double-blind treatment period, the management of glycemia will be left to the Investigator's and/or treating provider's judgment, informed by clinical guidelines and local/regional standards of care. Investigators will monitor the glycemic status and potassium levels of participants throughout the study. If treatment intensification is still considered necessary after dose increase of the background antihyperglycemic treatment, the Investigator can prescribe any other antihyperglycemic medication (according to its labeling), with the exception of a GLP-1 RA or a DPP4 inhibitor, that must not be used during the study.

Participants with a suspected renal event (reduction of eGFR) should have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained.

If a participant discontinues treatment with IMP prematurely, the participant will undergo a pEOT Visit, but every effort will be made to have the participants return to the site at the time corresponding to their scheduled visits, until the end of study. There must be at least 6 weeks of post-treatment safety follow-up between the last IMP administration and the Study Closeout Visit for participants who discontinue IMP prematurely.

Participants will continue taking IMP after a CV or renal outcome occurs. If the participant does not agree to continue taking IMP or to attend site visits, they will be contacted by telephone to inquire about safety status (including outcomes).

When 330 participants will have at least one primary event (3-point MACE) positively adjudicated by the CEC, all randomized participants will be scheduled to return to the site for a Study Closeout Visit (timing and window will be communicated to the sites).

All randomized participants, including those who prematurely discontinued from IMP, will be followed from Randomization until the Study Closeout Visit or death, whichever comes first. A post-treatment safety follow-up visit 6 weeks after the last dose of IMP will be implemented for participants still on study treatment at the Study Closeout Visit.

An independent DMC will review clinical study safety data and an independent CEC will review, assess and/or adjudicate all events of deaths, selected CV events (non-fatal MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), pancreatic events, and selected AEs. An independent ophthalmologist expert will review in a treatment-blinded manner all reported AEs suspected to be diabetic retinopathy to assess the presence of retinopathy and the relationship of reported AE to IMP. See Appendix 1 (Section 10.1) for further details of study committees.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Results from 4 CVOTs with GLP-1 agonists (LEADER, ELIXA, SUSTAIN-6 and EXSCEL) showed varying effects on cardiovascular outcomes (7, 8, 9, 10). In the LEADER trial liraglutide

significantly reduced the risk of the composite primary endpoint of CV death, non-fatal MI or non-fatal stroke by 13% vs placebo (95%CI: 0.78 to 0.97, p=0.01), when added to standard of care in patients with T2DM at high CV risk (7). ELIXA showed NI of lixisenatide to placebo (hazard ratio=1.02; 95%CI, 0.89 to 1.17) (p for NI <0.001) for the primary outcome of cardiovascular death, MI, stroke, or hospitalization for unstable angina after a recent acute coronary event (8). SUSTAIN-6 showed that semaglutide was noninferior to placebo on the composite primary endpoint of CV death, non-fatal MI (heart attack) or non-fatal stroke (hazard ratio=0.74; 95% CI: 0.58 to 0.95; p <0.001) in patients with T2DM at high CV risk. The study also showed superiority with p=0.02; however, this analysis was not prespecified in the hierarchical testing plan (9). EXSCEL showed that exenatide was noninferior to placebo on the composite primary endpoint of CV death, non-fatal MI or non-fatal stroke in patients with T2DM with or without cardiovascular disease (CVD) (hazard ratio, 0.91; 95% CI, 0.83 to 1.00; p <0.001 for NI) and was not superior (p=0.06 for superiority) (10). The CV effects of the various GLP-1 RAs in the 4 CVOTs discussed above cannot be directly compared due to differences in study design, duration of follow-up, and enrolled patient populations. The ELIXA trial, for example, was the only CVOT that investigated the CV effect of a GLP-1 RA in patients with a recent acute coronary syndrome. This population with very high CV risk was selected because it should be ideally suitable for demonstration of CV safety. However, the short duration of follow-up likely decreased the ability to detect potential cardioprotective effects of Lixisenatide (8).

In 2015, the EMPA-REG OUTCOME trial showed that the SGLT2 inhibitor empagliflozin, reduced the risk of 3-point MACE (CV death, non-fatal MI, or non-fatal stroke) compared to placebo (hazard ratio=0.86, p <0.001 NI and p=0.04 for superiority) in patients with T2DM and established CV disease (CVD). The CV benefit was primarily driven by a reduction of CV death (hazard ratio=0.62, p <0.001) (11). In 2017, the CANVAS program showed that another SGLT2 inhibitor, canagliflozin, also reduced the risk of 3-point MACE (CV death, non-fatal MI or non-fatal stroke) by approximately 14% (hazard ratio=0.86; p <0.001 for NI and p=0.02 for superiority) in patients with T2DM and established CVD or at high risk for CV events (12).

Of note, FDA recently approved a new indication for empagliflozin for reducing the risk of CV death in adult patients with T2DM and established CVD, and liraglutide for reducing the risk of non-fatal stroke, non-fatal MI and CV death in patients with T2DM and established CVD (13, 14). The EU Summaries of Product Characteristics (SmPCs) have also been updated to include the findings from the empagliflozin and liraglutide CVOT studies (15, 16).

This study is designed to assess the CV effects of efpeglenatide in patients with T2DM and high CV risk (see Section 5.1). Therefore it is important to mitigate any potential imbalance between the treatment arms in the use of concomitant medications that have been shown to affect the CV risk of the patient population. Therapies belonging to two classes of antihyperglycemic medications have been shown to be cardioprotective: the GLP1-RAs and the SGLT2 inhibitors. Since efpeglenatide is a GLP1-RA, treatment with other GLP1-RA will not be allowed during this study. Patients will be allowed to participate in this study even if they currently use an SGLT2 inhibitor, if deemed appropriate based on their comorbid profile. In order to mitigate an imbalance in the use of SGLT2 inhibitors, the Investigators will be asked to pre-specify before randomization whether they will consider starting an SGLT2 inhibitor should intensification of the background antihyperglycemic treatment be considered necessary for a specific patient during the study. Both the use at baseline and potential future use of SGLT2 inhibitor will be considered

in the randomization stratification, using the following 3 levels: Current use, Potential future use, Neither current nor potential future use.

The primary analysis will be performed in the ITT population, and all data from randomization to the Study Closeout Visit will be included. Patients who start or stop a SGLT2 inhibitor during the trial will continue study treatment, will remain in the study and their data will be included in the primary analysis. The supportive analysis will include the ITT population with censoring of patients at the time of starting or stopping a SGLT2 inhibitor.

4.3 JUSTIFICATION FOR DOSE

The selection of efpeglenatide 4 and 6 mg once-weekly doses is based on the results of early phase studies. Efpeglenatide Phase 2 studies have been conducted in both patients with T2DM as well as obese non-diabetic individuals, using a variety of dose regimens including weekly doses up to 4 mg (in patients with T2DM) and 6 mg (in non-diabetic overweight/obese patients) as well as monthly doses up to 16 mg (T2DM). These studies have demonstrated efpeglenatide's effect in glycemic improvement and weight reduction, with an overall favorable safety and tolerability profile.

The once-weekly doses of 4 and 6 mg were chosen for further evaluation based on their HbA1c lowering effects and the overall safety observed at these doses. The initial dose will be 2 mg, and dose increases to achieve maximum of 6 mg (in the corresponding arm) will be in 2-mg step interval every 4 weeks in order to minimize the GI adverse effects.

Please refer to the IB (6) for more details.

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed the Study Closeout Visit (in person or by phone) or has died prior to the Study Closeout Visit.

The study is event driven and will continue until it is projected that 330 participants will have at least one primary event (3-point MACE) positively adjudicated by the CEC.

All randomized patients will be asked to return to the study site for a Study Closeout Visit when approximately 330 participants have at least one primary event (3-point MACE) positively adjudicated by the CEC. The timing and window of this visit will be communicated to sites once the date on which the required number of events is projected to be positively adjudicated has been determined.

For patients who previously prematurely permanently discontinued IMP, the Study Closeout Visit, planned at least 6 weeks after the pEOT visit for post-treatment follow-up, will be the final study visit. Participants still taking the IMP at the time of the Study Closeout Visit will have their final study visit (Follow-up Visit) 6 weeks after their Study Closeout Visit.

5 STUDY POPULATION

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

5.1 INCLUSION CRITERIA

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

Age

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

Type of participant and disease characteristics

I 02. Participants with T2DM and HbA1c >7%

I 03. Participants who meet at least one of the 9 CVD criteria in Table 3
OR
male participants who are ≥50 years of age or female participants who are ≥55 years of age and have an eGFR ≥25 and <60 mL/min and have at least one of the 6 CV risk factors listed in Table 4

Table 3 - Established CVD criteria (need at least 1 from Section A, B or C)

Section A: Presence of Coronary Artery Disease (CAD)
1. Documented (with ECG changes or prior discharge hospital diagnosis) history of symptomatic myocardial infarction (>2 months prior to screening)
2. Evidence of multi-vessel coronary artery disease, ie, ≥2 major coronary arteries or the left main coronary artery, documented by any of the following: - Presence of a significant stenosis (imaging evidence of ≥50% narrowing of the luminal diameter measured during a coronary angiography or a multi-sliced computed tomography) - Previous revascularization of ≥2 major coronary arteries (percutaneous transluminal coronary angioplasty (with or without stent), or CABG) (>2 months prior to screening) - The combination of revascularization in one major coronary artery (>2 months prior to screening) and the presence of a significant stenosis in another major coronary artery {≥50% luminal narrowing during an angiography (coronary or multi-sliced computed tomography)}
3. Evidence of single vessel coronary artery disease of at least ≥50% luminal narrowing during a angiography (coronary or multi-sliced computed tomography) not subsequently successfully revascularized, with at least 1 of the following: - A positive non-invasive stress test for ischemia - Hospitalization for unstable angina within the prior 12 months
Section B: Presence of Cerebrovascular Disease
4. History of Ischemic or Haemorrhagic stroke (>2 months prior to screening)

Section C: Presence of Peripheral Arterial Disease (PAD) (symptomatic or not)
5. Previous limb angioplasty
6. Stenting or bypass surgery of peripheral artery
7. Previous limb or foot amputation due to circulatory insufficiency
8. Ankle-brachial index <0.9
9. Angiographic evidence of PAD

CABG: coronary artery bypass graft; ECG: electrocardiogram

Table 4 - CV Risk Factors (<u>at least 1</u> criterion must be met)

1. Body mass index ≥35 kg/m^2 at Screening
2. Dyslipidemia despite maximally-tolerated statin therapy: - Based on the last measured and documented laboratory measurement in the previous 6 months - LDL cholesterol >130 mg/dL (>3.36 mmol/L) - OR - HDL cholesterol <40 mg/dL (<1.03 mmol/L) for men or <50 mg/dL (<1.29 mmol/L) for women
3. Currently smoking tobacco (Consumes an average of at least 1 cigarette, pipe, or cigar per day, at Screening)
4. UACR ≥30 mg/g (3 mg/mmol) during Screening period, based on central laboratory (spot urine)
5. SBP >140 mmHg and DBP >90 mmHg despite antihypertensive therapy at the Screening Visit
6. Family history (in a male relative <55 years or in a female relative <65 years) of premature coronary heart disease (defined as MI or coronary revascularization procedure) in a first degree relative.

DBP: diastolic blood pressure; HDL: high density lipoprotein; LDL: low density lipoprotein; SBP: systolic blood pressure; UACR: urinary albumin-creatinine ratio

Sex

I 04. Male or Female

A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one of the following conditions applies:

- Not a WOCBP as defined in Appendix 4 (Section 10.4)

  OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) during the study and for at least 5 weeks after the last dose of study treatment and who agrees to refrain from donating ova for the duration of the study and at least 5 weeks after last dose of study treatment.

Informed Consent

I 05. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2) which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

5.2 EXCLUSION CRITERIA

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

Medical conditions

E 01. Clinically relevant history of GI disease associated with prolonged nausea and vomiting, including (but not limited to) gastroparesis, unstable and uncontrolled gastroesophageal reflux disease within 6 months prior to screening

E 02. History of pancreatitis (unless pancreatitis was related to gallstone and cholecystectomy has been performed) and pancreatitis during previous treatment with incretin therapies, chronic pancreatitis, and pancreatectomy

E 03. Personal or family history of medullary thyroid cancer (MTC) or genetic conditions that predisposes to MTC (eg, multiple endocrine neoplasia syndromes)

E 04. Estimated glomerular filtration rate <25 mL/min/1.73 m² by the 4 variable Modification of Diet in Renal Disease (MDRD) equation (at Screening, based on central laboratory)

E 05. Systolic BP >180 mmHg and/or DBP >100 mmHg at randomization

E 06. Hospitalization for hypertensive emergency within 3 months prior to randomization

E 07. Planned coronary revascularization procedures, electrophysiologic device implantation, cardiac mechanical support implantation or other cardiac surgery

E 08. History of solid organ transplant

E 09. Hypersensitivity to any of the study treatments, any components thereof, or any GLP-1 RAs (eg, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide)

E 10. No documented ophthalmologic exam with fundoscopy within 6 months prior to randomization (or within 3 months in patients with severe non proliferative diabetic retinopathy [NPDR]/ proliferative diabetic retinopathy [PDR]/Diabetic Macular Edema [DME])

E 11. Retinopathy or maculopathy with one of the following treatments, either recent (3 months prior to randomization) or planned during the study: intravitreal injections or laser or vitrectomy surgery

E 12. Patients with short life expectancy or with any clinically significant abnormality identified in their medical history (including severe anemia, congestive heart failure-New York Heart Association [NYHA] III/IV, respiratory, hepatic, neurological, psychiatric, active malignant tumor or other major systemic disease), during screening evaluation (eg, physical examination, laboratory tests, ECG, vital signs), or due to any AE during the screening period, which, in the judgement of the investigator, would preclude safe participation in the study or constrain efficacy assessment

E 13. History of drug or alcohol abuse within 6 months prior to the time of screening

Prior/concomitant therapy

E 14. Treated with any GLP-1 RA product alone (eg, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide) or in combination, within 3 months prior to screening

E 15. Use of any DPP4 inhibitor within 3 months prior to screening

E 16. Diabetic treatment has not been stable in the 3 months prior to screening, in the opinion of the investigator

Prior/concurrent clinical study experience

E 17. Exposure to any investigational drugs in the last 4 weeks or 5 half-lives, whichever is longer, prior to screening

E 18. Current enrollment in any other clinical study involving an investigational study treatment

E 19. Participation in any previous efpeglenatide/HM11260C clinical trial within 3 months prior to screening

Diagnostic assessments

E 20. Laboratory findings at the Screening Visit:

- ALT or AST >3 times the ULN
- Total bilirubin >1.5 times the ULN (except in case of documented Gilbert's syndrome)
- Amylase and/or lipase >3 times the ULN laboratory range
- Calcitonin ≥5.9 pmol/L (20 pg/mL)

Other exclusions

E 21. Presence of any other conditions (eg, geographic, social) actual or anticipated, that the Investigator feels would restrict or limit the patient's participation for the duration of the study

E 22. Participant is an employee of the Sponsor, or is the Investigator or any Subinvestigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the protocol

E 23. Participants unwilling or unable to comply with study procedures as outlined in the protocol

E 24. Participants who withdraw consent during the Screening Period (starting from signed ICF)

E 25. Any country-related specific regulation that would prevent the participant from entering the study (eg, individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities) – see Appendix 8 (Section 10.8) (country specific requirements)

5.3 LIFESTYLE CONSIDERATIONS

No restrictions are required.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

In cases where a patient fails Screening due to reasons expected to change upon rescreening based on the Investigator's clinical judgment, the patient can be rescreened once. In these cases, the patient should be registered as a screen failure in IRT. The patient will then need to sign a new ICF, be registered as a rescreen in IRT and assigned a new patient number, and again complete Screening Visit procedures/assessments.

6 STUDY INTERVENTION

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

The IMP includes efpeglenatide in 3 doses (2, 4 and 6 mg) and placebo for SC injection during the course of the study.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 5 - Overview of study interventions administered

Study intervention name	Efpeglenatide	Placebo
Dosage formulation	Sterile, non pyrogenic, clear, colorless solution in a 1 mL disposable PFS in the formulation buffer (containing citric acid monohydrate, L-methionine, polysorbate 20, D-mannitol, sodium hydroxide and water for injection).	Sterile, non pyrogenic, clear, colorless solution in a 1 mL disposable PFS in the formulation buffer (containing citric acid monohydrate, L-methionine, polysorbate 20, D-mannitol, sodium hydroxide and water for injection).
Unit dose strength(s)/Dosage level(s)	2, 4 and 6 mg/ 0.5 mL (at 4, 8 and 12 mg/mL concentrations, respectively)	Not applicable
Route of administration	SC Injection	SC Injection
Dosing instructions	The injection interval of the IMP is once weekly on the same week day (eg, each Monday) at any time of the day. Injections should be administered SC to the abdomen. Within this region, the site of the injection should be changed (rotated) at each time to prevent skin reactions.	
Packaging and labeling	Study intervention will be provided in different types of kit boxes. Each kit will be labeled as required per country requirement.	

INVESTIGATIONAL MEDICINAL PRODUCTS

The appropriate number of kits will be dispensed for the period until the next dispensing visit (please refer to SoA in Section 1.3). Storage conditions and use-by-end date (when required by country regulations) are part of the label text.

Participants will be trained on the use of the PFS by the study staff at Visit 2 (Week -1) and provided with an "instructions for use" leaflet which will describe the handling procedures for the PFS and administration technique. The injection training pads can be used, if needed. Initial injection technique training at Visit 2 will include mandatory self-injection with a training PFS and assessment of participant's skills and understanding by observing teach-back. If needed, an additional training PFS can be used for self-injection technique training any time prior to the day of randomization. In some cases, Visit 2 might be combined with Visit 3 (Randomization), as per Investigator's judgement, according to the patient's medical profile.

Review of injection technique can be done at any other visit as needed. Review of injection sites will be performed at all onsite visits. Injections should be administered SC to the abdomen. Within this region, the site of injection should be changed (rotated) at each time to prevent skin reactions.

Prefilled syringe related issues (malfunctions) should be reported to the Sponsor by the means of a procedure on Product Technical Complaint forms, which are described in a separate manual.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing.

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

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 (when required by country regulation), and storage conditions are written on the IMP labels and in the instruction leaflet.

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

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/device (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to

the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.8).

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

Under no circumstances will the Investigator supply IMP to a third party (except for direct to patient 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.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomization will be stratified by the current or potential future use of SGLT2 inhibitor (Current use, Potential future use, Neither current nor potential future use).

All participants will be centrally assigned to randomized study intervention using IRT. Before the study is initiated, instructions on how to access IRT will be provided to each site.

A randomized participant is a participant who has been allocated to a randomized intervention regardless whether the intervention kit was used or not. A participant cannot be randomized more than once in the study.

Study intervention will be dispensed at the study visits summarized in SoA.

Returned study intervention should not be re-dispensed to the participants.

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the Investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable. When documenting the reason for unblinding, the Investigator must not provide any detail regarding the nature of the IMP. The Investigator should not divulge IMP detail to the Sponsor's representative or to any staff members until database (DB) closure. Furthermore, when completing forms (eg, AE, SAE, adjudication information), the study treatment should not be disclosed on the forms. If the blind is broken by the Investigator, the patient must be permanently withdrawn from IMP administration but shall continue to be followed in the study.

Methods of blinding

During the double-blind treatment period, which includes titration, Investigators and participants will be blinded to the allocation of active or placebo treatment arms. Efpeglenatide and placebo will be provided in indistinguishable PFSs, in identical kits. Titration kits differ from treatment kits by the number of PFSs inside the kits. Each titration and treatment kit (and the corresponding

syringes) will be labeled with a unique number. The list of kit numbers will be generated by Sanofi.

In accordance with the double-blind design, Investigators will remain blinded to study treatment and will not have access to the randomization (treatment) codes except under exceptional medical circumstances.

Randomization code breaking will also be performed during the analysis of the ADA samples. Only the Project manager and lead scientist at the Bioanalytical laboratory will have access to the randomization code to allow for the sorting of the efpeglenatide blood samples. The Bioanalytical laboratory and responsible personnel will follow the standard procedures to ensure the protection of the blind within the Sponsor's clinical team. The randomization code or the individual analytical results will not be disclosed to any clinical team personnel prior to the DB lock.

Members of the CEC will review and adjudicate events in a blinded manner (please also refer to Appendix 1 [Section 10.1]).

The DMC receives unblinded safety data from an independent statistician for review, which will be handled strictly confidentially. None of these reports may be delivered to unauthorized persons (Appendix 1 [Section 10.1]).

Refer to Section 8.3.4 for suspected unexpected serious adverse drug reaction unblinding by the Sponsor.

6.4 STUDY INTERVENTION COMPLIANCE

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

- Proper recording of treatment kit number as required on appropriate electronic case report form (e-CRF) page for accounting purposes
- All medication treatment kits (whether empty or unused) are returned by the participant at each visit when a treatment dispensing is planned
- The Investigator or his/her delegate tracks treatment accountability/compliance comparing the treatment kit number with the treatment kit number of returned treatment kits (whether empty or unused) and fills in the participant treatment log
- The monitor in charge of the study then checks the data entered on the IMPs administration page of the e-CRF by comparing them with the IMPs that has been retrieved and the participant treatment log form

6.5 CONCOMITANT THERAPY

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with dates of administration including start and end dates.

During the study, the following treatments are prohibited:

- Any GLP-1 RA product alone (eg, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide) or in combination
- Any DPP-4 inhibitor
- Any investigational drug other than IMP for this study

Other medications which are unlikely to interfere with the IMP and the study procedures are allowed as needed and have to be recorded in the source data and in the e-CRF. However, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

Glucagon-like peptide-1 receptor agonists are known to decelerate gastric emptying. The delay of gastric emptying may impact absorption of concomitantly administered oral medicinal products. As drug-drug interaction data are not yet available for efpeglenatide, caution should be exercised. Drug levels of oral medications with narrow therapeutic index should be adequately monitored.

During the double-blind study treatment period, the management of glycemia will be left to the Investigator's judgment, informed by clinical guidelines. Investigators will monitor the glycemic status and potassium levels of patients throughout the study. For patients with HbA1c <7.5% at time of Screening, and who are treated with either insulin, glinide, or sulfonylurea, the doses of the glucose-lowering medications may be decreased at Randomization in order to prevent possible hypoglycemia. If treatment intensification is still considered necessary after dose increase of the background antihyperglycemic treatment, the Investigator can prescribe any other antihyperglycemic medication (according to its labeling), with the exception of a GLP-1 RA or a DPP4 inhibitor as mentioned above.

6.6 DOSE MODIFICATION

Up-titration of IMP from Randomization to Week 8 is described in Table 1. From Week 8 throughout the rest of the entire double-blind treatment period, participants will remain on the randomized IMP dose or placebo until the end of study, except in case of temporary treatment discontinuation if, at any time during the study, a participant does not tolerate the study treatment. If a maximum of 2 consecutive doses are missed, the IMP can be restarted with the latest dose given. In cases of 3 or more missed consecutive doses, the participant will restart treatment using a new titration kit (see Section 7.1.2.1).

6.7 INTERVENTION AFTER THE END OF THE STUDY

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

When a participant's participation in the trial ends, the subject will consult with his/her Investigator to decide on the best available treatment.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

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

7.1 DISCONTINUATION OF STUDY INTERVENTION

The IMP should be continued whenever possible. Patients who report a CV or renal endpoint as described in Section 3 should remain on IMP until the end of the study, unless there is a safety concern.

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 must be fully documented in the eCRF. In any case, the participant should remain in the study as long as possible and followed until study end to collect vital safety status and endpoint data.

7.1.1 Permanent discontinuation of study intervention

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

The participants may withdraw from treatment with IMP if they decide to do so, at any time and irrespective of the reason. Patients should discuss stopping study medication with the site before doing so in order that questions can be addressed, concomitant therapy can be adjusted if needed, and a follow-up assessment arranged. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the e-CRF.

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

- Intercurrent condition that requires discontinuation of IMP including:
  - laboratory abnormalities (see decision tree and general guidance for the follow up of laboratory abnormalities in Appendix 5 [Section 10.5])
  - diagnosis of acute pancreatitis confirmed by gastroenterologic evaluation and imaging, unless a clear cause unrelated to IMP is confirmed and the participant has recovered from pancreatitis (see Appendix 6 [Section 10.6])
  - calcitonin value ≥50 pg/mL (see Appendix 6 [Section 10.6])
- If, in the Investigator's opinion, continuation with the administration of IMP would be detrimental to the participant's well-being

- Pregnancy (in female patients)
- Confirmed intolerance to the allocated dose of IMP
- Any code breaking requested by the Investigator
- At the specific request of the Sponsor

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

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation (as soon as possible, preferably within 24 hours) before making a decision of permanent discontinuation of the IMP for the concerned participant.

Handling of participants after permanent intervention discontinuation

Every effort should be made to maintain patients in the study. Participants 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 intervention, the participant will undergo a pEOT Visit as soon as possible. Participants will then continue in the study with all study procedures/visits except those associated with IMP administration. Patients will continue to be followed after a CV or renal endpoint occurs irrespective of their treatment status. If the patient does not agree to site visits, he/she will be contacted by telephone to inquire about safety status (including hospitalizations and endpoints). See the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

As all data until the scheduled date of study completion will be used in statistical analyses, it is important to collect data for all participants, under treatment or not, during the whole duration of the study. A high rate of missing data could jeopardize efficacy results of the study. The Investigators should discuss with the participant key visits to attend. The value of critical study data collected during the participant's continued involvement will be emphasized as important to the public health value of the study. Site personnel will receive training regarding strategies for patient retention, and access to tools to assist with this during the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All cases of permanent intervention discontinuation must be recorded by the Investigator in the appropriate pages of the e-CRF when considered as confirmed.

If after permanent treatment discontinuation, a participant who has discontinued from treatment has reconsidered the decision to permanently discontinue treatment and wishes to later resume IMP, and if the Investigator has determined there is no safety reason prohibiting the patient from

resuming IMP and the selection criteria for the study are still met, the participant may resume IMP with Sponsor approval.

7.1.2 Temporary discontinuation of study intervention

Temporary intervention discontinuation corresponds to at least 1 dose not administered to the patient.

If, at any time during the study, a participant does not tolerate the study treatment, the IMP may be discontinued. All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol (see Section 7.1.1), and the Investigator should make best effort to resume IMP treatment as early as practically possible. There is no defined limit to the duration of temporary discontinuation.

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

7.1.2.1 Rechallenge

Participants who temporarily discontinue IMP should be reassessed at every visit to determine whether it is possible to safely resume IMP. Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely.

If a maximum of 2 consecutive doses are missed, the IMP can be restarted with the latest dose given. In cases of 3 or more missed consecutive doses, a new titration kit will be allocated to the participant (see Section 6.6).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

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

If participants no longer wish to take the IMP, they will be encouraged to remain in the study and attend the remaining visits (see Section 7.1).

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

If a participant withdraws consent for follow-up, the Investigator should still make best efforts to determine the patient's health status, including at least his/her vital status (including time of death), where permitted by local regulations. The patient's final vital status will be confirmed at the time of the study close-out visit.

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

7.3 LOST TO FOLLOW UP

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

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

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue to take IMP or permanently discontinue IMP while still continuing attend study visits.
- Before a participant is deemed potential lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, at least 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods, contact patient's family or private physician, review available registries, or health care DBs). These contact attempts should be documented in the participant's medical record and continue until DB lock.

The patient informed consent should mention that the study organization including the Sponsor will make every possible effort to determine this vital status during the scheduled duration of the study.

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA (Section 1.3), is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA (Section 1.3).

8.1 EFFICACY ASSESSMENTS

8.1.1 Primary endpoint: 3-point MACE

Cardiovascular death, non-fatal MI and non-fatal stroke events will be adjudicated by the CEC (see Appendix 1 [Section 10.1.4.3]).

8.1.2 Secondary efficacy endpoints

All cardiac events (see Section 3) will be adjudicated by the CEC (see Appendix 1 [Section 10.1.4.3]).

Renal events (see Section 3) will be reported by the Investigator in the eCRF. Participants with a suspected renal event (reduction of eGFR) should have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained.

8.1.3 Exploratory efficacy endpoint

HbA1c will be measured at different time points during study by a certified level I "National Glycohemoglobin Standardization Program" central laboratory.

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Physical examinations

- A complete physical examination will be performed as per clinical practice in order to assess the health status of the participant at Screening and evaluate the inclusion/exclusion criteria.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new adverse event.
- Height and body weight will be measured as described in the SoA (see Section 1.3).

8.2.2 Vital signs

- Blood pressure and pulse measurements will be assessed in a seated position using the same device (automated BP monitor or a manual sphygmomanometer) for each participant.

  At the Screening Visit (Visit 1), BP will be measured on both arms to identify and select the appropriate arm for future measurements. Seated BP should be measured in both arms after at least a 5-minute rest period, and then again after 1 minute in both arms in seated position. The arm with the highest systolic BP will be determined at this visit, and BP should be measured in this arm throughout the study. This highest value will be recorded in the e-CRF.
- At subsequent visits, BP and pulse measurements are to be done at participants' identified appropriate arm and should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Heart rate will be measured at the time of the measurement of seated BP.

8.2.3 Electrocardiograms

- The 12-lead ECG should be performed after at least 10 minutes in supine position and prior to other study procedures at that visit (eg, blood collection, IMP administration, etc). The Investigator should review the ECG and document the interpretation, sign and date it on the ECG print out and report it in the e-CRF. Each ECG trace is analyzed in comparison with the Screening ECG. All original ECG traces are kept as source data. The ECG assessment of "normal" or "abnormal" will be analyzed.

  Note: Any new ECG abnormality should be rechecked for confirmation and reported as an AE if considered clinically significant by the Investigator.

8.2.4 Clinical safety laboratory assessments

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

- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or medical monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.

All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.

- If local laboratory results are used to make a study treatment decision, for response evaluation, or to diagnose/follow-up an AE, then the results must be recorded in the eCRF.
- Recommended decision trees for the management of certain laboratory abnormalities are provided in Appendix 5 (Section 10.5).

8.2.5 Severe hypoglycemia

The definition of severe hypoglycemia is based on the American Diabetes Association workgroup on hypoglycemia classification (17, 18): severe hypoglycemia is an event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure, unconsciousness or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration. The definition of severe symptomatic hypoglycemia includes all episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place participants at risk for injury to themselves or others. Note that “requiring assistance of another person” means that the participant could not help himself or herself. Assisting a participant out of kindness, when assistance is not required, should not be considered a “requiring assistance” incident.

Severe hypoglycemia will be reported as an AE. Additional information will be recorded including symptoms and/or signs, associated glucose value (if available), whether assistance was required and the treatment.

Severe hypoglycemia will be qualified as an SAE only if it fulfills SAE criteria (see Appendix 3 [Section 10.3]). For example, events of seizure, unconsciousness or coma must be reported as SAEs.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

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

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP (see Section 8.3.5);
- Symptomatic overdose (serious or nonserious) with IMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the planned dose (e.g. two or more injections) if given within 3 days (72 hours).
  - Of note, asymptomatic overdose has to be reported as a standard AE.
- ALT ≥3 ULN (if baseline ALT <ULN) Or ALT ≥2 times the baseline value (if baseline ALT ≥ULN) (Please refer to related flowchart in Appendix 5 [Section 10.5])

Adverse events requiring specific monitoring

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

The AE requiring specific monitoring for this study are:

- Severe GI events
- Severe hypoglycemia (see Section 8.2.5)
- Pancreatic events (including abnormal values of pancreatic enzymes [see Appendix 6, Section 10.6])
- Calcitonin increase >5.9 pmol/L (20 pg/mL) and thyroid C-cell neoplasm (see Appendix 6, [Section 10.6])
- Acute renal failure (see Appendix 7 [Section 10.7])
- Diabetic retinopathy complications (will be reviewed by an independent ophthalmologist expert, see Appendix 1 [Section 10.1.4.4]); a written report from professional eye care provider will be required
- Severe injection site reactions
- Severe allergic reactions

- Severe immune complex disease

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

AE will be reported by the participant (or, when appropriate, by a caregiver or surrogate).

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

Expedited reporting of AE for primary or secondary endpoint is waived (see Section 8.3.7).

8.3.1 Time period and frequency for collecting AE and SAE information

All SAEs and AEs will be collected from the signing of the ICF until the follow-up visit at the time points specified in the SoA (Section 1.3).

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

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

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

8.3.2 Method of detecting AEs and SAEs

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

8.3.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the pre-specified study end-date, all SAEs, non-serious AEs of special interest (as defined in Section 8.3), and AEs requiring specific monitoring (as defined in Section 8.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Moreover, the ADA levels of subjects tested positive at the end of study associated with severe injection site reaction, or systemic allergic reaction will be monitored adequately over time up to 6 months from the last dose of IMP (see Section 8.8.1).

Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

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

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the follow-up visit.
- The Investigator may perform additional pregnancy tests at their discretion or as required by local regulations.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Pregnancy will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
- In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (See Appendix 4 [Section 10.4])
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Cardiovascular and death events

Cardiovascular and death events that are endpoints for the primary and secondary efficacy analysis will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE (see Section 8.3.7).

8.3.7 Disease-related events and other events not qualifying as AEs or SAEs

This study is designed to ascertain whether the following events (primary and secondary endpoints) are affected by efpeglenatide:

- CV death
- Non-fatal MI
- Non-fatal stroke
- Unstable angina requiring hospitalization
- New onset or progression to macro albuminuria (>300 mg/g) accompanied by a UACR value increase of ≥30% from Baseline
- Sustained ≥40% decrease in eGFR from Baseline (for ≥30 days)
- Chronic dialysis (for ≥90 days)
- Renal transplant
- Sustained eGFR <15 mL/min/1.73 m² (for ≥30 days)

Because these events will be reported and analyzed as efficacy endpoints, they will not be reported according to the standard process for expedited reporting of SAEs even though the event may meet the definition of a SAE. They are waived from expedited regulatory reporting to Health Authorities and they will not be reported to pharmacovigilance except if the Investigator, according to his/her best medical judgment, considers these events as related to the IMP taking into consideration the patient's underlying disease. In that case, the Investigator will report it within 24 hours to the Sponsor. These events will be recorded on the corresponding CRF page in the participant's CRF within the appropriate time frame. An independent CEC will review and adjudicate all events of death, MACE, other selected CV events and other selected AEs. In addition, an independent DMC will collect, track and monitor information regarding the endpoints. The members, roles and responsibilities of the CEC and DMC will be described in a separate charter.

8.3.8 Guidelines for reporting product complaints

Any defect in the IMP/device must be reported as soon as possible by the Investigator to the monitoring team that will complete a Product Complaint Form within required timelines.

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

8.4 TREATMENT OF OVERDOSE

Overdose is defined in Section 8.3.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Blood glucose levels, HR (telemetry) and liver enzymes should be monitored and appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
4. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

Pharmacokinetic parameters are not evaluated in this study.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated in this study.

8.7 GENETICS

Genetics are not evaluated in this study.

8.8 BIOMARKERS

Biomarkers are not evaluated in this study.

8.8.1 Immunogenicity assessments

Antibodies to efpeglenatide will be evaluated in serum samples collected from all participants according to the SoA (see Section 1.3). These samples will be tested by the Sponsor or Sponsor's designee.

Serum samples will be screened for antibodies binding to efpeglenatide and the titer of confirmed positive samples will be reported. Cross-reactivity of confirmed positive samples to endogenous GLP-1 (positive/negative), endogenous glucagon (positive/negative), neutralizing capacity of ADAs, and presence of anti-polyethylene glycol (PEG) antibodies (positive/negative) will also be evaluated in serum.

Participants with positive ADA at the end of study, and who experienced severe injection site or hypersensitivity reaction at whatever time during the study, will be asked to provide a sample for anti-efpeglenatide antibodies assessments 4 and 6 months after the end of the treatment.

The detection and characterization of antibodies to efpeglenatide will be performed using a validated assay method by or under the supervision of the Sponsor.

8.9 HEALTH ECONOMICS

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The statistical hypothesis for the primary endpoint of 3-point MACE is to test that efpeglenatide is noninferior (1.8 and 1.3 margin) to placebo at the two-sided 5% alpha level:

- H0: Hazard ratio of efpeglenatide versus placebo ≥1.8 vs. Ha: Hazard ratio of efpeglenatide versus placebo <1.8

and

- H0: Hazard ratio of efpeglenatide versus placebo ≥1.3 vs. Ha: Hazard ratio of efpeglenatide versus placebo <1.3

9.2 SAMPLE SIZE DETERMINATION

It is estimated that approximately 4000 participants are needed to obtain approximately 330 participants with a positively adjudicated event for the primary composite cardiovascular endpoint (3-point MACE), based on the following trial design characteristics assumptions:

- a recruitment period of approximately 12 months
- Study duration is estimated to be approximately 24 months of follow-up after the last randomized patient, estimated follow-up ranging from 24 to 36 months
- 2% annual early study discontinuation
- Yearly event rate in placebo group: 4.4% for participants not using a SGLT2 inhibitor, and 3.7% for participants using a SGLT2 inhibitor
- Treatment effect of efpeglenatide compared to placebo: 15% risk reduction for participants not using a SGLT2 inhibitor, and a neutral effect for participants using a SGLT2 inhibitor
- 20% of participants using a SGLT2 inhibitor at baseline, and additional 10% participants in placebo group and 5% participants in efpeglenatide group adding a SGLT2 inhibitor during the study period

This will provide:

- 90% power to demonstrate NI of efpeglenatide vs placebo with a 1.3 NI margin {UB of the 95% CI of the estimated hazard ratio <1.3} for the 3-point MACE (CV death, non-fatal MI or non-fatal stroke)
- >99% power to demonstrate NI with a 1.8 margin

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 6):

Table 6 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF
Randomized	All screened participants who have a treatment kit number allocated and recorded in IRT DB, regardless of whether the treatment kit was used or not.
ITT	All randomized participants irrespective of compliance with the study protocol and procedures. Participants will be analyzed in the treatment group to which they are randomized.
Safety	All randomized participants who have received at least 1 dose of double-blind treatment, regardless of the amount of treatment administered. Participants will be analyzed for safety analyses according to the treatment actually received.
ADA	All participants from the safety population with at least 1 post-baseline valid ADA sample after drug administration

ADA: anti-drug antibody; ICF: informed consent form; IRT: interactive response technology; ITT: intent to treat

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before DB lock and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

All efficacy analyses will be performed on the ITT population, unless otherwise specified.

Table 7 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary Time to the first occurrence of any of the following clinical events, positively adjudicated by the CEC: • CV death • Non-fatal MI • Non-fatal stroke	The time to the first occurrence of the primary composite CV endpoint event (CV death, non-fatal MI, or non-fatal stroke) will be analyzed using Cox proportional hazards model with treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo), region and randomization strata of current or potential future use of a SGLT2 inhibitor (Current use, Potential future use, Neither current nor potential future use) as the covariates. Participants who receive either 4 mg or 6 mg of efpeglenatide will be combined as one efpeglenatide treatment group when making comparisons using appropriate contrast for the purposes of the primary analysis. The hazard ratio between pooled efpeglenatide and placebo will be estimated along with the associated two-sided 95%CI. The NI with the 1.8 and 1.3 margin will be demonstrated on the primary endpoint if the UB of the two-sided 95% CI is <1.8 and 1.3, respectively.

Endpoint	Statistical Analysis Methods
	Kaplan-Meier curves of the cumulative incidence rate will also be provided by treatment groups. All participants will be followed up to the Study Closeout Visit or death, whichever comes first. The primary analysis will be based on the ITT approach that includes events occurring from randomization to the end of study, even after the participant has discontinued the study treatment. In the ITT approach, all randomized participants will be included and analyzed as randomized. The analysis will be based on the positively-adjudicated CV endpoint events. Time to the first occurrence of the primary CV event is the time from randomization to the first occurrence of cardiovascular death, non-fatal MI, or non-fatal stroke over the duration of the study (ie, randomization to the study end date inclusive). Participants who have not experienced any of these primary cardiovascular outcomes as positively adjudicated by the CEC during the study will be censored at the last date with available information on the CV outcomes on or before the study end date for the participant. If the NI with the 1.8 and 1.3 margin is demonstrated on the primary endpoint, the superiority of pooled efpeglenatide vs placebo for the primary endpoint will be tested in a hierarchical fashion. The superiority will be claimed if the UB of the 2-sided 95% CI of hazard ratio is less than 1. The p-value using the log-rank test will also be calculated. ***Sensitivity analysis:*** Sensitivity analyses will also be performed for the primary CV endpoint as appropriate, including the analyses that censor the events at the time a participant starts treatment with a SGLT2 inhibitor (for participants who were not receiving an SGLT2 inhibitor at baseline) or stops treatment with a SGLT2 inhibitor (for participants who were already receiving an SGLT2 inhibitor at baseline). ***Assessment of treatment effect by subgroup:*** For the primary composite cardiovascular endpoint, the treatment effects across the following subgroup factors will be examined based on ITT population: • Gender (Male, Female) • Age group (<65 and ≥65 years of age). • Race (White, Black or African American, Asian/Oriental, and Other) (any race groups with fewer than 5 participants may be combined with "Other" category as appropriate). • Ethnicity (Hispanic, Not Hispanic) • Duration of diabetes categories. • Use of SGLT2 inhibitor at baseline (Yes, No) The Cox proportional hazards model will be used to estimate the treatment effect across the above subgroups, with treatment (efpeglenatide 4 mg, efpeglenatide 6 mg, placebo), region, randomization strata of current or potential future use of a SGLT2 inhibitor (Current use, Potential future use, Neither current nor potential future use), subgroup factor, and treatment by subgroup factor interaction as the covariates. Hazard ratios between pooled efpeglenatide and placebo for categories from a subgroup factor in question will be estimated from this Cox model. The corresponding 95% CIs will be provided. Additional subgroups and analysis details will be provided in the statistical analysis plan.

Endpoint	Statistical Analysis Methods
Secondary Time to the first occurrence of any of the following clinical events, positively adjudicated by the CEC: • CV death • Non-fatal MI • Non-fatal stroke • Coronary revascularization • Hospitalization for unstable angina Time to the first occurrence of any of the following clinical events: • New onset or progression to macro albuminuria (>300 mg/g) accompanied by a UACR value increase of ≥30% from Baseline • Sustained ≥40% decrease in eGFR from Baseline (for ≥30 days) • Chronic dialysis (for ≥90 days) • Renal transplant, • Sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)	The two secondary endpoints will be analyzed using the same Cox proportional hazards model as used for the analysis of primary endpoint. The Cox model will include treatment (efpeglenatide 4mg, efpeglenatide 6 mg, placebo), region, and randomization strata of current or potential future use of a SGLT2 inhibitor (Current use, Potential future use, Neither current nor potential future use) as the covariates. The hazard ratio between pooled efpeglenatide and placebo will be estimated along with the associated two-sided 95%CI.
Tertiary/Exploratory	Will be described in the statistical analysis plan finalized before DB lock

9.4.1.1 Multiplicity adjustments

A hierarchical testing procedure will be used for adjustment of multiplicity for the testing of NI and superiority on the primary endpoint and in the analysis of the secondary endpoints to strongly control the overall Type-1 error rate at 0.05, with the hierarchy defined as:

- Non-inferiority (1.8 and 1.3 margin) of efpeglenatide versus placebo on 3-point MACE (CV death, non-fatal MI or non-fatal stroke), and then Superiority of efpeglenatide versus placebo on 3-point MACE (CV death, non-fatal MI or non-fatal stroke)
- Superiority of efpeglenatide versus placebo on time to the first occurrence of the expanded cardiovascular outcome of cardiovascular death, non-fatal MI, non-fatal stroke, coronary revascularization, or unstable angina
- Superiority of efpeglenatide versus placebo on time to the first occurrence of any of the following clinical events: new onset or progression to macro albuminuria (>300 mg/g) accompanied by a UACR value increase of ≥30% from Baseline, sustained ≥40% decrease in eGFR from Baseline (for ≥30 days), chronic dialysis (for ≥90 days) , renal transplant, sustained eGFR <15 mL/min/1.73 m^2 (for ≥30 days)

9.4.2 Safety analyses

All safety analyses will be performed on the Safety Population.

The **observation period of safety data** is divided into 3 main segments:

- The pre-treatment period is defined as the time from informed consent up to the time of the first injection of IMP
- The on-treatment period is defined as the time from the first injection of IMP up to 30 days after the last injection of IMP
- The post-treatment period is defined as the time starting 31 days after the last injection of IMP (after the on-treatment period)

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

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

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

In addition to the on-treatment period, all AEs, SAEs, AEs leading to permanent treatment discontinuation, and AEs leading to death will be summarized for the on-study period, which is defined as the time from randomization up to the day of recorded end of study or last contact.

Table 8 - Safety analyses

Endpoint	Statistical Analysis Methods
AE SAE AE leading to treatment discontinuation AE leading to death AESI AE requiring specific monitoring	All AEs will be coded to a lowest level term (LLT), preferred term (PT), high level term (HLT), and high level group term (HLGT) and associated SOC using the version of MedDRA currently in use by the Sponsor at the time of DB lock. Adverse event incidence tables will be presented by primary SOC (sorted by internationally agreed order), HLGT, HLT and PT (sorted in alphabetical order) for each treatment group, showing the number (n) and percentage (%) of participants experiencing an AE. Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment emergent SAEs, all TEAEs leading to permanent treatment discontinuation, all TEAEs leading to death, all AESI, and AE requiring specific monitoring. Adverse event incidence table for all types of TEAE will also be provided by treatment group in the subsets of participants on the background therapy of metformin + SGLT2, and on metformin + sulfonylurea.
Vital signs and laboratory data	For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from Baseline values by visit and treatment group.
ECG	The incidence of potentially clinically significant abnormalities (PCSA), defined as abnormal values

Endpoint	Statistical Analysis Methods
	considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review, will be summarized at any time during the on-treatment period. Results will be presented both in standard international and conventional US units The incidence of Normal and Abnormal ECG status at any time during the on-treatment period will be summarized by treatment group whatever the Baseline level and according to Baseline status.
Exploratory	Will be described in the statistical analysis plan finalized before DB lock

HLGT: higher-level grouped term; HLT higher-level term; LLT: lower-level term; PT preferred term; SOC: system organ class; TEAE treatment-emergent adverse event

9.4.3 Other analyses

Exploratory analyses will be described in the statistical analysis plan finalized before DB lock.

9.5 INTERIM ANALYSES

There is no interim analysis planned.

9.5.1 Data Monitoring Committee (DMC)

See Appendix 1 (Section 10.1.4) for details.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

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

10.1.1 Regulatory and Ethical Considerations

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

10.1.2 Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and

Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant.

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within the screening window (ie within 1 week of the previous screening).

10.1.3 Data Protection

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- Participants' race and ethnicity (race: Asian, Black or African American, White, Other not reported, Unknown; ethnicity: Hispanic, Not Hispanic) will be collected in this study because these data are required by several regulatory authorities (eg, on African American population for US FDA).
- 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.

10.1.4 Committees Structure

10.1.4.1 Steering Committee

The Steering Committee is responsible for providing study oversight. In this capacity, the Steering Committee shall address and resolve scientific issues encountered during the study. The Steering Committee is also responsible for ensuring accurate reporting of the study results.

10.1.4.2 Data Monitoring Committee

An independent DMC with members who are independent from the Sponsor and the Investigators will meet on a regular basis and will be responsible for:

- Review of accumulating clinical study safety data, and
- Making a recommendation to the Sponsor regarding the study following each meeting

The DMC reviews and analyzes, on a regular basis, unblinded safety data throughout the study, as well as safety data from the other ongoing clinical studies conducted with efpeglenatide (a single DMC for the whole efpeglenatide program). Details describing the DMC processes and procedures are outlined in the DMC Charter. To maintain continuous blinding and study integrity, the analysis will be conducted by an independent statistician who will directly transfer data to DMC members, and measures will be taken to ensure the validity of the data.

10.1.4.3 Clinical Endpoint Committee

An independent CEC will be composed of experts in the field of cardiology, neurology, and gastroenterology (and other appropriate medical specialties as needed). This committee will be independent from the Sponsor and the Investigators, and will be implemented to review, assess and/or adjudicate all events of death, selected CV events (non-fatal MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), pancreatic events and other selected AEs (to be defined in the CEC charter). This review will be conducted in a blinded manner with regard to study treatment.

10.1.4.4 Independent Expert

An independent ophthalmologist expert will review in a treatment-blinded manner all reported AEs suspected to be diabetic retinopathy to assess the presence of retinopathy and the relationship of reported AE to IMP.

Investigators are reminded that all patients should have eye examinations based on their retinopathy status, performed by a professional eye care provider according to International Council of Ophthalmology (ICO) guidelines (19) or local standards. Especially for patients at high risk, this should occur at minimum quarterly.

10.1.5 Dissemination of Clinical Study Data

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

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

publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

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

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

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

10.1.8 Study and Site Closure

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

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

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

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

10.1.9 Publication Policy

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

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

The tests detailed in Table 9 will be performed by the central laboratory.

- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.

Table 9 - Protocol-required safety laboratory assessments

Laboratory assessments	Parameters			
Hematology	Platelet count Red blood cell (RBC) count White blood cell (WBC) count Hemoglobin Hematocrit	RBC indices: Mean Corpuscular Volume (MCV) Mean Corpuscular Hemoglobin (MCH) %Reticulocytes	White blood cell (WBC) count with differential: Neutrophils Lymphocytes Monocytes Eosinophils Basophils	
Clinical chemistry[a]	Uric acid Glucose (non-fasting) Amylase Lipase	Potassium Sodium Calcitonin	Aspartate aminotransferase (AST Alanine aminotransferase (ALT) Alkaline phosphatase	Total bilirubin[b] Creatinine Estimated creatinine clearance
Lipid profile	Triglyceride(non-fasting)	Cholesterol: Total cholesterol Low-density lipoprotein cholesterol High-density lipoprotein cholesterol		
Anti-drug antibodies	• Treatment boosted and treatment induced ADA • ADAs cross-reacting to endogenous glucagon • ADAs directed against the PEG linker of efpeglenatide			
Routine urinalysis	• Specific gravity • pH, glucose, protein, blood, ketones, leukocyte • Microscopic examination (if blood or protein is abnormal)			
Other urinalysis	• Urinary albumin-to-creatinine ratio by spot urine			
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in women of non-childbearing potential only) • Serum human chorionic gonadotropin (HCG) pregnancy test (as needed for women of childbearing potential)[c] • Serology (hepatitis B surface antigen [HBsAg], and hepatitis C virus antibody) The results of each test will be transferred from Central Laboratory in the Clinical Database			

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Appendix 5 (Section 10.5). All events of ALT ≥3 × upper limit of normal (ULN) and bilirubin ≥2 × ULN (>35% direct bilirubin) or ALT ≥3 × ULN and international normalized ratio (INR) >1.5, if INR measured which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

b In case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin

c Urine pregnancy testing will be performed subsequent to Screening. If the urine test is positive, serum β-HCG should be tested for confirmation of the pregnancy

Investigators must document their review of each laboratory safety report.

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

DEFINITION OF AE

AE definition

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant’s condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition.

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen

DEFINITION OF SAE

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

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

a) Results in death

b) Is life-threatening

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

c) Requires inpatient hospitalization or prolongation of existing hospitalization

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

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

d) Results in persistent disability/incapacity

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

e) Is a congenital anomaly/birth defect

f) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize

the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.

Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor's representative in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor's representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor's representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

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

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

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.

- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor's representative. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to** the Sponsor's representative**.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor's representative to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the the Sponsor's representative within 24 hours of receipt of the information.
- Please refer to Section 8.3.3 for more details.

REPORTING OF SAES

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

- The primary mechanism for reporting an SAE to the Sponsor's representative will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE data collection tool (see next section).
- The site will enter the SAE data into the electronic system as soon as it becomes available.

- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor's representative by telephone.
  - Contacts for SAE reporting can be found in a separate study document.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

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

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

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

CONTRACEPTION GUIDANCE

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10 during the treatment period and for at least 5 weeks after the last dose of study treatment.

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

Table 10 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation • Oral[b] • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral[b] • Injectable
Highly effective methods that are user independent[a]
• Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

NOTES:

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b Pharmacokinetic drug interaction potential of oral hormonal contraception with the study treatment is low, but still unknown. Therefore, if the oral contraceptive cannot be replaced by another highly effective method of contraception, with a different route of administration, the hormonal contraception method must be supplemented with a male condom (for partner) during the treatment period and for at least 5 weeks after the last dose of study treatment..

PREGNANCY TESTING:

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

COLLECTION OF PREGNANCY INFORMATION:

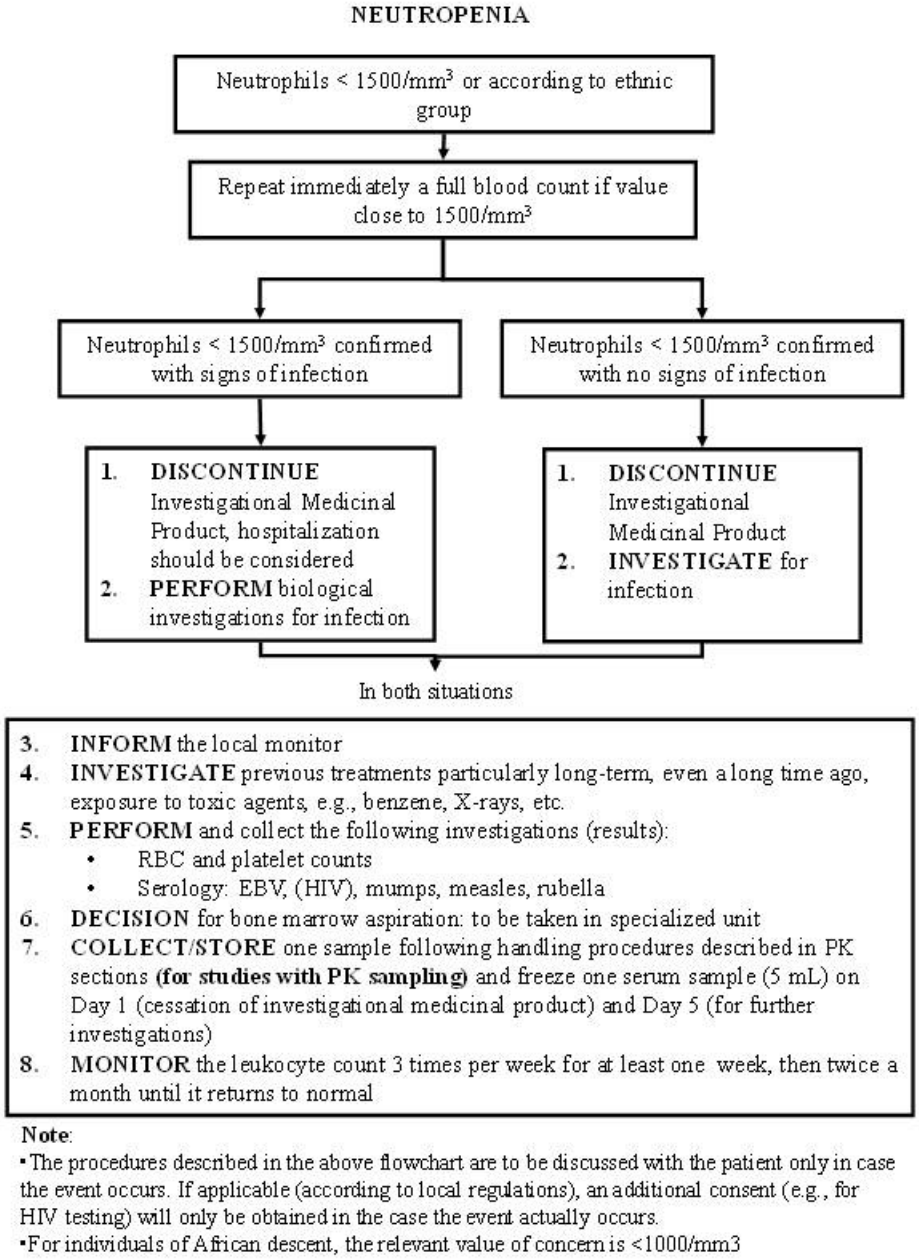
Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive IMP.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be for at least one year following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

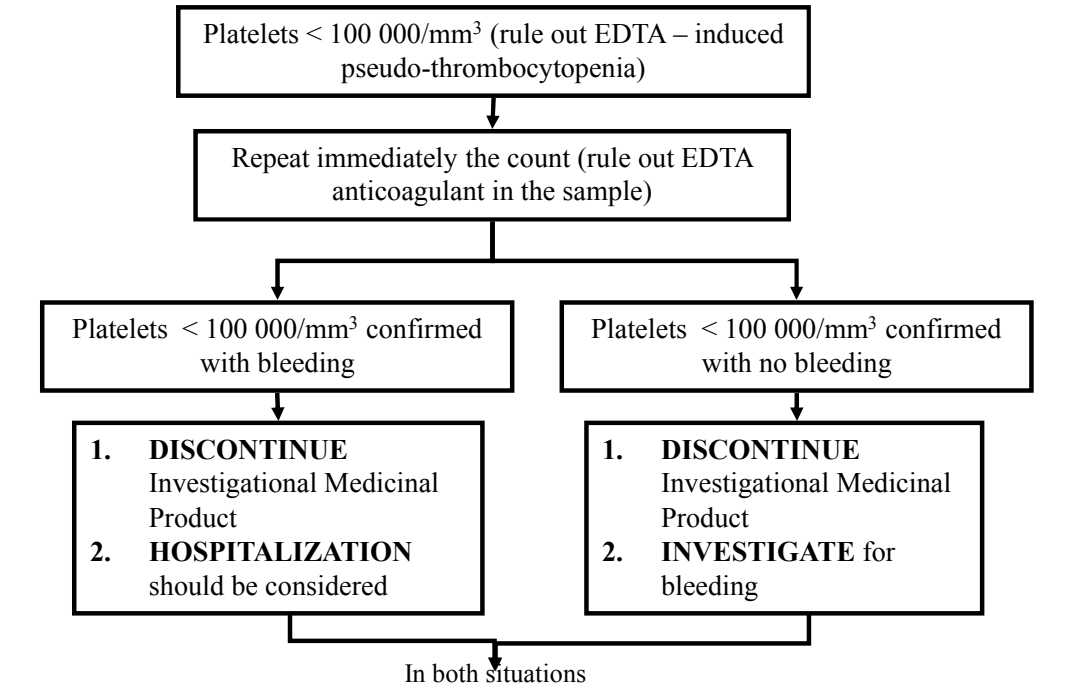
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed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

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



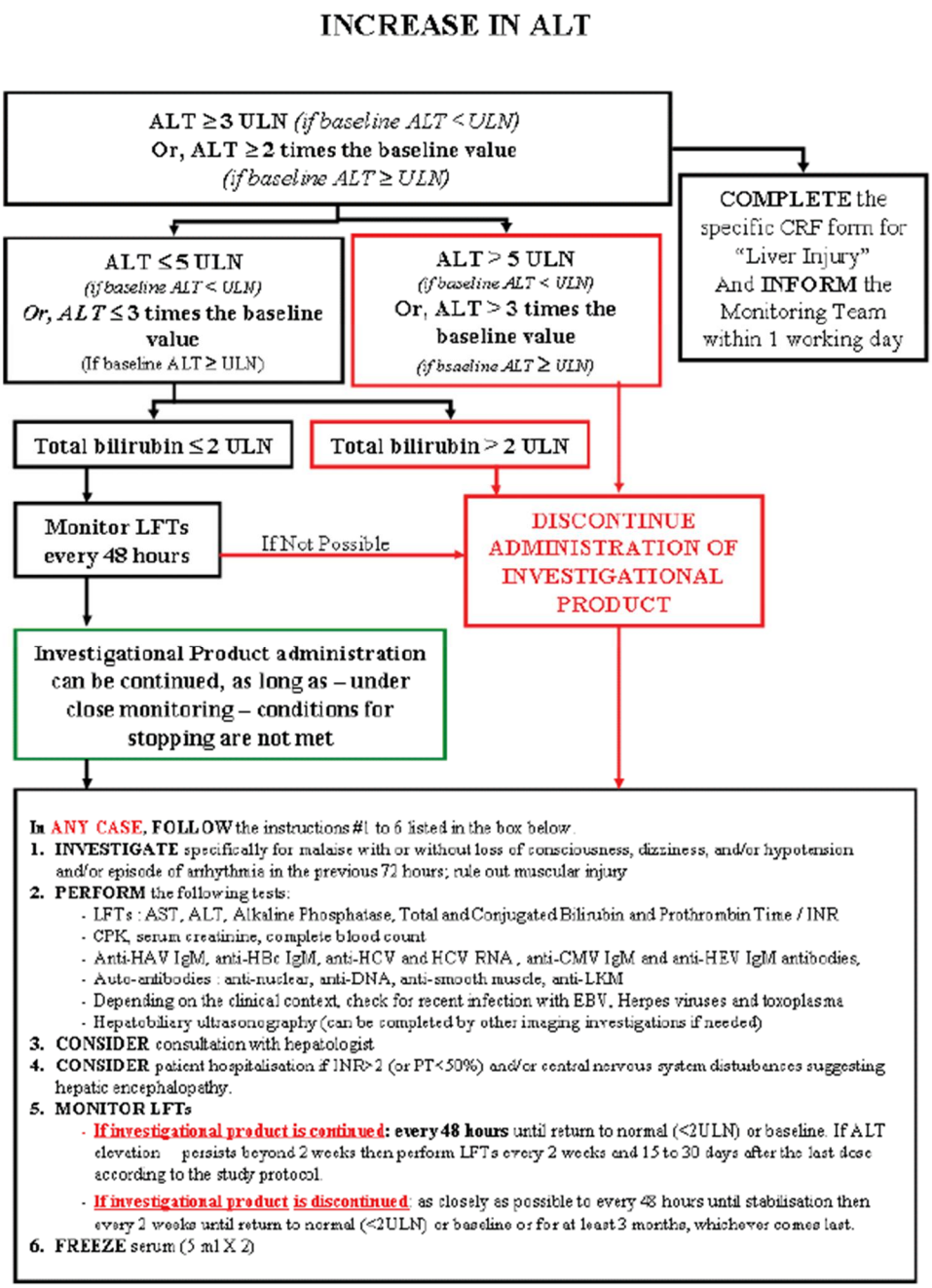
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Appendix 3 (Section 10.3) is met.

THROMBOCYTOPENIA



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

Thrombocytopenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Appendix 3 (Section 10.3) is met.

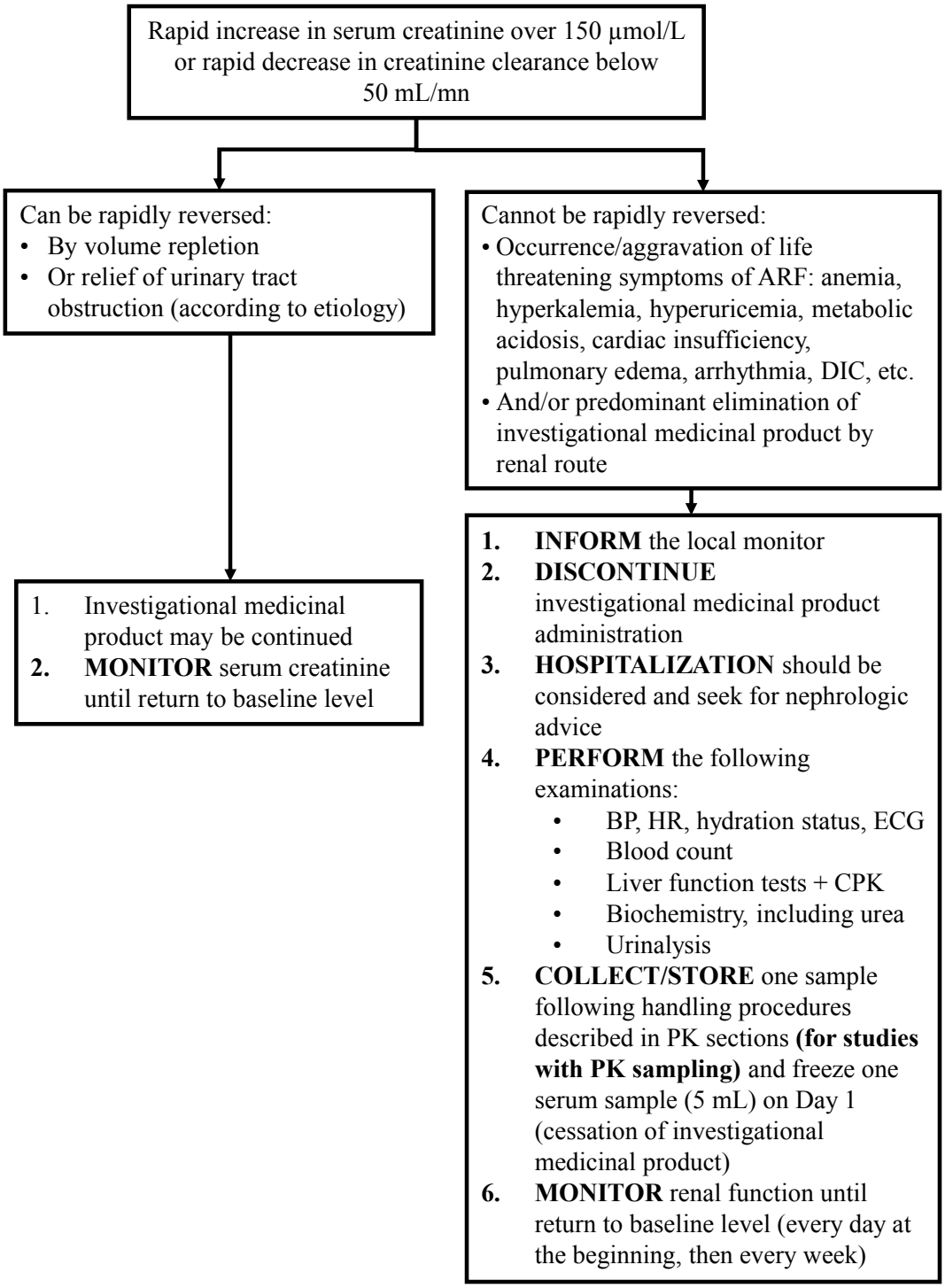


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

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

INCREASE IN SERUM CREATININE

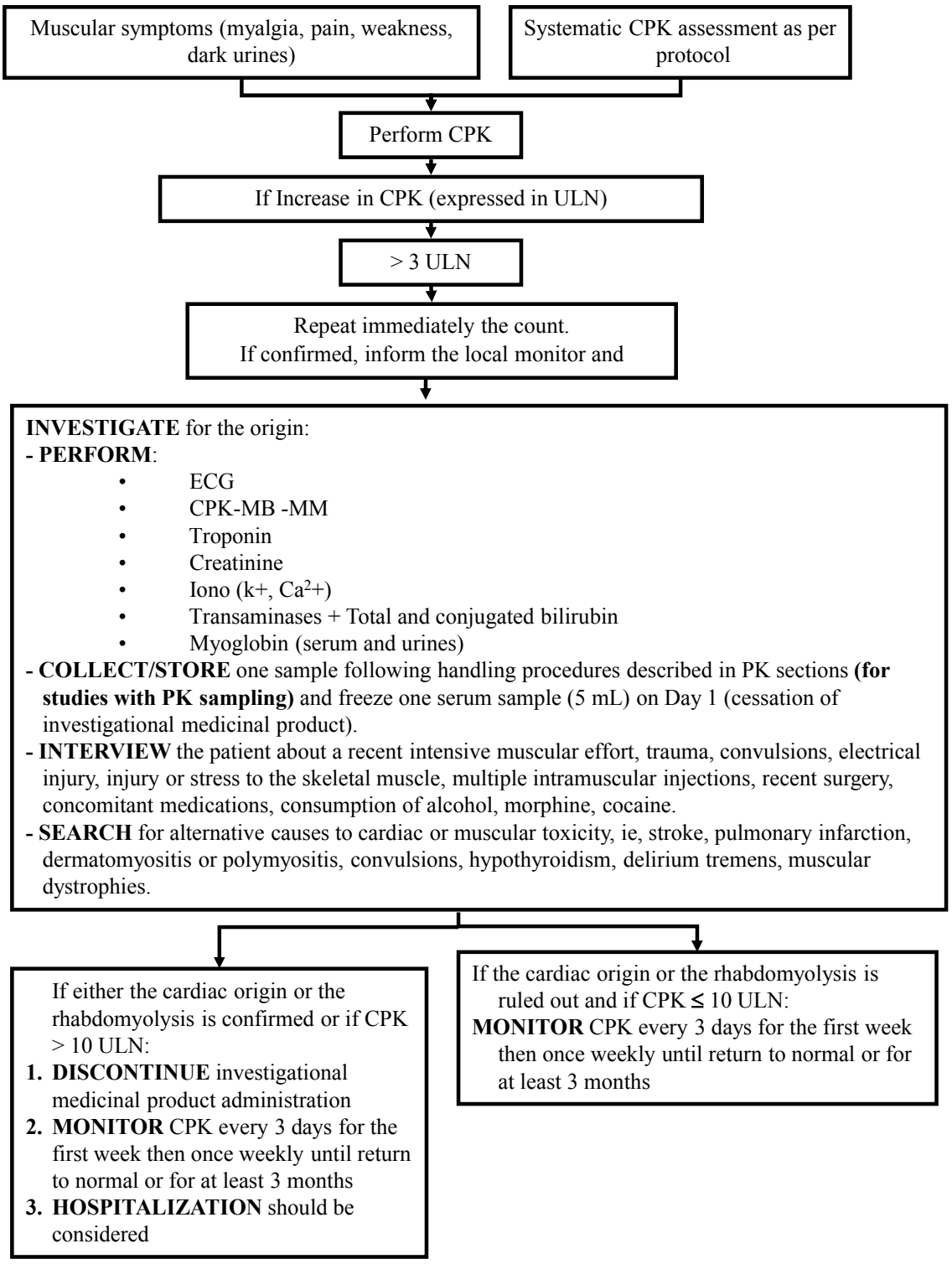


If any of the above conditions are met, the Investigator should take corrective measures to resolve and schedule an interim visit to evaluate the serum creatinine/GFR and the patient's clinical status

1 week from the institution of corrective measures. Patients with a suspected renal event (reduction of eGFR) should have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral.

Increase in serum creatinine is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting adverse events in Appendix 3 (Section 10.3) is met.

INCREASE IN CPK SUSPECTED TO BE OF NON-CARDIAC ORIGIN AND NOT RELATED TO INTENSIVE PHYSICAL ACTIVITY



Increase in CPK is to be recorded as an AE only if at least 1 of the criteria in the general guidelines for reporting adverse events in Appendix 3 (Section 10.3) is met.

10.6 APPENDIX 6: MONITORING AND MANAGEMENT OF PARTICIPANTS WITH INCREASED LIPASE AND/OR AMYLASE, OR CALCITONIN

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

GLP-1 RAs stimulate pancreatic beta-cell and suppress alpha-cell function. Some cases of acute pancreatitis have been reported with marketed GLP-1 RAs. Therefore participants enrolled in this study should be closely monitored 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.

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

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

- If value(s) is/are >2 to 3 x ULN: retest within 7 days,
- If value(s) is/are >3 x ULN: retest within 48 hours,
- If the value(s) remain(s) >2 x ULN upon retesting: amylase and/or lipase levels should be retested weekly until values are <2 x ULN.

In case a retest is >2 x ULN a gastroenterological evaluation and imaging (ultrasound and/or computed tomography [CT] or magnetic resonance imaging [MRI] with contrast, as appropriate) must be performed. The absence of clinical signs and/or symptoms should be documented in the source documents (if clinical signs and/or symptoms develop, please see Section 10.6.3 below).

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

10.6.3 Elevation of amylase and/or lipase >2 x 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 must 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 x ULN, then amylase and/or

lipase levels should be retested as described in Section 10.6.2 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 as clinically indicated and as per clinical practice and local guidelines. If a diagnosis of pancreatitis is confirmed, IMP should not be restarted and should be permanently discontinued. In both cases as described above under (1) and (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 e-CRF on the AE form and the specific complementary forms, 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.

10.6.4 Management of participants with increased calcitonin values

During the course of the study if calcitonin value is found ≥20 pg/mL (5.9 pmol/L):

- A retest should be performed by the central laboratory within 7 days.
- The following is to be collected and recorded as soon as possible:
  - Conditions other than C cell disease which may increase calcitonin levels, such as: smoking status, treatment with proton-pump inhibitor (eg, omeprazole), autoimmune thyroid diseases (Hashimoto's thyroiditis or Grave's disease), differentiated thyroid cancer, hypercalcemia, hypergastrinemia, chronic renal insufficiency (not on dialysis), other neuro-endocrine tumors (lung small cell carcinoma, intestinal carcinoid), acute pulmonary inflammatory conditions, or sepsis
  - Personal and/or familial medical history in relation with thyroid or other endocrine diseases
  - Specific physical examination (neck, thyroid gland)

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

- The event must be reported in the e-CRF on the AE form with all appropriate clinical and laboratory documentations.
- An ultrasound scan of thyroid should be performed and the participant may be referred to a Specialist if judged necessary.
- The participant should continue to be followed according to protocol schedule (including planned calcitonin measurements). The AE form should be updated with any new information collected during the follow up.
- If calcitonin value ≥50 pg/mL (14.75 pmol/L) is found at any time during further follow up, **the participant should be permanently discontinued from IMP** 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. As per

protocol, the participant should be followed according to study procedures up to the scheduled end of the study.

If at any time during follow-up calcitonin value ≥20 pg/mL increases by 20% or more between 2 assessments (while remaining below 50 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 representative should be initiated without delay for further guidance.

10.7 APPENDIX 7: GUIDANCE FOR THE FOLLOW-UP OF ACUTE WORSENING OF RENAL FUNCTION

Rapid change in renal function of greater than 30% as compared with the mean of the prior two study visits

- Evaluate if the patient is taking medications which alter serum creatinine such as: trimethoprim, fenofibrate, non-steroidal anti-inflammatory agents, cimetidine, cephalosporins, probenecid, aminoglycosides, amphotericin, ketoconazole, clofibrate, contrast agents
- Evaluate if any of the following conditions are present that may alter serum creatinine:
  - Significant increase or decrease in BP due to changes in antihypertensive therapy or diuretic treatment
  - Plasma volume depletion or expansion
  - Flu-like symptoms
  - Infected urine
  - Obstructive uropathy
  - New onset or exacerbation of heart failure
- If any of the above conditions are met, the Investigator should take corrective measures to resolve and schedule an interim visit to evaluate the serum creatinine/GFR and the patient's clinical status 1 week from the institution of corrective measures. Patients with a suspected renal event (reduction of eGFR) should have a repeat assessment of renal function 30 to 45 days following the onset of the event to confirm it is sustained. If acute renal failure is suspected, further clinical evaluation should be performed as per local standard of care, including confirmation of renal laboratory parameters, and consideration should be given to a nephrology referral.
- Permanent discontinuation of IMP should be a last resort, and if IMP needs to be withheld, it should be done so temporarily when possible.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.9 APPENDIX 9: ABBREVIATIONS

ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BP:	blood pressure
CABG:	coronary artery bypass graft
CAD:	coronary artery disease
CEC:	clinical endpoint committee
CFR:	Code of Federal Regulations
CI:	confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
CONSORT:	Consolidated Standards of Reporting Trials
CT:	computed tomography
CV:	cardiovascular
CVD:	cardiovascular disease
CVOT:	cardiovascular outcome trial
DB:	database
DBP:	diastolic blood pressure
DMC:	Data Monitoring Committee
DME:	diabetic macular edema
DPP4:	dipeptidyl peptidase-4
ECG:	electrocardiogram
e-CRF:	electronic case report form
eGFR:	estimated glomerular filtration rate
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
FSH:	follicle stimulating hormone
GCP:	good clinical practice
GI:	gastrointestinal
GLP-1:	glucagon-like peptide-1
HbA1c:	glycated hemoglobin A1c
HBsAg:	hepatitis B surface antigen
HCAb:	hepatitis C antibody
HCG:	human chorionic gonadotropin
HDL:	high density liporotein
HHF:	hospitalization for heart failure
HIPAA:	Health Insurance Portability and Accountability Act
HLGT:	high level group term
HLT:	high level term
HR:	heart rate
HRT:	hormonal replacement therapy

IB:	investigator's brochure
ICF:	informed consent form
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	intent-to-treat
IUD:	intrauterine device
IUS:	intrauterine hormone-releasing system
LDL:	low density lipoprotein
LLT:	lowest level term
MACE:	major adverse cardiac events
MCH:	mean corpuscular hemoglobin
MCV:	mean corpuscular volume
MDRD:	modification of diet in renal disease
MI:	myocardial infarction
MRI:	magnetic resonance imaging
MTC:	medullary thyroid cancer
NI:	noninferiority
NOAEL:	no observed adverse effect level
NPDR:	non proliferative diabetic retinopathy
NYHA:	New York Heart Association
PAD:	peripheral arterial disease
PCI:	percutanous coronary intervention
PCSA:	potentially clinically significant abnormalities
PDR:	proliferative diabetic retinopathy
PEG:	polyethylene glycol
pEOT:	premature end of treatment
PFS:	prefilled syringe
PT:	preferred term
QW:	once per week
R:	randomization
RA:	receptor agonist
RBC:	red blood cell
SAE:	serious adverse event
SBP:	systolic blood pressure
SC:	subcutaneous
SGLT2:	sodium-glucose linked transporter-2
SmPC:	summary of product characteristics
SoA:	schedule of activities
SOC:	system organ class
SUSAR:	suspected unexpected serious adverse reaction
T2DM:	type 2 Diabetes Mellitus
TEAE:	treatment-emergent adverse event
UACR:	urinary albumin-creatinine ratio

UB: upper bound
ULN: upper limit of normal
US: United States
WBC: white blood cell
WOCBP: woman of childbearing potential

10.10 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

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

Amended protocol 01 (28 May 2018)

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

OVERALL RATIONALE FOR THE AMENDMENT

Health Authorities' in Canada and Germany requested to update sections related to women of childbearing potential (WOCBP) participation, follow-up, and contraception. In addition, Sanofi uses this opportunity to edit other sections of the protocol, to update text with new available information, to align the procedures with those in other studies within the program and/or for better clarity. Main changes are listed below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria and Section 10.4 Appendix 4 Contraceptive guidance and collection of pregnancy information	Clarification of the contraception requirements for male and woman of childbearing potential (WOCBP): contraception for male participants not required, ova donation restrictions added, change in contraceptive methods to be used for WOCBP, follow-up of pregnancy extended to one year	Efpeglenatide was not genotoxic, and a fertility and early embryonic development study in rats revealed no effect on male and female fertility and mating performance. Furthermore exposure at risk to induce embryo-fetal toxicity in female partners of male subjects taking efpeglenatide after transfer via seminal fluid can be excluded based on an exposure assessment performed according to methods proposed by Banholzer et al. (20) and an FDA guidance of 2015 (21) based on numerous parameters such as exposure at no observed adverse effect level (NOAEL) in embryo-fetal studies in two animal species, cumulated dose administered vaginally and resulting female exposure. Using worst case assumptions for these factors a safety margin of approximately 1800 between exposure at NOAEL in the most sensitive species and estimated exposure in females after contamination with efpeglenatide via seminal fluid was calculated. Therefore use of condoms to avoid this contamination of female partners of male subjects taking efpeglenatide is considered as not required in clinical trials. WOCBP use contraception for the duration of the study and at least 5 weeks after last dose of study treatment, based on the reproductive toxicity profile of efpeglenatide. Since the potential fetal toxicity of efpeglenatide can extend to ova, WOCBP must refrain from donating ova for the duration of the study and at least 5 weeks after last dose of study drug (based on half-life of efpeglenatide). Contraceptive methods in Table 11 were updated based on the clarification that hormonal contraception drug interaction potential with the study treatment is low, but still unknown. Therefore, if the oral contraceptive cannot be replaced by another highly effective method of contraception, with a different route of administration, the hormonal contraception method must be supplemented with a male condom (for partner) during the treatment period and for at least 5 weeks after the last dose of study treatment. The section entitled, “Collection of pregnancy information” the duration of follow- up for the pregnancy was extended to one year to be consistent with the informed consent form (ICF)
Section 8.3.7 Disease-related events and other events not qualifying as AEs or SAEs	Clarification was added on reporting rules for the endpoints when they are considered per Investigators as Investigational Medicinal Product (IMP)-related	To clarify the rules of reporting of IMP-related endpoints to Sponsor

Section # and Name	Description of Change	Brief Rationale
10.3 Appendix 3: Adverse events: definitions and procedures for recording, evaluating, follow-up, and reporting	Lack of efficacy will not be reported as an adverse event (AE) but signs, symptoms and/or sequelae resulting from lack of efficacy will be reported if they fulfil the definition of an AE or serious adverse event (SAE)	Clarification done to comply with the Sponsor's reporting standard
Section 5.1 Inclusion Criteria and Section 5.2 Exclusion Criteria	Clarifications on Inclusion Criterion I03 and Exclusion Criteria E09, E10, E12, and E14: I03. Typo error corrected: 9 cardiovascular disease criteria instead of 8 E09. Exclusion of patients with hypersensitivity to any glucagon-like peptide-1 (GLP-1) receptor agonist (RA) E10. Wording correction, as should state "…within 6 months prior to randomization" rather than "screening" E12. Clarifications added E14. Clarification that prior treatment with GLP1 RAs is not allowed either alone or in combination E17 and E21 were removed	Clarifications for I03 and E10. E09. Clarification added to exclude the hypersensitivity to any GLP-1 RA as well E12 was amended to provide more details and clarify the patients' eligibility criteria. E14 was amended to clarify that GLP-1 RAs either alone or in combination are forbidden as prior treatment. E17 was removed since this cardiovascular outcome trial (CVOT) is not a glycemic control trial: the addition of glucocorticoids will not affect a primary or secondary endpoint and therefore is not needed as an exclusion criterion. E21 was redundant with E24
Section 1.1 Synopsis, Section 3 objectives and Endpoints, and Section 9.4.3 Other Analyses	Change in wording of anti-drug antibody endpoints and removal of percentages from endpoints	To align endpoints' wording within the efpeglenatide program
Section 9.4.2 Safety Analyses	All AEs, SAEs, AEs leading to permanent treatment discontinuation, and AEs leading to death will be summarized for the on-study period	Type of AEs to be summarized during the on-study period, as well as the definition, were clarified
Section 2.3 Benefit/Risk Assessment	Section rearranged for better clarity; diabetic retinopathy complications removed from exceptions to the known adverse events profile of currently marketed GLP-1 RAs	No case of diabetic retinopathy complication has been reported for efpeglenatide

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA) and Section 6.1 Study intervention(s) administered	Allowing the combination of Visit 2 and Visit 3, as per Investigator's judgment according to the patient's medical profile; the minimal time window of 2 weeks between screening visit and randomization has been removed and replaced with a maximum time window of 3 weeks + 3 days	To allow, in some cases and as per investigator's judgment, Visit 2 to be combined with Visit 3; clarification added for time window
Section 6.5 Concomitant Therapy	Dosage information removed from list of information collected for concomitant medications	This information is not collected
	Treatment with GLP1 RAs is not allowed either alone or in combination	To be consistent with E14
	Additional GLP-1 RAs: added lixisenatide, albiglutide and semaglutide to the following sentence for completion: "Any GLP-1 receptor agonist, eg, exenatide, liraglutide, dulaglutide"	Lixisenatide, albiglutide, and semaglutide have been approved by the health authorities
	Other therapy (drugs with a narrow therapeutic window) were added	To harmonize with the Investigator's Brochure
Section 7.3 Lost to Follow Up	Removed that unreachable patients are considered withdrawn from study	In accordance with the Sponsor's management of lost to follow-up patients
Section 1.3 Schedule of Activities (SoA)	Clarification on note related to the ophthalmologic exam with fundoscopy	To clarify that documented ophthalmologic examination with fundoscopy is to be available within 6 months prior to randomization
	Monthly home urine pregnancy tests added	To comply with Clinical Trial Facilitation Group recommendations related to pregnancy testing in clinical trials (22)
Section 10.1.3 Data protection	Text related to participants race and ethnicity collection added	In compliance with privacy regulations and given that these data are collected in the study
Section 8.2.5 Severe hypoglycemia and Section 11 References	New reference on hypoglycemia added	New reference available
Section 6.3 Measures to minimize bias: randomization and blinding	"The bioanalyses will be unblinded" has been deleted	It is already mentioned in the paragraph above that only the Project Manager and lead scientist at Bioanalytical laboratory will have access to randomization code
Section 8.2.4 Clinical safety laboratory assessments	Text on use of local laboratory results has been changed	Rewording done to provide better clarity on recording of local laboratory results

Section # and Name	Description of Change	Brief Rationale
Section 10.2 Appendix 2: Clinical Laboratory Tests	The results of protocol-required safety laboratory assessments (done by the Central laboratory): tests will be transferred from Central Laboratory in the Clinical Database	These results are not entered into the case report form (CRF)
Section 10.1.4.1 Steering Committee	Clarification on role of Steering Committee	Clarification
Section 10.1.4.4. Independent Expert Committee	The word “Committee” was removed from the heading	A single independent expert will review
Throughout	Minor editorial and document formatting revisions	Minor, therefore have not been summarized

11 REFERENCES

1. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes. 2008 Dec.

2. European Medicines Agency, 2015 Committee for Medicinal Products for Human Use (CHMP). Reflection paper on assessment of cardiovascular safety profile of medicinal products. 2016 Feb 25;EMA/CHMP/50549.

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EFC14828 16.1.1 Amendment 02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
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