NCT03353350

AMENDED CLINICAL TRIAL PROTOCOL 03

Protocol title:	**A 56-week, Multicenter, Double-blind, Placebo-controlled, Randomized Study to Evaluate the Efficacy and Safety of Efpeglenatide Once Weekly in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise**
Protocol number:	**EFC14822**
Amendment number:	**03**
Compound number (Trademark/INN):	**SAR439977/efpeglenatide**
Short title:	**Efficacy and Safety of Efpeglenatide Versus Placebo in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise (AMPLITUDE-M)**
Sponsor name:	
Legal registered address:	

Regulatory agency identifying number(s):

EudraCT number:	2016-001857-42
IND number:	112780
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Approval Date: 7-Jun-2018 Total number of pages: 100

Sponsor signatory:

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

Monitoring Team Representative's Name and Contact Information:

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY

Document		Date
Amended protocol 03	Version number: 1 (electronic 3.0)	07 June 2018
Amended protocol 02	Version number: 1 (electronic 2.0)	27 March 2018
Amendment 01[a]	Version number: 1 (electronic 1.0)	16 January 2018
Original Protocol	Version number: 1 (electronic 2.0)	26 September 2017

a Similar to Amended protocols, Amendment 01 contains the full amended text of the protocol plus description of changes versus the previous version of the protocol. The change of the name "amendment" to "amended protocol" is due to process change at the Sponsor company.

AMENDMENT 03 (07 JUNE 2018)

This amendment 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

In response to a BfArM (Germany) request, the protocol was updated to add the rationale for the selected efpeglenatide doses and to add an appendix subsection related to acute kidney failure as a consequence of severe gastrointestinal (GI) events and dehydration. In response to a request from the health authority (HA) in Poland, monthly home urine pregnancy tests have been added.

In addition, Sanofi uses this opportunity to edit other sections of the protocol as listed below, to update text with new available information (including statistical analysis update in response to an FDA request), to align the procedures with those in other studies within the program and/or for better clarity.

Inconsistencies, typographical, and spelling errors throughout the document were also corrected.

Section # and Name	Description of Change	Brief Rationale
Short title Section 1.1 Synopsis	Added study name 'AMPLITUDE-M'	A name was selected for the program and was added to the study title.
Section 1.1 Synopsis, Section 3 Objectives and Endpoints	Wording of tertiary objective (immunogenicity) and secondary objectives and corresponding endpoints of glycemic control, body weight, and safety are modified.	Reworded for clarity, and to harmonize with the other protocols in the program.
	Secondary objective and corresponding secondary endpoints which are not part of multiplicity analysis are deleted from secondary and added under tertiary/exploratory endpoints.	Only key efficacy endpoints included in the hierarchical testing and selected safety endpoints will be considered Secondary Endpoints; all others will be included in Tertiary/exploratory endpoints.
	Deletion of safety endpoints: laboratory variables, vital signs, and 12-lead ECG.	These are safety parameters assessed during the study and will be presented descriptively (detailed in SAP). At program level, it was decided not to consider them endpoints.
Section 1.1 Synopsis, Section 6 Study Interventions administered	Added placebo to IMP dose schedule table.	Placebo arm dosing was missing by mistake from the table.
Section 1.3 Schedule of activities	Minimum duration of screening (V1 to V2 and V2 to V3) has been clarified.	To clarify the minimum period needed between screening and randomization to allow IMP supply (triggered by screening confirmation in IRS).
	Added following text for pregnancy test: at on-site visits and monthly at home in between visits.	To add, at Polish HA request, monthly pregnancy tests to WOCBP included in the study.
Section 4.3 Justification for dose	Modified and provided additional information for dose justification.	To clarify, at BfArM request, rationale for efpeglenatide doses to be evaluated in the study.
Section 5.2 Exclusion criteria	Exclusion criteria E01 modified and added history of surgery affecting gastric emptying. Exclusion criteria E15 modified and added 'clinical study involving any other type of medical research'. Exclusion criteria E16 updated to clarify the exclusion of participants with previous GLP-1RA intolerance.	E01, E15, and E16 were amended to provide more details and clarify the patients' eligibility criteria.

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria Section 10.4 Appendix 4 Contraceptive guidance and collection of pregnancy information	Exclusion criteria E19 deleted details of male contraception. Deleted details of male contraception from Section 10.4 Appendix 4.	Efpeglenatide was not genotoxic, and a fertility and early embryonic development study in rats revealed no effect on male or female fertility and mating performance. Furthermore, risk of embryo-fetal toxicity in female partners of male subjects taking efpeglenatide (via seminal fluid) can be excluded. This is based on an exposure assessment performed according to methods prosed by Banholzer et al. (1) and an FDA guidance of 2015 (2) based on numerous parameters such as exposure at no-observed-adverse-effect level (NOAEL) in embryo-fetal studies in 2 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.
Section 6.3.2 Randomization code breaking during the study	Added following text, '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 closure. Furthermore, when completing forms (eg, AE, SAE, adjudication information), the IMP should not be disclosed on the forms.'	Protocol updated to reflect the actual instructions provided to the sites to ensure blinding preservation at Sponsor/CRO team level, to allow an unbiased analysis of data.
Section 6.5 Concomitant therapy	Added note for insulin use and also added DPP-4 inhibitors (eg, sitagliptin, saxagliptin, vildagliptin, or linagliptin), which are prohibited during the study.	This information was omitted in error from previous version of the protocol. DPP-4 inhibitors are not allowed to be taken during the study as this class is not approved for use in combination with a GLP1 RA. It was also clarified that short-time administration of prandial insulin (for acute illness, surgery etc) is allowed.
	Recommendation for concomitant use of drugs with a narrow therapeutic window was added.	To harmonize with the Investigator's Brochure for efpeglenatide.
Section 8.2.4 Clinical safety laboratory assessment	Modified the text pertaining to local laboratory results which are used to make study treatment decision.	Clarification of the local laboratory results that sites need to report in the eCRF to support medical evaluation of AEs.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis Section 9.4.1 Efficacy analysis	Updated the primary efficacy endpoint analysis method.	Following FDA request, the statistical methodology of the primary efficacy endpoint has been updated.
Section 9.4.1 Efficacy analysis	Added subgroups of duration of diabetes (<10, ≥10 years) and baseline estimated GFR categories (mL/min/1.73 m^2): (<30; [30-60]; >60) for assessment of treatment effect. Prioritized order has been changed for hierarchical testing procedure of secondary endpoints. Added following endpoint in hierarchical testing procedure 'change from baseline to Week 56 in body weight (kg) for efpeglenatide 2 mg versus placebo.'	For project harmonization, subgroups for statistical analysis have been added. Also the order of the secondary endpoints in multiplicity assessment was changed, to prioritize: • At Week 30, testing of body weight for 4mg dose before testing of FPG for 6mg dose and testing of HbA1c <7% for 2mg dose before testing of FPG for 4mg dose. • At Week 56, testing of HbA1c < 7% for 6 mg dose before testing of body weight for 4mg dose.
Section 9.4.1 Efficacy analysis	Added details of tertiary endpoint analysis under separate row.	Updated to follow the change in endpoints explained above (moved from secondary to tertiary endpoints).
Section 9.4.2 Safety analysis	Added the definition of 30-week on-study period. Specifications for hypoglycemia have been added in observation period of safety data.	Following FDA request, the 30 week on study period has been added. Clarification of study period definitions for hypoglycemia.
Section 10.5 Appendix 5 Liver and other safety: suggested actions and follow-up assessments Section 10.6 Appendix 6 Monitoring and management of participants with increased lipase and/or amylase, or calcitonin	All recommended actions regarding selected laboratory abnormalities and AEs were combined under the same section/appendix (Section 10.5 Appendix 5 Liver and other safety: suggested actions and follow-up assessments). A new subsection was added: Section 10.5.4. GI events in relation to acute renal failure Following sections have been also re-numbered. Section 10.6 Appendix 6 has been removed. Subheadings have been re-numbered accordingly.	Section 10.5.4 was added in response to BfArM question. Section was reorganized for better clarity and easy follow-up by the sites.
Section 10.7 Appendix 7 Country-specific requirements	A new section was added: Section 10.7 Country-specific requirements.	To keep the section as per the Sanofi standard format and harmonize with the other studies in the program.
Throughout	Minor editorial, typographical error corrections and document formatting revisions	Minor, therefore have not been summarized.

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title: A 56-week, Multicenter, Double-blind, Placebo-controlled, Randomized Study to Evaluate the Efficacy and Safety of Efpeglenatide Once Weekly in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise

Short title: Efficacy and Safety of Efpeglenatide Versus Placebo in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Diet and Exercise (AMPLITUDE-M)

Rationale:

This study is designed to demonstrate the efficacy and safety of efpeglenatide when used as monotherapy in participants with Type 2 diabetes mellitus (T2DM) who have inadequate glycemic control with diet and exercise. Efpeglenatide will be compared to placebo, consistent with regulatory guidance.

Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, or 6 mg in comparison to placebo in HbA1c change from baseline to Week 30 in participants with T2DM inadequately controlled with diet and exercise.	• Change from baseline to Week 30 in HbA1c
Secondary	
To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on glycemic control.	• Number of participants with HbA1c <7% at Week 30 • Change from baseline to Week 30 in fasting plasma glucose (FPG) • Change from baseline to Week 56 in HbA1c
To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on body weight.	• Change from baseline to Weeks 30 and 56 in body weight
To evaluate the safety of once-weekly injection of efpeglenatide 2, 4, and 6 mg.	• Number of participants with at least one hypoglycemic event during treatment period • Number of hypoglycemic events per participant-year during treatment period • Number of participants with AEs (see Section 8.3)

AE: adverse event; FPG: fasting plasma glucose; HbA1c: hemoglobin A1c; T2DM: type 2 diabetes mellitus.

Overall design:

This study is a Phase 3, multicenter, double-blind, placebo-controlled, randomized, 4-arm, parallel group study in participants with T2DM who have inadequate glycemic control with diet and exercise.

The randomization (1:1:1:1) to efpeglenatide 2 mg, efpeglenatide 4 mg, efpeglenatide 6 mg, or placebo will be stratified by Screening hemoglobin A1c (HbA1c; <8%, ≥8%) and Visit 3 (Baseline, Day 1) body mass index (BMI; <30 kg/m^2, ≥30 kg/m^2).

An independent Data Monitoring Committee (DMC) will review clinical study safety data and an Independent Clinical Endpoint Committee (CEC) will review, assess and/or adjudicate all events of death, selected cardiovascular adverse events (AEs), pancreatic events and other selected AEs (see Appendix 1 [Section 10.1] for further details of study committees).

Number of participants:

Sufficient participants will be screened to achieve 400 randomized participants assigned to study treatment for an estimated total of 100 participants per treatment group. All randomized participants will be included in the population analyzed for efficacy endpoints. Section 9.2 gives details of the sample size determination.

Intervention groups and duration:

The study will comprise 4 periods:

- An up to 3-week Screening Period (with a minimum of 11 days)
- A 30-week double-blind, placebo-controlled Core Treatment Period, for efficacy and safety assessment
- A 26-week double-blind, placebo-controlled Treatment Extension Period; participants will remain on the randomized investigational medicinal product (IMP) regimen
- A 6-week Follow-up Period to collect post-treatment safety information for all participants after last dose of IMP

The maximum study duration per participant will be 65 weeks.

Study interventions

Investigational medicinal product

Efpeglenatide

- Formulation: 500 µL of a sterile, non-pyrogenic, clear, colorless solution in a 1 mL disposable prefilled syringe (PFS)
- Route of administration: subcutaneous (SC)

- Dose regimen: SC injection once-weekly on the same week day (eg, each Monday) at any time of the day

Placebo

- Formulation: matching placebo (sterile, non-pyrogenic, clear, colorless solution in a 1 mL disposable PFS)
- Route of administration: SC
- Dose regimen: once-weekly on the same week day (eg, each Monday) at any time of the day

The dose will be titrated as shown in the table below. From Week 4 (Visit 5) through the rest of the double-blind treatment period, participants will remain on the randomized IMP dose or placebo until the end of treatment (EOT) at Week 56 (Visit 14).

Investigational medicinal product dose schedule

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5 onward
	Day 1 Visit 3	**Week 1**	**Week 2 Visit 4**	**Week 3**	**Week 4 Visit 5**
Dosing	*on-site*	*at home*	*at home*	*at home*	*on-site*
Efpeglenatide 2 mg	2 mg	2 mg	2 mg	2 mg	2 mg
Efpeglenatide 4 mg	2 mg	2 mg	4 mg	4 mg	4 mg
Efpeglenatide 6 mg	2 mg	2 mg	4 mg	4 mg	6 mg
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo

Noninvestigational medicinal products

Rescue therapy

Open-label rescue medication(s) to treat hyperglycemia will be at the discretion of the Investigator and in accordance with local standard of care and prescribing practice. Except for other glucagon-like peptide 1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase 4 (DPP-4) inhibitors, any approved medication(s), including oral antidiabetic drugs or insulin, can be prescribed to treat the hyperglycemia. If a participant requires glycemic rescue, the IMP received during the randomized, double-blind treatment period should continue and must remain blinded until the end of the study (unless the Investigator considers a change necessary for safety reasons). See Section 6.1.2.1 for full details of rescue therapy.

Statistical considerations:

- **Primary analysis:**

The primary efficacy endpoint (change from Baseline to Week 30 in HbA1c) will be analyzed using HbA1c values at Baseline and Week 30 (observed or imputed), regardless of treatment discontinuation or initiation of rescue therapy.

The primary analysis method for the primary efficacy endpoint will be an Analysis of Covariance (ANCOVA) model with missing values imputed by multiple imputation (MI) analysis methods in 2 parts as follows:

- Missing endpoint data in participants who prematurely discontinue the study treatment before the Week 30 visit will be imputed using a model estimated from participants in the same treatment arm who prematurely discontinue the study treatment before the Week 30 visit but have the measurements for the endpoint (retrieved dropouts). Considering that the number of participants in each treatment arm who discontinue the study treatment but have the measurement for the endpoint is expected to be small, a simple imputation model will be used, where only the baseline measurements are included as the predictor. Each treatment group will have their own imputation model. Missing data will be imputed using the regression method.
- Missing endpoint data in all participants, including those in the efpeglenatide arms, who stay on the study treatment until the Week 30 visit will be imputed separately, using a model estimated from participants in the placebo group who stay on the study treatment until the endpoint visit and have the Week 30 data available. The imputation model will include the randomization strata and corresponding baseline values but without including any intermediate values. Missing data will be imputed using the regression method.

In this analysis, missing endpoint values will be imputed 10 000 times to generate 10 000 data sets with complete data. Each of the complete datasets after the imputation will be analyzed by the ANCOVA model with the treatment groups (efpeglenatide 2, 4, or 6 mg, or placebo), randomization stratum of Screening HbA1c (<8%, ≥8%), randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30 kg/m^2, ≥30 kg/m^2), and geographical region as fixed effects, and Baseline HbA1c value as a covariate. The Baseline value is defined as the last available value prior to the first dose administration of IMP or the last available value on or before the date of randomization if not treated with the double-blinded IMP.

The results from the 10 000 analyses will be combined using Rubin's formula to provide the adjusted mean change in HbA1c from Baseline to Week 30 (regardless of treatment discontinuation or initiation of rescue therapy) for each treatment group, as well as the difference between each efpeglenatide dose and placebo and the 95% confidence interval (CI) for the difference.

The number of retrieved dropouts is expected to be small, and may not have sufficient data to support the imputation approach. If there are less than 5 participants in any arm who prematurely discontinue the study treatment before the Week 30 visit but have the measurement for the endpoint, a back-up imputation method for the primary efficacy analysis will be used.

In particular, missing endpoint data in all participants in both efpeglenatide and placebo groups, regardless of staying on the study treatment or not, will be imputed using a model estimated from participants in the placebo group with endpoint data, where randomization strata and baseline HbA1c value are included as the predictors. Missing data will be imputed using the regression method.

Hierarchical procedure will be done to adjust for the multiplicity of comparison. First, the highest dose of efpeglenatide (6 mg) will be compared to placebo. If the superiority is demonstrated, the superiority of 4 mg dose of efpeglenatide versus placebo will be tested. If demonstrated, the lowest dose (2 mg) will be tested. When the superiority is not obtained in a step, the sequential testing procedure will be stopped.

Summary statistics (for Screening value, Baseline value, observed values, and observed changes from Baseline) at scheduled visits will be provided for each treatment group over the whole treatment period including the 26-week Safety Extension Period. The summary will include the number of observations, mean, standard deviation, standard error (SE), minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from Baseline (±SE) at each of the scheduled visits (using observed cases).

- **Analysis of secondary and other efficacy endpoints:**

Continuous secondary efficacy endpoints will be analyzed using the same ANCOVA model with missing values imputed by similar MI method as the one used for the primary efficacy endpoint analysis. Differences between treatment groups and CIs will be estimated by this method. Categorical efficacy endpoints will be analyzed by Cochran-Mantel-Haenszel method stratified by the randomization strata. For the HbA1c <7.0% analysis, participants with missing HbA1c data at Week 30 or Week 56 will be considered non-responders in the ITT population.

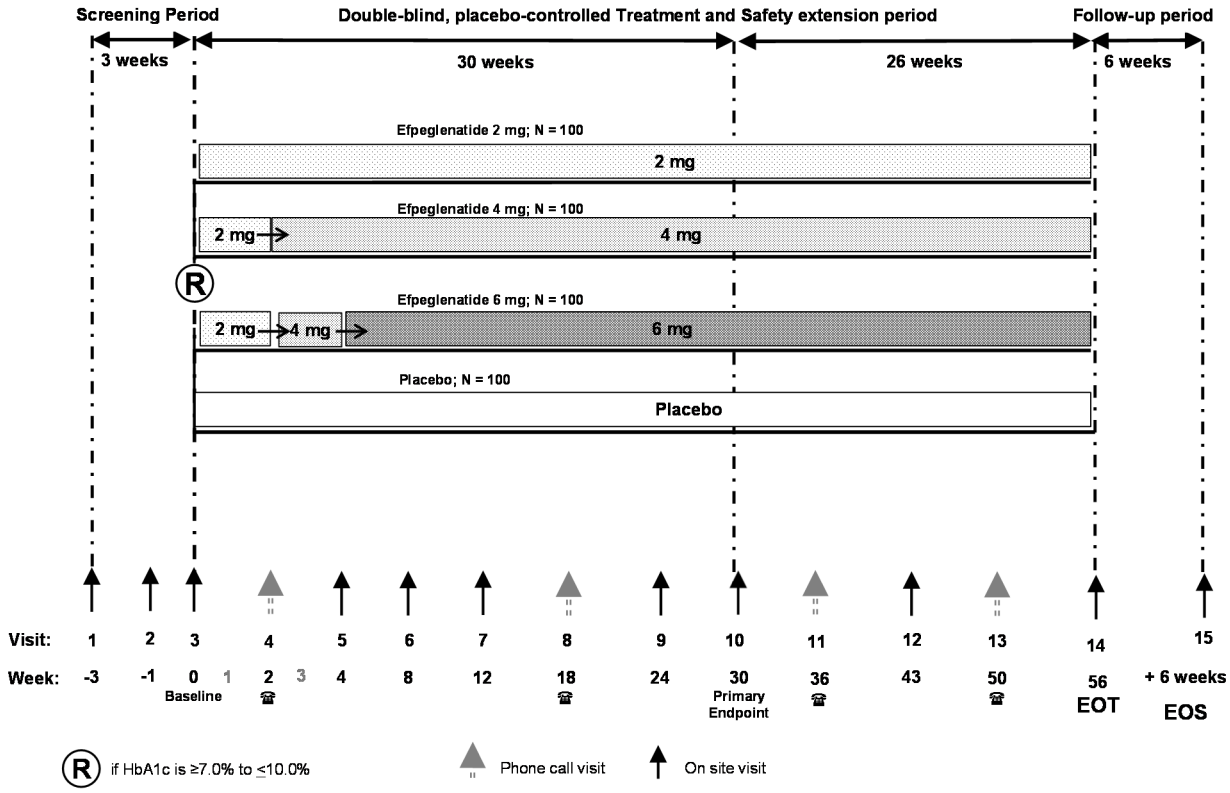
Comparisons of time to event endpoints between treatment groups will be performed using the Cox proportional hazards regression model with the treatment groups (efpeglenatide 2, 4, or 6 mg, placebo), randomization stratum of Screening HbA1c (<8%, ≥8%), randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30 kg/m^2, ≥30 kg/m^2), and geographical region as the factors.

Data Monitoring Committee: Yes

See Appendix 1 (Section 10.1) for details.

1.2 SCHEMA

Figure 1 - Graphical study design



1:1:1:1 randomization, stratified by HbA1c (<8%, ≥8%) and Visit 3 (Baseline, Day 1) BMI (<30 kg/m^2, ≥30 kg/m^2)
Visit schedule: from Visit 1 (Week -3) to Visit 15 (Week 56/EOT + 6 weeks).
BMI body mass index; EOS end of study; EOT end of treatment; N number of patients; R randomization.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
Acceptable range (days)	**-21 (up to)**	**-7 (±3)**	**1**	**14 (3±)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**210 (±3)**	**252 (±5)**	**301 (±5)**	**350 (±5)**	**392 (±5)**	**434 (±7)**	V2 can be done as soon as the Screening eligibility is confirmed and at least 7 days after screening visit (V1). V3 can be done 4 to 10 days after V2. V3 cannot be later than 21 days after V1 (except in case of Holter re-test when an additional 1 week is allowed).
Injection of weekly dose at day of visit			**X**		**X**		**X**		**X**	**X**						Participant will self-administer the injection only after blood samples have been drawn at the respective visit.
Injection of weekly dose may be on a different day than visit				**X**		**X**		**X**			**X**	**X**	**X**	**X**		See Table 2 for details of dosing windows
Informed consent	X															Informed consent taken prior to any study-related procedures being performed.
Inclusion and exclusion criteria	X	X	X													Check eligibility before Visit 2 and before Randomization.
Demography, medical/surgical history	X															Includes diabetes complications, CV and allergy history. Includes alcohol and smoking habits.
Physical examination	X		X		X	X	X		X	X		X		X	X	

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
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Vital signs	X		X		X	X	X		X	X		X		X	X	BP and HR in sitting position after at least 5 minutes of rest.
Height	X															
Body weight	X		X		X	X	X		X	X		X		X	X	
12-lead ECG			X				X			X				X		The 12-lead ECG recording should be obtained in supine position, prior to IMP dose administration
Injection training at Visit 2, retraining as needed; review of injection sites		X	X		X	X	X		X	X		X		X		See Section 6.1
Diary dispensation		X	X		X	X	X		X	X		X		X		
Diary review			X		X	X	X		X	X		X		X	X	
Glucose meter dispensation and training, training for hypoglycemia awareness and management		X														
Diet and lifestyle counseling	X		X		X	X	X		X	X		X		X		As per current practice, to be documented.
IRT contact	X	X	X		X	X	X		X	X		X		X	X	

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
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IMP dispensed		X	X		X	X	X		X	X		X				At Visit 2 placebo training kit(s) will be allocated; self-injection will be done at site.
IMP collection and accounting					X	X	X		X	X		X		X		
Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	SMPG, diary, and IMP.
Efficacy																
HbA1c	X		X				X			X		X		X		
FPG			X			X	X			X		X		X		For these visits, participants need to come in fasting condition as described in Section 5.3.1.
7-point SMPG profiles			X				X			X		X		X		Performed on at least 1 day in the week prior to visits indicated. See Section 8.1.3 for complete details.
Fasting (pre-breakfast) SMPG			X	X	X	X	X	X	X	X	X	X	X	X		Recommended daily, mandatory at least 3 days in the week prior to indicated visits with the study glucometer before breakfast and any intake of antihyperglycemic drug(s).

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
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Safety																
Rescue therapy assessment				X	X	X	X	X	X	X	X	X	X			Assessed by the Investigator after Randomization via fasting SMPG performed by the participants and/or via the central laboratory alerts received on FPG and on HbA1c (at Week 12 onward). See Section 6.1.2.1.
24-hour ECG (Holter) including diary		X								X				X		See Section 8.2.3.2 For 24-hour ECG (Holter) repeat procedure, Randomization may be delayed up to 7 days if needed.
Hematology	X		X				X			X		X		X	X	See Appendix 2 (Section 10.2).
Clinical chemistry	X		X				X			X		X		X	X	See Appendix 2 (Section 10.2).
Calcitonin	X		X				X			X				X	X	See Appendix 2 (Section 10.2).
Lipid profile			X							X				X		See Appendix 2 (Section 10.2).
Urinalysis			X							X				X		See Appendix 2 (Section 10.2).

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
Acceptable range (days)	**-21 (up to)**	**-7 (±3)**	**1**	**14 (3±)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**210 (±3)**	**252 (±5)**	**301 (±5)**	**350 (±5)**	**392 (±5)**	**434 (±7)**	V2 can be done as soon as the Screening eligibility is confirmed and at least 7 days after screening visit (V1). V3 can be done 4 to 10 days after V2. V3 cannot be later than 21 days after V1 (except in case of Holter re-test when an additional 1 week is allowed).
C-peptide (fasting)			X													For this visit, participants need to come in fasting condition as described in Section 5.3.1. See Appendix 2 (Section 10.2).
Pregnancy test (for WOCBP)	X		X		X	X	X		X	X		X		X	X	Serum pregnancy testing (β-HCG) at Screening for WOCBP (Appendix 4 [Section 10.4]), urine pregnancy testing subsequently (at on-site visits and monthly at home in between visits). If the urine test is positive, serum β-HCG should be tested for confirmation of the pregnancy.
Serum FSH and estradiol	X															For women of non-childbearing potential. In case the definition of postmenopausal or premenopausal cannot be satisfied (see Appendix 4, Section 10.4).
Anti-drug antibody sampling			X		X		X			X				X	X	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 sample for anti-efpeglenatide antibodies assessments 4 and 6 months after the end of the treatment.

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
Acceptable range (days)	**-21 (up to)**	**-7 (±3)**	**1**	**14 (3±)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**210 (±3)**	**252 (±5)**	**301 (±5)**	**350 (±5)**	**392 (±5)**	**434 (±7)**	V2 can be done as soon as the Screening eligibility is confirmed and at least 7 days after screening visit (V1). V3 can be done 4 to 10 days after V2. V3 cannot be later than 21 days after V1 (except in case of Holter re-test when an additional 1 week is allowed).
IMP concentration (PK) sampling					X		X		X	X						All participants will have 1 blood sample collected just before their weekly injection of the IMP (and at least 6 days after last dosing of the IMP) at selected clinical visits. For a subset of participants: 1 additional post-dose sample will be taken either 4 days (±1 day) after first IMP dose (Week 1), or 4 days (±1 day) after 4th dose (Week 4), or 4 days (±1 day) after 12th dose (Week 12). A separate consent will be signed. See Section 8.5.
Participant-reported outcomes																
PQATv2										X				X		PQATv2 should be completed by the participant as far as possible at home before on-site visits. See Section 8.1.6

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
Acceptable range (days)	**-21 (up to)**	**-7 (±3)**	**1**	**14 (3±)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**210 (±3)**	**252 (±5)**	**301 (±5)**	**350 (±5)**	**392 (±5)**	**434 (±7)**	V2 can be done as soon as the Screening eligibility is confirmed and at least 7 days after screening visit (V1). V3 can be done 4 to 10 days after V2. V3 cannot be later than 21 days after V1 (except in case of Holter re-test when an additional 1 week is allowed).
AE/SAE recording	Continuous assessment and recording throughout the study															
Concomitant medication review																
Reporting hypoglycemia (symptoms, SMPG)																Hypoglycemia eCRF page must be filled in for all SMPG ≤70 mg/dL (3.9 mmol/L) and/or in case of symptoms suggesting hypoglycemia (between V1 and V2, SMPG values measured with non-study glucometer can be used)

a **In case of premature permanent IMP discontinuation**, participants should have a visit as soon as possible with the assessments normally planned for the EOT visit (Visit 14; except for the 24-hour ECG and the 7-point SMPG, which will be performed as scheduled). These should be performed as soon as possible after last IMP administration. Afterwards, the participants should continue in the study up to the scheduled date of study completion and be followed up according to the study procedures as specified in the protocol (except for PK assessment). Every effort will be made to have participants complete the Visit 10 (Week 30) and Visit 14 (Week 56) assessments (primary and main secondary endpoints) at the minimum. For safety considerations, participants who wish to terminate all participation in the study should be assessed using the procedures normally planned for the post-treatment Follow-up Visit 15 at the minimum. At the time corresponding to their Visit 14 (Week 56), all attempts will be made to contact the participant to inquire about safety/vital status.

ADA: anti-drug antibody; AE: adverse event; BL: Baseline; β-HCG: beta-human chorionic gonadotropin; BP: blood pressure; CV: cardiovascular; ECG: electrocardiogram; e-CRF: electronic Case Report Form; EOS: end of study; EOT: end of treatment; FPG: fasting plasma glucose; FSH: follicle stimulating hormone; HbA1c: hemoglobin A1c; HR: heart rate; IMP: investigational medicinal product; IRT: interactive response technology; PK: pharmacokinetic; PQATv2: Patient Qualitative Assessment of Treatment version 2; R Randomization; SAE: serious adverse event; SMPG: self-monitored plasma glucose; WOCBP: women of childbearing potential.

2 INTRODUCTION

Efpeglenatide is a GLP-1 RA that is being developed for once-weekly treatment of T2DM.

2.1 STUDY RATIONALE

The primary objective of this study is to assess the effect of the different doses of efpeglenatide on glycemic control as measured by the change in HbA1c from Baseline at Week 30, a well-accepted benchmark of overall and longer-term glycemic control. Main secondary objectives include assessing the effect of efpeglenatide on treatment success factors (proportion of participants who achieve HbA1c goals of <7.0%), additional glycemic parameters (FPG, 7-point self-monitored plasma glucose [SMPG] profiles [24-hour profile, mean 24-hour SMPG, average pre-breakfast SMPG, prandial glucose excursions]), proportion of participants requiring rescue therapy, time to initiation of rescue therapy, and on body weight.

2.2 BACKGROUND

Several classes of pharmacological treatments are approved for glucose control in T2DM, but good glycemic control remains challenging for many patients and new therapy options are necessary.

In recent years, the GLP-1 RA class of pharmacotherapy for T2DM has evolved as an effective treatment option from multiple daily over daily to weekly injection. Glucagon-like peptide 1 (GLP-1) is an endogenous enteroendocrine hormone secreted by L-cells of the distal intestine in response to oral nutrient ingestion, 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 their glucose-dependent mechanism of action, GLP-1 RAs are generally associated with a low risk of hypoglycemia.

Efpeglenatide (SAR439977), a GLP-1 RA, is a novel long-acting form of CA exendin-4 (an exendin-4 analogue) that is being developed for the treatment of T2DM by once-weekly SC injection with an auto-injector. In clinical Phase 2 studies, it has shown effects on body weight and may therefore provide potential for development for use in obesity.

In total, 7 clinical studies (two Phase 1 studies and five Phase 2 studies) in approximately 1000 participants, with approximately 720 exposed to efpeglenatide, have been completed. The Phase 2 studies have been conducted in participants with T2DM and in obese non-diabetic individuals. In participants with T2DM, weekly doses between 0.3 to 4 mg or monthly doses between 8 to 16 mg were used, whereas in non-diabetic obese subjects, weekly doses of 4 to 6 mg and doses of 6 and 8 mg every other week were investigated. Overall, these studies have demonstrated that efpeglenatide effect improves glycemic control and reduce body weight, with an overall favorable safety and tolerability profile consistent with currently available GLP-1 RAs. Three weekly efpeglenatide doses (2, 4, or 6 mg) have been selected based on the Phase 1 and 2

study data which suggest that they will demonstrate efficacy in the target population while mitigating potential safety concerns and the incidence of AEs.

Details (nonclinical and clinical) about efpeglenatide can be found in the latest edition of the Investigator's Brochure (IB; 3).

2.3 BENEFIT/RISK ASSESSMENT

The non-clinical toxicological data and the safety data from clinical studies with efpeglenatide to date (with a cut-off date of 22 June 2017) suggest a safety profile consistent with the known AE profile of currently marketed GLP-1 RAs with the exception of potential liver toxicity. The following safety procedures are planned for the clinical study EFC14822:

- Potential AEs common to the GLP-1 RA drug class are mainly GI disorders such as nausea/vomiting and rarely pancreatitis. Thus far, no case of pancreatitis has been identified with efpeglenatide. The trend over time for nausea and vomiting events appeared dose-related with an increase after the first injection, and generally decreasing thereafter within a period of approximately 2 to 4 weeks. It is anticipated that the planned, gradual dose escalation scheme employed in study EFC14822 will reduce intensity and frequency of GI events, mainly such as nausea and vomiting.
- Increase in heart rate (HR) is a known side-effect of GLP-1 RAs. In the current study EFC14822, both periodic monitoring of vital signs including HR and blood pressure (BP) and 24-hour electrocardiogram (ECG) recording (Holter) will be performed to monitor for any effects on HR.
- The GLP-1 RA class has a box warning related to risk of thyroid C-cell tumors in the US label, based on findings in rodents. As the relevance for humans is unclear, GLP-1 RAs are contraindicated in participants with a personal or family history of medullary thyroid cancer (MTC) or in participants with multiple endocrine neoplasia syndrome Type 2 (MEN-2). In EFC14822, calcitonin will be monitored throughout the study, and participants with history of MTC or MEN-2 or with elevated calcitonin levels (≥5.9 pmol/L [20 pg/mL]) at Baseline will be excluded from the study.
- Diabetic retinopathy complications have been reported for one of the GLP-1RAs (as of 05 December 2017). No cases have been reported for efpeglenatide. Participants with a recent or planned retinal treatment for retinopathy or maculopathy will be excluded in the current study. Diabetic retinopathy complications will be monitored throughout the study.
- Additional safety monitoring in study EFC14822 includes the collection of AEs, anti-drug antibodies (ADAs; immunogenicity [4, 5]), as well as safety laboratory and 12-lead ECG.
- In the 3 Phase 2 clinical studies with efpeglenatide (HM-EXC-203, HM-EXC-204, and HM-EXC-205), overall a total of [redacted] out of 571 participants on efpeglenatide and [redacted] out of 183 participants on comparators had post-baseline ALT elevation ≥3 × ULN; most had confounding factors (3). In this study, patients with elevated liver enzymes >3 × upper limit of the normal (ULN) or total bilirubin >1.5 × ULN (except in cases of Gilbert's syndrome) will be excluded from participation. Liver function tests will be done regularly throughout the study.

Efpeglenatide concentrations will also be sampled in study EFC14822. These sparse pharmacokinetic (PK) samples will be used for population PK analyses to determine the PK characteristics of efpeglenatide in the target T2DM population.

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 monitor the glucose-lowering effects and to early detect eventual adverse reactions.

Placebo injections will not contribute to lower the plasma glucose, but the participation in the study may increase participant motivation and result in an improvement of glycemic control. In any case the close monitoring will detect early deterioration of glycemic control and allow initiation of "rescue therapy" as deemed necessary. The HbA1c and FPG tests will be performed approximately every 3 to 4 months. Participants will be provided with a glucose meter and test strips to regularly self-measure their plasma glucose. Glycemic control central laboratory alerts on FPG and on HbA1c (at Week 12 onwards) will be set up to ensure that glycemic parameters remain under predefined rescue thresholds.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of efpeglenatide may be found in the IB (3).

3 OBJECTIVES AND ENDPOINTS

Table 1 - Objectives and endpoints

Objectives	Endpoints
Primary	
To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, or 6 mg in comparison to placebo in HbA1c change from baseline to Week 30 in participants with T2DM inadequately controlled with diet and exercise	• Change from baseline to Week 30 in HbA1c
Secondary	
To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on glycemic control	• Number of participants with HbA1c <7% at Week 30 • Change from baseline to Week 30 in fasting plasma glucose (FPG) • Change from Baseline to Week 56 in HbA1c
To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on body weight	• Change from baseline to Weeks 30 and 56 in body weight
To evaluate the safety of once-weekly injection of efpeglenatide 2, 4, and 6 mg	• Number of participants with at least one hypoglycemic event during treatment period • Number of hypoglycemic events per participant-year during treatment period • Number of participants with AEs (see Section 8.3)
Tertiary/exploratory	
To characterize the PK of efpeglenatide	• Serum C_{trough} of efpeglenatide at pre-dose (Weeks 4, 12, 24, and 30) • Serum concentration of efpeglenatide at post-dose (either 4 days [±1 day] after first IMP dose [Week 1], 4 days [±1 day] after 4th dose [Week 4], or 4 days [±1 day] after 12th dose [Week 12] in a subset of participants, at least 10% of total: [N=12 per group])
To characterize the effect of once-weekly injection of efpeglenatide 2, 4, and 6 mg and placebo on participant perspective on the benefit/risk of treatment	• Participant perspective on benefit/risk of the drug using PQATv2 at Week 30 and Week 56
To compare the effects of once-weekly injection of efpeglenatide 2, 4, and 6 mg with placebo on immunogenicity	• Number of participants by ADA status (positive/negative) at scheduled visits • Number of participants with treatment-induced ADAs (among the participants ADA negative or missing at baseline) during the study period • Number of participants with treatment-boosted ADAs (among the participants with ADA positive at baseline) during the study period • ADA titer at scheduled visits

Objectives	Endpoints
To compare the effects of once-weekly injection of efpeglenatide 2, 4, and 6 mg with placebo on additional measures of glycemic control	• Number of participants by ADA cross-reactivity to endogenous GLP-1 at scheduled visits • Number of participants by ADA cross-reactivity to endogenous glucagon at scheduled visits • Number of participants with ADAs directed against PEG linker of efpeglenatide at scheduled visits • Number of participants with HbA1c <7% at Week 56 • Change from baseline to Week 56 in FPG • Change from baseline to Week 30 and Week 56 in mean 24-hour SMPG (7-point profile) • Change from baseline to Week 30 and Week 56 in plasma glucose excursions (2-hours PPG minus preprandial plasma glucose at breakfast, lunch, and dinner) based on 7-point SMPG data • Number of participants with rescue therapy used until Week 30 and Week 56 • Time to initiation of rescue therapy

ADA anti-drug antibody; AE adverse event; FPG: fasting plasma glucose; GLP-1 glucagon-like peptide 1; HbA1c hemoglobin A1c; PEG polyethylene glycol; PK pharmacokinetics; PQATv2 Patient Qualitative Assessment of Treatment version 2; SMPG self-monitored plasma glucose; T2DM type 2 diabetes mellitus.

3.1 APPROPRIATENESS OF MEASUREMENTS

Efpeglenatide monotherapy in participants with T2DM who have inadequate glycemic control with diet and exercise is expected to lower HbA1c over 30 weeks of treatment (primary efficacy analysis).

The concentration of HbA1c reflects the glycemic history of the previous 120 days and is thus an index of mean glycemia, documenting glycemic control over the past 2 to 3 months. Hemoglobin A1c has also been shown to correlate with the development of long-term complications of diabetes, and reduction of HbA1c is known to reduce the risk of long-term microvascular complications. Therefore, HbA1c is considered an appropriate primary endpoint for assessing the effect of a treatment on glycemic control.

The problem of weight gain in T2DM is widely recognized. More than 80% of individuals with T2DM are overweight, many at the time of diagnosis. Consequently, iatrogenic weight gain is not only unwelcome, but represents an important clinical issue that can become a barrier to the successful management of glycemic control. Therefore, in this study, assessing change in body weight from Baseline to Week 30 and Week 56 is a secondary endpoint.

Improvements in pre-prandial and post-prandial plasma glucose (PPG) have been observed with efpeglenatide in previous studies. Therefore, assessment of both pre-prandial plasma glucose and PPG (by 7-point SMPG profile) is relevant in this study. These 2 parameters are also considered by regulatory agencies to be supportive of efficacy of an antidiabetic agent.

The other efficacy and safety assessments in this study are standard, well-established measurements for a Phase 3 study evaluating the treatment of T2DM in adult participants.

The duration of the study is considered appropriate for enabling an adequate assessment of time dependent changes in HbA1c, and to evaluate the safety profile during the Treatment Extension Period.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The current protocol EFC14822, is a multicenter, 30-week, randomized, double-blind, placebo-controlled Phase 3 study with an additional 26-week controlled Safety Extension Period evaluating the efficacy and safety of efpeglenatide as a monotherapy in participants with inadequately controlled with diet and exercise.

Eligible participants will be randomized to 1 of 3 dose levels of efpeglenatide (2, 4, or 6 mg) or to placebo, to be administered SC once-weekly. Randomization will be stratified by HbA1c at Screening (<8%, ≥8%) and BMI (<30 kg/m^2, ≥30 kg/m^2) at Visit 3 (Baseline, Day 1). Masked weekly dose escalation over the course of 5 weeks will be used to reach the assigned 4 and 6 mg efpeglenatide weekly doses. Escalation will start from 2 mg once-weekly to the maximum of 4 or 6 mg once-weekly, as assigned at Randomization. Participants randomized to the efpeglenatide 2 mg dose arm will also initiate dosing at 2 mg once-weekly and remain on this dose for the treatment duration. In order to blind the treatments, both efpeglenatide and placebo will be provided in volume-matched, PFS.

The study will be comprised of 4 periods as follows:

- An up to 3-week Screening Period (with a minimum of 11 days)
- A 30-week double-blind, placebo-controlled Core Treatment Period, for efficacy and safety assessment
- A 26-week double-blind, placebo-controlled Treatment Extension Period; participants will remain on the randomized IMP regimen
- A 6-week Follow-up Period to collect post-treatment safety information for all participants after last dose of IMP

The maximum study duration per participant will be 65 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed to demonstrate the efficacy and safety of efpeglenatide when used as monotherapy in participants with T2DM who have inadequate glycemic control with diet and exercise. Efpeglenatide will be compared to placebo, consistent with regulatory guidance. Based on the study design, the protocol stipulates that participants can receive antidiabetic rescue therapy according to a predefined algorithm.

A placebo control will be used to allow for an unbiased assessment of treatment effects and safety data. Bias will be minimized by randomizing the participants to treatment groups, blinding the participants, the Investigators, and the Sponsor to the treatment allocations, and by adjudicating the selected AEs in a blinded fashion.

A parallel-group, randomized placebo-controlled design was selected because trial participants are exposed to a single treatment and dose, and assignment to that treatment is based solely on chance. This design is free of the limitations of competing designs such as crossover in which there may be a carryover of effect from the first to the second treatment. Although this carryover effect can be minimized with a washout period, it is possible that some longer-term effects may persist. While the sample size of the parallel group design is larger to account for more variability when participants cannot serve as their own control, the above-mentioned limitations of the crossover design have led the randomized controlled trial design to be the standard for therapeutic confirmatory trials for regulatory approval such as this trial.

4.3 JUSTIFICATION FOR DOSE

The selection of efpeglenatide 2, 4, and 6 mg once-weekly doses is based on the results of early phase studies.

Efpeglenatide has shown increasing efficacy up to the highest dose tested. Both once-weekly 2 mg and 4 mg doses have shown clinically relevant efficacy in study HM-EXC-203. The achieved Hb1Ac reduction indicates that the dose-response plateau has not been reached with the 4 mg dose; this may suggest higher efficacy of the 6 mg dose compared to the 4 mg dose can also be expected for glycemic control in diabetic patients. The once-weekly 6 mg dose tested in non-diabetic subjects in the Phase 2 study (HM-EXC-205) has shown higher efficacy in the decrease of body weight than the once-weekly 4 mg dose in this population.

Nausea and vomiting events appeared to be dose related and the trend over time showed an increase in incidence after the first injection with a general decrease thereafter for all tested doses. Based on the observed general decrease of GI event incidence after the first week of treatment with efpeglenatide, dose increases to achieve the higher doses of 4 and 6 mg (in the corresponding arm) will be in 2 mg step intervals every 2 weeks in order to minimize the GI adverse effects. The escalation step of 2 mg is small enough to contribute to improvement of GI tolerability at dose increase. With this dose escalation schedule, the dose of 4 mg once-weekly will be achieved 2 weeks and the maximal dose of 6 mg once-weekly will be achieved only 4 weeks after the first dose of efpeglenatide.

Please refer to the IB for more details (3).

4.4 END OF STUDY DEFINITION

The end of the study is defined as the date of the last visit of the last participant in the study (as scheduled per protocol or if trial is stopped prematurely based on the advice of the independent DMC or other unforeseen development).

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 type 2 diabetes mellitus (T2DM), and treated with diet and exercise

I 03. Hemoglobin A1c (HbA1c) between 7.0% and 10.0% (inclusive) measured by the central laboratory at Screening

Informed Consent

I 04. 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 not controlled gastroesophageal reflux disease within 6 months prior to Screening or history of surgery affecting gastric emptying

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

E 05. Body weight change of ≥5 kg within the last 3 months prior to Screening

E 06. Systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg at Randomization

E 07. End-stage renal disease as defined by estimated glomerular filtration rate (by Modification of Diet in Renal Disease [MDRD]) of <15 mL/min/1.73 m^2

E 08. Known presence of factors that interfere with the HbA1c measurement (eg, specific hemoglobin variants, hemolytic anemia) compromising the reliability of HbA1c assessment or medical conditions that affect interpretation of HbA1c results (eg, blood transfusion or severe blood loss in the last 3 months prior to Randomization, any condition that shortens erythrocyte survival)

E 09. Any clinically significant abnormality identified either in medical history, during physical examination, laboratory tests, electrocardiogram (ECG), or vital signs at the time of Screening or any adverse event (AE) during the Screening Period which, in the judgment of the Investigator, would preclude safe participation in the study and interpretation of the study results

E 10. Laboratory findings at the Screening Visit:

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3 times the upper limit of normal (ULN) or 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)

Prior/concomitant therapy

E 11. Participants receiving antidiabetic drug treatment within 3 months prior to Screening

E 12. Systemic glucocorticoid therapy (excluding topical, intra-articular, or ophthalmic application, nasal spray or inhaled forms) for more than 10 consecutive days in the last 3 months prior to Screening

E 13. Gastric surgery or other gastric procedures intended for weight loss within 2 years prior to Screening, or planned during study period

Prior/concurrent clinical study experience

E 14. Exposure to any investigational drugs in the last 4 weeks or 5 half-lives, whichever is longer, prior to Screening

E 15. Concomitant enrollment in any other clinical study involving an investigational study treatment or any other type of medical research

Other exclusions

E 16. Hypersensitivity to any of the study treatments, or components thereof, or to any GLP-1 RAs

E 17. History of drug or alcohol abuse within 6 months prior to the time of Screening

E 18. Pregnant (demonstrated by serum pregnancy test at Screening) or breast-feeding women

E 19. Women of childbearing potential (WOCBP) not willing to use highly effective method(s) of birth control (Appendix 4 [Section 10.4]) or who are unwilling to be tested for pregnancy during the study period and for at least 5 weeks after the last dose of study intervention

E 20. 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 21. Any country-related specific regulation that would prevent the participant from entering the study

E 22. Individuals committed to an institution by virtue of an order issued either by the judicial or the administrative authorities

Additional criteria at the end of the Screening Period

E 23. No confirmation of complete recording of the 24-hour ECG performed during Screening Period

E 24. Participants unwilling or unable to comply with study procedures as outlined in the protocol

E 25. Participants who withdraw consent during the Screening Period (starting from signed ICF)

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

Diet and exercise

Lifestyle and diet therapy provided before the time of Screening is to be continued during the study. Individualized dietary and lifestyle counseling will be given by a healthcare professional as per Schedule of Activities (SoA; Section 1.3) and should be consistent with international or local guidelines for participants with T2DM (for example, see 6).

Compliance with the diet and lifestyle counseling will be assessed in case of insufficient glucose control (please refer to Section 5.3).

Fasting conditions

- For Visits 3 (Day 1), 6 (Week 8), 7 (Week 12), 10 (Week 30), 12 (Week 43), and 14 (Week 56), participants need to come to the study center in a fasting condition after an overnight fast of no less than 8 hours that consisted of no food or liquid intake, other than water.
- For fasting (pre-breakfast) SMPG, to be performed per the SoA (Section 1.3).

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomized (randomly assigned to study treatment). 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 serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened once in cases where the original screen failure was due to reasons expected to change at rescreening (based upon the Investigator's clinical judgment). A participant should not be randomized more than once (ie, entering the randomized period twice).

6 STUDY INTERVENTION

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

The IMP includes efpeglenatide in 3 doses (2, 4, and 6 mg) and placebo for SC injection during the 56 weeks of treatment.

Non-IMP (NIMP) treatment is defined as the rescue medication(s) that will be used to treat hyperglycemia if a participant's glycemic values reach the applicable rescue threshold as defined in Section 6.1.2.1. Except for GLP-1 RAs and DPP-4 inhibitors, any approved medication(s), including oral antidiabetic drugs or insulin, can be prescribed at the Investigator's discretion to treat the hyperglycemia. The regimen of the rescue medications will be in accordance with local standard of care and prescribing practice.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 2 - Overview of study interventions administered

Study intervention name	Efpeglenatide	Placebo
Dosage formulation	0.5 mL of a 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 mg/500 µL, 4 mg/500 µL, and 6 mg/500 µL (at 4, 8, and 12 mg/mL concentrations, respectively)	NA
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 injection should be changed (rotated) at each time to prevent skin reactions. The site, date, and time of administration should be recorded for each injection administration. For selected visits during the Core Treatment Period up to Week 30 (corresponding to pre-dose PK sample collection) the weekly dose will be administered at the site after blood sample collection (see SoA, Section 1.3). For the other weekly administrations, if a dose is missed, participants must be instructed to administer the dose as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If less than 3 days remain before the next scheduled dose, participants should skip the missed dose and administer the next dose on the regularly scheduled day. In each case, participants should then resume their regular once-weekly dosing schedule. The day of weekly administration can be changed if necessary as long as the last dose was administered 3 or more days before.	

<table>
<tr><th>Study intervention name</th><td colspan="6">Efpeglenatide Placebo</td></tr>
<tr><td></td><td colspan="6">Pre-dose PK samples are expected to be collected at least 6 to 7 days after the last dose of IMP. The corresponding study visits (Visit 5, Visit 7, Visit 9 and Visit 10) and the timing of previous dose administration should be therefore scheduled to ensure as much as possible this duration.

IMP dose schedule
<table>
<tr><th></th><th>Dose 1</th><th>Dose 2</th><th>Dose 3</th><th>Dose 4</th><th>Dose 5</th></tr>
<tr><th></th><th>Day 1
Visit 3</th><th>Week 1</th><th>Week 2
Visit 4</th><th>Week 3</th><th>Week 4
Visit 5</th></tr>
<tr><th>Dosing</th><td>on-site</td><td>at home</td><td>at home</td><td>at home</td><td>on-site</td></tr>
<tr><th>Efpeglenatide 2 mg</th><td>2 mg</td><td>2 mg</td><td>2 mg</td><td>2 mg</td><td>2 mg</td></tr>
<tr><th>Efpeglenatide 4 mg</th><td>2 mg</td><td>2 mg</td><td>4 mg</td><td>4 mg</td><td>4 mg</td></tr>
<tr><th>Efpeglenatide 6 mg</th><td>2 mg</td><td>2 mg</td><td>4 mg</td><td>4 mg</td><td>6 mg</td></tr>
<tr><th>Placebo</th><td>Placebo</td><td>Placebo</td><td>Placebo</td><td>Placebo</td><td>Placebo</td></tr>
</table>
From Week 4 (Visit 5) through the rest of the double-blind treatment period, participants will remain on the randomized IMP dose or placebo until the EOT at Week 56 (Visit 14).</td></tr>
<tr><td>Storage conditions</td><td colspan="6">Store between +2°C and +8°C (36°F and 46°F). Do not freeze, protect from light.</td></tr>
<tr><td>Packaging and labeling</td><td colspan="6">Study treatment will be provided in different types of kit boxes (open-label training kits, double-blind titration kits and double-blind treatment kits), in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.</td></tr>
</table>

The details of this table are specific to IMP, information of non-IMP is described in Section 6.1.2

EOT: end-of-treatment, IMP investigational medicinal product; NA not applicable; PFS prefilled syringe; PK: pharmacokinetic; SC subcutaneous; SoA: schedule of activities.

6.1.1 Investigational medicinal product(s)

The appropriate number of kits will be dispensed for the period until the next dispensing visit (please refer to SoA 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 (Week -1) 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.

Review of injection technique can be done at any other visit as needed (self-injection with IMP at site during selected visits until Week 30). Review of injection sites will be performed at all on-site visits.

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 study document.

6.1.2 Noninvestigational medicinal products

6.1.2.1 Rescue therapy

Rescue medication(s) that will be used to treat unacceptable hyperglycemia if a participant's glycemia reaches an applicable rescue threshold is considered NIMP for this study. The threshold values are defined as follows in Table 3, dependent on study period.

Table 3 - Rescue criteria

Time in study	Threshold
From Randomization up through the scheduled Week 8 visit (Visit 6)	FPG >15.0 mmol/L (>270 mg/dL)
After the Week 8 visit up through the scheduled Week 12 visit (Visit 7)	FPG >13.3 mmol/L (>240 mg/dL)
After the Week 12 visit (Visit 7) through the end of the 30-week Core Treatment Period	FPG >11.1 mmol/L (>200 mg/dL) **or** HbA1c ≥8.0%
After the Week 30 visit (Visit 10) through the end of the treatment period (Week 56 [Visit 14])	FPG >8.9 mmol/L (>160 mg/dL) **or** HbA1c ≥7.0%

FPG fasting plasma glucose; HbA1c hemoglobin A1c

Routine fasting SMPG and central laboratory alerts on FPG (and HbA1c at Week 12 [Visit 7] onward) are set up to ensure that glycemic parameter results remain below the predefined thresholds.

- If 1 fasting SMPG value exceeds the specific glycemic limit on 1 day, the participant checks it again during the 2 following days. If all the values in 3 consecutive days exceed the specific limit, the participant should contact the Investigator and a central laboratory FPG measurement (and HbA1c at Week 12 [Visit 7] onward) be performed as soon as possible for confirmation
- Upon receipt of a central laboratory rescue alert, a central laboratory re-test must be completed and confirmed as exceeding the threshold for rescue before rescue therapy is initiated. The re-test confirmation should be performed as soon as possible by unscheduled visit

In the event that a confirmatory FPG and/or HbA1c exceed the threshold, the Investigator should ensure that no reasonable explanation exists for insufficient glucose control and in particular that:

- The increased FPG has been tested at a fasted state (ie, no food intake or liquid intake [except water] for ≥8 hours)
- IMP was appropriately injected (as per weekly schedule)
- There was no intercurrent disease, which may jeopardize glycemic control (eg, infectious disease)

- Compliance to treatment was appropriate
- Compliance to diet and lifestyle was appropriate

If any of the above mentioned reasons can reasonably explain the insufficient glycemic control, the Investigator should consider not initiating rescue medication and should undertake appropriate action, ie:

- Assess FPG (ie, after ≥8 hours fast)
- Initiate an evaluation and treatment of intercurrent disease (to be reported in AE/concomitant medication parts of the electronic Case Report Form [e-CRF] and the medical record)
- Stress the absolute need to be compliant with treatment
- Organize a specific interview with the participant and a Registered Dietician or other qualified nutrition professional to reinforce the absolute need to be compliant with diet and lifestyle recommendations, and schedule an FPG/HbA1c assessment at the next visit

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

If a participant needs to start rescue therapy, an unscheduled in-person visit will be scheduled to perform pre-rescue assessments (as specified for EOT; Week 56/Visit 14], except the 7-point SMPG and 24-hour ECG), prior to starting the rescue medication(s).

Prescription of open-label rescue medication(s) to treat hyperglycemia will be at the discretion of the Investigator and in accordance with local standard of care and prescribing practice. With the exception of other GLP-1 RAs and DPP-4 inhibitors, any approved medication(s), including oral antidiabetic drugs or insulin, can be prescribed to treat the hyperglycemia. If a participant requires glycemic rescue, the IMP received during the randomized, double-blind treatment period should continue and must remain blinded until the end of the study (unless the Investigator considers a change necessary for safety reasons).

All rescue medications will be documented in the e-CRF. The cost of rescue therapy not covered by health insurance will be reimbursed by the study Sponsor where permitted by local regulations.

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 IMP received and any discrepancies are reported and resolved before use of the study IMP.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study IMP. All study IMP 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 IMP accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study IMP are provided in 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/NIMP/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/NIMP/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/NIMP/device and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP/NIMP/device to a third party, allow the IMP/NIMP/device to be used other than as directed by this clinical trial protocol, or dispose of IMP/NIMP/device in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

6.3.1 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 and doses included in 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.

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

The Investigator will not have access to the data of the primary efficacy endpoint (ie, HbA1c) or FPG obtained after Baseline/Randomization visit (Visit 3) as those data will be masked. If the central laboratory detects FPG above the rescue thresholds, the Investigator will receive an alert from the central laboratory (see Section 6.1.2.1). The HbA1c alerts will also be sent if a value is above threshold at the Week 12 visit (Visit 7) onwards.

6.3.2 Randomization code breaking during the study

The blind may be broken if, in the opinion of the Investigator, it is in the participant's best interest for the Investigator to know the IMP assignment. The Sponsor must be notified before the blind is broken unless identification of the IMP is required for a medical emergency in which the knowledge of the specific blinded IMP will affect the immediate management of the participant's condition (eg, antidote available). In this case, 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 e-CRF, as applicable.

Code breaking can be performed at any time by using the proper module of the interactive response technology (IRT) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day, and reason for code breaking. If the code is broken by the Investigator, the participant must withdraw from IMP administration. 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 closure. Furthermore, when completing forms (eg, AE, SAE, adjudication information), the IMP should not be disclosed on the forms.

Randomization code breaking will also be performed during the analysis of the PK serum concentration samples and ADA samples in order to enable the laboratory to sort the samples (verum [dose group], placebo) and start analyzing the samples (verum group only) while the study is still ongoing. Only the Project manager and lead scientist at the Bioanalytical laboratory, as well as the population PK analyst, 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 database lock.

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 the following:

- Proper recording of treatment kit number as required on appropriate 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 recorded on the participant diary 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
- For the NIMP not provided by the Sponsor, tracking and reconciliation will be documented in participant's source documents and medication reported in appropriate e-CRF pages

6.4.1 Return and/or destruction of treatments

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the used and unused IMP unless the Sponsor provides written authorization. For NIMP reimbursed by the Sponsor, tracking and reconciliation will be achieved by the Investigator (or the pharmacist, if appropriate) as per local requirements.

Sharp containers containing all used PFS will be brought back to the site by the study participant for the purpose of destruction.

Destruction is strongly encouraged at site level, nevertheless, if the site is not able to destroy or destruction is not allowed in the country, all treatments kits will be retrieved by the Sponsor.

6.5 CONCOMITANT THERAPY

The following treatments are prohibited during the study (including Screening Period and the 56 weeks of treatment):

- Initiation of any antidiabetic agents, including oral or injectable antihyperglycemic agents other than the IMP before pre-rescue assessments and initiation of rescue therapy

  Note: (short-term use [<10 consecutive days] of short-acting insulin for treatment of acute illness or surgery is allowed)
- Initiation of any GLP-1 RAs (eg, exenatide, liraglutide, dulaglutide, or semaglutide) and DPP-4 inhibitors (eg, sitagliptin, saxagliptin, vildagliptin, or linagliptin)
- Initiation of any prescription weight loss drugs (eg, phentermine, lorcaserin, or orlistat)
- Gastric surgery or other gastric procedures for weight loss
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, nasal spray, and inhaled or intra-articular applications are allowed)
- Any investigational drug other than IMP for this study

Glucagon-like petide-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.

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:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

6.6 DOSE MODIFICATION

Up-titration of IMP from Randomization to Week 5 is described in Table 2. From Week 5 throughout the rest of the entire double-blind treatment period, participants will remain on the randomized IMP (efpeglenatide assigned dose or placebo) until the EOT at Week 56.

6.7 INTERVENTION AFTER THE END OF THE STUDY

The IMPs will not be provided after the EOT period.

When a participant's participation in the trial ends, the participant 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 should be distinguished from (additional) withdrawal of consent for follow-up visits and from withdrawal of consent for non-participant contact (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.

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 e-CRF. In any case, the participant should remain in the study as long as possible to collect endpoint data at Week 30 and Week 56 and vital safety status at the scheduled end of study time.

7.1.1 Permanent discontinuation

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. Participants 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: eg, laboratory abnormalities (see decision tree and general guidance for the follow-up of laboratory abnormalities in Appendix 5 [Section 10.5.1]), 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 5 [Section 10.5.2]), or calcitonin value ≥50 pg/mL (see Appendix 5 [Section 10.5.3])
- If, in the Investigator's opinion, continuation with the administration of IMP would be detrimental to the participant’s well-being
- Pregnancy (in female participants)
- Confirmed intolerance to the allocated dose of IMP

- Any code breaking requested by the Investigator
- At the specific request of the Sponsor

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 56 weeks of the study. A high rate of missing data could jeopardize efficacy results of the study. See the SoA (Section 3.1) 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 participants 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, the participants will be assessed using the procedure normally planned for the EOT Visit including a PK sample when the permanent discontinuation occurred during the core treatment period and visit can be scheduled 7 days after the permanent discontinuation of intervention. For participants who discontinue IMP but remain in the study, the remaining visits should occur as scheduled where possible. The Investigators should discuss with them key visits to attend. All efforts should be made to continue to follow the participants for primary and secondary endpoints, after the discontinuation of treatment.

The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study. 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.

7.1.2 Temporary discontinuation

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

All IMP discontinuation should initially be considered as temporary unless permanent discontinuation is mandated by the protocol (see Section 7.1), and the Investigator should make best effort to resume IMP treatment as early as practically possible. There is no defined limit to the duration of temporary discontinuation.

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs (including intolerance to IMP planned dose). For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the e-CRF.

7.1.2.1 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely. In case of IMP intolerance, a one-time re-challenge is recommended following temporary discontinuation before deciding to permanently discontinue the IMP. If a maximum of 2 consecutive doses are missed, the IMP can be restarted with the last dose given. In cases of 3 or more consecutive doses are missed, the titration is highly recommended to be re-initiated to minimize the risk of GI events (especially if the temporary discontinuation was related to a GI event).

Participants who temporarily discontinue IMP should be reassessed at every visit to determine whether it is possible to safely resume IMP. If a decision has been made that the discontinuation is permanent, then the participant should be considered as permanently discontinued and the corresponding e-CRF page should be completed. Please note that permanent discontinuation should be a last resort.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

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

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

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

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

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

Participants who have withdrawn from the study cannot be 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 lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

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

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

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

- 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 before confirming Visit 2 in IRT, to confirm that potential participants meet all eligibility criteria. Eligibility criteria will be evaluated again before randomization, including additional criteria at the end of Screening Period (see Section 5.2). 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.

8.1 EFFICACY ASSESSMENTS

8.1.1 Hemoglobin A1c

The primary efficacy endpoint and 2 secondary efficacy endpoints are assessed by measurement of HbA1c. For the eligibility and efficacy assessments of the study, HbA1c is measured at different time points during study, by a certified level I "National Glycohemoglobin Standardization Program" central laboratory.

If a participant needs to receive rescue antidiabetic medication (see Section 6.1.2.1), assessment of HbA1c should be performed before the introduction of the rescue medication(s).

8.1.2 Fasting plasma glucose

Plasma glucose will be assessed in the fasting state (as defined in Section 5.3.1) according to the schedule detailed in the SoA (Section 1.3). If participant is not fasting at the time of the visit a re-test should be scheduled in fasting status for the next day (or as soon as possible). For the efficacy assessments of the study, FPG is measured at a central laboratory.

8.1.3 7-point self-monitored plasma glucose profiles

The 7-point SMPG will be performed over a single 24-hour period, on at least 1 day within the weeks prior to selected study visits (see SoA, Section 1.3), and must be recorded in the participant diary. Participant should repeat the 7-point SMPG profile if any time point is missed.

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

On days when 7-point profiles are done, fasting pre-breakfast SMPG will be considered as the first point of measurement, ie, "pre-breakfast" time point.

8.1.4 Body weight

Body weight will be measured to allow the estimation of change from Baseline to Weeks 30 and 56 in body weight.

Body weight is measured according to the schedule detailed in the SoA (Section 1.3) with the participant wearing only undergarments or very light clothing and no shoes, and with an empty bladder.

The same scale should be used throughout the study, and calibrated on a regular basis as recommended by the manufacturer. Calibration should be documented in source documents. The use of balance scales is recommended; if digital scales are used, testing with standard weights is of particular importance. The floor surface on which the scale rests must be hard and should not be carpeted or covered with other soft material. The scale should be balanced with both weights at zero and the balance bar aligned. The participant should stand in the center of the platform as standing off-center may affect measurement. The weights are moved until the beam balances (the arrows are aligned). The weight is read and recorded in the e-CRF and source documents. Self-reported weights are not acceptable; participants must not read the scales themselves.

8.1.5 Use of rescue therapy

The use of rescue medications for hyperglycemia will be assessed and reported throughout the treatment period to allow determination of the start of rescue treatment and the percentage of participants using rescue therapy at Weeks 30 and 56. Routine fasting SMPGs will be measured by the participants, and alerts on FPG and/or HbA1c will be sent to the Investigator from the central laboratory to ensure that glycemic parameter results remain within predefined thresholds. For details and further actions should FPG and/or HbA1c values rise above thresholds, refer to Section 6.1.2.1.

8.1.6 Patient Qualitative Assessment of Treatment

The Patient Qualitative Assessment of Treatment version 2 (PQATv2; see Appendix 9; Section 10.9) is intended for the collection of participant-perceived benefit-risk of glucose-lowering treatment with IMP.

This participant qualitative assessment should take between 10 and 20 minutes to complete. The participants will be asked to complete it from home just before the on-site visits planned at Weeks 30 and 56. They will be asked to do it by themselves without any help from friends or relatives. Use of this questionnaire will be limited to participants in countries where PQATv2 is available in the local language.

At the beginning of the Weeks 30 (Visit 10) and 56 (Visit 14) patient visits, Investigators will have to review participant's answers in order to identify any potential AEs reported by participants within the open-ended questions. Investigators will discuss with the participant's potential AEs identified; Investigators will not discuss any other aspects of the answers with the participant, and will not ask participants to change their answers. If AEs that were previously not captured are identified during this process, they should be reported as described in Appendix 3 (Section 10.3).

If a participant discontinues treatment with IMP during the Treatment Period, the participant will be asked to complete the PQATv2 at the time of discontinuation. Even if he/she remains in the study, the participant will not need to complete it again at the following scheduled visits: Week 30 and/or Week 56.

8.2 SAFETY ASSESSMENTS

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

8.2.1 Physical examinations

- A complete physical examination will be performed as per clinical practice in order to assess the health status of the participant at Screening and evaluate the inclusion/exclusion criteria.
- At the following on-site visits, a limited physical examination focused on any affected body area or organ system and other symptomatic or related organ system(s) will be performed.
- Height will be measured at Screening only. If for any reason it was not measured at this visit, it can be measured at any other visit in the study.
- 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 AE.

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 5-minute rest period, and then again after 1 minute in both arms while the participant is in a 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

8.2.3.1 12-lead electrocardiogram

A 12-lead ECG recording will be performed locally as scheduled in SoA (see Section 1.3).

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). The Investigator should review the ECG trace and document the interpretation, sign and date the ECG print out and record it in the e-CRF. Each ECG trace must be compared with the Screening ECG results. All original ECG traces must be 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.

8.2.3.2 24-hour Holter electrocardiogram including diary

Holter ECG will be collected over approximately 24 hours starting on selected visits as presented in the SoA (see Section 1.3). Twenty–four hour average and night time average HR will be derived based on the Holter monitoring.

Instruction and diary for participants' notes while they are wearing the ECG device will be provided by the Investigator.

Holter recordings will be sent to an ECG reading center for further analysis. If the Holter memory cards are to be downloaded to compact discs (CDs)/digital versatile discs (DVDs) at the study site and the CDs/DVDs are then shipped to the reading center, the study site will keep a copy of the CDs/DVDs and will not erase the memory cards until being notified by the reading center to do so (when Holter recordings will be correctly downloaded into the reading center system).
Paper copies of all notifications will be kept as source documents on the study site. The digital recording, data storage, and transmission need to comply with all applicable regulatory requirements (eg, Food and Drug Administration 21 Code of Federal Regulation [CFR] Part 11).

A complete recording is to be confirmed prior to Randomization.

If the Holter ECG needs to be repeated to get a complete evaluation, Randomization may be delayed by up to 7 days.

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 (Section 1.3) for the timing and frequency of sample collection.

- 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 e-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 or Baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA (Section 1.3).
- If local laboratory results are used to make study treatment decision, for response evaluation, or to diagnose/follow-up and AEs, then the results must be recorded in the e-CRF.
- Recommended decision trees for the management of certain laboratory abnormalities are provided in Appendix 5 (Section 10.5.1).

8.2.5 Hypoglycemia

During the study, participants must be instructed to document any hypoglycemic episodes in their study diary. Hypoglycemia will be reported in the specific hypoglycemia event information form in e-CRF with onset date and time, symptoms and/or signs, the SMPG value if available, and the treatment. Hypoglycemia fulfilling the seriousness criteria will be documented in addition on the SAE form in the e-CRF.

Hypoglycemic events will be categorized (7, 8, 9) as follows (also see Appendix 8 [Section 10.8]):

- **Severe hypoglycemia:** Severe hypoglycemia is an event that requires the 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 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.

- **Documented symptomatic hypoglycemia:** Documented symptomatic hypoglycemia is an event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration ≤3.9 mmol/L (≤70 mg/dL). Clinical symptoms that are considered to result from a hypoglycemic episode are, eg, increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma

- **Asymptomatic hypoglycemia:** Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration ≤3.9 mmol/L (≤70 mg/dL)

- **Probable symptomatic hypoglycemia:** Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration ≤3.9 mmol/L (≤70 mg/dL); symptoms treated with oral carbohydrate

- **Relative hypoglycemia:** (recently termed "pseudo-hypoglycemia") is an event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration >3.9 mmol/L (>70 mg/dL)

In addition to the threshold of plasma glucose of ≤3.9 mmol/L (≤70 mg/dL), documented hypoglycemia with a measured plasma glucose concentration < 3.0 mmol/L (<54 mg/dL) will also be analyzed (9).

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

In addition, hypoglycemia events will be evaluated at the following time periods defined by time of the day:

- **Nocturnal hypoglycemia defined by time of the day:** any hypoglycemia of the above categories that occurs between 00:00 and 05:59, regardless of whether the participant was awake or woke up because of the event
- **Daytime hypoglycemia:** any hypoglycemia of the above categories that occurs between 06:00 and 23:59

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An adverse event of special interest (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. The classification of AESI may be changed during the study by protocol amendment (eg, further AE classified as AESI, or AE losing their AESI status).

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP/NIMP (see Section 8.3.5);
  - In the event of pregnancy in a female participant, IMP should be discontinued.
- Symptomatic overdose (serious or nonserious) with IMP/NIMP;
  - 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 (eg, two or more injections) if given within 3 days (72 hours)
  - An overdose (accidental or intentional) with the NIMP is an event suspected by the Investigator or spontaneously notified by the participant and defined as at least twice the recommended dose during the planned interval(s)
  - Of note, asymptomatic overdose has to be reported as a standard AE
- Increase in ALT >3 × ULN (see Appendix 5 [Section 10.5])

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

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

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

Adverse events requiring specific monitoring

An AE requiring specific monitoring is a serious or 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 AEs 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 5, Section 10.5.2] pancreatitis, and pancreatic neoplasm) – will be adjudicated by CEC
- Major adverse cardiovascular events (MACE; cardiovascular (CV) death, myocardial infarction (MI), or stroke) and other specific CV events (eg, heart failure leading to hospitalization) – will be adjudicated by CEC
- Calcitonin increase >5.9 pmol/L (20 pg/mL) and thyroid C-cell neoplasm (see Appendix 5, [Section 10.5.3])
- Acute renal failure (see Appendix 5 [Section 10.5.4] for definition)
- Diabetic retinopathy complications (will be reviewed by an independent ophthalmologist expert; see Appendix 1 [Section 10.1.4.3]); a written report from professional eye care provider will be required
- Severe injection site reaction
- Severe allergic reactions
- Severe immune complex disease

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs, SAEs, AESIs, and AEs requiring specific monitoring will be collected from the date of signing the ICF until the end of the study as defined by the protocol for that participant, at the time points specified in the SoA (Section 1.3).

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 AEs and SAEs 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. All SAEs, non-serious AESIs, and AEs requiring specific monitoring (as defined in Appendix 3 [Section 10.3]), 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). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

The following are requirements for reporting of SAEs:

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing an 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 (Visit 15).
- 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).
- In the event of pregnancy in a female participant, IMP should be discontinued.
- A pregnancy will be qualified as an SAE only if it fulfills 1 of the seriousness criteria (see Appendix 3 [Section 10.3]).
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Cardiovascular and death events

For cardiovascular events, see Section 8.3.

8.3.7 Disease-related events and/or disease-related outcomes not qualifying as AEs or SAEs

Not applicable.

8.3.8 Guidelines for reporting product complaints/medical device incidents (including malfunctions)

Any defect in the IMP/NIMP/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

The Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.
3. 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

- Blood samples will be collected for measurement of serum concentrations of efpeglenatide as specified in the SoA (see Section 1.3). Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded along with the date, time, and site (abdomen) of drug administration. Samples not collected, missed or lost, for any reason should be recorded
- For a subset of participants, 10% of total (N=12 per group): 1 additional post-dose sample will be taken either 4 days (±1 day) after 1st IMP dose (Week 1), or 4 days (±1 day) after 4th dose (Week 4), or 4 days (±1 day) after 12th dose (Week 12). To reach this number and due to the blind design of the study, PK post-dose sample will be collected in the first 80 randomized participants who will accept this additional sampling, sign the separate section of the main consent form and provide a valid post-dose sample
- The collected blood samples will be used to determine concentration of efpeglenatide in serum and these concentration data will be summarized and reported in the CSR
- The concentrations data will be used to perform a population PK analysis by non-linear mixed effects modeling and the results will be reported in a separate population PK report
- Samples collected for analyses of efpeglenatide serum concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study if warranted upon agreement with the Sponsor

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel.

8.6 PHARMACODYNAMICS

Pharmacodynamic parameters are not evaluated as a part of 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

Blood samples are taken to assess the ADA status (positive/negative) and level (titer). 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 at the time points specified in the SoA (Section 1.3).

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 sample for anti-efpeglenatide antibodies assessments 4 and 6 months after the end of the treatment.

8.9 HEALTH ECONOMICS

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

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

For the primary efficacy variable of change from Baseline to Week 30 in HbA1c, the following statistical null hypothesis and alternative will be tested for each efpeglenatide dose:

- H0: No treatment difference
- H1: efpeglenatide has a higher reduction in HbA1c from Baseline than placebo

Based on data from previous Phase 1 and 2 studies and modeling, a minimum treatment effect difference of -0.6% in HbA1c change from Baseline to Week 30 was considered as reasonable for this study.

9.2 SAMPLE SIZE DETERMINATION

The sample size calculations are performed based on the primary endpoint, change in HbA1c (%) from Baseline to Week 30.

A sample size of approximately 100 participants per arm (ie, 100 participants for each of the efpeglenatide doses and 100 for the placebo group) has 89% (96%) power to detect a treatment difference of -0.5% (-0.6%) between each dose of efpeglenatide and placebo in HbA1c change from Baseline to Week 30, assuming a common standard deviation of 1.1% (2-sided, α=0.05) for each comparison.

Hence, there are 4 parallel dosing arms:

- Efpeglenatide 2 mg, N=100
- Efpeglenatide 4 mg, N=100
- Efpeglenatide 6 mg, N=100
- Efpeglenatide placebo, N=100

Hierarchical procedure will be done to adjust the multiplicity of comparison.

9.3 POPULATIONS FOR ANALYSES

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

Table 4 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF.
Randomized	All screened participants who have a treatment kit number allocated and recorded in in IRT database, regardless of whether the treatment kit was used or not.
ITT	All randomized participants irrespective of rescue therapy use and compliance with the study protocol and procedures. Participants will be analyzed in the treatment group to which they are randomized.
Safety	All participants randomly assigned to IMP and who take at least 1 dose of IMP. Participants will be analyzed according to the treatment they actually received.
ADA	All participants from the safety population with at least 1 post-Baseline valid ADA sample after drug administration
PK	All participants from the safety population with at least 1 valid PK sample available for analysis.

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

9.4 STATISTICAL ANALYSES

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

9.4.1 Efficacy analyses

Table 5 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary	Primary analysis:
Change in HbA1c from Baseline to Week 30	The primary efficacy endpoint will be analyzed using all HbA1c values at Baseline and Week 30 (observed or imputed), regardless of treatment discontinuation or initiation of rescue therapy (ITT estimand). The primary analysis method for the primary efficacy endpoint will be an ANCOVA model with missing values imputed by MI analysis method in two parts as follows: • Missing endpoint data in participants who prematurely discontinue the study treatment before the Week 30 visit will be imputed using a model estimated from participants in the same treatment arm who prematurely discontinue the study treatment before the Week 30 visit but have the measurement for the endpoint (retrieved dropouts). Considering that the number of participants in each treatment arm who discontinue the study treatment but have the measurement for the endpoint is expected to be small, a simple imputation model will be used, where only the baseline measurements are included as the predictor. Each treatment group will have their own imputation model. Missing data will be imputed using the regression method. • Missing endpoint data in all participants, including those in the efpeglenatide arms, who stay on the study treatment until the Week 30 visit will be imputed separately, using a model estimated from participants in the placebo group who stay on the study treatment until the Week 30 visit and have the endpoint data available. The imputation model will include the randomization strata and corresponding baseline values without including any intermediate. Missing data will be imputed using the regression method. In this analysis, missing endpoint values will be imputed 10 000 times to generate 10 000 data sets with complete data. The completed data sets will be analyzed using an ANCOVA model with treatment groups, randomization strata, and geographical regions as fixed effects and the corresponding baseline values as a covariate. The Baseline value is defined as the last available value prior to the first dose administration of IMP or the last available value on or before the date of Randomization if not treated with the double-blinded IMP. The results from the 10 000 analyses will be combined using Rubin's formula and provide the adjusted mean change in HbA1c from Baseline to Week 30 (regardless of treatment discontinuation or initiation of rescue therapy) for each treatment group, as well as the difference between each efpeglenatide dose and placebo and the 95% CI for the difference. A hierarchical procedure will be applied to adjust for the multiplicity of comparison on the primary endpoint: • First, the highest dose of efpeglenatide (6 mg) will be compared to placebo to demonstrate superiority of this dose versus placebo • If superiority is demonstrated for efpeglenatide 6 mg, the superiority of 4 mg dose of efpeglenatide versus placebo will be tested • If superiority is also demonstrated for 4 mg dose, the lowest dose (2 mg) will be tested for superiority over placebo When the superiority is not obtained in a step, the sequential testing procedure will be stopped. As noted, the number of retrieved dropouts is expected to be small, and may not have sufficient data to support the imputation approach in item 1 described above. If there are less than 5 participants in any arms who prematurely discontinue the study treatment before the Week 30 visit but have the measurement for the endpoint, a back-up imputation method for the primary efficacy analysis will be used. In particular, missing endpoint data in all participants in both

Endpoint	Statistical Analysis Methods

efpeglenatide and placebo groups, regardless of staying on the study treatment or not, will be imputed using a model estimated from participants in the placebo group with endpoint data, where randomization strata and corresponding baseline values are included as the predictors. Missing data will be imputed using the regression method.

Sensitivity analysis:

Tipping point analysis based on the same MI method as described above will be performed to examine the robustness of the results from the primary analysis. A penalty δ will be added to participants in efpeglenatide groups (2, 4, or 6 mg) who have no HbA1c data at Week 30. The penalty will be gradually increased to evaluate at which level the conclusion of the analyses in terms of statistical significance is changed for each efpeglenatide dose group. The tipping point is the penalty level, at which the magnitude of efficacy reduction in participants without HbA1c data at Week 30 creates a shift in the treatment effect of efpeglenatide from being statistically significantly better than placebo to a non-statistically significant effect. The penalty δ will start at 0 and increase by 0.01 at each imputation until non-statistically significance is found. Least square mean difference between each efpeglenatide dose and placebo and its associated p-value will be provided for each penalty level.

The primary endpoint will be assessed too by an ANCOVA model with missing values imputed by Control-based MI method (copy to reference) under the MNAR framework in the ITT population. Data will be imputed 10 000 times.

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

In particular, a 2-step approach will be used:

- **Step 1:** Use the Markov Chain Monte Carlo method conjunction with the IMPUTE=MONOTONE option in PROC MI to create an imputed data set with a monotone missing pattern
- **Step 2:** Based on the MONOTONE data sets obtained from Step 1, build the imputation model using the regression method on data from the placebo group, and use the built model conditional on the participant's previous observed data to impute the missing data in both placebo and efpeglenatide groups. The imputation model will include the randomization stratum of HbA1c value at Screening (<8%, ≥ 8%), and the randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30 kg/m^2, ≥30 kg/m^2). This will be implemented using MNAR statement in PROC MI

Each of the complete datasets after the imputation will be analyzed using the same ANCOVA model as used for the primary analysis. Results from each complete dataset will be combined using Rubin's formula.

Descriptive analyses will be conducted to explore missing data patterns for HbA1c in the primary efficacy analysis, with number and percentage of participants in each of the following categories presented by treatment group.

- Pattern 1: participants without Baseline if any
- Pattern 2: participants with Baseline but without post-Baseline value during the 30-week Core Treatment Period
- Pattern 3: participants with Baseline and at least 1 post-Baseline value during the 30-week Core Treatment Period but not at Week 30
- Pattern 4: participants with Baseline and Week 30 value during the 30-week Core Treatment Period

HbA1c values by visit will be presented by missing data pattern for each treatment group, using descriptive statistics and/or graphs

Endpoint	Statistical Analysis Methods
	Assessment of treatment effect by subgroup: Primary efficacy endpoint will be further analyzed to examine the consistency of the treatment effect across the subgroups defined by the following Baseline covariates: • Race (White, Black or African American, Asian, Other) (any race groups with fewer than 5 participants may be combined with "Other" category as appropriate) • Ethnicity (Hispanic, Not Hispanic) • Age group (<50, ≥50 to <65, ≥65 years) (any category with fewer than 5 participants may be combined with another category as appropriate) • Gender (Male, Female) • Duration of diabetes (<10, ≥10 years) • Baseline HbA1c (<8.0%, ≥8.0%) • Baseline BMI (<30 kg/m^2, ≥30 kg/m^2) • Country • United States/non-United States • Baseline estimated GFR categories (mL/min/1.73m^2): (<30; [30-60]; ≥60) The treatment effects (efpeglenatide 2, 4, or 6 mg, versus placebo) across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 30 in HbA1c in the ITT population, and using a similar approach as applied to the analysis for the primary efficacy endpoint. The ANCOVA model will include treatment groups (efpeglenatide 2, 4, or 6 mg, placebo) and randomization stratum of Screening HbA1c (<8%, ≥8%), randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30 kg/m^2, ≥30 kg/m^2), subgroup factor, treatment-by-subgroup factor, and region as fixed factors and using Baseline HbA1c value as a covariate. The adjusted estimates of treatment mean differences (each efpeglenatide dose versus placebo) with SE and 95% CIs will be provided as appropriate across the subgroups. A graphical presentation of the results (ie, forest plot) will also be provided. In the case that the subgroup factor is identical or similar to a randomization strata factor (eg, Baseline HbA1c, Baseline BMI), only the subgroup factor (as a single factor or an interaction term) will be included in the model in order to avoid the issue of collinearity in the analysis. The corresponding strata factor will not be included in the model. In case that the subgroup factor is country, the region will not be included in the model. Summary statistics (for Screening value, Baseline value, observed values, and observed changes from Baseline) at scheduled visits will be provided by treatment group for HbA1c value over the whole treatment period including the 26-week Safety Extension Period. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from Baseline (±SE) at each of the scheduled visits (using OC).
Secondary - Change from baseline to Week 56 in HbA1c - Change from baseline to Week 30 in FPG - Number of participants with HbA1c <7.0% at Week 30 - Change from baseline to Weeks 30 and 56 in	Continuous secondary efficacy endpoints will be analyzed using the same ANCOVA model with missing values imputed as the one used for the primary efficacy endpoint analysis. Differences between treatment groups and CIs will be estimated by this method. Categorical efficacy endpoints will be analyzed by Cochran Mantel Haenszel method stratified by the randomization stratum of Screening HbA1c (<8%, ≥8%) and randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30 kg/m^2, ≥30 kg/m^2). For the HbA1c <7.0% analysis, participants with missing HbA1c data at Week 30 or Week 56 will be considered non-responders in the ITT population. Summary statistics (for Screening value, Baseline value, observed values, and observed changes from Baseline) at scheduled visits will be provided for continuous efficacy endpoints for each treatment group over the whole treatment period including the 26-week Safety Extension Period. The summary will include the number of observations, mean, SD, SE, minimum, median, and

Endpoint	Statistical Analysis Methods
body weight	maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from baseline (±SE) at each of the scheduled visits (using OC).
Multiplicity considerations	To control the family-wise type I error, a step-down testing procedure will be applied. For the primary efficacy endpoint (change from Baseline to Week 30 in HbA1c), the 3 efpeglenatide doses will be tested in the order of 6 mg, 4 mg, and 2 mg. once the primary endpoint is statistically significant at α=0.05 (2-sided) for all 3 efpeglenatide doses, a hierarchical testing procedure will be performed to test the following study secondary efficacy endpoints by the following prioritized order: 1. HbA1c <7% at Week 30 for efpeglenatide 6 mg versus placebo (yes/no) 2. HbA1c <7% at Week 30 for efpeglenatide 4 mg versus placebo (yes/no) 3. Change from Baseline to Week 30 in body weight (kg) for efpeglenatide 6 mg versus placebo 4. Change from Baseline to Week 30 in body weight (kg) for efpeglenatide 4 mg versus placebo 5. HbA1c <7% at Week 30 for efpeglenatide 2 mg versus placebo (yes/no) 6. Change from Baseline to Week 30 in FPG (mmol/L, mg/dL) for efpeglenatide 6 mg versus placebo 7. Change from Baseline to Week 30 in FPG (mmol/L, mg/dL) for efpeglenatide 4 mg versus placebo 8. Change from Baseline to Week 56 in body weight (kg) for efpeglenatide 6 mg versus placebo 9. Change from Baseline to Week 56 in HbA1c (%) for efpeglenatide 6 mg versus placebo 10. Change from Baseline to Week 56 in body weight (kg) for efpeglenatide 4 mg versus placebo 11. Change from Baseline to Week 56 in HbA1c (%) for efpeglenatide 4 mg versus placebo 12. Change from Baseline to Week 56 in HbA1c (%) for efpeglenatide 2 mg versus placebo 13. Change from Baseline to Week 56 in body weight (kg) for efpeglenatide 2 mg versus placebo The testing will stop as soon as an endpoint for an efpeglenatide dose is found to be not statistically significant at α=0.05 (2-sided) for 1 efpeglenatide dose. No multiplicity adjustment will be made on other secondary efficacy variables or the comparison of other efpeglenatide dose versus placebo than mentioned above.
Tertiary - 7 point SMPG profile - HbA1c <7.0% at Week 30 and Week 56 - Rescue therapy used during the treatment period until Weeks 30 and 56 (yes/no) - Time to initiation of rescue therapy (weeks)	Comparisons of time to event endpoints between treatment groups will be performed using the Cox proportional hazards regression model with the treatment groups (efpeglenatide 2, 4, or 6 mg, placebo), randomization stratum of Screening HbA1c (<8%, ≥8%), randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30 kg/m^2, ≥30 kg/m^2), and region as the factors. The curve of the cumulative incidence of participants with rescue initiation will be estimated using Kaplan-Meier method by study treatment group. Summary statistics (for Screening value, Baseline value, observed values, and observed changes from Baseline) at scheduled visits will be provided for continuous efficacy endpoints for each treatment group over the whole treatment period including the 26-week Safety Extension Period. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from Baseline (±SE) at each of the scheduled visits (using OC).

ANCOVA Analysis of Covariance; BMI body mass index; CI confidence interval; FPG fasting plasma glucose; HbA1c hemoglobin A1c; ITT intent to treat; MI multiple imputation; MNAR missing not at random; OC observed cases; SD standard deviation; SE standard error; SMPG self-monitoring plasma glucose.

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 whole on-treatment period is defined as the time from the first injection of IMP up to 30 days (7 days for hypoglycemia) after the last injection of IMP;
  - The 30-week core on-treatment period is defined as the time from the first injection of IMP up to Visit 10 (Week 30) (or Day 210 if Visit 10 [Week 30] visit is missing) or up to 30 days (7 days for hypoglycemia) after the last injection of IMP, whichever comes earlier
- The 30-week on-study period is defined from the first injection of IMP up to Week 30, irrespectively if IMP was still used or already discontinued at Week 30.
- The post-treatment period is defined as the time starting 31 days (8 days for hypoglycemia) after the last injection of IMP (after the whole 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 (TEAEs)** are AEs that developed or worsened or became serious during the on-treatment period
- **Post-treatment AEs** are AEs that developed or worsened or became serious during the post-treatment period.

Table 6 - Safety analyses

Endpoint	Statistical Analysis Methods
AEs	All AEs will be coded to a "LLT", “PT”, "HLT", and “HLGT” and associated “SOC” using the version of MedDRA currently in use by the Sponsor at the time of database 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. The primary focus of AE reporting will be on TEAEs. Pretreatment and posttreatment AEs will be described separately. Adverse event incidence table will be provided by treatment group for all types of TEAEs: all TEAEs, all treatment-emergent SAEs, all TEAEs leading to permanent treatment discontinuation and all TEAEs leading to death. Tables will be presented on the “30-week main on-treatment period” and on the “whole on-treatment period including the 26-week controlled Treatment Extension Period”.

Endpoint	Statistical Analysis Methods
	Adverse events, SAEs and AEs leading to death tables also will be presented on the 30-week on-study period too.
Hypoglycemia	The number (%) of participants with at least 1 hypoglycemia event during the whole on-treatment period will be assessed per type of hypoglycemic event (see Section 8.2.5) and according to time of occurrence (nocturnal [ie, 00:00 to 05:59 am], any time of the day). Documented hypoglycemia (symptomatic or asymptomatic) will be also evaluated for the more stringent SMPG threshold of <54 mg/dL (3.0 mmol/L). Summaries will be presented overall and by type of event for each treatment group. The total number of events (per 100 participant-years) will be computed and summarized overall and by type of event for each treatment group. Similar summaries will also be provided for the 30-week core on-treatment period.
Vital signs and laboratory data ECG & Holter 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. The incidence of potentially clinically significant abnormalities (PCSA), defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review, will be summarized at any time during the 30-week core on-treatment period and during the whole 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 on-treatment period will be summarized by treatment group whatever the Baseline level and according to Baseline status. Tables will be presented on the “30-week main on-treatment period” and on the “whole on-treatment period including the 26-week controlled Treatment Extension Period”
Exploratory	Will be described in the statistical analysis plan finalized before database lock

AE adverse event; ECG electrocardiogram; HLGT higher-level grouped term; HLT higher-level term; LLT lower-level term; MedDRA Medical Dictionary for Regulatory Activities; PCSA potentially clinically significant abnormalities; PT preferred term; SAE serious adverse event; SOC system organ class; TEAE treatment-emergent adverse event.

9.4.3 Other analyses

Pharmacokinetic exploratory analyses will be described in the statistical analysis plan finalized before database lock. Analyses of other endpoints are detailed in Table 7.

Table 7 - Other analyses

Endpoint	Statistical Analysis Methods
Efpeglenatide ADA	Summaries of ADA data will be for participants treated with efpeglenatide only. All summaries related to kinetics of ADA response (ADA status and magnitude, ADA attributes, participant status, ADA incidence) will be descriptive; no statistical significance tests will be performed on ADA data: • Number and percentage of participants by ADA status (positive/negative) at scheduled visits • Number and percentage of participants with treatment-induced ADAs (among the participants with ADA negative or missing at baseline) during the study period • Number and percentage of participants with treatment-boosted ADAs (among the participants with ADA positive at baseline) during he study period • ADA titer at schedule timepoint will be summarized by visit using descriptive statistics by number (n), median, quartiles, minimum, and maximum. • Number and percentage of participants by ADA cross-reactivity to endogenous GLP-1 (positive or

Endpoint	Statistical Analysis Methods
	negative) at scheduled visits • Number and percentage of participants by ADA cross-reactivity to endogenous glucagon (positive or negative) at scheduled visits • Number and percentage of participants with ADAs directed against the PEG linker of efpeglenatide at scheduled visits. Correlation, scatterplots and/or subgroup analyses will be conducted as appropriate to assess the relationship between immunogenicity endpoints and efficacy/safety assessments.
PK endpoints: serum concentration of efpeglenatide at pre-dose and post-dose	Efpeglenatide pre-dose and post-dose serum concentrations of participants in the efpeglenatide groups will be listed and summarized by visit in the PK population, using descriptive statistics by N, geometric mean, coefficient of variation, median, minimum and maximum.
PRO:	The analysis of PRO endpoints will be descriptive with no formal testing. Summary statistics at scheduled visits will be provided by treatment group. Graphical presentations will also be used to illustrate trends over time. Participants' answers to the open-ended questions of PQATv2 will be analyzed qualitatively and quantitatively, as relevant, using appropriate data analysis software. The analysis method for this exploratory analysis will be provided in a separate SAP and the analyses results will be documented in a separate report.

ADA anti-drug antibodies; GLP-1 glucagon-like peptide 1; PEG polyethylene glycol, PK pharmacokinetic; PQATv2 Patient Qualitative Assessment of Treatment version 2; PRO participant-reported outcome ; SAP statistical analysis plan.

9.5 INTERIM ANALYSES

Not applicable.

9.5.1 Data Monitoring Committee

See Appendix 1 (Section 10.1) 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 Council for 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 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 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.
- Participants who are rescreened are required to sign a new ICF.
- The ICF will contain a separate section that addresses the participation in the post-dose PK assessment sub-study. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

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 of 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 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.

10.1.4.2 Clinical Endpoint Committee

Independent CEC(s) 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, the CRO and the Investigators, and will be implemented to review, assess and/or adjudicate all events of death, selected cardiovascular events (non-fatal myocardial infarction, 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.

10.1.4.3 Independent Expert

An independent ophthalmologist expert will review in a treatment-blinded manner all reported AEs suspected to be diabetic retinopathy-related to assess the presence of retinopathy and 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 ICO guidelines (10) 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 participants 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 e-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 e-CRF 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 or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

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

10.1.9 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 8 will be performed by the central laboratory, except urine pregnancy tests and urinalysis by dipstick, which will be performed locally.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at a local laboratory at any time during the study as determined necessary by the Investigator or required by local regulations. If they are used to evaluate an AE (diagnostic, follow-up, outcome), the results must be entered into the e-CRF.

Table 8 - Protocol-required safety laboratory assessments

Laboratory assessments[a]	Parameters			
Hematology	Platelet count	WBC count with differential:		
	Red blood cell count	Neutrophils		
	Hemoglobin	Lymphocytes		
	Hematocrit	Monocytes		
		Eosinophils		
		Basophils		
Clinical chemistry	Creatinine	Potassium	Aspartate aminotransferase	Total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin)
	Sodium	Alkaline phosphatase	Alanine aminotransferase	Estimated glomerular filtration rate (MDRD formula)
	Amylase	Lipase		
Routine urinalysis	pH, glucose, protein, blood/hemoglobin, ketones, leucocyte, by dipstick			
Lipid profile	Triglyceride	Cholesterol:		
		Total cholesterol		
		Low-density lipoprotein cholesterol		
		High-density lipoprotein cholesterol		
Anti-drug antibodies	Serum anti-drug antibody sample			
Calcitonin	Calcitonin			
Other Screening tests	• Follicle-stimulating hormone and estradiol (as needed in unconfirmed postmenopausal women) • NOTE: For women of non-childbearing potential (Appendix 4, Section 10.4), follicle-stimulating hormone and estradiol levels should be tested in case the definition of postmenopausal or premenopausal cannot be satisfied; eg, no medical document of hysterectomy or cessation of menses <12 months without an alternative medical cause. • Serum human β-HCG pregnancy test (as needed for women of childbearing potential)[b] • C-peptide			

NOTES :

a All study-required laboratory assessments will be performed by a central laboratory except urine pregnancy tests and urinalysis by dipstick, which will be performed locally; the results of each test must be entered into the e-CRF.

b 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.

β-HCG human beta-chorionic gonadotropin; MDRD Modification of Diet in Renal Disease; WBC white blood cell; WOCBP women of childbearing potential.

Investigators must document their review of each laboratory safety report.

Hemoglobin A1c and FPG values that could unblind the study will not be reported to study sites or other blinded personnel after Visit 3 (Day 1), until the study has been unblinded. Details of the conditions in which unblinding can occur, and the procedure, are detailed in Section 6.3.2.

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 participant 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. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.

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).

An 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/AESI 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 e-CRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to Sponsor representative in lieu of completion of the SAE/AESI e-CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor representative. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor representative.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- The Investigator will submit any initial SAE/AESI data to the Sponsor representative within 24 hours of its acknowledgement.

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

Follow-up of AEs and SAEs

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

REPORTING OF SAEs/AESIs

SAE reporting to Sponsor representative via an electronic data collection tool

- The primary mechanism for reporting an SAE/AESI to Sponsor representative will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE/AESI data collection tool.

- The site will enter the SAE/AESI 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/AESI from a study participant or receives updated data on a previously reported SAE/AESI after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE/AESI form or to the Sponsor representative by telephone.
- Contacts for SAE/AESI 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. Post-menopausal female:
   - A post-menopausal 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 9.

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 9 - 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 other highly effective method of contraception, with 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 at each on-site visit during the treatment period, at the last study visit (6 weeks ±7days after the last dose of study treatment), 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 no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure

Female participants who become pregnant

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

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

10.5.1 Laboratory abnormalities

NEUTROPENIA

Neutrophils < 1500/mm^3 or according to ethnic group

Repeat immediately a full blood count if value close to 1500/mm^3

Neutrophils < 1500/mm^3 confirmed with signs of infection	Neutrophils < 1500/mm^3 confirmed with no signs of infection
1. **DISCONTINUE** Investigational Medicinal Product, hospitalization should be considered 2. **PERFORM** biological investigations for infection	1. **DISCONTINUE** Investigational Medicinal Product 2. **INVESTIGATE** for infection

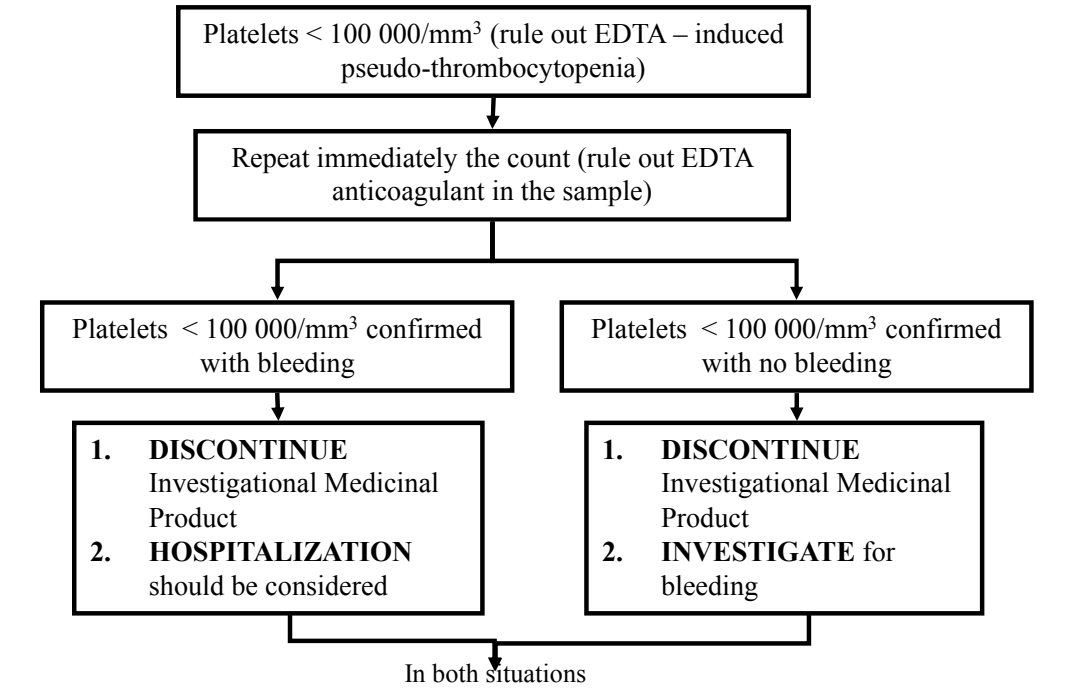
In both situations

3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts
   - Serology: EBV, (HIV), mumps, measles, rubella
6. **DECISION** for bone marrow aspiration: to be taken in specialized unit
7. **COLLECT/STORE** one sample following handling procedures described in PK sections **(for studies with PK sampling)** and freeze one serum sample (5 mL) on Day 1 (cessation of investigational medicinal product) and Day 5 (for further investigations)
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

Note:
•The procedures described in the above flowchart are to be discussed with the patient only in case the event occurs. If applicable (according to local regulations), an additional consent (e.g., for HIV testing) will only be obtained in the case the event actually occurs.
•For individuals of African descent, the relevant value of concern is <1000/mm3

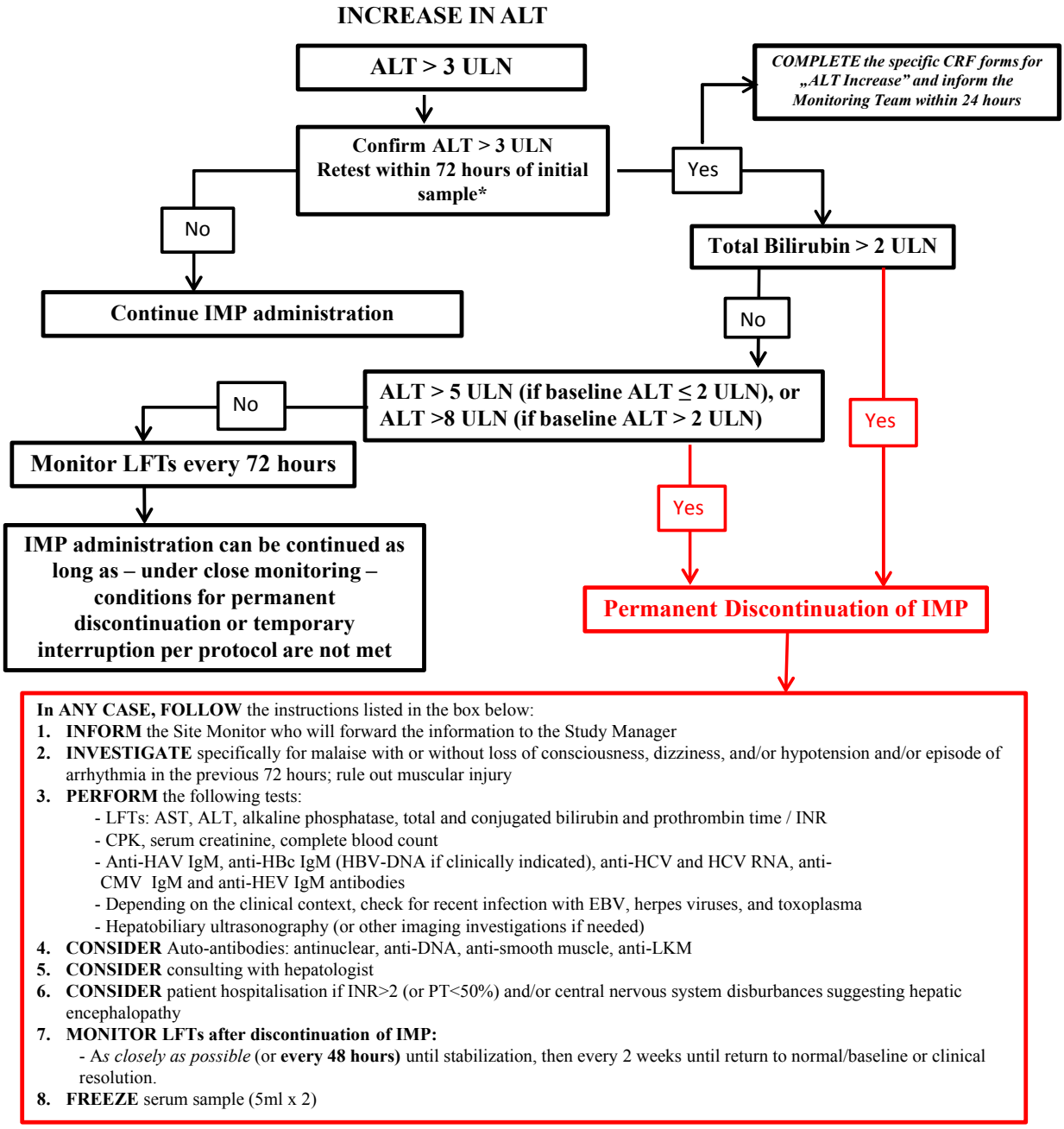
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

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 AEs in Appendix 3 (Section 10.3) is met.

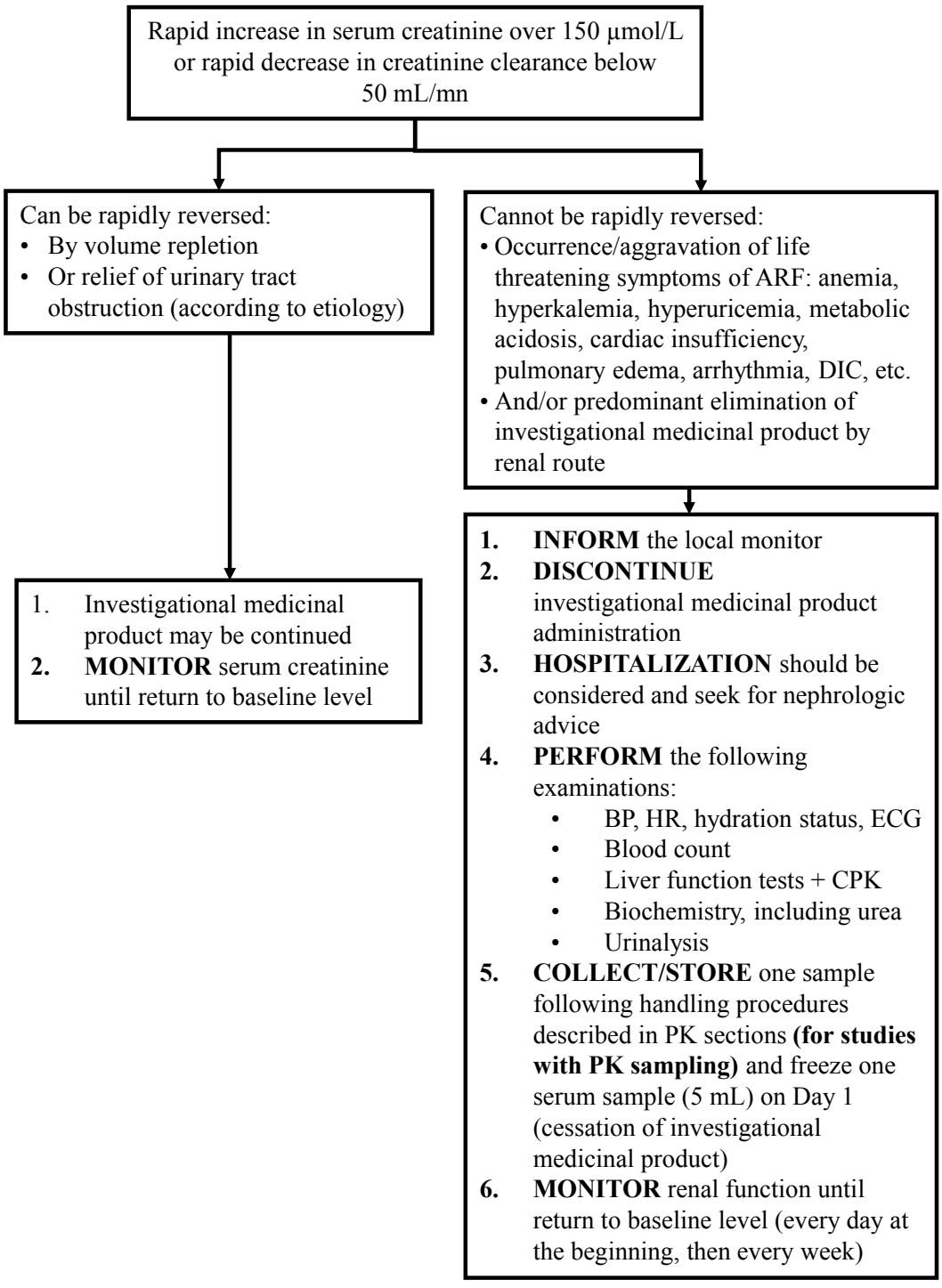


*If unable to retest in 72 hours, use original laboratory results to decide on further reporting/monitoring/discontinuation.

Note:

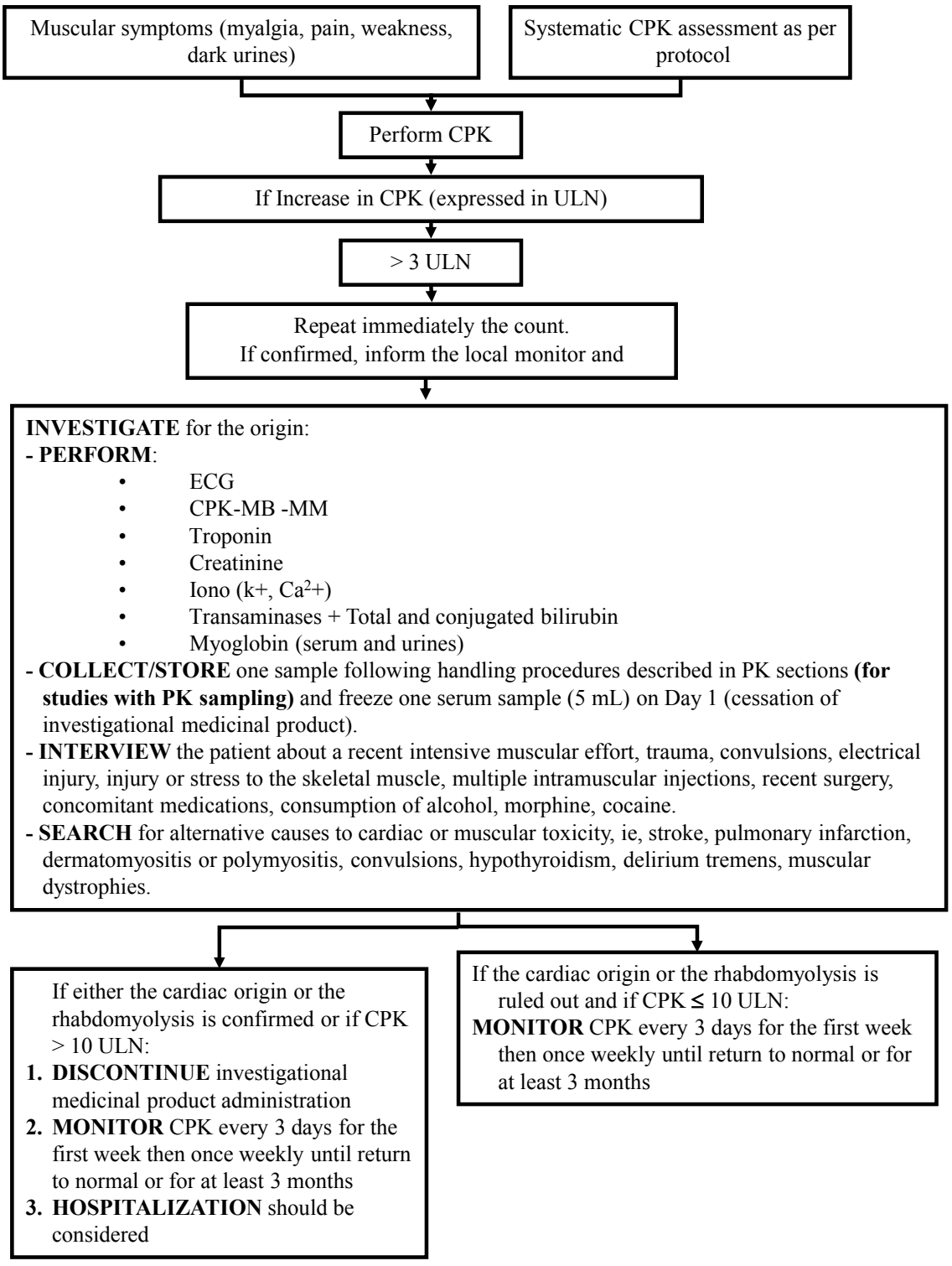
- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Appendix 3 (Section 10.3) for guidance on safety reporting.
- Normalization is defined as ≤ ULN or baseline value, if baseline value is > ULN.

INCREASE IN SERUM CREATININE



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

10.5.2 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.

10.5.2.1 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 × ULN, a retest (centrally assessed as far as possible) must be performed as follows:

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

In case a retest is >2 × ULN a gastroenterological evaluation and imaging (ultrasound and/or computed tomography [CT] or magnetic resonance imaging [MRI] with contrast, as appropriate) is highly recommended. The absence of clinical signs and/or symptoms should be documented in the source documents (if clinical signs and/or symptoms develop, please see Appendix 5 Section 10.5.2.2 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.

10.5.2.2 Elevation of amylase and/or lipase >2 × ULN with clinical signs and/or symptoms.

In the presence of clinical signs and/or symptoms evocative of pancreatitis (as previously described) 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 × ULN, then amylase and/or lipase levels should be retested as described in Appendix 5 Section 10.5.2.1 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 (Section 10.5.2.1 and Section 10.5.2.2) as previously described, 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 specific 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.

10.5.3 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 (as final diagnostic if available or as “increased calcitonin”); all appropriate clinical and laboratory documentations should also be reported in the corresponding eCRF pages

- An ultrasound scan of the thyroid is highly recommended to be performed and the participant may be referred to a Specialist if judged necessary (per clinical practice and local guidelines)
- The participant should continue to be followed according to protocol schedule (including planned calcitonin measurements). The AE form and all other related eCRF pages 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 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.

10.5.4 Gastrointestinal events in relation to acute renal failure

Acute renal impairment caused by dehydration is a potential risk described for other GLP-1 RA. Acute renal impairment is not thought to be caused directly by GLP-1 RA (including efpeglenatide) without dehydration.

In case of prolonged or severe nausea and vomiting, if clinically indicated, serum creatinine measurement should be performed at the central laboratory. If there is an acute increase of serum creatinine, metformin must be discontinued (if concomitantly taken) until resolution of renal dysfunction. Please also refer to Appendix 5 (Section 10.5.1), increase in serum creatinine flowchart for further recommendations.

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

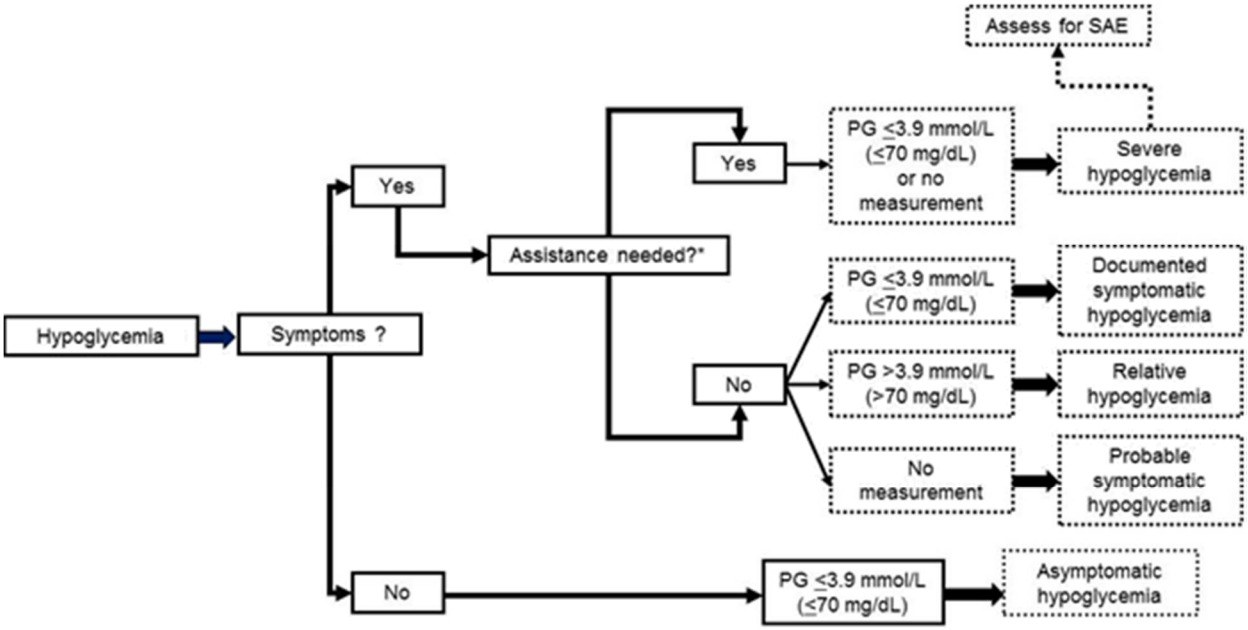
Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.8 APPENDIX 8: HYPOGLYCEMIA CLASSIFICATION

Figure 2 - Hypoglycemia classification



*The patient is not able to treat her/himself because of the acute neurological impairment and requires another person to actively administer sugar, glucagon or intravenous glucose

10.9 APPENDIX 9: PATIENT QUALITATIVE ASSESSMENT OF TREATMENT VERSION 2

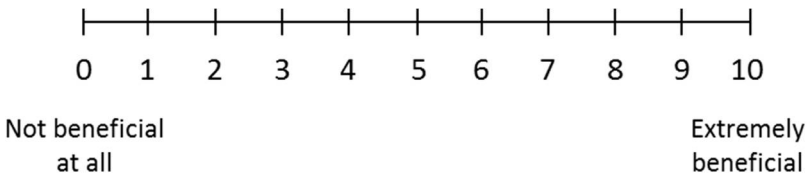
The following questions ask for your opinion on the drug you received during this clinical study.

There are no right or wrong answers; we would like to better understand your own experience of the drug.

1. During this trial, what were the main benefits you experienced with the drug you received?

Free-text

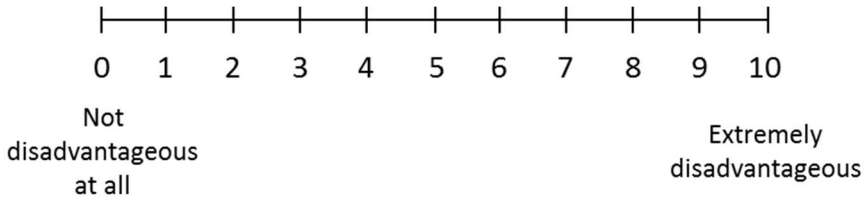
2. On a scale of 0 to 10, how beneficial was the drug you received during this trial?



3. During this trial, what were the main disadvantages you experienced with the drug you received?

Free-text

4. On a scale of 0 to 10, how disadvantageous was the drug you received during this trial?



5. After this trial, would you be willing to continue using the drug you received during this trial?

Yes ☐ No ☐

Please explain why?

Free-text

6. Based on your own experience in this trial, please select a response on the scale below

☐ - 3	☐ - 2	☐ - 1	☐ 0	☐ 1	☐ 2	☐ 3
The disadvantages of the drug I received significantly outweigh the benefits			There were equal benefits and disadvantages of the drug I received			The benefits of the drug I received significantly outweigh the disadvantages

10.10 APPENDIX 10: ABBREVIATIONS

ADA:	anti-drug antibody
AE:	adverse event
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	Analysis of Covariance
AST:	aspartate aminotransferase
BMI:	body mass index
BP:	blood pressure
CDs:	compact discs
CEC:	clinical endpoint committee
CFR:	Code of Federal Regulation
CI:	confidence interval
CIOMS:	Council for International Organizations of Medical Sciences
CT:	computed tomography
DMC:	data monitoring committee
DPP-4:	dipeptidyl peptidase 4
DVDs:	digital versatile disc
ECG:	electrocardiogram
e-CRF:	electronic Case Report Form
EOT:	end of treatment
FPG:	fasting plasma glucose
GCP:	Good Clinical Practice
GI:	gastrointestinal
GLP-1:	glucagon-like peptide 1
GLP-1 RA:	glucagon-like peptide 1 receptor agonist
HA:	health authority
HbA1c:	hemoglobin A1c
HR:	heart rate
HRT:	hormonal replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committees
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
MDRD:	modification of diet in renal disease
MEN-2:	multiple endocrine neoplasia syndrome type 2
MI:	multiple imputation
MRI:	magnetic resonance imagine
MTC:	medullary thyroid cancer
NIMP:	noninvestigational medicinal product

NOAEL:	no-observed-adverse-effect level
PEG:	polyethylene glycol
PFS:	prefilled syringe
PK:	pharmacokinetic
PPG:	post-prandial plasma glucose
PQATv2:	patient qualitative assessment of treatment version 2
SAE:	serious adverse event
SC:	subcutaneous
SE:	standard error
SMPG:	self-monitored plasma glucose
SoA:	schedule of assessments
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
ULN:	upper limit of the normal
WOCBP:	women of childbearing potential

10.11 APPENDIX 11: PROTOCOL AMENDMENT HISTORY

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

10.11.1 Amendment 01: 16 January 2018

This amendment 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

Following US IRB Protocol review, it was requested to update sections related to male contraception and legally authorized representative. Updates to the following sections were also made, based on US FDA advice: statistical analysis and methods of unblinding.

In addition, Sanofi uses this opportunity to edit other sections of the protocol as listed below, to update text with new available information, to align the procedures with those in other studies within the program and/or for better clarity:

- Schedule of activities, exploratory endpoints and dosing instructions (for PK pre-dose),
- Benefit/Risk assessment,
- Exclusion criteria,
- Anti-drug antibody measurements,
- Committee Structure.

Inconsistencies, typographical, and spelling checks were also run throughout the document and corrected.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, 9.4.1 Efficacy analyses	Control-based MI method for analysis of primary/secondary efficacy endpoints for missing data changed to retrieve drop-out method Control-based imputation method moved to sensitivity analysis	To update analysis of primary/secondary efficacy endpoints with retrieve drop-out method to handle missing values following US FDA recommendation To update sensitivity analysis

Section # and Name	Description of Change	Brief Rationale
Section 5.2 Exclusion criteria, Section 10.4 Appendix 4 Contraceptive guidance and collection of pregnancy information	Exclusion criteria E19 modified to add required contraception duration to study period and at least 5 weeks after last dose of study treatment for women and required contraception duration for male for at least 5 weeks after the last dose of study intervention and sperm donation restriction during this period is added	To add male exclusion criteria related to required contraception during the study
Section 6.3.1 Methods of blinding, 6.3.2 Randomization code breaking during the study	The text for bioanalyst unblinding deleted from Section 6.3.1 and additional text pertaining to PK analyst unblinding is added	To clarify, at US FDA request, the samples to be analyzed for PK and ADA during the study
Section 9.4.2 Safety analyses	Text included to add 30-week core treatment period for safety analysis	Clarification of treatment periods for which safety tables will be provided as per US FDA recommendation
Appendix 1 Section 10.1.2. Informed consent process	Involvement of legally authorized representative in informed consent process deleted	The age of majority is not >18 in any participating country. Protocol procedures require participants to be able to self-manage different activities so a legally authorized representative is not accepted. Legally authorized representative has been removed following US IRB request
Section 1.1 Synopsis, Section 3 Objectives and endpoints, Section 9.4.3 Other analyses	Text for ADA measurement schedule modified	ADA endpoints wording was changed following additional team discussion and recommendation
Section 1.3 Schedule of activities	Permitted window of up to -21 days added to Screening period Visit 1 and ±3 days deleted for Visit 3. Notes for permitted window for Visits 2 and 3 added	To clarify the permitted window for visits during Screening period (Visit 1 and Visit 2) and remove window from Visit 3 (Randomization, Day 1)
Section 1.3 Schedule of activities	Diary dispensation schedule added on Visits 3, 5, 6, 7, 9, 10, 12, and 14 (EOT)	To clarify in Scope of Activities the requirement for dispensation of paper diary at all visits
Section 1.3 Schedule of activities Table 1 Objectives and Endpoints	PK pre-dose was removed from Baseline and was added at Week 24 visit. PK endpoint has been updated accordingly	Participants in this study should not have been treated with any antidiabetic medication within 3 months prior to the study. For this reason the baseline PK pre-dose sampling was considered non-informative and was replaced with a sample at Week 24 to better characterize the PK profile of the patients.

Section # and Name	Description of Change	Brief Rationale
Table 2 Overview of study interventions administered	Additional instructions have been provided for the timing of IMP administration prior to PK pre-dose (expected to be 6 to 7 days)	We need PK samples which are far enough removed from the period between time of injection and C_{max} (T_{max}) such that the large, random fluctuations in concentration which typically occur during that period will not confound our estimates. Because for efpeglenatide C_{max} typically occurs around 4 days after injection, PK samples taken during the first 5 to 6 days after dosing will still be heavily influenced by random fluctuations in C_{max} and T_{max}, and essentially uninformative with regard to clearance.
Section 2.3 Benefit/Risk assessment	Cut-off date of 22 June 2017 for safety information was included	To clarify this information and to be able to make a correct time reference for safety data presented in this section.
Section 2.3 Benefit/Risk assessment	Following text: • The GLP-1 RA class has a box warning related to risk of thyroid C-cell tumors in the label, based on findings in rodents. Replaced with: • The GLP-1 RA class has a box warning related to risk of thyroid C-cell tumors in the US label, based on findings in rodents.	To clarify that only US label for GLP-1 RA has a box warning for thyroid C-cell tumors
Section 2.3 Benefit/Risk assessment	Following text added about diabetic retinopathy complication: Diabetic retinopathy complications have been reported for one of GLP-1 RAs (as of 05 December 2017). No case has been reported for efpeglenatide. Participants with a planned retinal treatment for retinopathy or maculopathy will be excluded in the current study. Diabetic retinopathy complications will be monitored throughout the study.	To add new available data on retinopathy and methods to mitigate the participant's risk during the study
Section 2.3 Benefit/Risk assessment	Text for ALT increase in overall a total of 12 out of 571 subjects on efpeglenatide and 3 out of 183 subjects on comparators for Phase 2 clinical studies added	To clarify prior ALT increase events in Phase 2 studies
Section 5.2 Exclusion criteria	Exclusion criteria 04 modified to detail description for exclusion of retinopathic participants	To clarify the retinopathy exclusion criteria
Section 5.2 Exclusion criteria	Hematological laboratory results deleted from Exclusion Criteria 10	To remove hematology laboratory results from exclusion criteria as there is no related safety signal to efpeglenatide so far

Section # and Name	Description of Change	Brief Rationale
Section 7.1.2.1 Rechallenge	"Consecutive" was added to the text: If a maximum of 2 (two) consecutive doses are missed, the IMP can be restarted with the last dose given. In cases of 3 (three) or more consecutive doses are missed, the titration should be re-initiated.	To clarify the conditions when the re-titration with IMP is needed following temporary discontinuation.
Section 8.3 Adverse events and serious adverse events	Text to define symptomatic overdose with the IMP as at least twice the planned dose given within 3 days (72 hours) is added	To separately define the overdose of IMP considering longer half-life of efpeglenatide
Sections 8.3.8.1 Appendix 6	These sections have been removed Appendix 6 has been made "Not applicable"	It was clarified that the study intervention is not a medical device per regulatory definition so no related information and reporting rules are applicable. It is a combined product. Sponsor's procedures for product technical complaints will be followed.
Section 10.1.3 Data protection	Text for collection of participants race and ethnicity added	Race is collected in this trial as it is requested by regulatory authorities and the information was missing from the Protocol
Section 10.1.4 Committees Structure	Addition of pancreatic events (and need for gastroenterologist) to events adjudicated by CEC Addition of Independent Expert for review of all reported AEs suspected to be diabetic retinopathy-related	Both pancreatic events and diabetic retinopathy complications are included in the Adverse Events requiring specific monitoring. Pancreatic events were planned be adjudicated by the CEC, but by mistake they were omitted from description of the Committee. Based on the recent reporting of diabetic retinopathy complication for another drug in same class, it was decided to add an independent expert to review all reported events for confirmation and causality assessment.
Section 6.1 Study intervention(s) administered Table 2	Content of formulation buffer for IMP corrected from "sodium citrate, polysorbate 20, mannitol, and methionine" to "citric acid monohydrate, L-methionine, polysorbate 20, D-mannitol, sodium hydroxide and water for injection"	Initial formulation was incorrectly entered in the initial protocol
Throughout	Minor editorial, typo error corrections and document formatting revisions	Minor, therefore have not been summarized

10.11.2 Amendment 02: 27 March 2018

This amendment 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

Following Medicines and Healthcare products Regulatory Agency (MHRA) request, the protocol was updated to clarify the contraception requirements for women of childbearing potential (WOCBP).

Section # and Name	Description of Change	Brief Rationale
Section 10.4 Appendix 4 Contraceptive guidance and collection of pregnancy information	Appendix modified to add ova donating restriction for female participants for the duration of the study and at least 5 weeks after last dose of study treatment. Change of wording in Table 9 related to drug-interaction potential of oral hormonal contraception and recommended measures.	To clarify, at UK MHRA request, the recommendations for methods of contraception and ova donating restriction for WOCBP.

11 REFERENCES

1. Banholzer ML, Wandel C, Barrow P, Mannino M, Schmitt G, et al. Clinical trial considerations on male contraception and collection of pregnancy information from female partner: update. Clin Transl Med. 2016;5(1):23.

2. US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) (2015) Assessment of male-mediated developmental risk for pharmaceuticals guidance for industry: guidance for industry (draft guidance).

3. Investigator's Brochure, SAR439977, latest edition.

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ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	Clinical Approval	[redacted]
[redacted]	Clinical Approval	[redacted]
[redacted]	Regulatory Approval	[redacted]