NCT03713684

AMENDED CLINICAL TRIAL PROTOCOL 01

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 basal insulin alone or in combination with oral antidiabetic drug(s)**
Protocol number:	**EFC14893**
Amendment number:	**01**
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 basal insulin alone or in combination with oral antidiabetic drug(s) (AMPLITUDE-L)**
Sponsor name:	
Legal registered address:	

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

Monitoring Team's Representative Name and Contact Information:

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 01	All	30 September 2019, version 1 (electronic 1.0)
Original Protocol		20 June 2018, version 1 (electronic 2.0)

AMENDED PROTOCOL 01 (30 September 2019)

This amended protocol is considered to be nonsubstantial because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The protocol was updated to make the pharmacokinetic (PK) dataset more robust by timing the postdose sample collection to coincide with the absorption phase of efpeglenatide, and by collecting additional PK samples postdose.

In addition Sanofi took this opportunity to clarify other sections of the protocol as listed below.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 2.1 Study rationale	Specified the patient population and mentioned that patients with T2DM should be inadequately controlled with basal insulin alone or in combination with OAD(s)	Clarification on the studied population.
Section 1.1 Synopsis (Noninvestigational medicinal product) and Section 6.1.2.1 Background medication	The Lantus starting dose should be based on HbA1c at screening instead of at randomization	Clarification
Section 1.1 Synopsis (Statistical consideration-Primary analysis) and Section 9.4.1 Efficacy analysis	Clarified that the primary efficacy endpoint will be analyzed in all participants randomized	Clarification
Section 1.3 Schedule of activities - ADA	The following text was added in the notes section: "or as soon as possible after study database lock whichever comes later."	Clarification
Section 1.3 Schedule of activities - IMP concentration (PK) sampling	Modified postdose PK sampling time from "4 days (±1 day)" to "3 days (±1 day)" and specified the sample collection window as "preferably between Week 8 and Week 12" Description of PK note has been changed from: "All participants will have one blood sample collected just before their weekly injection of the IMP at selected clinical visits. For a subset of participants, 1 additional postdose sample will be taken either 4 days (±1 day) after 1st IMP dose, or 4 days (±1 day) after 4th dose, or 4 days (±1 day) after 12th dose). A separate consent will be signed. See Section 8.5." To: "All participants will have 1 blood sample collected just before their weekly injection (and at least 6 days after last IMP dose administration) for the predose serum concentration (C_{trough}) of efpeglenatide at selected clinical visits. For participants who consent, at least 1 additional postdose sample will be taken 3 days (±1 day) after administration of IMP, preferably between Week 8 and Week 12. See Section 8.5."	Postdose PK sampling time changed from 4 days (±1 day) to 3 days (±1 day) in order to collect more PK data in the absorption phase. The timeline of PK predose sample collection from the previous IMP dose administration has been clarified; Sample collection time points have been specified to allow higher flexibility with regard to postdose sample collection window in order to facilitate additional postdose sampling. A preferred interval for PK postdose sampling (between Week 8 and Week 12) was defined considering the balance between two requirements: PK steady state and limited risk of antidrug antibodies (ADA) formation.
Section 1.3 Schedule of Activities - rescue therapy	The following detail has been added for rescue therapy notes: "Participants must have an unscheduled in-person visit prior to rescue therapy initiation, with the assessment normally planned for the EOT visit."	The note has been updated for clarity. The visits and procedures are detailed in different cases (rescue treatment introduction).

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities - footnote "a"	Footnote "a" has been updated from: "In case of premature permanent IMP discontinuation, the participant should have a visit as soon as possible after the last IMP administration with the assessments normally planned for EOT visit." To "In case of premature permanent IMP discontinuation, the participant should have a visit as soon as possible after the last IMP administration with the assessments normally planned for EOT visit (including a PK sample if the visit can be scheduled 6-7 days after the permanent IMP discontinuation)." "For safety reasons, participant who wish to terminate participation in the study, should be assessed 6 weeks (±1 week) from the last IMP dose (at the minimum) using the procedure normally planned for the posttreatment follow-up visit at EOS." To: "For safety reasons, participants who do not want to continue to be followed in the study after IMP discontinuation should be assessed 6 weeks (±1 week) from the last IMP dose (at the minimum) using the procedure normally planned for the posttreatment follow-up visit (EOS)."	The footnote has been reworded for clarity.
Section 2.2 Background	Under diabetic retinopathy bullet point, the text was updated from "No cases have been reported for efpeglenatide" To "No cases have been reported for efpeglenatide in completed Phase 1 and 2 studies". Specified the section numbers of the IB (Section 5 Nonclinical Studies and Section 6 Effects in humans) that contains nonclinical and clinical information of efpeglenatide, respectively.	Clarification To clarify the reference source of information.
Section 2.3 Benefit/risk assessment	Specified the section numbers of the IB (Section 2 Summary and Section 7 Summary of data and guidance for the Investigator) that contains information of known and expected benefits and risks and reasonably expected AEs of efpeglenatide, respectively.	To clarify the reference source of information.
Section 3 Table 1 - Objectives and endpoints	The PK endpoint regarding serum concentration of efpeglenatide at postdose has been modified from: "Serum concentration of efpeglenatide at postdose (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] in a subset of participants, at least 10% of total: [N = 12 per group])." To: "Postdose serum concentration of efpeglenatide in participants who consent"	The endpoint has been updated to remove the operational instruction language.

Section # and Name	Description of Change	Brief Rationale
Section 5.3.1 Meals and dietary restrictions	Under fasting conditions, the following wording has been added to the first and second bullet, respectively: • "The participants should not take any antidiabetic medication before blood sampling." • "and before administration of antidiabetic medication"	To add clarity on the definition of fasting for the purpose of sample collection for glycemic parameters.
Section 6.1 Study intervention(s) administered Table 2 Overview of Study Interventions Administered	The following text was added under dosing instructions: "Participants will be asked to administer the last 2 consecutive weekly dose injections prior to PK sampling at the same body region (eg, at Week 2 and Week 3 before the planned PK visit at Week 4; see Section 8.5)."	To clarify the site of IMP administration before PK sampling.
Section 6.1.1 Investigational medicinal products	Specified the name of reference document "Pharmacy Manual". The following text was added "In case of emergency only, for scheduled or unscheduled visits, the IMP and Lantus might be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations. Direct-To-Patient (DTP) remains an option and the participant/Investigator can refuse this option."	Clarification. To include DTP, a new process regarding IMP dispensation in case of emergency.
Section 6.1.2.1 Background medication	The following text added for Lantus: "Lantus is the only background therapy provided by the Sponsor. The appropriate number of kits will be dispensed for the period until the next dispensing visit (please refer to the SoA Section 1.3). Lantus will be provided until the end of study even in case of premature end of treatment for patients attending the safety follow-up visits. Storage conditions and use-by-end date (when required by country regulations) are part of the label text."	Clarification of Lantus allocation during treatment period and after premature treatment discontinuation
Section 6.2 Preparation/ handling/storage/ accountability	Specified the name of reference document "Pharmacy Manual". The following text was added "except for IMP and Lantus in case of DTP shipment, for which a courier company has been approved by the Sponsor"	Clarification. To include DTP, a new process regarding IMP dispensation in case of emergency.
Section 6.3 measure to minimize bias: randomization and blinding	Adjusted the wordings for allocated IMP from: "Returned study intervention should not be redispensed to the participants." To: "Previously allocated IMP should not be redispensed to the participants."	Clarification.

Section # and Name	Description of Change	Brief Rationale
Section 6.3.2 Randomization code breaking during the study	The following text was changed from: Only the Project Manager and lead scientist at the Bioanalytical laboratory, as well as the popPK analyst, will have access to the randomization code to allow for the sorting of the efpeglenatide blood samples. To Only the predefined designated personnel from Sponsor and Bioanalytical laboratory will have access to the randomization code to allow for the sorting of the efpeglenatide blood samples.	Clarification and simplification as process is detailed in the applicable standard procedure for PK analysis
	The following text was changed from: "Refer to Section 8.3.4 for suspected unexpected serious adverse reaction (SUSAR) unblinding by the Sponsor." To "Randomization code breaking will be performed for reporting to the Health Authorities of any suspected unexpected serious adverse reaction (SUSAR). Refer to Section 8.3.4 for regulatory reporting requirements. The unblinding information will not be disclosed to patients, sites or any clinical team personnel prior to the database lock."	Clarification of the unblinding process for SUSARs
Section 6.4.1 Return and/or destruction of treatments	The following sentences were modified from: "The Investigator will not destroy the used and unused IMP and Lantus unless the Sponsor provides written authorization." To: "The Investigator will not destroy the used and unused IMP and Lantus unless the Sponsor or delegate provides written authorization."	Clarification on who can provide authorization for destruction of IMP
Section 7.1.1 Permanent discontinuation	The following text was modified from: "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. Refer to the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed." To: "As all randomly assigned participants, under treatment or not, will be included in the study data analyses, it is important to collect efficacy and safety data from all participants, during the entire 56 weeks of the study. Collection of Week 30 data is of highest importance as they are needed for primary endpoint analysis. A high rate of missing data could jeopardize robustness of efficacy and safety findings and should be avoided. Refer to the SoA (Section 1.3) for data to be collected at the	Clarification and reinforcing the importance of data collection for primary and main secondary endpoints after permanent IMP discontinuation.

Section # and Name	Description of Change	Brief Rationale
	time of intervention discontinuation and follow-up and for any further evaluations that need to be completed." The following text was modified from: "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 the 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." To: "If possible, the participants who discontinue IMP 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 the visit can be scheduled 6 to 7 days after the permanent discontinuation of IMP. For participants who discontinue IMP, but who remain in the study, the remaining visits should occur as scheduled, where possible, until Week 56 (Visit 13), and all planned procedures should be performed."	Clarification of the schedule of assessments after permanent IMP discontinuation
Section 8.1.1 Hemoglobin A1c	Reference to SoA Section 1.3 added	Clarification
Section 8.2.2 Vital signs	Added clarification for heart rate measurement, text modified from: "Heart rate will be measured at the time of the measurement of seated BP" To: "Heart rate will be measured at the time of the seated BP measurement from a pulse point (as per current practice)"	Clarification on heart rate measurement.
Section 8.2.3 12-lead electrocardiogram	The text updated from: "Each ECG trace must be analyzed in comparison with the screening ECG results." To "Each ECG trace must be analyzed in comparison with the baseline ECG results."	Text corrected for consistency with the SoA.
Section 8.2.5 Hypoglycemia	Added analysis of documented hypoglycemia with a measured plasma glucose concentration "≥3.0 and ≤3.9 mmol/L (≥54 and ≤70 mg/dL)".	To align with new FDA recommendations regarding hypoglycemia definition.
Section 8.3 Adverse Event and Serious Adverse Event	The reference to Appendix 1 (Section 10.1.4.3) has been deleted from the diabetic retinopathy complications bullet.	Maintaining consistency among the sections.

Section # and Name	Description of Change	Brief Rationale
Section 8.3.1 Time period and frequency for collecting AE and SAE information	The following text was added: "All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available."	Added per Common Protocol Template.
Section 8.5 Pharmacokinetics	The following text has been added pertaining to predose PK sampling: "Blood samples for measurement of serum concentrations of efpeglenatide will be collected for all participants in order to keep blinding and analyzed for participants in efpeglenatide arms only. Participants will be asked to administer the last 2 consecutive weekly dose injections prior to PK sampling at the same injection region (eg, at Week 2 and Week 3 before the planned PK visit at Week 4)."	Clarification on the general predose PK sampling process.
	The following text has been modified from: "For a subset of participants, 10% of total (N = 12 per group): 1 additional postdose sample will be taken either 4 days (±1 day) after 1st IMP dose, or 4 days (±1 day) after 4th dose, or 4 days (±1 day) after 12th dose. To reach this number and due to the blind design of the study, PK postdose sample will be collected in the first 80 randomly assigned participants who will accept this additional sampling, sign the separate consent form, and provide a valid postdose sample." To: "For participants who consent for additional postdose PK sampling, at least 1 additional postdose sample will be taken 3 days (±1 day) after administration of efpeglenatide or placebo, preferably between Week 8 and Week 12, but other weeks are also acceptable (eg, after 1st dose, 4th dose, or 12th dose). A minimum of 120 evaluable postdose samples (in participants on efpeglenatide) are needed to contribute to popPK analysis. To reach this number and due to the blind design of the study, PK postdose samples will be collected in participants who will accept this additional sampling, sign the separate consent in the main ICF and provide a valid postdose sample until the above number of evaluable samples is confirmed."	To allow collection of more PK data in the drug absorption phase and to allow higher flexibility with regard to postdose sample collection window in order to facilitate additional postdose sampling.

Section # and Name	Description of Change	Brief Rationale
Section 8.8.1 Immunogenicity Assessments	The following wording changed: From "Blood samples are taken to assess the ADA status (positive or negative) and level (titer)." To "Blood samples for assessment of ADA status (positive or negative) and level (titer) will be collected for all participants in order to keep blinding and analyzed for participants in efpeglenatide arms only."	Clarification provided for ADA sampling requirements.
	And from "Participants positive for ADAs at the end of study, and who experienced severe injection site or hypersensitivity reaction at any 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." To "Participants positive for ADAs at EOS, and who experienced severe injection site or hypersensitivity reaction at any time during the study, will be asked to provide additional samples for anti efpeglenatide antibodies assessments approximately 4 and 6 months after the end of the treatment or as soon as possible after study database lock whichever comes later."	Clarification on the ADA follow-up sampling for patients who are ADA positive at the EOS and experienced predefined severe events while on treatment
Section 9.4.3, Table 8 Other analyses	Clarified text pertaining to postdose PK samplings, text changed from: "Efpeglenatide predose and postdose 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." To "Efpeglenatide predose and postdose 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."	Clarification of PK statistical analysis

Section # and Name	Description of Change	Brief Rationale
Section 10.1.3 Data protection	The following text was added: "All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the GDPR (Global Data Protection Regulation)." "When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party."	To update the section with reference to GDPR and archiving requirements.
Section 10.1.6 Data quality assurance	Text was updated for retaining records and documents from 15 years to 25 years after the signature of the final study report	To update in accordance with new document retention requirements
Section 10.1.4.3 Independent expert Section 10.5.5. Guidance for monitoring of participants with diabetic retinopathy	Section 10.1.4.3 pertaining to independent ophthalmologist expert review has been deleted. Added the following details of management of participants with retinopathy in Section 10.5.5. "Investigators are reminded that all participants should have eye examinations based on their retinopathy status, performed by a professional eye care provider according to International Council of Ophthalmology (ICO) guidelines or local standards; all efforts to be done to collect all medical documents from ophthalmologic examination(s) related to potential diabetic retinopathy events."	Adverse event of diabetic retinopathy complications will be reviewed as per current medical review process without an independent ophthalmologist expert review.
Section 10.1.7 Source documents	Specified the name of reference document "GCP training module"	Clarification.
Section 10.3 Appendix 3	Specified the name of reference document "the site file (detailed Study Contact List)".	Clarification.
Section 10.5 Appendix 5	Flowchart for neutropenia was updated	To update in accordance with new follow-up recommendations
Section 10.5.2.1 Elevation of amylase and/or lipase >2 x ULN without clinical signs and/or symptoms	The following bullet points were updated From "If value(s) is/are >2 to 3 × ULN: retest within 7 days. If value(s) is/are >3 × ULN: retest within 48 hours." To "If value(s) is/are >2 to 3 × ULN in a participant with baseline amylase and/or lipase values <2 × ULN: retest within 7 days. If value(s) is/are >3 × ULN: retest within 48 hours, regardless of baseline amylase and/or lipase values."	Clarification on the recommendations for amylase/lipase retest according to baseline values
Throughout	Editorial, typographical error corrections and document formatting revisions	To improve readability and overall quality of the document.

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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 basal insulin alone or in combination with oral antidiabetic drug(s)

Short title: Efficacy and safety of efpeglenatide versus placebo in patients with Type 2 diabetes mellitus inadequately controlled with basal insulin alone or in combination with oral antidiabetic drug(s) (AMPLITUDE-L)

Rationale:

The aim for the present trial is to compare efpeglenatide once weekly versus placebo once weekly in addition to Lantus alone or with oral antidiabetic drug(s) OAD, in a population of patients with type 2 diabetes mellitus (T2DM) inadequately controlled with basal insulin alone or in combination with OAD(s), in terms of glycemic control, weight control, and other efficacy and safety parameters.

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 basal insulin alone or in combination with OAD(s)	• 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 Week 30 and Week 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, OAD: oral antidiabetic drug, T2DM: type 2 diabetes mellitus

Overall design:

This study is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel-group study in participants with T2DM inadequately controlled with basal insulin alone or in combination with OAD(s).

The randomization (1:1:1:1) to efpeglenatide 2 mg, efpeglenatide 4 mg, efpeglenatide 6 mg, or placebo will be stratified by screening HbA1c (<8%, ≥8%) and sulfonylurea (SU) use at screening (Yes/No).

An independent Data Monitoring Committee (DMC) will review accumulating clinical study safety data throughout the study 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 randomly assigned participants assigned to study intervention for an estimated total of 100 participants per treatment group. All randomly assigned 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 comprises 4 periods as follows:

- A 2-week Screening Period.
- 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 posttreatment Follow-up Period to collect safety information after last dose of IMP.

The maximum study duration per participant will be 64 weeks.

Study interventions

Investigational medicinal product

Efpeglenatide/Matching placebo

- Formulation: 500 µL of a sterile, nonpyrogenic, 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.

The dose will be titrated as shown in the table below. From Week 4 (Visit 4) through the rest of the double-blind treatment period, participants will remain on the randomized IMP until the end of treatment (EOT) at Week 56 (Visit 13).

Investigational medicinal product dose schedule

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
	Day 1	**Week 1**	**Week 2**	**Week 3**	**Week 4**
	Visit 2		**Visit 3**		**Visit 4**
Dosing	*(on-site)*	*(at home)*	*(on-site)*	*(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 product

Lantus

- Formulation: Lantus will be supplied as a sterile, nonpyrogenic, clear, colorless solution in the marketed Lantus SoloStar prefilled (disposable) pen (insulin glargine 100 U/mL solution for SC injection). Each Lantus SoloStar contains in total 300 units of insulin glargine (3.0 mL of 100 units/mL insulin glargine solution). The pen allows dose setting in the range of 1 to 80 units with minimum of 1 unit increment. Lantus must not be diluted or mixed with any other insulin or solution.
- Route of administration: SC.
- Dose regimen: Injections should be administered once daily at any time of the day, but at the same time every day SC to the abdomen, thigh, or upper arm. Within these regions, the sites of injection should be changed (rotated) at each administration to prevent skin reactions.

Lantus starting dose at beginning of treatment period

- At randomization, the prestudy dose of basal insulin (glargine 100 U/mL) should be converted to an equivalent dose of Lantus on a 1:1 unit basis. If HbA1c at screening is ≤8.0%, the daily dose of Lantus should be reduced by 20% at randomization in order to avoid hypoglycemia when the participant starts the combination therapy with IMP.
- The starting dose of Lantus can be further adjusted as per Investigator's discretion based on most recent fasting self-monitored plasma glucose (SMPG) values and HbA1c value before randomization.

Lantus dose adjustment

- **After randomization**, the Lantus dose should be kept stable within the first 8 weeks after addition of study treatment unless a dose adjustment is required in case of, eg, repeated hypoglycemia. After Week 8 (Visit 5), the Lantus dose should be adjusted according to the algorithm or local titration standards as needed based on the median of the 3 most recent fasting (prebreakfast) SMPG values measured by the participant using the glucose meter and accessories supplied by the Sponsor. The SMPG values and all Lantus dose adjustments must be documented in the patient diary.
- **Daily fasting (prebreakfast) SMPG** measurements are required during first 8 weeks after randomization, when the study treatment is added and increasingly contributing to the glucose-lowering activity. After Week 8 (Visit 5), three fasting (prebreakfast) SMPG values per week are mandatory prior to each visit (these may include the day of the visit). During the other weeks, fasting SMPG values are to be measured at the discretion of the Investigator.

Recommended Lantus dose adjustment algorithm

Median of the 3 most recent fasting (prebreakfast) SMPG values	Lantus dose adjustments (U/day)*
≥10 mmol/L (≥180 mg/dL)	+8
≥7.8 mmol/L to <10.0 mmol/L (≥140 to <180 mg/dL)	+6
≥6.7 to <7.8 mmol/L (≥120 and <140 mg/dL)	+4
>5.6 to <6.7 mmol/L (>100 and <120 mg/dL)	+2
Glycemic target: ≥4.4 to 5.6 mmol/L (≥80 to 100 mg/dL), inclusive	No change
≥3.3 and <4.4 mmol/L (≥60 to <80 mg/dL)	-2
<3.3 mmol/L (<60 mg/dL) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) in the preceding week.	- 3 to -4 or at the discretion of the Investigator or medically qualified designee**

* Dose adjustment should not be done more often than every 3 to 4 days.
** in case of SU background treatment, SU reduction or discontinuation might also be considered
SMPG: self-monitored plasma glucose, SU: sulfonylurea

In case of any concerns with the treatment, more visits (telephone contact or clinic visits) than those scheduled may be arranged as needed.

Oral antidiabetic drug(s) (OAD[s])

- Route of administration: Oral.
- Dose regimen: Administered as per Investigator prescription and in accordance with local labeling. If metformin is taken as the only OAD in addition to the basal insulin, it should be at a dose of ≥1500 mg/day (or maximum tolerated dose or as per country regulation if less). Dose(s) of background OAD(s) should be kept stable throughout the study unless dose reduction is needed for safety reasons.

Rescue therapy

- Route of administration: Oral, injectable.
- Dose regimen: Open-label rescue medication(s) to treat hyperglycemia will be prescribed at the discretion of the Investigator and in accordance with local standard of care and prescribing practice. Adjustments of the Lantus dose will not be considered as rescue therapy. If adjustment of the Lantus dose does not result in further improvement of glycemic control, the recommended approach is addition of prandial insulin. With the exception of other glucagon-like peptide 1 receptor agonists (GLP-1 RA) and dipeptidyl peptidase 4 (DPP-4) inhibitors, any approved medication(s), including OADs 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 be continued and must remain blinded until the end of the study (unless the Investigator considers a change necessary for safety reasons). Refer to Section 6.1.2.2 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 in all participants randomized, using HbA1c values measured 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 method in 2 parts as follows:

1. Missing endpoint data in participants who prematurely discontinue the IMP before the Week 30 visit will be imputed using a model estimated from participants in the same treatment arm who prematurely discontinue the IMP 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 IMP 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.
2. Missing endpoint data in all participants, including those in the efpeglenatide arms, who stay on the IMP until the Week 30 visit, will be imputed separately, using a model estimated from participants in the placebo group who stay on the IMP 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 completed 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 SU (yes/no) 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.

As noted, the number of retrieved dropouts is expected to be small, and there may not be sufficient data to support the imputation approach in item 1 described above. If there are fewer than 5 participants in any treatment arms who prematurely discontinue the IMP before the Week 30 visit but have the HbA1c measurements 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 IMP 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.

A hierarchical procedure will be performed 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 for the 6 mg dose of efpeglenatide, then the superiority of the 4 mg dose of efpeglenatide versus placebo will be tested. If superiority is also demonstrated for the 4 mg dose of efpeglenatide, then the lowest dose (2 mg) versus placebo will be tested. When the superiority is not obtained in a step, then 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 Treatment Extension Period. The summary will include the number of observations, mean, standard deviation (SD), 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 [OC]).

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

Continuous secondary efficacy endpoints will be analyzed using the same ANCOVA model with missing values imputed by MI method as the method 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 the 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 nonresponders in the intent-to-treat (ITT) population.

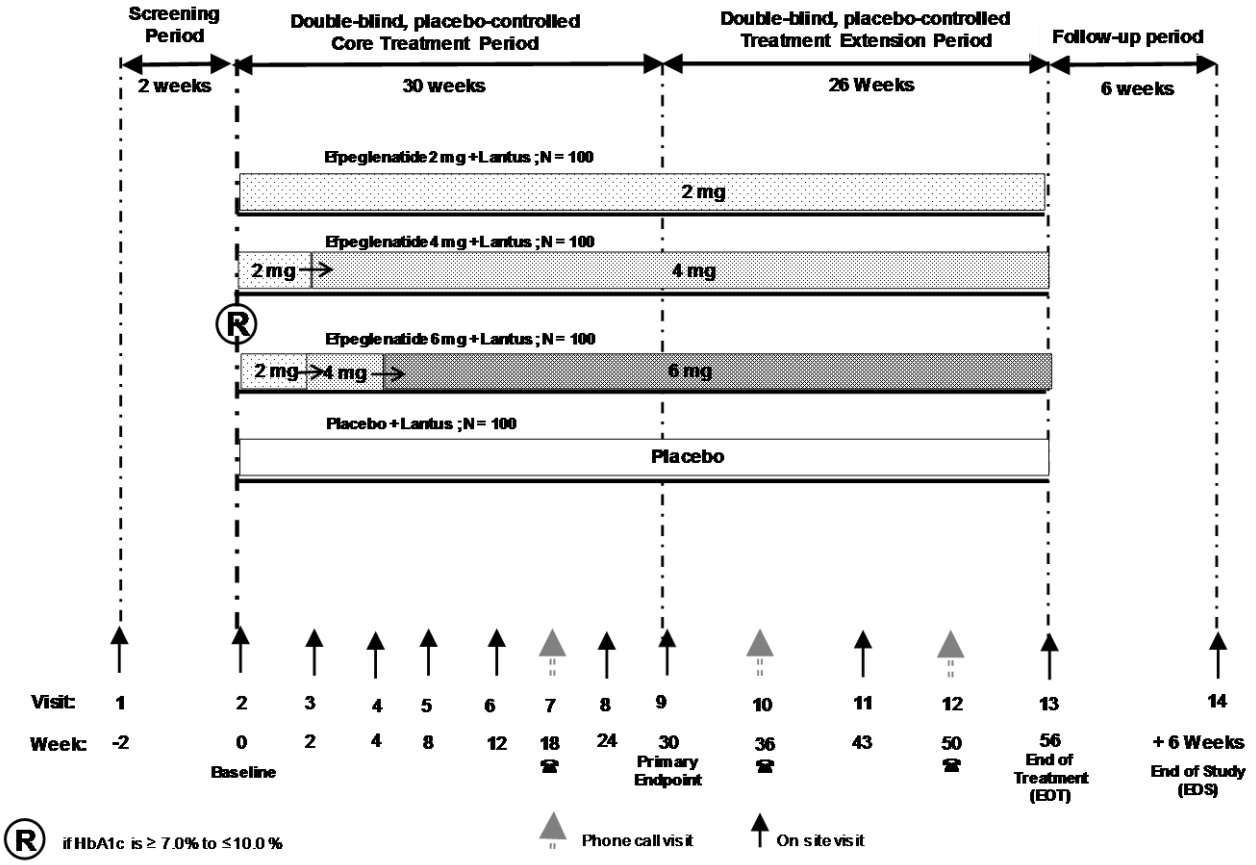
Comparisons of time-to-event endpoints between treatment groups will be performed using the Cox proportional hazards regression model with the treatment groups (efpeglenatide 2, 4, or 6 mg, or placebo), randomization stratum of screening HbA1c (<8%, ≥8%), randomization stratum of SU use (yes/no), and 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 (<8.0% and ≥8.0%) at Week -2 and SU use (Yes/No) at screening.
Visit schedule: From Visit 1 (Week -2) to Visit 14 (Week 56/EOT + 6 weeks)
EOS, end of study; EOT, end of treatment; HbA1c, hemoglobin A1c; R, Randomization; SU, sulfonylurea.

1.3 SCHEDULE OF ACTIVITIES (SOA)

Procedure	Screening (2 weeks)	Double-blind, placebo-controlled Core Treatment Period (30 weeks)								Double-blind, placebo-controlled Treatment Extension Period (26 weeks)				Post-treatment Follow-up Period (6 weeks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
		R					☎			☎		☎	**EOT**	**EOS**	
Week	**-2**	**0** Baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**[a]	**36**	**43**	**50**	**56**	Last IMP+ 6 weeks	
Acceptable range (days)	-14 to -11	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)	
Injection of weekly dose on the day of visit		X	X	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													Check eligibility before randomization
Demography, medical/surgical history	X														Includes diabetes complications, cardiovascular (CV) and allergy history, alcohol and smoking habits
Physical examination	X	X				X			X		X		X		
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	

Procedure	Screening (2 weeks)	Double-blind, placebo-controlled Core Treatment Period (30 weeks)								Double-blind, placebo-controlled Treatment Extension Period (26 weeks)				Post-treatment Follow-up Period (6 weeks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
		R					☎			☎		☎	**EOT**	**EOS**	
Week	**-2**	**0** Baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**[a]	**36**	**43**	**50**	**56**	Last IMP+ 6 weeks	
Acceptable range (days)	-14 to -11	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)	
Waist circumference		X							X				X		See Section 8.1.4
12-lead ECG		X				X			X				X		The 12-lead ECG recording should be obtained in supine position prior to IMP dose administration (see Section 8.2.3).
Transition from prestudy insulin glargine 100 U/mL to Lantus		X													See Section 6.1.2.1 of NIMPs.
IMP injection training/retraining with prefilled syringe if needed	X	X	X	X	X	X		X	X		X				See Section 6.1.1.
Review of injection sites		X	X	X	X	X		X	X		X		X	X	
Diary dispensation	X	X	X	X	X	X		X	X		X		X		
Diary collection		X	X	X	X	X		X	X		X		X	X	
Review of SMPG and Lantus dose adjustments		X	X	X	X	X	X	X	X	X	X	X	X	X	
Glucose meter dispensation and training	X														Will include training for hypoglycemia awareness and management.
Diet and lifestyle counselling		X	X	X	X	X		X	X		X		X		As per current practice, to be documented (Section 5.3.1).
IRT contact	X	X	X	X	X	X		X	X		X		X	X	
Lantus dispensation		X	X	X	X	X		X	X		X				
Lantus collection and accounting			X	X	X	X		X	X		X		X		

Procedure	Screening (2 weeks)	Double-blind, placebo-controlled Core Treatment Period (30 weeks)								Double-blind, placebo-controlled Treatment Extension Period (26 weeks)				Post-treatment Follow-up Period (6 weeks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
		R					☎			☎		☎	**EOT**	**EOS**	
Week	**-2**	**0** Baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**[a]	**36**	**43**	**50**	**56**	Last IMP+ 6 weeks	
Acceptable range (days)	-14 to -11	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)	
IMP dispensation		X	X	X	X	X		X	X		X				
IMP collection and accounting			X	X	X	X		X	X		X		X		
Compliance		X	X	X	X	X	X	X	X	X	X	X	X		SMPG, IMP, Lantus, diary
Efficacy:															
HbA1c	X	X				X			X		X		X		
FPG		X			X	X			X		X		X		For these visits, participants need to come in fasting conditions as described in Section 5.3.1 and Section 8.1.2.
C-peptide (fasting)		X													For these visits, participants need to come in fasting conditions as described in Section 5.3.1.
7-point SMPG profiles (on at least 1 day in the week prior to the visit)		X				X			X				X		Performed on at least 1 day in the week prior to clinical visits indicated. See Section 8.1.5 for complete details.
Fasting (prebreakfast) SMPG		X	X	X	X	X	X	X	X	X	X	X	X	X	Daily within first 8 weeks after randomization and at least 3 days in the other weeks, prior to visits indicated. See Section 8.1.5.
Safety:															
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)

Procedure	Screening (2 weeks)	Double-blind, placebo-controlled Core Treatment Period (30 weeks)								Double-blind, placebo-controlled Treatment Extension Period (26 weeks)				Post-treatment Follow-up Period (6 weeks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
		R					☎			☎		☎	**EOT**	**EOS**	
Week	**-2**	**0** Baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**[a]	**36**	**43**	**50**	**56**	Last IMP+ 6 weeks	
Acceptable range (days)	-14 to -11	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)	
Lipid profile		X							X				X		See Appendix 2 (Section 10.2)
Urinalysis		X							X				X		See Appendix 2 (Section 10.2)
Pregnancy test (for women of childbearing potential)	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 nonchildbearing potential. In case the definition of postmenopausal or premenopausal cannot be satisfied. See Appendix 4 (Section 10.4).
ADA		X		X		X			X				X	X	Participants positive for ADAs at the end of study, and who experienced severe injection site or hypersensitivity reaction at any time during the study will be asked to provide samples for anti-efpeglenatide antibodies assessments 4 and 6 months after the end of the treatment or as soon as possible after study database lock whichever comes later.
IMP concentration (PK)				X		X		X	X						All participants will have 1 blood sample

Procedure	Screening (2 weeks)	Double-blind, placebo-controlled Core Treatment Period (30 weeks)								Double-blind, placebo-controlled Treatment Extension Period (26 weeks)				Post-treatment Follow-up Period (6 weeks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
		R					☎			☎		☎	**EOT**	**EOS**	
Week	**-2**	**0** Baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**[a]	**36**	**43**	**50**	**56**	Last IMP+ 6 weeks	
Acceptable range (days)	-14 to -11	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)	
Sampling															collected just before their weekly injection (and at least 6 days after last IMP dose administration) for the predose serum concentration (C_{trough}) of efpeglenatide at selected clinical visits. For participants who consent, at least 1 additional postdose sample will be taken 3 days (±1 day) after administration of IMP, preferably between Week 8 and Week 12. See Section 8.5.
Rescue therapy assessment		Continuous assessment and recording during treatment periods													After randomization, the need of rescue therapy should be assessed by the Investigator via fasting SMPG performed by the participants and the central laboratory alerts received on FPG and on HbA1c (from Week 12 onwards). Participants must have an unscheduled in-person visit prior to rescue therapy initiation, with the assessments normally planned for EOT visit. See Section 6.1.2.2.

Procedure	Screening (2 weeks)	Double-blind, placebo-controlled Core Treatment Period (30 weeks)								Double-blind, placebo-controlled Treatment Extension Period (26 weeks)				Post-treatment Follow-up Period (6 weeks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
		R					☎			☎		☎	**EOT**	**EOS**	
Week	**-2**	**0** Baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**[a]	**36**	**43**	**50**	**56**	Last IMP+ 6 weeks	
Acceptable range (days)	-14 to -11	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)	
Concomitant medication review	Continuous assessment and recording throughout the study														
AE/SAE recording															
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.

a **In case of premature permanent IMP discontinuation**, the participant should have a visit as soon as possible after the last IMP administration with the assessments normally planned for EOT visit (including a PK sample if the visit can be scheduled 6-7 days after the permanent IMP discontinuation). Afterwards, the participant should continue in the study up to the scheduled date of study completion and be followed according to the study procedures as specified in the protocol. Every effort should be made to have the participant complete the Week 30 and Week 56 visits' assessments (primary and main secondary endpoints) as the minimum.
For safety reasons, participants who do not want to continue to be followed in the study after IMP discontinuation should be assessed 6 weeks (±1 week) from the last IMP dose (at the minimum) using the procedure normally planned for the posttreatment follow-up visit (EOS). At the time corresponding to their Week 56 visit, all attempts will be made to contact the participant to inquire about safety and/or vital status.

Abbreviations: ADA: antidrug antibody, AE: adverse event, β-HCG: beta-human chorionic gonadotropin, BP: blood pressure, CV: cardiovascular, ECG: electrocardiogram, eCRF: 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, NIMP: noninvestigational medicinal product, PK: pharmacokinetic, 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 aim for the present trial is to compare efpeglenatide once weekly versus placebo once weekly in addition to Lantus alone or with OAD(s), in a population of patients with T2DM inadequately controlled with basal insulin alone or in combination with OAD(s), in terms of glycemic control, weight control, and other efficacy and safety parameters.

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 through daily to weekly injections. Glucagon-like peptide-1 is an endogenous enteroendocrine hormone secreted by L-cells of the distal intestine in response to oral nutrient ingestion. It has multiple physiologic effects that contribute to controlling hyperglycemia, such as 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 exendin-4 (exenatide) analogue that is being developed for the treatment of T2DM by once-weekly SC injection. 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) including approximately 1000 participants (~720 exposed to efpeglenatide) have been completed. The Phase 2 studies have been conducted in participants with T2DM and in obese nondiabetic 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 nondiabetic obese subjects, weekly doses of 4 to 6 mg and doses of 6 mg and 8 mg every other week were investigated. Overall, these studies have demonstrated that efpeglenatide improves glycemic control and reduces body weight, with an overall favorable safety and tolerability profile consistent with currently available GLP-1 RAs. Based on Phase 1 and 2 study data, 3 weekly efpeglenatide doses (2, 4, or 6 mg) have been selected for use in Phase 3 studies. These doses are expected to demonstrate efficacy in the target population while mitigating potential safety concerns and the incidence of adverse events (AEs).

Details of nonclinical and clinical information on efpeglenatide can be found in Section 5 Nonclinical studies and Section 6 Effects in humans, respectively, of the Investigator's Brochure (IB) (1).

2.3 BENEFIT/RISK ASSESSMENT

The nonclinical 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 EFC14893:

- Gastrointestinal (GI) disorders such as nausea/vomiting and rarely pancreatitis are the most common AEs to the GLP-1 RAs class. 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 EFC14893 will reduce intensity and frequency of GI events, mainly nausea and vomiting.
- Increase in heart rate is a known side-effect of GLP-1 RAs. In study EFC14893, periodic monitoring of vital signs including heart rate and blood pressure will be regularly performed.
- 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, GLP1-RAs are contraindicated in patients with a personal or family history of medullary thyroid cancer (MTC) or in patients with multiple endocrine neoplasia syndrome Type 2 (MEN-2). In study EFC14893, patients with history of MTC or MEN-2 or with elevated calcitonin levels (≥5.9 pmol/L [20 pg/mL]) at screening will not be randomized. Calcitonin will be monitored throughout the study and guidelines for follow-up are provided if this threshold will be reached after randomization.
- Diabetic retinopathy complications have been reported for one of GLP-1 RAs (as of 05 December 2017). No cases have been reported for efpeglenatide in completed Phase 1 and 2 studies. Patients 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 EFC14893 includes the collection of AEs, antidrug antibodies (ADA, immunogenicity, [2, 3]), as well as safety laboratory and 12-lead electrocardiogram (ECG).
- In 3 large Phase 2 clinical studies with efpeglenatide (HM EXC-203, HM-EXC-204, and HM-EXC-205), overall a total of 12 out of 571 participants on efpeglenatide and 3 out of 183 participants on comparators had postbaseline alanine aminotransferase (ALT) elevation ≥3 × ULN; most had confounding factors (1). 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 EFC14893. These sparse PK samples will be used for population PK (popPK) analyses to determine the PK characteristics of efpeglenatide in the target T2DM population.

The risks to the study participants will be minimized by careful patient 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. Suggested actions and follow-up measurements for laboratory abnormalities and other safety findings are provided in Appendix 5 (Section 10.5) of the protocol.

Placebo injections will not contribute to lower the plasma glucose but the participation in the study may increase patient 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 fasting plasma glucose (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. Central laboratory alerts on FPG and on HbA1c (from Week 12 and 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 Section 2 Summary and Section 7 Summary of data and guidance for the Investigator, respectively, of the IB (1).

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 basal insulin alone or in combination with OAD(s).	• 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 Week 30 and Week 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 pharmacokinetics (PK) of efpeglenatide in dose regimen of once weekly injection of 2, 4, and 6 mg.	• Serum concentration (C_{trough}) of efpeglenatide at predose (Weeks 4, 12, 24, and 30). • Postdose serum concentration of efpeglenatide in participants who consent.
To evaluate the immunogenicity of once weekly injection of efpeglenatide 2, 4, and 6 mg.	• Number of participants by ADA status (positive/negative) at scheduled visits. • Number of participants with treatment-induced ADAs (among the participants with 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. • 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 polyethylene glycol (PEG) linker of efpeglenatide at scheduled visits.

Objectives	Endpoints
To compare the effects on once weekly injection of efpeglenatide 2, 4 and 6 mg with placebo on additional parameters of glycemic control	• Change from baseline to Week 30 and Week 56 in mean 24-hour SMPG (7-point SMPG 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 HbA1c <7.0% at Week 30 and Week 56 without weight gain. • Time to initiation of rescue therapy. • Number of participants with rescue therapy used until Week 30 and Week 56. • Change from baseline to Week 56 in FPG. • Number of participants with HbA1c <7.0% at Week 56.
To compare the effects on once weekly injection of efpeglenatide 2, 3 and 6 mg with placebo on waist circumference	• Change from baseline to Week 30 and Week 56 in waist circumference.
To compare the effect of once weekly injection of efpeglenatide 2, 4, and 6 mg with placebo on insulin dose	• Change from baseline to Week 30 and 56 in daily basal insulin dose.

ADA: antidrug antibody, AE: adverse event, FPG: fasting plasma glucose, GLP-1: glucagon-like peptide-1, HbA1c: hemoglobin A1c, OAD: oral antidiabetic drug, PK: pharmacokinetic, PEG: polyethylene glycol, PPG: post prandial glucose, SMPG: self-monitored plasma glucose, T2DM: type 2 diabetes mellitus

3.1 APPROPRIATENESS OF MEASUREMENTS

Efpeglenatide added to basal insulin alone or in combination with OAD(s) in participants with T2DM who have inadequate glycemic control on their previous antidiabetic therapy 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 measurement for assessing the efficacy of a novel treatment for Type 2 diabetes.

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 preprandial and postprandial plasma glucose (PPG) have been observed with efpeglenatide in previous studies. Therefore, assessment of both preprandial 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 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 EFC14893, is a multicenter, 30-week, double-blind, randomized, placebo-controlled Phase 3 study with an additional 26-week Treatment Extension Period evaluating the efficacy and safety of efpeglenatide addition in participants with T2DM inadequately controlled with basal insulin alone or in combination with OAD(s).

Eligible participants will be randomly assigned 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 SU use at screening (Yes/No). Masked weekly dose escalation over the course of 4 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 randomly assigned 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 PFSs.

The study will be comprised of 4 periods as follows:

- A 2-week screening period.
- 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 posttreatment Follow-up Period to collect safety information after last dose of IMP.

The maximum study duration per participant will be 64 weeks.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This study is designed to demonstrate the efficacy and safety of efpeglenatide when used as added antidiabetic treatment in participants with T2DM inadequately controlled with basal insulin alone or in combination with OAD(s). Efpeglenatide will be compared to placebo. 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 so most likely, 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 (1).

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 T2DM.

I 03. Diabetes diagnosed at least 1 year before screening.

I 04. Participants on a background antidiabetic treatment for which all of the below apply:

a) Participants on basal insulin regimen alone or in combination with OAD(s) for at least 6 months prior to screening,

b) Participants on insulin glargine 100 U/mL as only basal insulin for at least 3 months prior to screening,

c) Participants on stable daily dose of insulin glargine 100 U/mL (±20% total dose) for at least 2 months prior to screening.

I 05. HbA1c between 7.0% and 10.0% (inclusive) measured by the central laboratory at screening.

Informed consent

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

E 02. 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 03. 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 requiring medical treatment within 6 months prior to screening or history of surgery affecting gastric emptying.

E 04. History of pancreatitis (unless pancreatitis was related to gallstones and cholecystectomy has been performed), pancreatitis during previous treatment with incretin therapies, chronic pancreatitis, pancreatectomy.

E 05. Personal or family history of MTC or genetic conditions that predisposes to MTC (eg, multiple endocrine neoplasia syndromes).

E 06. Body weight change of ≥5 kg within the last 3 months prior to screening.

E 07. Systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg at randomization.

E 08. End-stage renal disease as defined by estimated glomerular filtration rate (eGFR, by Modification of Diet in Renal Disease [MDRD]) of <15 mL/min/1.73 m^2.

E 09. Laboratory findings at the Screening Visit:

- ALT or aspartate aminotransferase (AST) >3 × ULN or total bilirubin >1.5 × ULN (except in case of documented Gilbert's syndrome).
- Amylase and/or lipase: >3 × ULN.
- Calcitonin ≥5.9 pmol/L (20 pg/mL).

E 10. 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 11. Any clinically significant abnormality identified either in medical history or during screening evaluation (eg, physical examination, laboratory tests, ECG, vital signs) or any AE during screening period which, in the judgment of the Investigator, would preclude safe participation in the study or constrains efficacy assessment.

Prior/concomitant therapy

E 12. Participants not on stable daily dose of OAD(s) (any change in total dose) within 3 months prior to screening.

E 13. Participants on a GLP-1 RA and/or DPP-4 inhibitor in the last 3 months prior to screening.

E 14. If treatment with metformin as the only OAD: not at a stable dose of at least 1500 mg/day (except for South Korea/Taiwan: at least 1000 mg/day) or individually tolerated maximum dose for at least 3 months prior to screening.

E 15. 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 16. 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 17. Participation in any previous clinical trial of efpeglenatide/HM11260C.

E 18. Exposure to any investigational drugs in the last 4 weeks or 5 half-lives, whichever is longer, prior to screening.

E 19. Concomitant enrollment in any other clinical study involving an investigational study treatment or any other type of medical research.

Other exclusions

E 20. Any contraindication to use Lantus and OAD (if taken) as defined in the national product label(s).

E 21. Participants not willing to switch to once daily injections of Lantus.

E 22. Hypersensitivity to any of the study treatments, or components thereof, or to any GLP-1-RAs.

E 23. History of drug or alcohol abuse within 6 months prior to the time of screening.

E 24. Pregnant (confirmed by serum pregnancy test at screening) or breast-feeding women.

E 25. 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 26. 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 27. Any country-related specific regulation that would prevent the participant from entering the study.

E 28. 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 29. Participants unwilling or unable to comply with study procedures as outlined in the protocol.

E 30. 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 [4]).

Fasting conditions

- For Visits 2 (Day 1), 5 (Week 8), 6 (Week 12), 9 (Week 30), 11 (Week 43), and 13 (Week 56), participants need to come to the study center in a fasting condition after an overnight fast of no less than 8 hours, which consists of no food or liquid intake other than water. The participants should not take any antidiabetic medication before blood sampling.
- Fasting (prebreakfast and before administration of antidiabetic medication) SMPG must 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 intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

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 randomly assigned 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) includes Lantus for SC injections, OAD(s) administered as per Investigator prescription and in accordance with local labeling, and 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 6.1.2.2. Except for GLP-1 RAs and DPP-4 inhibitors, any approved medication(s) can be prescribed at the Investigator's discretion to treat the hyperglycemia. The regimen of the rescue medication(s) 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	Sterile, nonpyrogenic, 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, nonpyrogenic, 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, preferably on the same week day (eg, each Monday) at any time of the day. Injections should be administered SC to any of the following body regions: abdomen, thigh or upper arm. For each injection, the date, time, and region of administration should be recorded. Within any selected region, the site of injection should be changed (rotated) at each time to prevent skin reactions. For selected visits during the Core Treatment Period up to Week 30 (corresponding to predose PK sample collection), the weekly dose will be administered at the study 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 it 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, the participant should skip the missed dose and administer the next dose on the regularly scheduled day. In each case, participants should then	

Study intervention name	Efpeglenatide	Placebo

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.

Participants will be asked to administer the last 2 consecutive weekly dose injections prior to PK sampling at the same body region (eg, at Week 2 and Week 3 before the planned PK visit at Week 4; see Section 8.5).

Predose PK samples are expected to be collected at least 6 to 7 days after the last dose of IMP. The corresponding study visits (Visit 4, Visit 6, Visit 8, and Visit 9) and the timing of dose administration before each of these visits should be scheduled to ensure, as much as possible, the duration of 6 to 7 days between them is maintained.

IMP dose schedule

	Dose 1	Dose 2	Dose 3	Dose 4	Dose 5
	Day 1	**Week 1**	**Week 2**	**Week 3**	**Week 4**
	Visit 2		**Visit 3**		**Visit 4**
Dosing	*(on-site)*	*(at home)*	*(on-site)*	*(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

From Week 4 (Visit 4) 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 13).

Storage conditions	Store between +2°C and +8°C (36°F and 46°F). Do not freeze, protect from light.
Packaging and labeling	Study treatment will be provided in boxes, in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

The details of this table are specific to IMP; information of non-IMP is described separately in this section.

EOT: end of treatment, IMP: investigational medicinal product, NA: not applicable, PK: pharmacokinetic, PFS: prefilled syringe, SC: subcutaneous, SoA: Schedule of Activities.

6.1.1 Investigational medicinal products

The appropriate number of kits will be dispensed for the period until the next dispensing visit (please refer to the 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 1 (Screening) 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 1 (Screening) may include self-injection with a training PFS and assessment of participant's skills and understanding by observing teach-back (if needed). Also, 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 43, under close supervision).

Review of injection sites will be performed at all on-site visits.

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

In case of emergency only, for scheduled or unscheduled visits, the IMP and Lantus might be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations. Direct-To-Patient (DTP) remains an option and the participant/Investigator can refuse this option.

6.1.2 Noninvestigational medicinal products

6.1.2.1 Background medication

Lantus

Lantus is the only background therapy provided by the Sponsor. The appropriate number of kits will be dispensed for the period until the next dispensing visit (please refer to the SoA Section 1.3). Lantus will be provided until the end of study even in case of premature end of treatment for patients attending the safety follow-up visits. Storage conditions and use-by-end date (when required by country regulations) are part of the label text.

- Formulation: Lantus will be supplied as a sterile, nonpyrogenic, clear, colorless solution in the marketed Lantus SoloStar prefilled (disposable) pen (insulin glargine 100 U/mL solution for SC injection). Each Lantus SoloStar contains in total 300 units of insulin glargine (3.0 mL of 100 units/mL insulin glargine solution). The pen allows dose setting in the range of 1 to 80 units with minimum of 1 unit increment. Lantus must not be diluted or mixed with any other insulin or solution.
- Route of administration: SC.
- Dose regimen: Injections should be administered once daily at any time of the day, but at the same time every day SC to the abdomen, thigh, or upper arm. Within these regions, the sites of injection should be changed (rotated) at each administration to prevent skin reactions.

Lantus starting dose at beginning of Treatment Period

- At randomization, the prestudy dose of basal insulin (glargine 100 U/mL) should be converted to an equivalent dose of Lantus on a 1:1 unit basis. If HbA1c at screening is ≤8.0%, the daily dose of Lantus should be reduced by 20% at randomization in order to avoid hypoglycemia when the participant starts the combination therapy with IMP.
- The starting dose of Lantus can be further adjusted as per Investigator's discretion based on most recent fasting SMPG values and HbA1c value before randomization.

Lantus dose adjustment

- After randomization, the Lantus dose should be kept stable within the first 8 weeks after addition of study treatment unless a dose adjustment is required in case of, eg, repeated hypoglycemia. After Week 8 (Visit 5), the Lantus dose should be adjusted according to the algorithm (Table 3) or local titration standards as needed based on the median of the 3 most recent fasting (prebreakfast) SMPG values measured by the participant using glucose meter and accessories supplied by the Sponsor. The SMPG values and all Lantus dose adjustments are to be documented in the patient diary.
- **Daily fasting (prebreakfast) SMPG** measurements are required during first 8 weeks after randomization, when the study treatment is added and increasingly contributing to the glycemic control. After Week 8 (Visit 5), three fasting (prebreakfast) SMPG values per week are mandatory prior to each visit (these may include the day of the visit). During the other weeks fasting SMPG values are to be measured at the discretion of the Investigator.

Table 3 - Recommended Lantus dose adjustment algorithm

Median of the 3 most recent fasting (prebreakfast) SMPG values	Lantus dose adjustments (U/day)*
≥10 mmol/L (≥180 mg/dL)	+8
≥7.8 mmol/L to <10.0 mmol/L (≥140 to <180 mg/dL)	+6
≥6.7 to <7.8 mmol/L (≥120 and <140 mg/dL)	+4
>5.6 to <6.7 mmol/L (>100 and <120 mg/dL)	+2
Glycemic target: ≥4.4 to 5.6 mmol/L (≥80 to 100 mg/dL), inclusive	No change
≥3.3 and <4.4 mmol/L (≥60 to <80 mg/dL)	-2
<3.3 mmol/L (<60 mg/dL) or occurrence of 2 (or more) symptomatic hypoglycemic episodes or one severe hypoglycemic episode (requiring assistance) in the preceding week.	- 3 to -4 or at the discretion of the Investigator or medically qualified designee**

* Dose adjustment should not be done more often than every 3 to 4 days.
** in case of SU background treatment, SU reduction or discontinuation might also be considered
SMPG: self- monitored plasma glucose, SU: sulfonylurea

In case of any concerns with the treatment, additional unscheduled visits (telephone contact or clinic visits) may be arranged as needed.

Oral antidiabetic drug(s) (OAD[s])

- Route of administration: Oral.
- Dose regimen: Administered as per Investigator prescription and in accordance with local labeling. If metformin is taken as the only OAD in addition to the basal insulin, it should be at a dose of ≥1500 mg/day (or maximum tolerated dose or as per country regulation if less). Dose(s) of background OAD(s) should be kept stable throughout the study unless dose reduction is needed for safety reasons.

6.1.2.2 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 in Table 4 and are dependent on study period.

Table 4 - Rescue criteria

Time in study	Threshold
From randomization up through the scheduled Week 8 visit (Visit 5).	FPG >15.0 mmol/L (>270 mg/dL)
After the Week 8 visit up through the scheduled Week 12 visit (Visit 6).	FPG >13.3 mmol/L (>240 mg/dL)
After the Week 12 visit (Visit 6) through the end of the 30-week Core Treatment Period.	FPG >11.1 mmol/L (>200 mg/dL) or HbA1c ≥8.5%
After the Week 30 Visit (Visit 9) through the end of the Treatment Extension Period.	FPG >8.9 mmol/L (>160 mg/dL) or HbA1c ≥8.0%

FPG: fasting plasma glucose, HbA1c: hemoglobin A1c

Routine fasting SMPG and central laboratory alerts on FPG (and HbA1c from Week 12 [Visit 6] onwards) will be set up to ensure that glycemic parameter results remain below the predefined thresholds.

If a fasting SMPG value exceeds the specific glycemic limit on 1 day, the participant must check it again during the following 2 days. If all the SMPG values in 3 consecutive days exceed the specific limit, the participant should contact the Investigator and a central laboratory FPG measurement (and HbA1c from Week 12 onwards) be performed as soon as possible for confirmation.

Upon receipt of a central laboratory alert for either FPG or HbA1c, a central laboratory retest must be completed and confirmed as exceeding the threshold for rescue before rescue therapy is initiated. The retest confirmation should be performed as soon as possible during an unscheduled visit.

In the event that a confirmatory FPG and/or HbA1c value exceeds 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 fasting status (ie, no food or liquid intake [except water] for ≥8 hours).
- IMP was given at the planned dose and was appropriately injected (as per weekly schedule).
- Lantus dose was appropriately adjusted.
- 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 explanations can reasonably explain the insufficient glycemic control, the Investigator should consider not initiating rescue medication(s) and should undertake appropriate action as follows, ie:

- Assess FPG (ie, after the participant has fasted for ≥8 hours).
- Initiate an evaluation and treatment of intercurrent disease (to be reported in the AE/concomitant medication parts of the electronic Case Report Form (eCRF) and the medical record).
- Stress the absolute need for the participant 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 a FPG/HbA1c assessment at the next visit.

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

If a participant needs to start rescue therapy, an unscheduled in-person visit will be scheduled to perform prerescue assessments (which are the same as those specified for EOT, Week 56, Visit 13), prior to starting the rescue medication(s).

If adjustment of the Lantus dose does not result in further improvement of glycemic control, the recommended approach is addition of prandial insulin.

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. Adjustment in the Lantus dose will not be considered as rescue therapy. With the exception of other GLP-1 RAs and DPP-4 inhibitors, any approved medication(s) can be prescribed to treat the hyperglycemia.

If a participant requires glycemic rescue, the IMP received during the randomized, double-blind treatment period should be continued and must remain blinded until the end of the study (unless the Investigator considers a change necessary for safety reasons).

All concomitant antidiabetic medications (background OAD[s] and/or rescue therapy) will be documented in the eCRF.

The cost of background OADs and/or 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

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

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

The expiry date is mentioned on the IMP and Lantus labels (when required by country regulation), and storage conditions are written on the IMP and Lantus labels and in the instruction leaflet.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP and Lantus will be responsible for ensuring that the IMP and Lantus used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements. All IMPs and Lantus will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP and Lantus 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 by the sites 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 (except for IMP and Lantus in case of DTP shipment, for which a courier company has been approved by the Sponsor), 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

All participants will be centrally assigned to randomized study intervention using IRT as summarized in the SoA (Section 1.3). Before the study is initiated, instructions on how to access IRT will be provided to each site.

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

Previously allocated IMP should not be redispensed to the participants.

6.3.1 Methods of blinding

During the entire double-blind treatment period, Investigators and participants will be blinded to the allocation of active doses of efpeglenatide or placebo treatment arms. Efpeglenatide and placebo will be provided in indistinguishable PFSs in identical 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 IMP 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 also 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 the baseline/randomization visit (Visit 2) as those data will be masked. If the central laboratory detects FPG greater than the rescue thresholds, the Investigator will receive an alert from the central laboratory (see Section 6.1.2.2). The HbA1c alerts will also be sent if a value is greater than the threshold from the Week 12 visit (Visit 6) 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 eCRF, as applicable.

Code breaking can be performed at any time by using the proper module of the 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 predefined designated personnel from Sponsor and Bioanalytical laboratory will have access to the randomization code to allow for the sorting of the efpeglenatide blood samples. The Bioanalytical laboratory and responsible personnel will follow the standard procedures to ensure the protection of the blind within the Sponsor's clinical team. The randomization code or the individual analytical results will not be disclosed to any clinical team personnel prior to the database lock.

The DMC will receive 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]).

Randomization code breaking will be performed for reporting to the Health Authorities of any suspected unexpected serious adverse reaction (SUSAR). Refer to Section 8.3.4 for regulatory reporting requirements. The unblinding information will not be disclosed to patients, sites or any clinical team personnel prior to the database lock.

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 eCRF page for accounting purposes.
- All medication treatment kits (whether empty or unused) will be returned by the participant at each visit when treatment dispensing is planned.
- The Investigator or his/her delegate will track treatment accountability/compliance by comparing the treatment kit number recorded on the patient diary with the treatment kit number of returned treatment kits (whether empty or unused) and completes in the participant treatment log.
- The monitor in charge of the study will then checks the data entered on the IMPs administration page of the eCRF by comparing them with the IMPs that have 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 eCRF pages.

6.4.1 Return and/or destruction of treatments

A detailed treatment log of the destroyed IMP (and Lantus, as provided by the Sponsor) 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 and Lantus unless the Sponsor or delegate provides written authorization. For NIMP reimbursed by the Sponsor, tracking and reconciliation will be completed by the Investigator (or the pharmacist, if appropriate) as per local requirements.

Sharp containers containing all used PFSs 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 treatment kits will be retrieved by the Sponsor.

6.5 CONCOMITANT THERAPY

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

- Initiation of any antidiabetic agents (short-term use [<10 consecutive days] of short-acting insulin for treatment of acute illness or surgery is allowed) other than the IMP and Lantus or change in dose or preexisting OAD(s) before prerescue assessments and initiation of rescue therapy.
- Initiation of any GLP-1 RAs (eg, exenatide, lira-, dula-, or semaglutide) and DPP-4 inhibitors (eg, sita-, saxa-, vilda-, 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, 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 4 is described in Table 2. From Week 4 (Visit 4) through the rest of the double-blind treatment period, participants will remain on the randomized IMP (efpeglenatide assigned dose or placebo) until the EOT at Week 56 (Visit 13).

6.7 INTERVENTION AFTER THE END OF THE STUDY

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

When a participant's participation in the trial ends, the 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 nonparticipant contact follow-up (eg, medical record checks). 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 eCRF. 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.

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 treatment 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 eCRF.

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]), 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 randomly assigned participants, under treatment or not, will be included in the study data analyses, it is important to collect efficacy and safety data from all participants, during the entire 56 weeks of the study. Collection of Week 30 data is of highest importance as they are needed for primary endpoint analysis. A high rate of missing data could jeopardize robustness of efficacy and safety findings and should be avoided. Refer to the SoA (Section 1.3) for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

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

Handling of participants after permanent intervention discontinuation

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

If possible, the participants who discontinue IMP 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 the visit can be scheduled 6 to 7 days after the permanent discontinuation of IMP. For participants who discontinue IMP, but who remain in the study, the remaining visits should occur as scheduled, where possible, until Week 56 (Visit 13), and all planned procedures should be performed. The Investigators should discuss with them the 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 study intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Temporary discontinuation

Temporary intervention discontinuation corresponds to at least 1 (one) 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 eCRF.

7.1.2.1 Rechallenge

Re-initiation 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 it is safe for the participant to re-start the IMP. In case of IMP intolerance, a one-time rechallenge 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 where 3 or more consecutive doses are missed, the titration should be re-initiated.

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 eCRF 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.

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

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

Participants who have withdrawn from the study cannot be rerandomized (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/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 as 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 (randomization) in IRT, to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

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 (see SoA Section 1.3).

If a participant needs to receive rescue therapy (see Section 6.1.2.2), then HbA1c assessment should be performed before the introduction of rescue medication(s).

8.1.2 Fasting plasma glucose

Plasma glucose will be assessed in a fasted 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 retest should be scheduled in fasting state 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 Body weight

Body weight will be measured to allow the determination of change from baseline to Week 30 and Week 56 in body weight.

Body weight is measured at every on-site study visit (see 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 must be moved until the beam balances (the arrows are aligned). The weight must be read and recorded in the eCRF and source documents. Self-reported weights are not acceptable; participants must not read the scales themselves.

8.1.4 Waist circumference

Waist circumference will be measured at the midpoint between the lower rib margin and the iliac crest, in centimeters (cm).

The calibrated metric tape will be held firmly in a horizontal position and will be placed around the waist. It is recommended that the observer sits beside the participant while taking the measurements.

The tape should be loose enough to allow the recorder to place 1 finger between the tape and the participant's body.

Participants will be asked to breathe normally and the measure is taken at the end of a normal exhalation, while ensuring that the participant does not contract the abdominal muscles.

8.1.5 7-point self-monitored plasma glucose profiles

The 7-point SMPG profile 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 patient diary. Participants 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: prebreakfast and 2 hours postbreakfast, prelunch and 2-hour postlunch, predinner and 2-hour postdinner, and at bedtime. Two hours postprandial (breakfast, lunch, and dinner) is defined as 2 hours after the start of the meal.

On days when 7-point SMPG profiles are measured, the fasting prebreakfast SMPG profile will be considered as the first point of measurement (ie, "prebreakfast" time point).

8.1.6 Use of rescue therapy

The use of rescue medication(s) for hyperglycemia will be assessed and reported throughout the treatment period to allow determination of the start of rescue therapy and the percentage of participants using rescue therapy at Weeks 30 and 56. Routine fasting SMPG will be measured by the participants, and alerts on FPG and/or HbA1c from the central laboratory will be sent to the Investigator to ensure that glycemic parameter results remain within predefined thresholds. For details and further actions should FPG and/or HbA1c values rise values greater than the predefined thresholds, refer to Section 6.1.2.2.

8.2 SAFETY ASSESSMENTS

The 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 other selected 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 measurements will be assessed while participant is in a seated position using the same device (automated BP monitor or a manual sphygmomanometer) for each participant.
- Heart rate will be measured at the time of the seated BP measurement from a pulse point (as per current practice).
- At the Screening Visit (Visit 1), BP will be measured on both arms to identify and select the appropriate arm for future measurements. Seated BP should be measured in both arms after at least a 5 minute rest period, and then again after 1 minute in both arms while 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 eCRF.
- At subsequent visits, BP and pulse measurements are to be performed using the 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).

8.2.3 12-lead electrocardiogram

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

The 12-lead ECG should be performed after the participants has been in the supine position for at least 10 minutes 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 printout, and record it in the eCRF. Each ECG trace must be analyzed in comparison with the baseline 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.

8.2.4 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 eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal 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 an AE, then the results must be recorded in the eCRF.
- Recommended decision trees for the management of certain laboratory abnormalities are provided in Appendix 5 (Section 10.5).

8.2.5 Hypoglycemia

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

Hypoglycemic events will be categorized (5, 6, 7) as follows
(also see Appendix 8 [Section 10.8]):

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

episodes in which neurological impairment was severe enough to prevent self-treatment and which were thus thought to place participants at risk for injury to themselves or others.

Note that "requiring assistance of another person" means that the participant could not help himself or herself. Assisting a participant out of kindness, when assistance is not required, should not be considered a "requiring assistance" incident.

Severe hypoglycemia will be reported 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 less than or equal to 3.9 mmol/L (70 mg/dL). Clinical symptoms that are considered to result from a hypoglycemic episode are, eg, increased sweating, nervousness, asthenia/weakness, tremor, dizziness, increased appetite, palpitations, headache, sleep disorder, confusion, seizures, unconsciousness, or coma.
- **Asymptomatic hypoglycemia:** Asymptomatic hypoglycemia is an event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL).
- **Probable symptomatic hypoglycemia:** Probable symptomatic hypoglycemia is an event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 3.9 mmol/L (70 mg/dL); symptoms are 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 greater than 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 and ≤3.9 mmol/L (≥54 and ≤70 mg/dL) and less than 3.0 mmol/L (<54 mg/dL) will also be analyzed (5).

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

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

- 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]) will be adjudicated by CEC.
- Major adverse cardiovascular events (MACE; CV death, myocardial infarction, 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] for definition).
- Diabetic retinopathy complications; 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).

All SAEs and AESIs will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs 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 nonleading 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, nonserious 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 (IECs), and Investigators.
- Investigator safety reports must be prepared for SUSARs 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 the report along with 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 14).
- 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 CV events, see details of the AEs requiring specific monitoring above.

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 the 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 do the following:

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 for measurement of serum concentrations of efpeglenatide will be collected for all participants in order to keep blinding and analyzed for participants in efpeglenatide arms only. Participants will be asked to administer the last 2 consecutive weekly dose injections prior to PK sampling at the same injection region (eg, at Week 2 and Week 3 before the planned PK visit at Week 4).

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 dates, times, and body regions (abdomen, thigh, or arm) of drug administration. Samples not collected, missed or lost, for any reason should be recorded.

- For participants who consent for additional postdose PK sampling, at least 1 additional postdose sample will be taken 3 days (±1 day) after administration of efpeglenatide or placebo, preferably between Week 8 and Week 12, but other weeks are also acceptable (eg, after 1st dose, 4th dose, or 12th dose). A minimum of 120 evaluable postdose samples (in participants on efpeglenatide) are needed to contribute to popPK analysis. To reach this number and due to the blind design of the study, PK postdose samples will be collected in participants who will accept this additional sampling, sign the separate consent in the main ICF and provide a valid postdose sample until the above number of evaluable samples is confirmed.
- The collected blood samples will be used to determine concentrations of efpeglenatide in serum and these concentration data will be summarized and reported in the CSR.
- The concentrations will be used to perform a popPK analysis by nonlinear mixed effects modeling and the results will be reported in a separate popPK 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 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 for assessment of ADA status (positive or negative) and level (titer) will be collected for all participants in order to keep blinding and analyzed for participants in efpeglenatide arms only. Cross-reactivity of confirmed positive samples to endogenous GLP-1 (positive or negative), endogenous glucagon (positive or negative), neutralizing capacity of

ADAs, and presence of antibodies against polyethylene glycol (PEG) (positive or negative) will also be evaluated in serum at the time points specified in the SoA (Section 1.3).

Participants positive for ADAs at EOS, and who experienced severe injection site or hypersensitivity reaction at any time during the study, will be asked to provide additional samples for anti-efpeglenatide antibodies assessments approximately 4 and 6 months after the end of the treatment or as soon as possible after study database lock whichever comes later.

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 were 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% power to detect a treatment difference of -0.5% (and 96% power to detect a treatment difference of -0.6%) between each dose of efpeglenatide and placebo in HbA1c change from baseline to Week 30, assuming a common SD of 1.1% (2-sided, $\alpha = 0.05$) for each comparison.

Hence, there are 4 parallel dosing arms as follows:

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

A hierarchical procedure will be performed to adjust the multiplicity of comparison.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 5):

Table 5 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF.
Randomized	All screened participants who have a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not.
ITT	All participants randomized 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 randomly assigned.
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 postbaseline valid ADA sample after drug administration.
PK	All participants from the safety population with at least 1 valid PK sample available for analysis.

ADA: antidrug 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 6 - Efficacy analyses

Endpoint	Statistical Analysis Methods
Primary Change from baseline to Week 30 in HbA1c.	Primary analysis: The primary efficacy endpoint will be analyzed in all participants randomized, using all HbA1c values measured 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 ANCOVA model with missing values imputed by MI analysis method in 2 parts as follows: 1. Missing endpoint data in participants who prematurely discontinue the IMP before the Week 30 visit will be imputed using a model estimated from participants in the same treatment arm who prematurely discontinue the IMP 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 IMP 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.

Endpoint	Statistical Analysis Methods

2. Missing endpoint data in all participants, including those in the efpeglenatide arms, who stay on the IMP until the Week 30 visit, will be imputed separately, using a model estimated from participants in the placebo group who stay on the IMP 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. Each of the completed datasets after the imputation will be analyzed by the ANCOVA model with treatment groups, randomization strata, and geographical regions as fixed effects and the corresponding baseline HbA1c 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 as follows:

- 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 there may not be sufficient data to support the imputation approach in item 1 described above. If there are fewer than 5 participants in any treatment arms who prematurely discontinue the IMP before the Week 30 visit but have the HbA1c measurements 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 IMP 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.

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 Treatment 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 OCs).

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

Endpoint	Statistical Analysis Methods
	without HbA1c data at Week 30 creates a shift in the treatment effect of efpeglenatide from being statistically significantly better than placebo to a nonstatistically significant effect. Least squares 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 participants in the placebo group, 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 as follows: • 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 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 SU use (Yes, No). 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 values, if any. • Pattern 2: participants with baseline values but without postbaseline values during the 30-week Core Treatment Period. • Pattern 3: participants with baseline values and at least 1 postbaseline value during the 30-week Core Treatment Period but not at Week 30. • Pattern 4: participants with baseline values and a 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 <u>Assessment of treatment effect by subgroup:</u> The 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 to <75, ≥75 years) (any category with fewer than 5 participants may be combined with another category as appropriate). • Gender (Male, Female). • Baseline HbA1c (<8.0%, ≥8.0%).

Endpoint	Statistical Analysis Methods
	• Baseline BMI (<30 kg/m^2, ≥30 kg/m^2). • Diabetes duration (<10 years, ≥10 years). • Country. • United States/non-United States. • Antidiabetic drugs at the time of screening (Lantus, Lantus + OAD). • SU use at screening (Yes, No). 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 SU use (Yes, No), subgroup factor, treatment-by-subgroup factor, and region as fixed factors and using the 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 across the subgroups, as appropriate. 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, SU use), 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 colinearity 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.
Secondary Change from baseline to Week 56 in HbA1c Change from baseline to Week 30 in FPG Change from baseline to Weeks 30 and 56 in body weight Number of participants with HbA1c <7.0% at Week 30 (yes/no)	Continuous secondary efficacy endpoints will be analyzed using the same ANCOVA model with missing values imputed by MI method as the method 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 the 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 nonresponders 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 each treatment group over the whole treatment period including the 26-week Treatment 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 OCs).
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 $\alpha = 0.05$ (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. Change from baseline to Week 30 in body weight (kg) for efpeglenatide 6 mg versus placebo. 3. HbA1c <7% at Week 30 for efpeglenatide 4 mg versus placebo (yes/no). 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).

Endpoint	Statistical Analysis Methods
	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 body weight (kg) for efpeglenatide 4 mg versus placebo. 10. Change from baseline to Week 56 in HbA1c (%) for efpeglenatide 6 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. 14. Change from baseline to Week 30 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 $\alpha = 0.05$ (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.
Exploratory endpoints See Section 3	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 SU use (yes/no) and geographical region as the factors. The curve of the cumulative incidence of participants with rescue therapy initiation will be estimated using Kaplan-Meier method by treatment group. 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 Treatment 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 OCs).

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-monitored plasma glucose, SU: sulfonylurea.

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 as follows:

- The pretreatment 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 9 (Week 30) (or Day 210 if Visit 9 [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 posttreatment 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 the following:

- **Pretreatment AEs** are AEs that developed or worsened or became serious during the pretreatment period.
- **Treatment-emergent AEs (TEAEs)** are AEs that developed or worsened or became serious during the on-treatment period.
- **Posttreatment AEs** are AEs that developed or worsened or became serious during the posttreatment period.

Table 7 - 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 who experienced an AE. The primary focus of AE reporting will be on TEAEs. Pretreatment and posttreatment AEs will be described separately. Adverse event incidence tables 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 for the "30-week core on-treatment period" and for the "whole on-treatment period including the 26-week controlled Treatment Extension Period". AE, SAE, and AEs leading to death tables will be presented for the 30-week on-study period too.
Hypoglycemia	The number (%) of participants with at least 1 hypoglycemic event during the 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], daytime [06:00 to 23:59]). Documented hypoglycemia (symptomatic or asymptomatic) will be also evaluated for the more stringent SMPG threshold of <3.0 mmol/L (<54 mg/dL). Summaries will be presented overall and by type of event for each treatment group. The total number of events (per participant-years) will be computed and summarized overall and by type of event for each treatment group. Similar summaries will be also provided for the 30-week core on-treatment period.

Endpoint	Statistical Analysis Methods
Vital signs and laboratory data ECG data	For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and changes 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 on-treatment period. Results will be presented both in standard international and conventional US units. The incidence of normal and abnormal ECG status at any time during the on-treatment period will be summarized by treatment group whatever the baseline level and according to baseline status. Tables will be presented on the "30-week core 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, SMPG: self-monitored plasma glucose, SOC: system organ class, TEAE: treatment-emergent adverse event.

9.4.3 Other analyses

Analyses of other endpoints are detailed in Table 8.

Table 8 - 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 ADA (among the participants with ADA negative or missing at baseline) during the study period. • Number and percentage of participants with treatment-boosted ADA (among the participants with ADA positive at baseline) during the study period. • ADA titer at scheduled time points will be summarized by visit using descriptive statistics by number (N), median, quartiles, minimum, and maximum. • Number and percentage of participants with ADA cross-reactivity to endogenous GLP-1 at scheduled visits. • Number and percentage of participants with ADA cross-reactivity to endogenous glucagon at scheduled visits. • Number and percentage of participants with ADAs directed against PEG linker of efpeglenatide at schedule visits. Correlation, scatterplots, and/or subgroup analyses will be conducted as appropriate to assess the relationship between immunogenicity endpoints and efficacy/safety assessments.

Endpoint	Statistical Analysis Methods
PK endpoints: serum concentration of efpeglenatide at predose and postdose	Efpeglenatide predose and postdose serum concentrations of participants in the efpeglenatide groups will be listed and summarized in the PK population, using descriptive statistics by n geometric mean, coefficient of variation, median, minimum and maximum.

ADA: antidrug antibody, GLP-1: glucagon-like peptide 1, PEG: polyethylene glycol, PK: pharmacokinetic.

9.5 INTERIM ANALYSES

Not applicable.

9.5.1 Data Monitoring Committee (DMC)

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

10.1.2 Informed Consent Process

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

- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be reconsented 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 postdose PK assessment sub-study.
- A separate signature will be required to document 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. 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.

10.1.3 Data Protection

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

- 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: white, black or African American, Asian, Other) will be collected in this study because these data are required by several regulatory authorities (eg, on African American population for US Food and Drug Administration [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.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.4 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 the following:

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

The DMC will review and analyze, 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 CV events (nonfatal MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), pancreatic events, and other selected AEs (to be defined in the CEC charter). This review will be conducted in a blinded manner with regard to IMP.

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 clinical trial register (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, the Sponsor continues to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.6 Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7 Source documents

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

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 9 will be performed by the central laboratory, except urine pregnancy tests and urinalysis by dipstick, which will be performed locally (at the study site).
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed locally at any time during the study as determined necessary by the Investigator or required by local regulations. If the local laboratory test results are used to make a study treatment decision or response evaluation or to diagnose and/or follow-up an AE, the results must be entered into the eCRF.

Table 9 - Protocol-required safety laboratory assessments

Laboratory assessments[a]	Parameters			
Hematology	Platelet count		WBC count with differential:	
	RBC count		Neutrophils	
	Hemoglobin		Lymphocytes	
	Hematocrit		Monocytes	
			Eosinophils	
			Basophils	
Clinical chemistry	Creatinine	Potassium	AST	Total bilirubin (in case of values above the normal range, differentiation in conjugated and nonconjugated bilirubin).
	Sodium	ALP	ALT	eGFR (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	
Antidrug antibodies	Serum antidrug antibody			
Calcitonin	Calcitonin			
Other screening tests	• Follicle-stimulating hormone and estradiol (as needed in unconfirmed postmenopausal women). • NOTE: For women not of 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 eCRF.
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.
ALT: alanine aminotransferase, ALP: alkaline phosphatase, AST: aspartate aminotransferase, β-HCG: human beta-chorionic gonadotropin, eGFR: estimated glomerular filtration rate, MDRD: Modification of Diet in Renal Disease, RBC: red blood cells, WBC: white blood cell, WOCBP: women of childbearing potential.

Investigators must document their review of each laboratory safety report.

The HbA1c and FPG values that could unblind the study will not be reported to study sites or other blinded personnel after Visit 2 (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 patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.

  NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

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

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

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

Assessment of causality

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

Follow-up of AEs and SAEs

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

REPORTING OF SAEs and AESIs

SAE/AESI reporting to Sponsor representative via an electronic data collection tool

- The primary mechanism for reporting an SAE/AESI to the Sponsor representative will be the electronic data collection tool.
- If the electronic system is unavailable for more than 24 hours, then the site will use the paper SAE/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 (see next section) or to the Sponsor representative by telephone.
- Contacts for SAE/AESI reporting can be found in the site file (detailed Study Contact List).

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 postmenopausal unless permanently sterile (see below).

Women in the following categories are not considered WOCBP

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

   Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

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

CONTRACEPTION GUIDANCE

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly as described in Table 10.

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

Table 10 - Highly effective contraceptive methods

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

NOTES:

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

b Pharmacokinetic drug-interaction potential of oral hormonal contraception with the study treatment is low, but still unknown. Therefore, if the oral contraceptive cannot be replaced by 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 (ie, until Follow-up Visit 15) after the last dose of IMP.

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 ±7 days after the last dose of study intervention), 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.

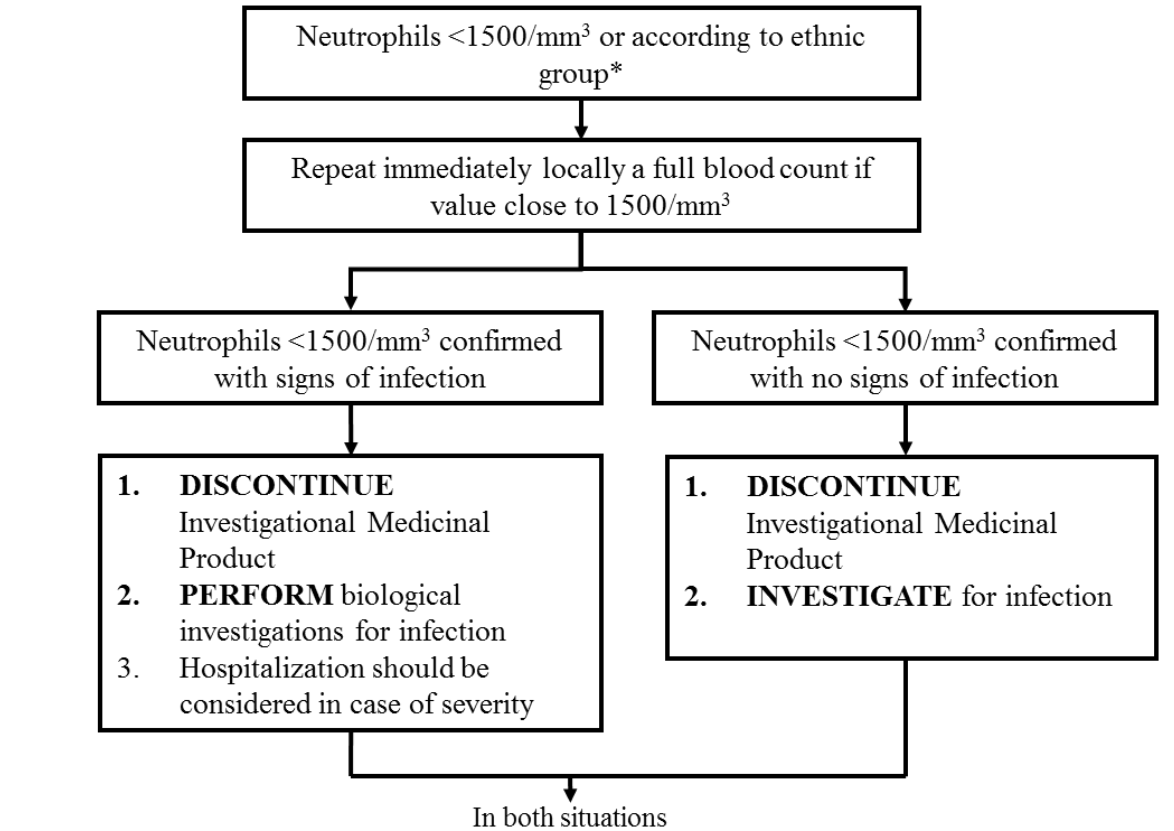
Female participants who become pregnant:

- 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 poststudy 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/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

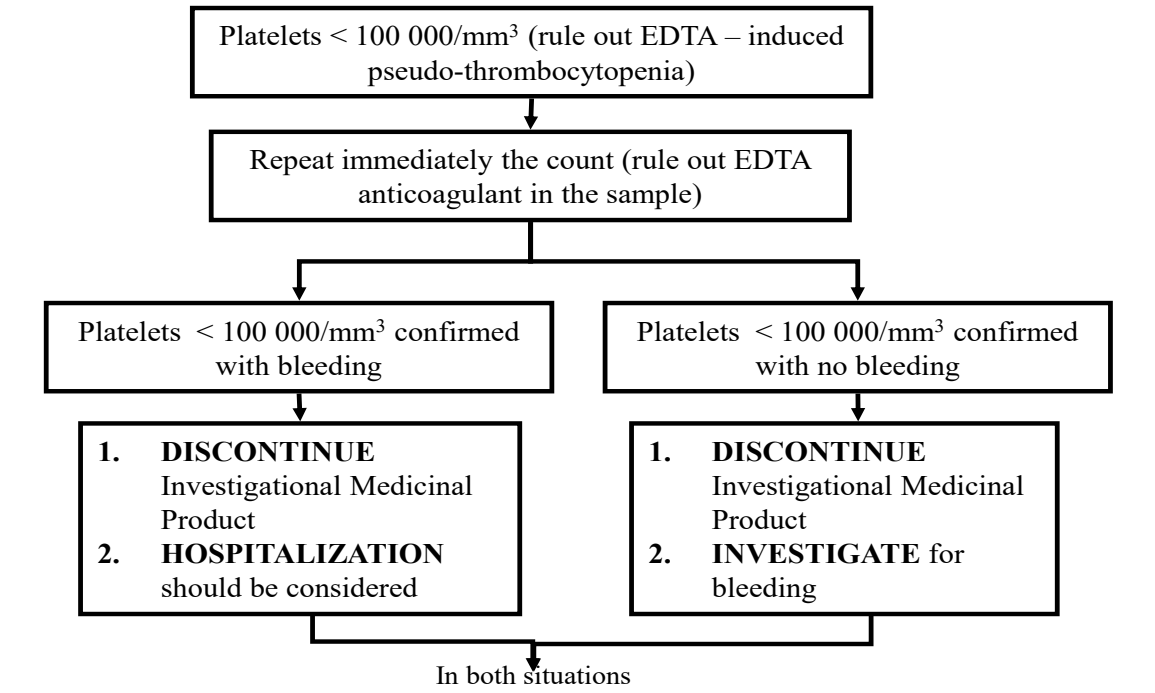


3. **INFORM** the local monitor
4. **INVESTIGATE** previous treatments particularly long-term, even a long time ago, exposure to toxic agents, e.g., benzene, X-rays, etc.
5. **PERFORM** and collect the following investigations (results):
   - RBC and platelet counts, Absolute Neutrophil Count (ANC)
   - Infectious serologies to be performed locally, according to clinical symptoms / medical history
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)**
8. **MONITOR** the leukocyte count 3 times per week for at least one week, then twice a month until it returns to normal

***** For individuals of African descent, the relevant value of concern is <1000/mm³

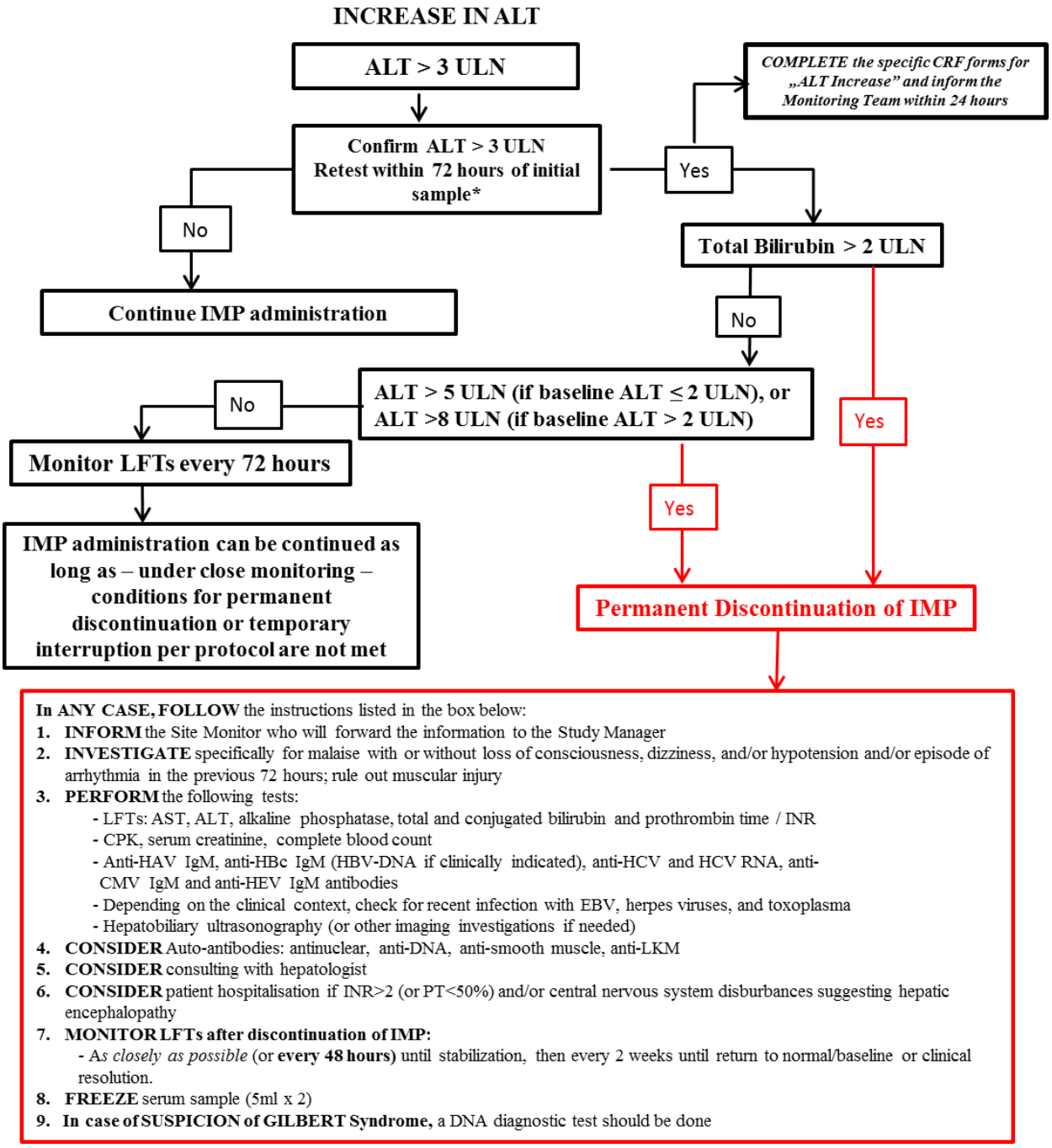
Neutropenia is to be recorded as an AE only if at least 1 of the criteria listed in the general guidelines for reporting AEs in Appendix 3 (Section 10.3) is met.

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.

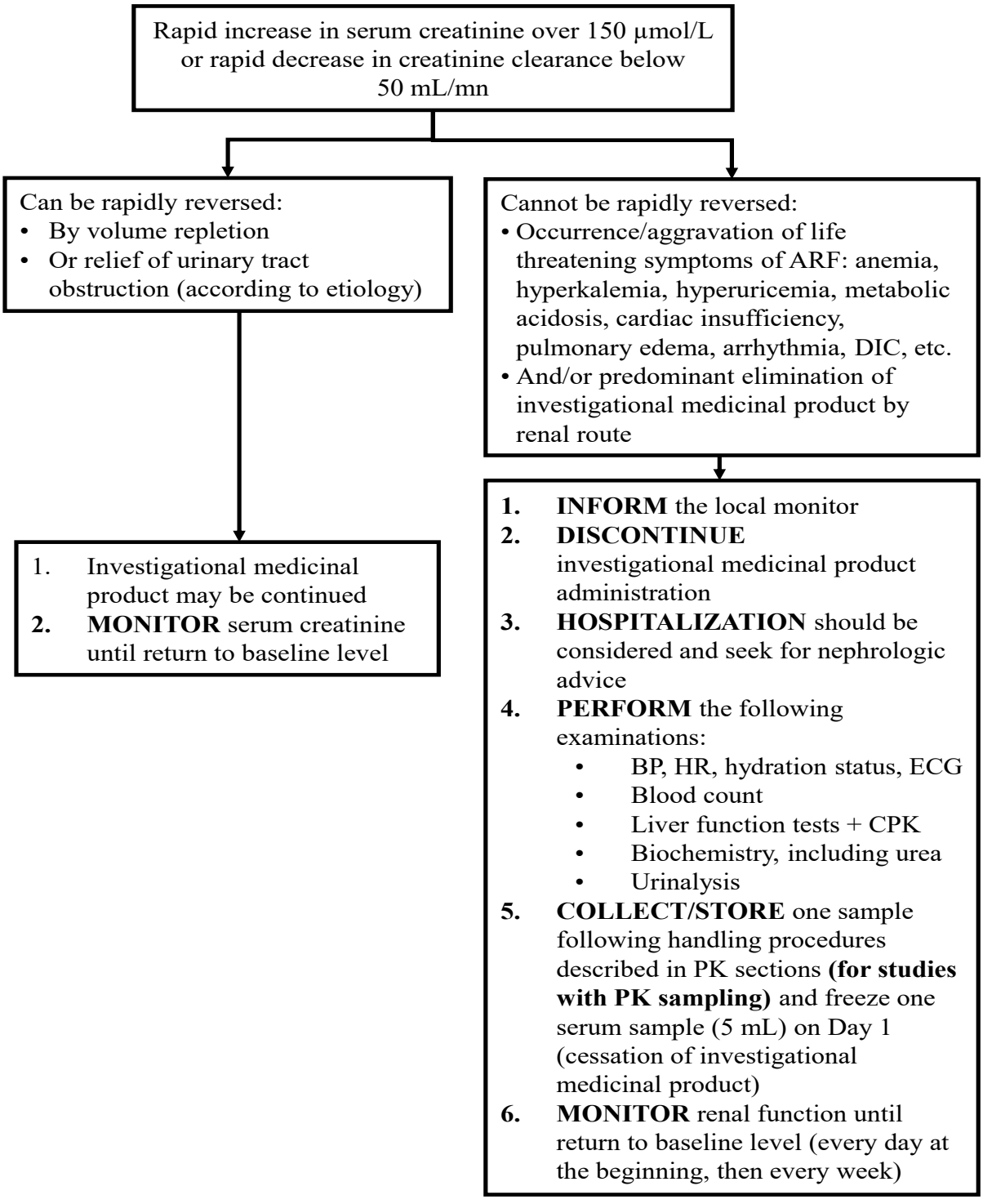


*If unable to retest in 72 hours, use original lab results to decide on further reporting/monitoring/discontinuation.

Note:

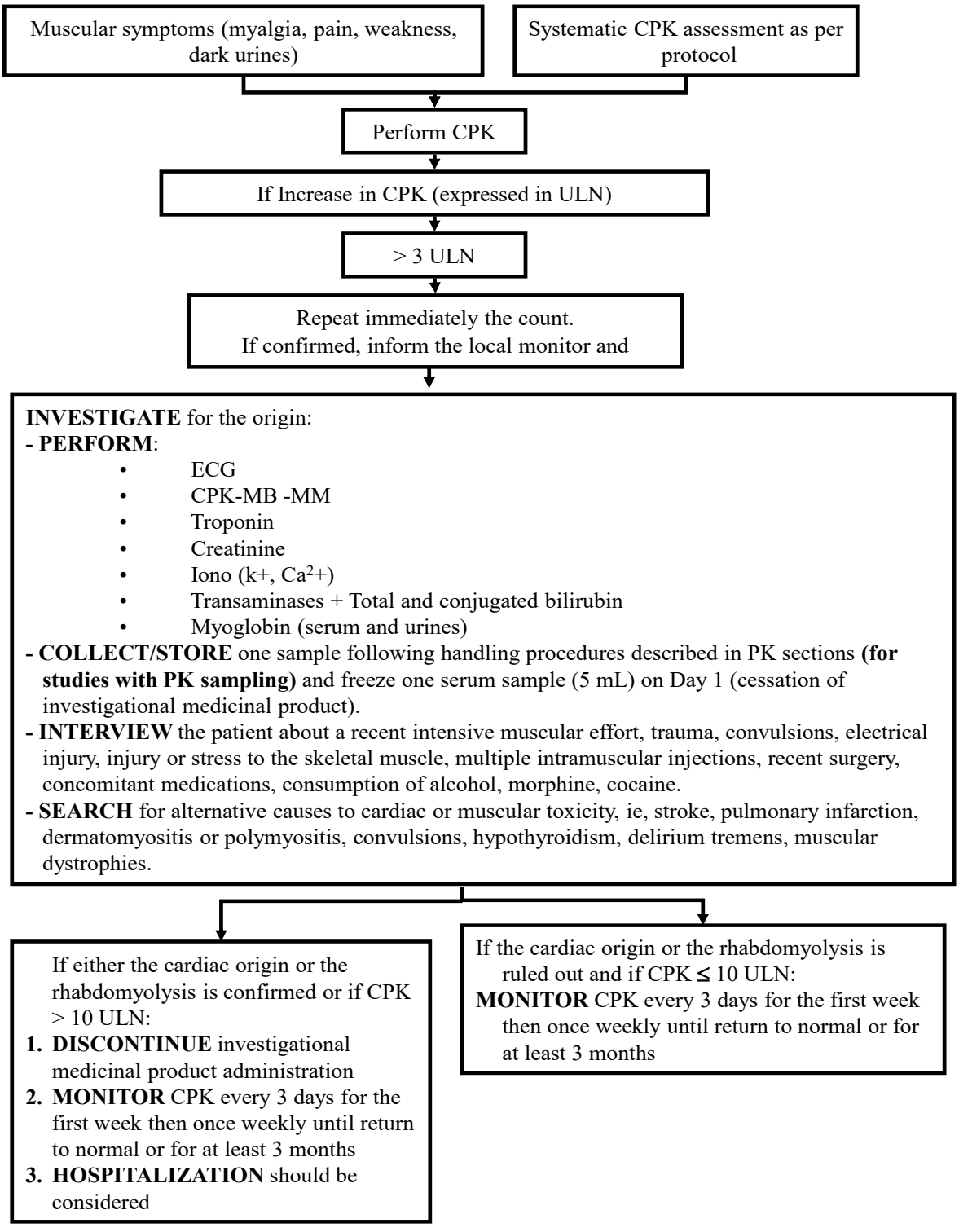
- "Baseline" refers to ALT sampled at baseline visit; or if baseline value unavailable, to the latest ALT sampled before the baseline visit. The algorithm does not apply to the instances of increase in ALT during screening.
- See Section 8.3 for guidance on safety reporting.
- Normalization is defined 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 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 intervention 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 leukocytosis, further measurement of amylase and lipase should be performed. The clinical signs and/or symptoms should be documented in the source data documentation.

Refer to Section 10.5.2.1 and Section 10.5.2.2 below for actions to take in case of elevation of amylase and/or lipase with or without clinical signs and/or symptoms evocative of pancreatitis, respectively.

In any situation as described below, all laboratory or clinical documentations must be collected. If the retest result confirms lipase and/or amylase values are >2 × ULN, the event must be reported in the eCRF 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.

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

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

- If value(s) is/are >2 to 3 × ULN in a participant with baseline amylase and/or lipase values <2 × ULN: retest within 7 days.
- If value(s) is/are >3 × ULN: retest within 48 hours, regardless of baseline amylase and/or lipase values.
- 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 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 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.

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 are 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 (≥5.9 pmol/L):

- The event must be reported in the eCRF 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 RAs. Acute renal impairment is not thought to be caused directly by GLP-1 RAs (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), Increase in serum creatinine flowchart for further recommendations.

10.5.5 Guidance for monitoring participants with diabetic retinopathy

Investigators are reminded that all participants should have eye examinations based on their retinopathy status, performed by a professional eye care provider according to International Council of Ophthalmology (ICO) guidelines or local standards; all efforts to be done to collect all medical documents from ophthalmologic examination(s) related to potential diabetic retinopathy events.

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

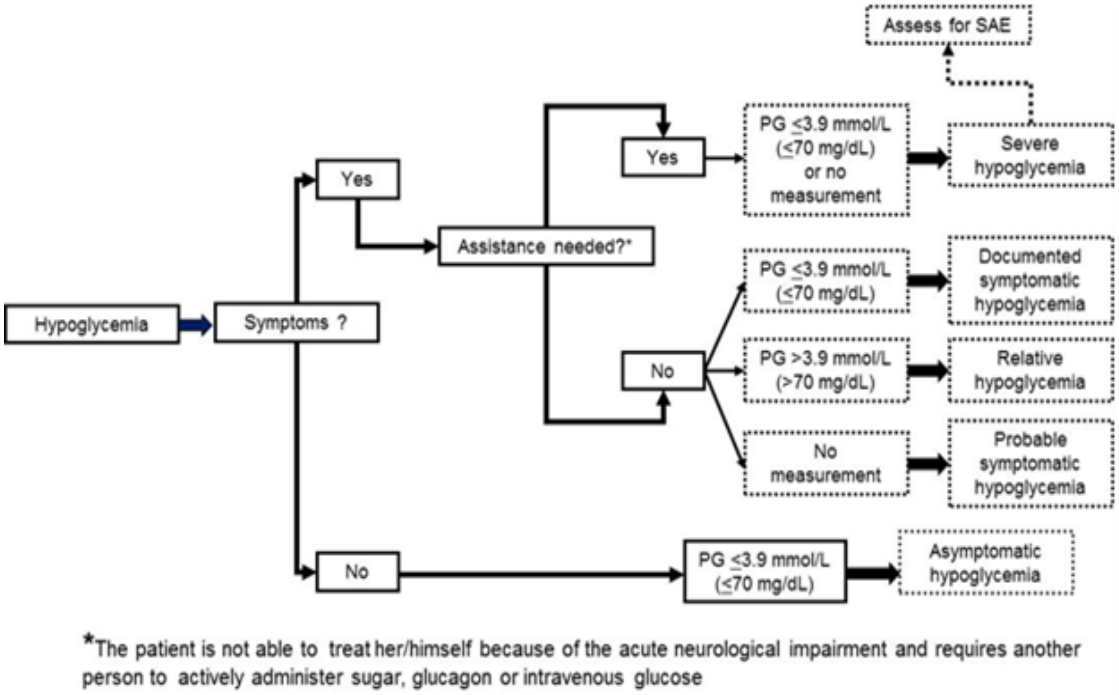
Not applicable.

10.7 APPENDIX 7: COUNTRY-SPECIFIC REQUIREMENTS

Not applicable.

10.8 APPENDIX 8: HYPOGLYCEMIA CLASSIFICATION

Figure 2 - Hypoglycemia classification



PG: plasma glucose, SAE: serious adverse event

10.9 APPENDIX 9: ABBREVIATIONS

ADA:	antidrug antibody
AEs:	adverse events
AESI:	adverse event of special interest
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
AST:	aspartate aminotransferase
CEC:	Clinical Endpoint Committee
CFR:	Code of Federal Regulations
CI:	confidence interval
CT:	computed tomography
CV:	cardiovascular
DMC:	Data Monitoring Committee
DPP-4:	dipeptidyl peptidase 4
DTP:	Direct-To-Patient
ECG:	electrocardiogram
eCRF:	electronic Case Report Form
eGFR:	estimated glomerular filtration rate
EOT:	end of treatment
FDA:	Food and Drug Administration
FPG:	fasting plasma glucose
FSH:	follicle stimulating hormone
GCP:	Good Clinical Practice
GI:	gastrointestinal
GLP-1 RA:	glucagon-like peptide 1 receptor agonists
HbA1c:	hemoglobin A1c
HRT:	hormone replacement therapy
IB:	Investigator's Brochure
ICF:	informed consent form
IEC:	Independent Ethics Committees
IMP:	Investigational Medicinal Product
IRB:	Institutional Review Board
IRT:	interactive response technology
ITT:	intent-to-treat
MACE:	major adverse cardiovascular events
MDRD:	modification of diet in renal disease
MEN-2:	multiple endocrine neoplasia syndrome type 2
MI:	multiple imputation
MRI:	magnetic resonance imaging
MTC:	medullary thyroid cancer
NIMP:	noninvestigational medicinal product
OAD:	oral antidiabetic drug

OC:	observed cases
PEG:	polyethylene glycol
PFS:	prefilled syringe
PK:	pharmacokinetic
popPK:	population pharmacokinetic
PPG:	postprandial plasma glucose
SAE:	serious adverse event
SC:	subcutaneous
SD:	standard deviation
SE:	standard error
SMPG:	self-monitored plasma glucose
SoA:	schedule of activities
SU:	sulfonylurea
SUSAR:	suspected unexpected serious adverse reaction
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
ULN:	upper limit of normal
WOCBP:	women of childbearing potential

10.10 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

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

11 REFERENCES

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