NCT03353350

STATISTICAL ANALYSIS PLAN

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

SAR439977-EFC14822

STATISTICIAN: [redacted]

Statistical Project Leader: [redacted]

DATE OF ISSUE: 19-Aug-2020

Total number of pages: 74

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
AE:	adverse event
ALT:	alanine aminotransferase
ANCOVA:	analysis of covariance
BLQ:	below quantitation limit
BMI:	body mass index
CI:	confidence interval
CMH:	Cochran-Mantel-Haenszel
ECG:	electrocardiogram
EOS:	end of study
EOT:	end of treatment
FPG:	fasting plasma glucose
GI:	gastrointestinal
HbA1C:	hemoglobin A1c
HLGT:	high-level group term
HLT:	high-level term
IMP:	investigational Medicinal Product
IRT:	interactive response technology
LLT:	lower-level term
NIMP:	noninvestigational medicinal product
OC:	observed cases
PCSA:	potentially clinically significant abnormality
PRO:	patient reported outcome
PT:	preferred term
R:	randomization
SOC:	system organ class
T2DM:	type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter and multinational, double-blind, placebo-controlled, randomized, 4-arm, parallel group study in participants with type 2 diabetes mellitus (T2DM).

After a Screening phase of up to 3 weeks, participants will be centrally randomized (using permuted block randomization schedule) via Interactive Response Technology (IRT) in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:

- Efpeglenatide 2 mg;
- Efpeglenatide 4 mg;
- Efpeglenatide 6 mg;
- Efpeglenatide placebo.

Randomization will be stratified by Screening hemoglobin A1c (HbA1c) (<8.0, ≥8.0%) and Visit 3 (Baseline, Day 1) body mass index (BMI) (<30, ≥30 kg/m^2). Participants will receive double-blinded treatment for 56 weeks. Additional details on the study design and plan are located in Section 1.4.

Approximately 400 participants (100 participants per treatment group) [details in Section 1.3] will be randomized.

1.2 OBJECTIVES

1.2.1 Primary objectives

The primary objective of this study is to demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, or 6 mg in comparison to placebo in HbA1c change from Baseline to Week 30 in participants with T2DM inadequately controlled with diet and exercise.

1.2.2 Secondary objectives

Secondary objectives of this study include:

- To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on glycemic control parameters (number of participants who achieve HbA1c goal of <7.0%, HbA1c, fasting plasma glucose [FPG]);
- To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on body weight;
- To evaluate the safety of once-weekly injection of efpeglenatide 2, 4, and 6 mg.

1.3 DETERMINATION OF SAMPLE SIZE

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

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

Hence, there are 4 parallel dosing arms:

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

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

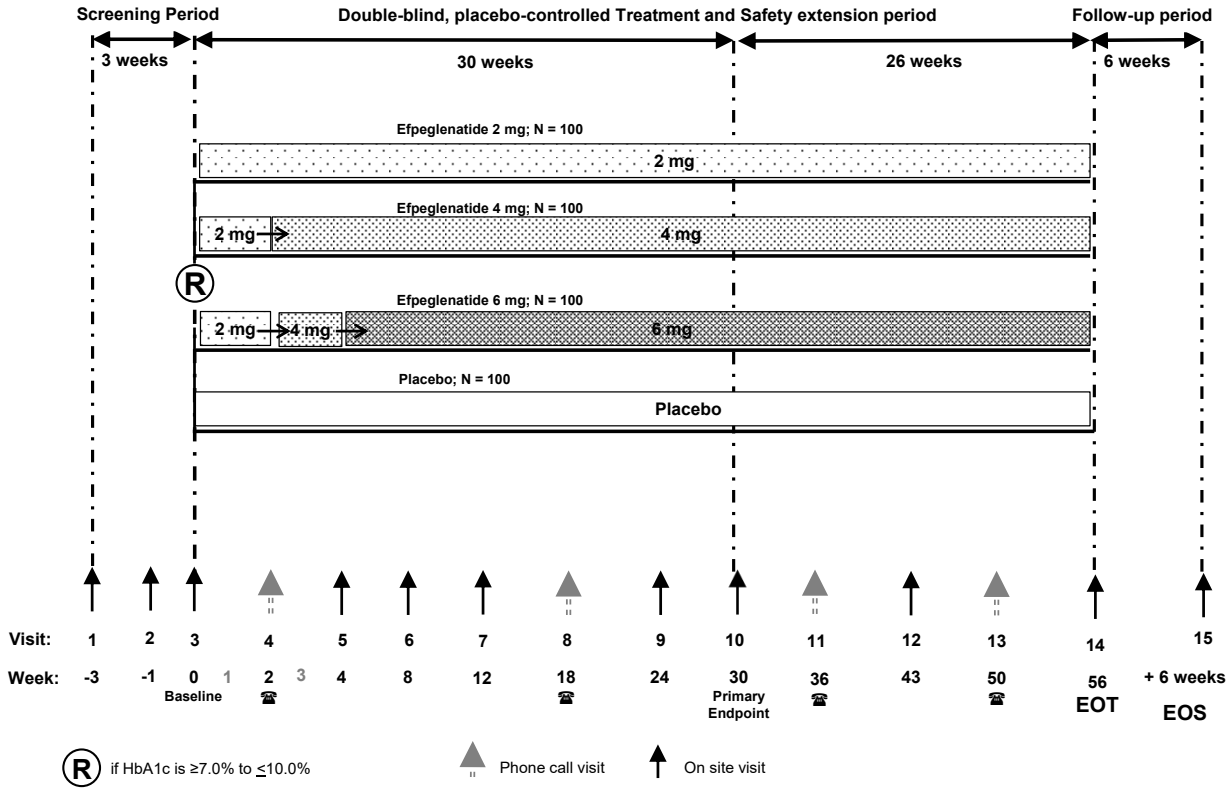
1.4 STUDY PLAN

This is a multicenter, 56-week, randomized, double-blind, placebo-controlled Phase 3 study consisting of 4 study periods:

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

The maximum study duration per participant will be 65 weeks with treatment lasting for 56 weeks (a 30-week core treatment period and a 26-week extension period). The graphical study design is shown in Figure 1.

Figure 1 - Study design overview



Abbreviations: EOS, end of study; EOT, end of treatment; R, Randomization.
Note: The telephone symbol is used to designate visits conducted by telephone interview.

The end of the study is defined as the date of the last visit of the last participant in the study.

1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

The original protocol (dated: 26 September 2017) was updated to amendment 01 (dated: 16 January 2018), amendment 02 (dated: 27 March 2018) and amendment 03 (dated: 07 June 2018). In protocol amendment 01, the analysis of primary/secondary efficacy endpoints was updated with retrieve dropout method to handle missing values following health authority recommendation. In protocol amendment 02, no changes were made in statistical section. In protocol amendment 03, wording of some secondary and tertiary objective was modified, the secondary objective and corresponding secondary endpoints which are not part of multiplicity analysis moved to tertiary/exploratory endpoints, the primary efficacy endpoint analysis method updated, subgroups of duration of diabetes and baseline estimated GFR categories added, the order for hierarchical testing procedure of secondary endpoints changed and new endpoints added into hierarchical testing procedure.

The Table 1 below gives the timing, rationale, and key details of major changes to the protocol statistical section.

Table 1 - Protocol amendment statistical changes

Amendment number	Date approved	Rationale	Description of statistical changes
01	16-Jan-2018	To update analysis of primary/secondary efficacy endpoints with retrieve dropout method to handle missing values following health authority recommendation	Control-based multiple imputation method for analysis of primary/secondary efficacy endpoints for missing data changed to retrieve dropout method
		To update sensitivity analysis	Control-based imputation method moved to sensitivity analysis
03	07-Jun-2018	To use different primary analysis missing data imputation method following by health authority recommendation	Primary analysis missing data imputation method: retrieved dropouts, washout-imputation, and back-up imputation method
		The order of the secondary endpoints in multiplicity assessment was changed,	To use different order/endpoints in hierarchical testing procedure of secondary endpoints
		To add additional subgroups for statistical analysis for project harmonization	Subgroups of duration of diabetes and baseline estimated GFR categories
		To update the wording of some secondary and tertiary objectives	Only key efficacy endpoints included in the hierarchical testing and selected safety endpoints will be considered Secondary Endpoints; all others will be included in Tertiary/exploratory endpoints

The first participant was enrolled on 20th of December 2017. There are no planned interim analyses.

1.6 STATISTICIAL MODIFICATIONS MADE IN STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan and/or protocol. Changes listed under SAP Version 1 are additional analysis not defined in the protocol and/or protocol amendments at the time of that SAP version.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
3	19-Aug-2020	Additional analyses provided due to COVID-19 pandemic.	2.2 COVID-19 impact on disposition data to be presented
			2.2.1 COVID-19 related PDs to be presented
			2.4.4.2.2 HbA1c/weight sensitivity analysis due to COVID-19 at Week 56 added. Assessment of missing data due to COVID-19 added
			2.4.5.1 COVID-19 related AEs added
			Appendix C Diagram for identifying missing data due to COVID-19 added
		Clarified on- and post-study period definitions. Removed control-based multiple imputation sensitivity analyses for the primary efficacy endpoint. Removed model-based analyses for the change from baseline in mean 24-hour SMPG and time to initiation of rescue medication. Clarified AERSM definitions.	2.1.4 Clarified on-study and post-study observation period definitions
			2.1.5.1 Added definitions for Persistent and Transient ADA response
			2.4.4.1 Control-based multiple imputation sensitivity analysis for primary efficacy endpoint removed
			2.4.4.4.3 Removed ANCOVA analysis for changes from baseline in mean 24-hour SMPG. Removed Cox proportional hazard model for time to initiation of rescue analysis
			2.4.5 Table 3 Clarified pancreatic event, selected cardiovascular event definitions, and diabetic retinopathy complications
			2.5.4 Clarified analysis window for efficacy endpoints at Weeks 30 and 56 in case of missing scheduled visits
2	25-Feb-2020	Clarification of baseline definitions, updated compliance definition, some imputation rules for missing data, definitions of some study periods, efficacy subgroup and sensitivity analyses, anti-drug antibodies analyses, use of certain populations, clarification of AERSM definitions.	Clarified definition of baseline when IMP time is missing.
			Clarified the handling of race categories throughout.
			Clarified baseline microvascular complications.
			Clarified on-study observation period and 30-week on-study observation period.
			Clarified definitions for anti-drug antibodies analyses.
			Clarified the safety population when missing exposure information and when discontinued during the titration phase.
			Demographics and Baseline characteristics updated to be presented by the ITT population.
			Included cumulative exposure (patient-years) summary.
			Updated compliance equation.
			Sensitivity analyses for primary model was updated.

SAP version number	Date approved	Rationale	Description of statistical changes
			Additional data presentations included for overall adverse event tables.
			Updated definitions of AESI and AERSM events to include CMQs and additional clarifications.
			Removed reference to adjudicated diabetic retinopathy data.
			Handling of missing baseline medication missing/partial dates updated.
			Added “back-up plan” code for multiple imputation analyses.
			Updated analysis of deaths.
			Definition updated for “duration of study”.
			Imputation rule added for missing efficacy data at Baseline.
			Clarified that intermediate data will be included in control-based MI.
			TTE censoring rules added.
			Analysis of hypoglycemia events updated.
			Titration period categories amended.
			All non-primary analysis pseudo code removed.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The Baseline value (with the exception of serum creatinine and eGFR) 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 study treatment. Note: any assessment undertaken on the day of first dose administration of IMP with missing assessment time will be considered as Baseline.

For serum creatinine and eGFR baseline is defined as the average of all values before the first dose of double-blind IMP for those randomized and exposed or before randomization for those who were randomized but never exposed to IMP

All Baseline safety parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety sections (Section 2.4.5).

Summary statistics of baseline efficacy parameters by treatment group and overall will be provided in randomized population.

Demographic characteristics

Demographic variables are gender (Male, Female), race (Asian, Black or African American, White, Multiple, Other, Not reported, Unknown), age in years (quantitative and qualitative variable: <50, ≥50 and <65, ≥65 and <75, ≥75 years), ethnicity (Hispanic or Latino, not Hispanic or Latino, Not reported, Unknown), region (North America, Western Europe, Eastern Europe), randomization strata, Baseline BMI (quantitative and qualitative variable : <30, ≥30 and <40, ≥40 kg/m^2), and HbA1c (%) at screening.

Participants counted as multiple races will not be counted in other race categories.

Medical history

Medical history includes medical or surgical history, alcohol and smoking habits.

Medical and surgical history will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at the time of database lock.

Alcohol and smoking habit variables include:

- Alcohol status in the last 12 months (Never, Occasional, At least monthly, At least weekly, At least daily),
- Smoking status (Never, Current, Former);
- Cigarettes smoked (per day).

Disease characteristics at Screening or Baseline

Diabetes history includes:

- Duration of diabetes (years) derived as: (Date of informed consent – Date of diagnosis of diabetes + 1)/365.25;
- Categories of duration of diabetes (<10, ≥10 years);
- Age at diagnosis of diabetes (years) derived as: Year of diagnosis of diabetes - Year of birth;
- Baseline diabetic microvascular complications (Yes, No) (ie, retinopathy, non-proliferative/proliferative retinopathy, nephropathy, neuropathy, and macular edema);
- Estimated Glomerular Filtration Rate (eGFR) at baseline (mL/min/1.73 m^2);
- Estimated glomerular filtration rate (eGFR) categories at baseline (<15 mL/min/1.73 m^2 [End stage renal Disease], ≥15 to <30 mL/min/1.73 m^2 [Severe decrease in glomerular filtration rate (GFR)], ≥30 to <60 mL/min/1.73 m^2 [Moderate decrease in GFR], ≥60 to <90 mL/min/1.73m^2 [Mild decrease in GFR], and ≥90 mL/min/1.73 m^2 [Normal]).

Baseline efficacy variables

The baseline efficacy variables include:

- HbA1c (%, mmol/mol);
- HbA1c category (<8.0%, ≥8.0%);
- FPG (mmol/L, mg/dL);
- Body weight (kg);
- Mean 24-hour SMPG (mmol/L, mg/dL).

Any technical details related to computation, dates, and imputation for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

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 during the study must be recorded in the corresponding case report form page.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at the time of database lock.

Medications will be classified into the following 3 groups:

- Prior medications are those the participant used prior to first IMP administration. Prior medications can be discontinued before first IMP administration or can be ongoing during treatment phase.

- Concomitant medications are any treatments received by the participant concomitantly to the IMP(s), from first dose to the end of treatment + 30 days (+ 7 days for antidiabetic drugs). A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the posttreatment period (as defined in the observation period in Section 2.1.4).
- Post-treatment medications are those the participant took in the period running from the 31st day (8 days for antidiabetic drugs) after the last injection of IMP up to the end of the study.

Rescue medication(s) is considered Non-IMP (NIMP) treatment. Except for GLP-1 RA and DDP-4i, any approved medication(s) including oral antidiabetic drugs or insulin can be prescribed at the Investigator's discretion to treat the hyperglycemia.

The rescue therapy medications will be included in the concomitant medication summaries. A special list of rescue therapy medications will be generated.

Prohibited medication(s)

All prohibited medications are based on sponsor-defined Customized Drug Grouping (CDG).

The following treatments are prohibited during the Screening Period and the 56 weeks of treatment period:

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

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Efficacy endpoints are defined in Section 2.1.3.1, Section 2.1.3.2, Section 2.1.3.3.

Efficacy variables will be summarized in both standard international units and conventional units when applicable.

2.1.3.1 Primary efficacy endpoint

- Change in HbA1c (%) from Baseline to Week 30.

2.1.3.2 Secondary efficacy endpoints

- HbA1c < 7.0% at Week 30 (yes/no);
- Change in FPG from Baseline to Week 30;
- Change in HbA1c (%) from Baseline to Week 56;
- Changes in body weight from Baseline to Weeks 30 and 56.

2.1.3.3 Exploratory efficacy endpoint(s)

- Patient qualitative assessment of treatment version 2 (PQAT v2) at Weeks 30 and 56;
- HbA1c <7.0% at Week 56 (yes/no);
- Change in FPG from Baseline to Week 56;
- Changes in 7-point SMPG profiles (mmol/L, mg/dL: mean 24-hour SMPG) from Baseline to Weeks 30 and 56;
- Change in plasma glucose excursions (2-hours PPG minus preprandial plasma glucose at breakfast, lunch, and dinner) based on 7-point SMPG data from baseline to Week 30 and Week 56;
- Rescue therapy used during the treatment period until Weeks 30 and 56 (yes/no);
- Time to initiation of rescue therapy (weeks).

Mean 24-hour SMPG is the average over the available plasma glucose values from the 7 time points and can only be calculated if at least 4 points are available.

Prandial glucose excursions are calculated by subtracting the preprandial value from the postprandial value respectively for breakfast, lunch, and dinner.

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events (AE), hypoglycemia and other safety information, such as clinical laboratory data, vital signs, and ECG.

Observation period

The period related to treatment will be divided into 3 main segments:

- The **pre-treatment** period is defined as the time from informed consent up to the time of first injection of IMP.
- The whole **on-treatment** period is defined as the time from the first injection of the IMP up to 30 days (7 days for hypoglycemia) after the last injection of the IMP.

- The 30-week core on-treatment period is defined as the time from the first injection of IMP up to Visit 10 (Week 30) (or Day 210 if Visit 10 [Week 30] visit is missing) or up to 30 days (7 days for hypoglycemia) after the last injection of IMP, whichever comes earlier.

- The **post-treatment** period is defined as the period from the end of the whole on-treatment period.

The **on-study observation period** is defined as the time from first injection of IMP up to either the last protocol-planned visit or the date of last available information if participants discontinue the study prematurely (ie, the date collected on e-CRF page "Completion of End of Study/Follow-up"), whichever is later.

- The **30-week on study observation period** is defined as the time from first injection of IMP up to Visit 10 (Week 30) (or Day 210 if Week 30 visit 10 is missing), irrespective of whether subject had discontinued, or IMP was still being used at Week 30.

The post-study observation period is defined as the time after the end of the on-study observation period until the date of resolution/stabilization of all SAE, AESI and/or AERSM, up to database lock.

Adverse event observation period

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

All AEs (including SAEs, AEs of special interest and AEs requiring specific monitoring) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of MedDRA currently in effect at the time of database lock.

Adverse events of special interest (AESIs) include the following:

- 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;
- Symptomatic overdose (serious or nonserious) with IMP/NIMP;
- Increase in alanine aminotransferase (ALT) >3 x upper limit normal (ULN).

Adverse events requiring specific monitoring include the following terms:

- Severe gastrointestinal (GI) events;
- Severe hypoglycemia;

- Pancreatic events (including abnormal values of pancreatic enzymes, pancreatitis and pancreatic neoplasm);
- Selected cardiovascular events (CV death, MI, stroke, heart failure leading to hospitalization, unstable angina, and transient ischemic attack [TIA]);
- Calcitonin increase (≥5.9 pmol/L (20 pg/mL)) and thyroid C-cell neoplasm;
- Acute renal failure;
- Diabetic retinopathy complications;
- Severe injection site reaction;
- Severe allergic reactions;
- Severe immune complex disease.

Independent Clinical Endpoint Committee(s) [CEC(s)] will review, assess and/or adjudicate all events of death, selected CV events and pancreatic events.

2.1.4.1 Deaths

Deaths will be analyzed according to the following observation periods:

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

2.1.4.2 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry and urinalysis. Clinical laboratory values will be summarized in both standard international units and conventional units (US) when applicable.

Blood samples for clinical laboratories will be collected at designated visits (see Schedule of Activities in Appendix C). The following laboratory parameters will be measured at central laboratory:

- Hematology
  - Red blood cells and platelets: Platelet count, Red blood cell count, Hemoglobin, Hematocrit;
  - White blood cells: White blood cell count, differential count (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils).
- Clinical chemistry
  - Pancreatic enzymes: Amylase, Lipase;

- Electrolytes: Potassium, Sodium;
- Renal function: Creatinine, Estimated glomerular filtration rate (MDRD formula);
- Liver function: Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Total bilirubin;
- Lipid profile:
  - Triglyceride, Total cholesterol, Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol;

  For triglycerides, only values assessed in fasted participants will be analyzed.
- Calcitonin.

Technical formulas are described in Section 2.5.1.

2.1.4.3 Vital signs variables

Vital signs include: sitting heart rate (bpm), as well as sitting systolic and diastolic blood pressures (mmHg).

2.1.4.4 Electrocardiogram variables

ECG variables include 12-lead ECG interpretation (normal/abnormal) provided by the investigator, 24-hour mean heart rate (bpm) and night-time mean heart rate (bpm) provided by reading center. 12-lead ECG recording will be performed locally at Randomization, Week 12, Week 30 and Week 56. Investigator's interpretation of normal and abnormal will be reported in the eCRF.

24-hour Holter ECGs will be recorded automatically by the device and will be sent to an ECG reading center for further analysis. A minimum of 19 hours (80%) of evaluable data are needed for analysis of the 24-hour ECG record.

2.1.4.5 Hypoglycemia

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

Hypoglycemic events will be categorized as follows:

- **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 qualified as an SAE only if it fulfills SAE criteria. 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 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 less than or equal to 3.9 mmol/L (≤70 mg/dL), documented symptomatic and asymptomatic hypoglycemic events with 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.

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.

2.1.5 Immunogenicity endpoints

2.1.5.1 Anti-drug (efpeglenatide) antibody

Blood samples are taken to assess the Anti-drug antibody (ADA) status (positive/negative) and level (titer). Mapping the ADA epitopes of confirmed positive samples to different moieties of efpeglenatide, (ie, HMC001, exendin-4 and polyethylene glycol (PEG)) and cross-reactivity to endogenous GLP-1 (positive/negative), endogenous glucagon (positive/negative), neutralizing capacity of ADAs will also be evaluated for efpeglenatide groups in serum, at the time points specified in protocol.

Subjects with pre-existing ADAs are those with a positive ADA at Baseline. Non-missing post-Baseline titer values are deemed treatment-induced ADAs if the subject had a negative or missing ADA status at Baseline. Treatment-boosted ADAs are defined as a post-Baseline minimum 2-fold increase in Baseline titer value for subjects with pre-existing ADA at Baseline.

Persistent ADA response is defined as: Treatment-induced or treatment-boosted ADA detected at two or more sampling time points during the study (ie, including post-study observation period), where the first and last treatment-induced or treatment-boosted ADA samples (irrespective of any negative samples in between) are separated by at least 16 weeks.

Transient ADA response is defined as: (1) Treatment induced or treatment-boosted ADA detected only at 1 sampling time point during the study (excluding the last sampling time point); or (2) Treatment induced or treatment-boosted ADA detected at 2 or more sampling time points during the study, where the first and last treatment-induced or treatment-boosted ADA samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks and the last time point is ADA-negative.

Indeterminate ADA response: Only the last sampling time point is treatment-induced or treatment-boosted ADA sample and all previous samples are negative.

The data will be presented as:

- 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)
- Number of participants with treatment-boosted ADAs (among the participants with ADA positive at Baseline)
- ADA titer at scheduled visits
- Number of participants by ADA cross-reactivity to endogenous GLP-1 (positive/negative) at scheduled visits
- Number of participants by ADA cross-reactivity to endogenous glucagon (positive/negative) at scheduled visits

- Number of participants with ADAs directed against PEG linker of efpeglenatide at scheduled visits
- Number of participants with ADAs directed against the HMC001 moiety of efpeglenatide at scheduled visits
- Number of participants with ADAs directed against the exendin-4 moiety of efpeglenatide at scheduled visits
- Number of participants by status of anti-efpeglenatide neutralizing antibodies (positive/negative) at scheduled visits
  - Number of participants by status of neutralizing antibodies against endogenous GLP-1 (positive/negative) at scheduled visits
  - Number of participants by status of neutralizing antibodies against endogenous glucagon (positive/negative)

2.1.6 Pharmacokinetic endpoints

Pharmacokinetic variables include the concentration of efpeglenatide in the efpeglenatide groups:

- Serum C_{trough} of efpeglenatide at pre-dose (Weeks 4, 12, 24, 30);
- Serum concentration of efpeglenatide at post-dose (either 4 days [±1 day] after first IMP dose, 4 days [±1 day] after 4th dose, or 4 days [±1 day] after 12th dose in a subset of participants). All valid samples collected will be sent to the laboratory to be analyzed, even if out of the specified window.

2.1.7 Pharmacodynamic/genomics endpoints

Pharmacodynamic parameters are not evaluated in this study.

2.2 DISPOSITION OF PARTICIPANTS

This section describes participants' disposition for both participant study status and the participant analysis populations.

Screened participants are defined as any participants who signed the informed consent form.

Randomized participants consist of all participants with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

The total number of participants in each of the following categories will be presented in the clinical study report using a flowchart diagram or summary table:

- Screened participants;
- Screen failure participants and reasons for screen failure;

- Nonrandomized but treated participants;
- Randomized participants;
- Randomized but not treated participants;
- Randomized and treated participants;
- Participants who have completed the 30-week core treatment period as per protocol;
- Participants who did not complete the 30-week core treatment period, and main reasons for permanently treatment discontinuation;
- Participants who have completed the whole study treatment period including the 26-week extension period as per protocol;
- Participants who did not complete the whole study treatment period, and main reason for permanent treatment discontinuation;
- Participants who completed the study as per protocol;
- Participants who discontinued the study by main reason for permanent study discontinuation;
- Status at last study contact.

For all categories of participants (except for the screened, screen failure and nonrandomized but treated categories) percentages will be calculated using the number of randomized participants as the denominator. Reasons for treatment and study discontinuation will be supplied in tables giving numbers and percentages by treatment group. Number and percent of participants: screened, screen failed, randomized, randomized and treatment, ended treatment prematurely, and ended study prematurely will be provided by treatment group within each country and site as applicable.

List of participants who discontinued treatment and/or study will be provided with reasons for discontinuation, including reasons related to COVID-19.

Kaplan-Meier cumulative incidence of early IMP, premature discontinuation of treatment due to AE and study discontinuation will be provided.

Additionally, the following analysis populations will be summarized in a table by number of participants in the randomized population.

- Efficacy population: intent-to-treat (ITT) population
- Safety population
- ADA population
- Pharmacokinetics population

2.2.1 Protocol deviations

All significant deviations, potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, as well as other selected significant deviations will be summarized

in tables giving numbers and percentages of deviations by treatment group in randomized population. Listing of participants with at least one significant deviation will be provided.

Additionally, participants with any protocol deviations due to COVID-19 will be summarized and listed separately.

2.3 ANALYSIS POPULATIONS

Participants treated without being randomized will not be considered randomized and will not be included in any efficacy population.

The randomized population includes any participant who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

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

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

2.3.1 Efficacy populations

The efficacy analysis population will be the ITT population.

2.3.1.1 Intent–to-treat population

The ITT population is defined as all randomized participants, irrespective of compliance with the study protocol and procedures analyzed, according to the treatment group allocated by randomization.

2.3.2 Safety population

The safety population is defined as:

- Randomized population who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment actually received

In addition:

- Nonrandomized but treated participants will not be part of the safety population; however, their safety data will be presented separately.
- Randomized participants for whom it is unclear whether they took the IMP will be included in the safety population as randomized according to their planned treatment.
- For participants receiving 1 or more injections of efpeglenatide during the trial, regardless of being assigned to the efpeglenatide groups or not, the treatment group allocation for

as-treated analysis will be included in the efpeglenatide dose group that they are exposed for longer duration. In case of tie, highest dose group will be used.

- Participants, who premature discontinued study treatment during the titration phase, will be summarized in their planned treatment group for as-treated analysis too.
- Randomized participants will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that participants have not taken the study treatment. If a participant is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the participant will be considered exposed.

2.3.3 ADA population

ADA population is defined as:

- All participants from the safety population with at least 1 post-Baseline valid ADA sample after drug administration.

2.3.4 PK population

PK population is defined as:

- All participants from the safety population with at least 1 measurable serum efpeglenatide concentration available for PK analysis.

2.4 STATISTICAL METHODS

In general, descriptive statistics of quantitative efficacy and safety endpoints (result and change from baseline) by scheduled visit will be provided on observed cases (OC), ie, only including participants having a non-missing assessment at a specific visit.

2.4.1 Demographics and baseline characteristics

Parameters described in Section 2.1.1 will be summarized on the ITT population by randomized treatment group and overall using descriptive statistics.

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum, and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of participants in each treatment group. Missing data will not be categorized in the summaries.

Medical history will be summarized on the ITT population by treatment group (and overall), primary SOC, and HLT, with events sorted by primary SOC in internationally agreed order and decreasing frequency of HLT in the overall group.

Technical formulas are described in Section 2.5.1.

P-values on demographic and Baseline characteristic data will not be calculated.

2.4.2 Prior or concomitant medications

The prior, concomitant, and post-treatment medications will be presented for the ITT population and the following two summaries will be produced for each:

- All medications (excluding anti-diabetic), and
- Anti-diabetic medications.

Medications will be summarized by treatment group (and overall) according to the WHO-DD, considering the first digit of the ATC class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). Anti-diabetic medications will be summarized by the ATC categories, pharmacological class and chemical class. Prohibited medications will be summarized by category of prohibited medication and chemical class.

All ATC codes corresponding to a medication will be summarized, and participants will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore, participants may be counted several times for the same medication. The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

The tables for concomitant and posttreatment medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the Efpeglenatide 6 mg treatment group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Similar to concomitant medications, prohibited medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the Efpeglenatide 6 mg treatment group.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by cumulative exposure (patient years), duration (days), and category (weeks).

Duration of IMP exposure is defined as last dose date – first dose date + 7, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following

categories and cumulatively according to these categories: 1 to 2 weeks, 3 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, 13 to 18 weeks, 19 to 24 weeks, 25 to 30 weeks, 31 to 43 weeks, 44 to 56 weeks, and >56 weeks. The duration of treatment exposure in weeks will be the duration (in days)/7, rounded to the nearest integer.

Duration of study will be summarized separately and analyzed descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). The duration of study is defined as date of completion or discontinuation – date of first dose of IP + 1. In the case of not treated participants, the randomization date will be used for calculation purposes.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the participant did not take the planned dose of treatment as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of compliance for a participant will be defined as the number of injections (partial injection will be counted as 1 injection) that the participant was compliant divided by the total number of injections that the participant was planned to take during the treatment period defined from the first to the last dose injection. Number of planned injections is calculated as following:

1 + (last dose date – first dose date + 1) / 7, rounded to the nearest integer.

Treatment compliance will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of participants whose compliance is <60, ≥60 and <80, ≥80% and ≤100%, or >100% will be summarized.

Cases of overdose will constitute AESIs and will be listed as such.

2.4.3.3 Frequency of injections

The frequency of injections during the whole on-treatment period will be summarized separately by time of day (morning, afternoon, evening, night) and location of injection (Abdomen, Other, Missing). For analysis purposes, morning is defined as the time between 06:00-11:59, afternoon as between 12:00-17:59, evening as between 18:00-23:59, and night as between 00:00-05:59.

2.4.4 Analyses of efficacy endpoints

Efficacy analyses will be performed on the ITT population using efficacy assessment collected during the study, including those obtained after IMP discontinuation and/or introduction of rescue therapy, unless otherwise specified (see Section 2.5.4).

Due to COVID-19 pandemic, participants may not be able to maintain their regular clinical visits according to the study protocol, with the closure of facilities, safety concern for the participants to go to the sites, unavailability of the investigators for treating participants, interruption of transportation or other COVID-19 related reasons. Data missingness due to these reasons is likely to be missing at random. For a continuous endpoint, all observed data of participants within the

same treatment group can be used for imputation in an MAR approach. Sensitivity analyses will be performed to take into consideration of the impact of COVID-19 if the number of participants with missing endpoint data due to COVID-19 is above the threshold as specified in the following sections.

Of note, it is unlikely that the efficacy analyses at Week 30 in EFC14822 would be impacted by COVID-19 as the last Week 30 visit was performed on 29Jan2020**.** However, the efficacy analyses at Week 56 is likely to be impacted.

2.4.4.1 Analysis of primary efficacy endpoint

The statistical test will be 2-sided tests at a nominal 5% significance level.

Hypothesis Testing of the Primary Endpoint

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 population LS mean treatment difference in reduction in HbA1c from Baseline;
- H1: Efpeglenatide has a higher population LS mean reduction in HbA1c from Baseline than placebo.

Primary Analysis

The statistical analysis for the primary endpoint is described below.

The Baseline value is defined in Section 2.1.1.

The primary analysis will be an analysis of covariance (ANCOVA) modeling with missing values imputed based upon retrieved dropouts in 2 separates parts as follows:

1. Missing endpoint data in participants who prematurely discontinue the study treatment before the Week-30 visit will be imputed using a model built separately in each arm and estimated from participants in the same treatment arm who prematurely discontinue the study treatment before the Week-30 visit but have the measurement for the endpoint (retrieved dropouts). Considering that the number of participants in each treatment arm who discontinue the study treatment but have the measurement for the endpoint is expected to be small, a simple imputation model will be used, where only the Hb1Ac 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 study treatment until the Week-30 visit will be imputed separately. The washout-imputation method will be used, where missing endpoint data in the efpeglenatide arms, as well as the missing data in the placebo arm, are imputed from a model estimated from participants in the placebo group with endpoint data without including any intermediate values. The imputation model will include the randomization strata and corresponding Hb1Ac baseline 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. The completed data sets will be analyzed using an ANCOVA model with the treatment group (efpeglenatide 2, 4, or 6 mg, or placebo), randomization stratum of Screening HbA1c (<8.0, ≥8.0%), BMI at Visit 3 (<30, ≥30 kg/m²), and geographical region as fixed classification effects, and Baseline HbA1c value as a continuous covariate.

For subjects with missing efficacy endpoint data at Baseline, values will be imputed using the population mean at Baseline.

SAS pseudo-codes are provided in Appendix A.

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. This will be implemented using MIANALYZE procedure in SAS.

A hierarchical procedure will be applied to adjust for the multiplicity of comparison on the primary endpoint:

- First, the highest dose of efpeglenatide (6 mg) will be compared to placebo to demonstrate superiority of this dose to placebo
- If superiority is demonstrated for efpeglenatide 6 mg, the superiority of 4 mg dose of efpeglenatide to placebo will be tested
- If superiority is also demonstrated for 4 mg dose, the lowest dose (2 mg) will be tested for superiority to 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 have sufficient data to support the imputation approach in item 1 described above. If there are less than 5 participants in any arms who prematurely discontinue the study treatment before the endpoint visit but have the measurement for the endpoint, a back-up imputation method for the primary efficacy analysis will be used. In particular, missing endpoint data in all participants in both efpeglenatide and placebo groups, regardless of staying on the study treatment or not, will be imputed using a model estimated from participants in the placebo group with endpoint data without including any intermediate values, where randomization strata and corresponding baseline values are included as the predictors. Missing data will be imputed using the regression method.

Sensitivity Analysis

Tipping point analysis

Tipping point analysis based on the same multiple imputation (MI) method as applied above will be performed to examine the robustness of the results from the primary analysis. A penalty δ will be applied to participants in the efpeglenatide group who have no HbA1C data at Week 30. The penalty will be gradually increased to determine at which level (if any) the conclusion of the

analyses in terms of statistical significance is changed for each efpeglenatide dose group. The tipping point is the penalty level at which the magnitude of efficacy reduction in participants without HbA1c data at Week 30 creates a shift in the treatment effect of efpeglenatide from being statistically significantly better than placebo to a non-statistically significant effect. The penalty δ will start at 0 and increase by 0.1 (unit: %) until non-statistical significance is found. Least square mean difference between each efpeglenatide dose and placebo and its associated p-value will be provided for each penalty level.

Analysis on completers

For participants in ITT population who completed the 30-week core treatment period and did not start any rescue therapy before the end of the period, the primary endpoint will be assessed too by the same ANCOVA model as used for the primary analysis using the observed values.

Assessment of missing data

The availability of primary and secondary efficacy data (yes, no) at the endpoint visit (Week 30 or Week 56) will be summarized by treatment status (discontinued, completed) and by treatment group.

Assessment of treatment effect by subgroup

Primary efficacy endpoint will be further analyzed to examine the consistency of the treatment effect across the subgroups defined by the following Screening or 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)

  Note: For all efficacy and safety subgroup analyses, race groups "Not reported", "Unknown", and participants who report more than one race will be considered "Other".
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Age group (<50, ≥50 to <65, ≥65)
- Gender (Male, Female)
- Duration of diabetes (<10, ≥10 years)
- Baseline HbA1c (<8.0, ≥8.0%)
- Baseline BMI (<30, ≥30 to <40, ≥40 kg/m²)
- Region (North America, Western Europe, Eastern Europe)
- Baseline estimated GFR categories (mL/min/1.73m²): (<60; ≥60 to <90; ≥90)

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 the same imputation approach (retrieve dropout) as applied to the primary analysis of the primary efficacy endpoint. The ANCOVA model will include treatment groups (efpeglenatide 2, 4, or 6 mg, placebo) and randomization stratum of Screening HbA1c

(<8.0, ≥8.0%), randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30, ≥30 kg/m^2), subgroup factor, treatment-by-subgroup factor, and region as fixed factors and using Baseline HbA1c value as a covariate. The adjusted estimates of treatment mean differences (each efpeglenatide dose versus placebo) with SE and 95% CIs will be provided as appropriate across the subgroups. A graphical presentation of the results (ie, forest plot) will also be provided.

In the case that the subgroup factor (eg, Baseline HbA1c, Baseline BMI) is identical or similar to a randomization strata factor, only the subgroup factor (as a single factor or an interaction term) will be included in the model in order to avoid the issue of collinearity in the analysis. The corresponding strata factor will not be included in the model.

Descriptive statistics for change from baseline in Hba1c to Week 30 will be presented by ADA status for the 3 efpeglenatide groups:

- ADA status (positive, negative) at Baseline, if ≥ 5% of participants are ADA positive;
- Treatment-emergent ADA status (positive, negative).

Summary statistics at scheduled visits

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 treatment period. The last on-treatment value will be presented in a separate row. The summary will include the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be used to examine trends over time using mean values (±SE) and mean changes from Baseline (±SE) at each of the scheduled visits (using OC).

2.4.4.2 Analyses of secondary efficacy endpoints

For secondary efficacy endpoints included in the multiplicity procedure described in Section 2.4.4.3, 2-sided statistical tests for the superiority of efpeglenatide to placebo will be performed at the alpha level of 0.05.

2.4.4.2.1 HbA1c <7.0 % at Week 30 (yes/no)

Proportions of participants achieving the HbA1c target value of <7.0% at Week 30 will be compared by treatment group using a Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratum of Screening HbA1c (<8.0, ≥8.0%) and Visit 3 (Baseline, Day 1) BMI (<30, ≥30 kg/m^2) in the ITT population. All HbA1c values at Week 30 will be used to determine whether a participant is a responder (HbA1c <7.0%) or not, even if they are measured after IMP discontinuation or introduction of rescue therapy. Participants with missing HbA1c data at Week 30 will be considered not achieving HbA1c <7.0%. The nominal p-value from the CMH test will be presented. No rounding for HbA1c will be done.

2.4.4.2.2 Changes from baseline in FPG to Week 30 and in body weight to Weeks 30 and 56 and in HbA1c to Week 56

Changes from Baseline in FPG to Week 30, in body weight to Weeks 30 and 56 and in HbA1c to Week 56 will each be analyzed by the same ANCOVA model with missing values imputed by MI method as described in Section 2.4.4.1 the primary analysis. The least squares (LS) means, standard errors of LS means within each treatment group and the adjusted mean and associated two-sided 95% CI of the difference between efpeglenatide 2, 4, and 6 mg and placebo group will be presented.

Summary statistics at protocol scheduled visits and for the last on-treatment value will also be provided for FPG and body weight.

Additional Analysis

Analysis on completers at Week 30 (body weight)

For participants in ITT population who completed the 30-week core treatment period and did not start any rescue therapy before the end of the period, the secondary endpoint of change from Baseline in body weight to Weeks 30, will be assessed too by the same ANCOVA model as used for the primary analysis using the observed values.

Analysis on completers at Week 56 (HbA1c and body weight)

For participants in ITT population who completed the whole on-treatment period and did not start any rescue therapy before the end of the period, the change from Baseline in HbA1c and body weight to Weeks 56, will be assessed by the same ANCOVA model as used for the primary analysis using the observed values.

Sensitivity analysis due to COVID-19 at Week 56 (HbA1c and body weight)

Sensitivity analysis will be performed using ANCOVA (as specified in Section 2.4.4.1) with missing values imputed based upon retrieved dropouts, washout and MAR approach as described below, if there are more than 10 participants in total (regardless of treatment group) with missing endpoint data due to COVID-19. Participants with missing endpoint data due to COVID-19 are identified in Appendix C.

1. Missing endpoint data in participants who prematurely discontinue the study treatment before the Week-56 visit will be imputed using a model built separately in each arm and estimated from participants in the same treatment arm who prematurely discontinue the study treatment before the Week-56 visit but have the measurement for the endpoint (retrieved dropouts). Considering that the number of participants in each treatment arm who discontinue the study treatment but have the measurement for the endpoint is expected to be small, a simple imputation model will be used, where only the Hb1Ac/weight 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. a) Missing endpoint data not due to COVID-19 in participants in all groups, who stay on the study treatment until the Week-56 visit will be imputed using the washout-imputation method, where missing endpoint data in the efpeglenatide arms, as well as the missing data in the placebo arm, are imputed from a model estimated from participants in the placebo group with endpoint data without including any intermediate values. The imputation model will include the randomization strata and corresponding Hb1Ac/weight baseline values. Missing data will be imputed using the regression method.

   b) Missing endpoint data due to COVID-19 in participants in each group, who stay on the study treatment until the Week-56 visit, will be imputed using separate models including the data at all scheduled visits within the same treatment group assuming missing at random.

   - Step 1: Use the Markov Chain Monte Carlo method in 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 sequentially for each scheduled visit. The imputation model will include the randomization stratum of Hba1c value at Screening (<8.0, ≥8.0%), the randomization stratum of Visit 3 (Baseline, Day 1) BMI (<30, ≥30 kg/m²), corresponding baseline values and preceding scheduled postbaseline values.

Similar to what is specified in Section 2.4.4.1, only Step 2 a) and b) will be applied if there are insufficient data to support the imputation approach in Step 1 above (ie, fewer than 5 participants in any arms who prematurely discontinue the study treatment before the endpoint visit but have the measurement for the endpoint).

Participants without data at the endpoint visit will be summarized by treatment status (discontinued, completed) and by impact of COVID-19 on participant (yes, no) for each treatment group.

2.4.4.3 Multiplicity issues

To protect the family-wise error rate for the secondary endpoint, the adjustment for multiplicity of comparison will be applied.

For secondary endpoints, a step-down testing procedure will be applied. For the primary efficacy endpoint (change from Baseline to Week 30 in HbA1c), the 3 efpeglenatide doses will be tested in the order of 6 mg, 4 mg, and 2 mg. Once the primary endpoint is statistically significant at α=0.05 (2-sided) for all 3 efpeglenatide doses, a hierarchical testing procedure will be performed to test the following study secondary efficacy endpoints by the following prioritized order:

1. HbA1c <7% at Week 30 for efpeglenatide 6 mg versus placebo (yes/no)
2. HbA1c <7% at Week 30 for efpeglenatide 4 mg versus placebo (yes/no)
3. Change from Baseline to Week 30 in body weight (kg) for efpeglenatide 6 mg versus placebo

4. Change from Baseline to Week 30 in body weight (kg) for efpeglenatide 4 mg versus placebo
5. HbA1c <7% at Week 30 for efpeglenatide 2 mg versus placebo (yes/no)
6. Change from Baseline to Week 30 in FPG (mmol/L, mg/dL) for efpeglenatide 6 mg versus placebo
7. Change from Baseline to Week 30 in FPG (mmol/L, mg/dL) for efpeglenatide 4 mg versus placebo
8. Change from Baseline to Week 56 in body weight (kg) for efpeglenatide 6 mg versus placebo
9. Change from Baseline to Week 56 in HbA1c (%) for efpeglenatide 6 mg versus placebo
10. Change from Baseline to Week 56 in body weight (kg) for efpeglenatide 4 mg versus placebo
11. Change from Baseline to Week 56 in HbA1c (%) for efpeglenatide 4 mg versus placebo
12. Change from Baseline to Week 56 in HbA1c (%) for efpeglenatide 2 mg versus placebo
13. Change from Baseline to Week 56 in body weight (kg) for efpeglenatide 2 mg versus placebo

Based on the hierarchical testing above, the testing will stop as soon as an endpoint for an efpeglenatide dose is found to be not statistically significant at α=0.05 (2-sided). No multiplicity adjustment will be made on other secondary efficacy variables or the comparison of other efpeglenatide dose versus placebo than mentioned above.

2.4.4.4 Exploratory efficacy analysis

2.4.4.4.1 HbA1c <7.0 % at Week 56 (yes/no)

Proportions of participants achieving HbA1c target values of <7.0% at Week 56 will be analyzed by same approach described in secondary endpoint: HbA1c < 7% at Week 30.

2.4.4.4.2 Change in FPG from baseline to Week 56

Change in FPG concentrations from Baseline to Week 56 will be analyzed by same approach described in secondary endpoint: Change in FPG from baseline to Week 30.

2.4.4.4.3 Changes in 7-point SMPG from baseline to Weeks 30 and 56

The 7-point SMPG profile should be measured at the following 7 points: pre-breakfast and 2 hours post-breakfast, pre-lunch, 2-hour post-lunch, pre-dinner, 2-hour post-dinner, and at bedtime. Two hours postprandial (breakfast, lunch and dinner) is defined as 2 hours after the start of the meal. On days when 7-point profiles are done, fasting pre-breakfast SMPG will be considered as the first point of measurement, ie, “pre-breakfast” time point.

Normally, investigator can only record one entry in the eCRF. In case of multiple records per visit for some participants, the most complete one should be selected; in case of a tie, the one closest to the visit will be selected for analysis. Descriptive statistics and graphical presentations will be presented by treatment group over time at each visit and for each time point.

- **Changes in mean 24-hour SMPG from Baseline to Weeks 30 and 56**

  The mean 24-hour SMPG (7-point profile) will be calculated as the mean of the plasma glucose values over the 7 time points. The daily average data will be calculated only if at least 4 plasma glucose values are available. Only available plasma glucose values will be used for the calculation. For example, if the available data are pre-breakfast, post-breakfast, pre-lunch, and pre-dinner, then the daily average will be calculated as (pre-breakfast + post-breakfast + pre-lunch + pre-dinner)/4.

  Descriptive statistics and graphical presentations will be presented by treatment group over time.

- **Changes in prandial glucose excursion from Baseline to Weeks 30 and 56**

  The prandial glucose excursion, defined as the change in plasma glucose value after each meal (breakfast, lunch, or dinner), will be calculated by subtracting the preprandial value from the postprandial value.

  Prandial glucose excursion will be summarized by treatment group and over time. Additionally, graphical presentations will be provided as appropriate.

Rescue therapy used during the treatment period until Weeks 30 and 56 (yes/no)

Proportions of participants who used rescue therapy during the treatment period until Week 30 and Week 56 will be compared by treatment group using a CMH test stratified by the randomization stratum of Screening HbA1c (<8.0, ≥8.0%) and Visit 3 (Baseline, Day 1) BMI (<30, ≥30 kg/m²) in ITT population.

Time to initiation of rescue therapy (weeks)

Time to initiation of rescue therapy is defined as the time from the date of randomization to the date of first rescue therapy in weeks. Participants who did not take any rescue therapy during the study will be censored at the date of study completion/discontinuation. The curve of the cumulative incidence of participants with rescue initiation will be estimated using Kaplan-Meier method by study treatment group.

Patient reported outcome

The Patient Qualitative Assessment of Treatment version 2 (PQATv2) is intended for the collection of participant-perceived benefit-risk of glucose-lowering treatment with efpeglenatide. The participants will be asked to complete it from home just before the on-site visits planned at Weeks 30 and 56. If a participant discontinues treatment with IMP during the treatment period, the participant will be asked to complete the PQATv2 at the time of discontinuation.

The analysis of participant-reported outcome (PRO) endpoints will be descriptive with no formal testing. For categorical data, frequency and percentage will be provided by treatment group and overall at scheduled visits. Participants' answers to the open-ended questions of PQATv2 (items #1, 3 and 5) will be analyzed qualitatively and quantitatively, as relevant, using appropriate data analysis software. The analysis method for the open-ended questions will be provided in a separately and the analyses results will not be included in the CSR.

Other exploratory analysis

- Analysis to investigate whether the HbA1c decrease depends on the decrease in weight will be assessed by scatter plots of HbA1c reduction versus weight loss. A cumulative distribution plot will be provided for each of changes in HbA1c and in body weight from Baseline to Week 30 and 56.
- Proportion of participants with HbA1c <7.0% at Week 30 and 56 with no severe or documented symptomatic hypoglycemia will be assessed by number of participants and percentage by treatment group.
- Analysis of change in weight as a function of baseline BMI will be assessed by descriptive summary statistics at scheduled visits, by baseline BMI categorization (<19, [≥19 to <25], [≥25 to <30], [≥30 to <40], ≥40 kg/m^2) and by treatment group.
- Analysis of proportions of participants with 5% and 10% weight loss at Weeks 30 and 56 will be assessed by number of participants and percentage by treatment group.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group on the "30-week core on-treatment period" and on the "whole on-treatment period" as defined in Section 2.1.4. Selected tables will be displayed by treatment group on the "30-week on study observation period" as defined in Section 2.1.4.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the common rules noted below. Safety data in participants who do not belong to the safety population (eg, treated but not randomized) will be listed separately.

- The Baseline value is defined in Section 2.1.1. For WBC and differential counts, the baseline is defined as the last available value before the first injection of IMP where no differential component is missing.
- Last on-treatment value is defined as the value collected at or just prior to the last IMP intake.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version 3 date dated 21 May 2014 effective date 24 May 2014 [Appendix B]).
  - PCSA criteria will determine which participants had at least 1 PCSA during the 30-week core on-treatment period and whole on-treatment period, taking into account all evaluations performed during the 30-week core on-treatment period and whole on-treatment period, including nonscheduled or repeated evaluations. The number of all such participants will be the numerator for the 30-week core on-treatment period and whole on-treatment period PCSA percentage.
  - The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of participants assessed for that given parameter in the 30-week core on-treatment period and whole on-treatment period by treatment group on the safety population.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from Baseline values by visit and treatment group.
- The analysis of the safety variables will be, essentially, descriptive and no systematic testing is planned. Relative risks versus placebo and their 95% CIs may be provided, if relevant.
- Selected safety analyses will be summarized by age group, gender, racial subgroups, and any pertinent subgroups as appropriate.

2.4.5.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs. Pretreatment and posttreatment AEs will be described separately.

If an AE date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the AE as pretreatment, treatment-emergent, or posttreatment. The algorithm for imputing date/time of onset will be conservative and will classify an AE as treatment emergent unless there is definitive information to determine it is pretreatment or posttreatment. Details on classification of AEs with missing or partial onset dates are provided in Section 2.5.3.

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

Sorting within tables ensures the same presentation for the set of all AEs within the observation period (pretreatment, treatment-emergent, and posttreatment). For that purpose, the table of all TEAEs presented by primary SOC and PT sorted by the internationally agreed SOC order and decreasing frequency of PTs within SOCs will define the presentation order for all other tables unless otherwise specified. In case of equal frequencies of PTs within a SOC, the alphabetic order will be applied. Sorting will be based on the incidence in the efpeglenatide 6 mg group.

The internationally agreed order of SOCs shown below was described in the Introductory Guide MedDRA Version 19.1, September 2016 International Conference on Harmonisation for SOC:

1. Infections and infestations
2. Neoplasms benign and malignant (including cysts and polyps)
3. Blood and lymphatic system disorders
4. Immune system disorders
5. Endocrine disorders
6. Metabolism and nutrition disorders
7. Psychiatric disorders
8. Nervous system disorders
9. Eye disorders
10. Ear and labyrinth disorders
11. Cardiac disorders
12. Vascular disorders
13. Respiratory, thoracic, and mediastinal disorders
14. Gastrointestinal disorders
15. Hepato-biliary disorders
16. Skin and subcutaneous tissue disorders
17. Musculoskeletal, connective tissue, and bone disorders
18. Renal and urinary disorders
19. Pregnancy, puerperium, and perinatal conditions
20. Reproductive system and breast disorders
21. Congenital and familial/genetic disorders
22. General disorders and administration site conditions
23. Investigations
24. Injury, poisoning, and procedural complications
25. Surgical and medical procedures
26. Social circumstances
27. Product issues

Analysis of all treatment-emergent adverse events

The following TEAE summaries will be generated for the safety population.

- Overview of TEAEs, summarizing number (%) of participants with any
  - TEAE
  - Serious TEAE
  - TEAE leading to death
  - TEAE leading to permanent treatment discontinuation
  - Treatment-related TEAE
  - TEAEs of special interest (AESI)
  - TEAEs requiring specific monitoring (AERSM)
- All TEAEs by primary SOC, HLGT, HLT, and PT, showing number (%) of participants with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order. This sorting order will be applied to all other tables by SOC, HLGT, HLT, and PT, unless otherwise specified.
- All TEAEs by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC. This sorting order will be applied to all other tables by SOC and PT, unless otherwise specified.
- All TEAEs related to IMP by primary SOC, HLGT, HLT and PT, showing the number (%) of participants with at least 1 TEAE
- All TEAEs by maximal intensity, presented by primary SOC and PT, showing the number (%) of participants with at least 1 TEAE by intensity (ie, mild, moderate, or severe)
- Summary of common TEAEs (eg, PTs with incidence ≥2% in any treatment group) will also be presented by primary SOC, and PT
- Summaries of common TEAEs (eg, PTs with an incidence ≥2% in any treatment group) will be provided as appropriate by primary SOC and PT and by demographic factors including gender (Male, Female), age group (<50, ≥50 to <65, ≥65 to <75, ≥75 years), and race (Asian, Black or African American, White, Other)

Note: For all efficacy and safety subgroup analyses, race groups “Not reported”, “Unknown”, and participants who report more than one race will be considered “Other”.

- Kaplan-Meier curves will be provided for the time to first onset of the following PTs: nausea, vomiting, and diarrhea
- The frequency of TEAEs over time will be provided for nausea, vomiting, and diarrhea, using weekly time intervals through Week 8 and then every 4 weeks through Week 56, ie, [0-1] week, [1-2] weeks, [2-3] weeks, [3-4] weeks, etc. In each time interval, the numerator in the calculation of percentages will be the number of participants with at least 1 TEAE occurring in this time interval. Two types of analyses will be included: (1) only

the first event will be counted for each participant and all recurrent events will not be included, and the denominator for the calculation of percentages will be the number of participants at risk at the beginning of the time interval who did not experience a first event in the preceding intervals; and (2) the recurrent events in subsequent intervals will be counted once for each participant in the numerator of the corresponding interval, and the denominator for the calculation of percentages will be the number of participants at risk at the beginning of the time interval. A histogram of the frequency over time (by weekly intervals) will also be presented as appropriate.

- All TEAEs by BMI subgroup ($< 30, \geq 30$ kg/m^2)
- All TEAEs by Anti-Efpeglenatide Antibody Status (Positive, Negative)

Analysis of all treatment emergent serious adverse event(s)

- All serious TEAEs by primary SOC, HLGT, HLT, and PT, showing the number (%) of participants with at least 1 serious TEAE

All serious TEAEs related to IMP, by primary SOC and PT, showing the number (%) of participants with at least 1 serious TEAE.

Analysis of all treatment-emergent adverse event(s) leading to treatment discontinuation

All TEAEs leading to treatment discontinuation, by primary SOC, HLGT, HLT, and PT, showing the number (%) of participants

Analysis of adverse events of special interest and adverse events requiring specific monitoring

Adverse events of special interest (AESI) and adverse events requiring specific monitoring (AERSM) include AE defined in Section 2.1.4 and the criteria of AESI and AERSM are in Table 3.

Table 3 - Criteria for AESI and AERSM

AE Grouping		Criteria
AESI		
	Pregnancy	"Pregnancy" or "Partner pregnancy" checked
	Symptomatic Overdose	"Overdose" checked and symptomatic (AEOVSYMP) ="Yes"
	Increase in ALT >3 ULN	"ALT Increase" checked and Yes to the question "Is the event an AESI?" in eCRF form "Adverse Events"
AERSM		
	Severe GI event	AE severity= "severe" using Gastrointestinal disorders CMQ
	Severe hypoglycemia	Any hypoglycemia event which required assistance (from hypoglycemia page)
	Pancreatic event	Cases reported in eCRF "Suspected or confirmed Pancreatitis" page or AE Category="Pancreatic Neoplasm"

AE Grouping	Criteria
Selected cardiovascular event	Cases reported in the following specific eCRF pages: • "Suspected or confirmed MI/Unstable Angina" • "Suspected or confirmed cerebrovascular event" • "Suspected or confirmed heart failure" led to unplanned hospitalization, led to urgent/unscheduled visit to emergency room or an urgent/unscheduled outpatient heart failure treatment unit, or infusion center, or office/practice visit, not followed by hospitalization, or occurred while patient was hospitalized for another reason • Primary cause of death in eCRF "Death (CV)" as Acute MI, Sudden cardiac death, Heart failure or cardiogenic shock, Stroke, Complication of cardiovascular procedure, Other cardiovascular cause, or Undetermined cause of death
Calcitonin and thyroid C-cell neoplasm	Using Calcitonin increase CMQ Using Medullary thyroid cancer CMQ
Acute renal failure	Using Acute renal failure CMQ
Severe injection site reaction	Intensity = "Severe" + Using Injection site reaction_ CMQ.
Severe allergic reaction	Intensity = "Severe" + CMQs for anaphylactic reaction, angioedema, severe cutaneous adverse reaction, anaphylactic/anaphylactoid shock conditions (under SMQ "Shock"), and hypersensitivity.
Severe immune complex disease	Intensity = "Severe" using Immune complex disease CMQ
Diabetic retinopathy complications	Cases reported in eCRF "Diabetic Retinopathy Complementary Form"

The following TEAE summaries will be generated for the safety population:

- All AESI by prespecified grouping and PT, showing number (%) of participants with at least 1 AESI, with PTs sorted by decreasing order in Efpeglenatide 6 mg group.
- All AERSM by prespecified grouping and PT, showing number (%) of participants with at least 1 AERSM, with PTs sorted by decreasing order in Efpeglenatide 6 mg group.

Separate AESI listings will be provided for pregnancy, overdose, and ALT increase, as well as an overall listing for AERSM.

Analysis of adjudicated events

All events of death, selected cardiovascular events (MI, stroke, unstable angina leading to hospitalization, and heart failure leading to hospitalization), any pancreas-related events, and other selected AEs (as defined in the CEC charter) will be reviewed, assessed and adjudicated by CEC.

The number of events confirmed by adjudication, will be summarized by treatment group.

Analysis of pretreatment and posttreatment adverse events

- All pretreatment AEs by primary SOC and PT, showing the number (%) of participants with at least 1 pretreatment AE
- All posttreatment AEs by primary SOC and PT, showing the number (%) of participants with at least 1 posttreatment AE
- All pretreatment SAEs by primary SOC and PT, showing the number (%) of participants with at least 1 pretreatment SAE
- All posttreatment SAEs by primary SOC and PT, showing the number (%) of participants with at least 1 posttreatment SAE.

Analysis of adverse events during the 30-week on study observation period

The following selected AE will also be summarized for the 30-week on-study observation period as defined in Section 2.1.4:

- Overview of AEs
- AEs (by primary SOC, HLGT, HLT, and PT, showing number (%) of participants with at least 1 adverse event)
- SAE (by primary SOC, HLGT, HLT, and PT, showing number (%) of participants with at least 1 serious adverse event)
- AEs leading to death.

Analysis of COVID-19 related adverse events

COVID-19 related AEs during the whole on-treatment period will be presented for the number (%) of participants with at least one event and by primary SOC and PT.

Listings

Supportive AE listings will be provided for all SAEs, AESIs/AERSM, AEs leading to death, and AEs leading to treatment discontinuation. These listings will include at least the following information, sorted by treatment, participant identification, and onset date: treatment, participant identification, country, age, gender, race, primary SOC, PT, reported term, onset date, study day (relative day to the start date of IMP), AE duration, duration of exposure, intensity, corrective treatment, action taken with IMP, relationship to IMP/NIMP/study procedures, outcome, date of death (if any), seriousness, seriousness criteria, and AE status (“Pre” for a pre-treatment AE; “T” for a TEAE; and “Post” for a post-treatment AE).

Similar to the AE listing, a listing for all adjudicated AEs will be provided with adjudication outcome.

2.4.5.2 Analysis of hypoglycemia

Treatment-emergent hypoglycemia events will be tabulated separately from the AEs.

Event frequency and incidence of hypoglycemia events will be summarized by treatment for all reported hypoglycemia and per type of hypoglycemic event described in Section 2.1.4.5 (ie, severe, documented symptomatic, asymptomatic, probable symptomatic, relative) for safety population. Incidence of severe or documented symptomatic hypoglycemia events will be summarized by study period (≤4 weeks (titration period), >4 weeks to ≤8 weeks, >8 weeks to ≤30 weeks, >30 weeks) and according to time of occurrence (nocturnal [ie, 00:00 to 05:59 am], daytime [ie, 06:00 am to 23:59]) for safety population. Documented hypoglycemia (symptomatic or asymptomatic) will be also evaluated for the more stringent plasma glucose threshold of <54 mg/dL (3.0 mmol/L), as well as for ≥3.0 and <3.9 mmol/L (≥54 and <70 mg/dL). Frequency and percentage of participants with at least one hypoglycemia event will be summarized as well.

Event rate of hypoglycemia per participant year will be calculated by treatment using the total number of hypoglycemia events from all participants (denoted as n) divided by the total exposures from all participants expressed in years (ie, participant exposure in days divided by 365.25, denoted as t). Multiple events from an individual participant will all count. Event rates of hypoglycemia per participant year (all reported hypoglycemia, severe, documented symptomatic, asymptomatic, probable symptomatic, relative hypoglycemia, and documented hypoglycemia with plasma glucose <54 mg/dL [3.0 mmol/L]) will be presented by treatment group for the 30-week core on-treatment period and the whole on-treatment period.

The summary of frequency and event rate in participant years for severe or documented symptomatic hypoglycemia will be provided as appropriate by gender (Male, Female), age group (<50, ≥50 to <65, ≥65 to <75, ≥75 years), and race (Asian, Black or African American, White, Other).

A KM curve will also be provided by treatment group for the time to first severe or documented symptomatic hypoglycemia during the whole on-treatment period.

A listing of participants for all severe or documented symptomatic hypoglycemia events reported on the specific eCRF “Hypoglycemic Event Information” page will be provided and sorted by participants.

2.4.5.3 Deaths

The following summaries of deaths will be generated:

- TEAE leading to death (death as an outcome on the AE case report form page as reported by the Investigator) during whole on-treatment period by primary SOC, HLGT, HLT, and PT showing number (%) of participants (Safety population)
- AE leading to death (death as an outcome on the AE case report form page as reported by the Investigator) during whole 30-week on-study observation period by primary SOC, HLGT, HLT, and PT showing number (%) of participants (Safety population)
- Number (%) of participants who died by study period (on-study, on-treatment, post-study) (Safety population)
- Pre-treatment AEs, TEAEs and post-treatment AEs leading to death (death as an outcome on the AE case report form page as reported by the Investigator) by study period

(pre-treatment period, on-treatment period, and post-treatment period) showing number (%) of participants

- Listing of all Deaths (Screened participants)

2.4.5.4 Product complaints

All product complaint summaries during the on-treatment period will be generated in the safety population with number (%) of participants experiencing at least one event as well as number of events and rate per participant-years.

Rate per participant-years will be defined as the number of events divided by the cumulative duration of participants' exposure expressed in years.

The overview of product complaints with the details below will be generated:

- Any product complaint
- Any product complaint related to AEs

In addition, the analysis below will be conducted.

- Any product complaint categorized by type of complaint
- AE(s) leading to product complaints by primary SOC and PT
- Listing of all product complaints

2.4.5.5 Analyses of laboratory variables

All hematology and clinical chemistry results will be listed by treatment group, participants and visit, including scheduled and unscheduled/repeat measurements.

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all protocol-required laboratory variables (central laboratory values and changes from Baseline) will be calculated for each scheduled visit and last value on treatment by treatment group.

The incidence of PCSAs at any time during the whole on-treatment period will be summarized by biological function and treatment group whatever the Baseline level and/or according to the following Baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided. For calcitonin, no PCSA criterion is defined. Similar summaries will be provided using the pre-defined categories: ≤ULN, >ULN - <20 ng/L, ≥20 - <50 ng/L, and ≥50 ng/L (Note that ng/L is the standard international unit and is equivalent to pg/mL).

All measurements collected during the whole on-treatment period, including values from unscheduled visits, will be considered for the PCSA summaries. These summaries will include participants in the safety population who have at least 1 assessment performed during the whole on-treatment period. When a PCSA definition involves only a change from baseline value, participants must also have a baseline value to be included in the summaries, and when required by the definition of the abnormality, participants must also have available laboratory normal ranges.

For some parameters, such as liver enzymes, the lower limit of normal (LLN) is not considered clinically relevant, and values below this limit are considered normal. When there are multiple PCSA criteria for a specific parameter (eg, ALT), the participant will be counted once during the whole on-treatment period for the specific parameter in question under the worst/maximum PCSA category.

Elevated liver parameters will be summarized by treatment group in safety population.

For PCSA, both central and local lab data will be used.

A listing of participants with at least 1 post-baseline PCSA (or out of normal range when no PCSA criterion is defined) will be provided and will display the entire participants' profile across time for all parameters belonging to the corresponding biological function. Individual data listings will include flags when applicable:

- Baseline values will be flagged "B".
- Normal laboratory ranges, available for most laboratory parameters, will be identified as ULN and LLN. Baseline, and individual data will be flagged "L" if the value is below the LLN and will be flagged "H" if it is above the ULN.
- Laboratory PCSA criteria will be used for the corresponding laboratory parameters. Values reaching a PCSA limit will be flagged (+, ++, -, or – depending upon the direction and level of the abnormality). Flags for WBC and differential counts will be determined using data expressed in international units.

For parameters whose PCSA criteria are multiples of the ULN, the parameter's value will also be expressed as a multiple of the ULN in the individual data provided.

2.4.5.6 Analyses of vital sign variables

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of all vital sign variables will be calculated for each scheduled visit by treatment group.

The incidence of PCSAs at any time during the whole on-treatment period will be summarized by treatment group irrespective of the Baseline level and/or according to the following Baseline status categories:

- Normal/missing,
- Abnormal according to PCSA criterion or criteria.

A listing of participants with at least 1 post-baseline PCSA will be provided and will display the participant's profile over time of all vital sign parameters. Individual data listings will include the following flags:

- Baseline values will be flagged "B",
- Parameter values reaching a PCSA limit will be flagged (+, or - depending of the direction).

2.4.5.7 Analyses of electrocardiogram variables

The frequency and percentage of 12-lead ECG interpretation (normal, abnormal) will be provided at each scheduled visit by treatment group.

2.4.5.8 24-hours Holter ECG

The summary statistics (including number, mean, median, standard deviation, minimum and maximum) of Holter ECG variables (24-hour mean heart rate and night-time mean heart rate, and changes from baseline) will be calculated for each applicable visit by treatment group and overall.

2.4.5.9 Analyses of other safety endpoints

Anti-drug Antibody

An anti-drug antibody positive participant is defined as a participant with at least one treatment-induced or treatment-boosted ADA-positive sample at any time.

Summaries of ADA data will be provided 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. The incidence of ADA status (positive/negative/inconclusive) will be summarized by visit, treatment, and individual titer for the ADA population. Incidence of treatment induced and treatment-boosted (treatment emergent) ADA during on-study period will be summarized by treatment. Incidence of participants with ADA cross-reactivity to endogenous GLP-1 (positive/negative), and to endogenous glucagon (positive/negative) will be summarized by visit and treatment. Incidence of participants with ADA directed against PEG linker, HMC001 moiety and exendin-4 moiety (positive/negative), will be summarized by visit and treatment.

Incidence of participants with neutralizing antibodies against efpeglenatide and against endogenous GLP-1 and Glucagon will be summarized by visit and treatment.

ADA data from unscheduled visits (due to SAE for example) will not be included in summary and will be presented only in ADA values listing.

2.4.6 Analyses of pharmacokinetic variables

Serum concentrations of efpeglenatide, pre-dose (C_{trough}) and post-dose, will be summarized (mean, SD, CV%, median, minimum, and maximum) over time and by treatment. All below quantitation limit (BLQ) concentration will be treated as zero and all missing concentrations will be treated as missing for descriptive statistics.

Serum concentrations of efpeglenatide, pre-dose (C_{trough}) and post-dose, will be listed.

Population PK analysis will be discussed in a separate analysis plan.

2.4.7 Analyses of quality of life/health economics variables

Not Applicable.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

The participant's duration of diabetes (years) is calculated using the date of informed consent and the date of diabetes diagnosis.

If date of diabetes diagnosis is a complete date, then the duration of diabetes is (date of informed consent - date of diabetes diagnosis + 1) / 365.25. If date of diabetes diagnosis is a partial date:

- Year and month are not missing, but day is missing, then day = 01
- Year is not missing, but month and date are both missing, then month = January and day = 01.

Renal function formulas

eGFR will be calculated using the 4-variable Modification of Diet in Renal Disease (MDRD-4) formula below (1):

- eGFR (mL/min/1.73 m^2) = 175 × serum creatinine (mg/dL)$^{-1.154}$ × Age(year)$^{-0.203}$ × 1.212 [*if black*] × 0.742 [*if female*]

2.5.2 Data handling conventions for secondary efficacy variables

No special data handling.

2.5.3 Missing data

For categorical variables, participants with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of participants with missing data is presented.

Derived variables will be considered missing if any of the original variables required to calculate them are missing. For example, if either a baseline assessment or an endpoint assessment is missing for a particular participant, then change from baseline at endpoint will be missing. Depending upon the assessment, analyses may not include all participants in the analysis population, because certain participants in the intended population may have missing data.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the treatment status case report form page. If this date is missing, the exposure duration should be left as missing.

In the definition of the whole on-treatment period, the date of the last dose of IMP is equal to the date of the last administration reported on the treatment status case report form page. If this date is missing, the date of the last IMP injection in the exposure page will be used for participants with at least 1 injection or the date of visit 3/randomization visit will be used for participants who were lost to follow-up after the initial dispensation of IMP.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing, and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior, concomitant, and post-treatment medication.

For time to event (TTE) analysis, partial rescue medication dates will be imputed using the following rules:

- If year and month are not missing, but day is missing, then day = 15
- If year is not missing, but month and date are both missing, then month = June and day = 15.

Note: if it's possible that the partial date is within the whole on-treatment period, but the imputed date falls outside of the whole on-treatment period, then imputed date will be set to the nearest date inside the whole on-treatment period.

Handling of adverse events/hypoglycemia with missing or partial date/time of onset

Missing or partial AE/hypoglycemia onset dates and times will be imputed so that if the partial AE/hypoglycemia onset date/time information does not indicate that the AE/hypoglycemia started prior to treatment or after the whole on-treatment period, the AE/hypoglycemia will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data

imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

Handling of adverse events/hypoglycemia when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all AEs/hypoglycemia that occurred on or after the day of randomization should be considered as TEAEs. The exposure duration should be kept as missing.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the AE considered as such in the frequency tables of possibly related AEs, but no imputation should be done at the data level.

Handling of missing intensity of adverse events

If the intensity is missing for 1 of the treatment-emergent occurrences of an AE, the maximal intensity on the remaining occurrences will be considered. If the intensity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a participant has a missing Baseline, he or she will be grouped in the category "normal/missing at Baseline."

For PCSAs with 2 conditions, one based on a change from Baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

Handling of missing screening value to derive actual randomization strata

In case of missing data at screening visit for HbA1c and BMI, unscheduled data before randomization visit can be used. If the sample is confirmed as being for the purpose of a re-screen, then the result is sent to be integrated into IRT. In case of several data collected, the earliest is used.

2.5.4 Windows for time points

Nominal post-baseline visits will be used for descriptive statistics and time course plots.

Display of safety data by visit (laboratory variables and vital signs)

Descriptive statistics (N, mean, SD, minimum, median, maximum) of quantitative laboratory variables and vital signs (observed data and change from baseline) during the whole on-treatment period for all scheduled visits as per protocol will be provided (ie, only including participants having non-missing assessments at a nominal visit). Summaries showing data by visit will be presented according to the visit number and labeled with the targeted approximate day/week.

As specified in the study protocol, laboratory data from scheduled visits are reported by central laboratories. When both central and local laboratories report values from the same blood sample (ie, sample collected at the same date and time), only measurements from the central laboratory will be included in the analyses. When only local laboratory results are reported, and central laboratory results are unavailable, the local results will not be used in the efficacy analyses. In the safety analyses, local results will only be used in the PCSA summary if they are accompanied by a local laboratory normal range.

When a participant has more than 1 measurement from the central laboratory for the same laboratory parameter on the same date, the average of the measurements will be used. For the same laboratory parameter, if a participant has more than one measurement on different dates for the same scheduled visit, the value closest to the scheduled visit will be used for the scheduled visit. When the values for the same scheduled visit are equidistant, the last value should be used for the scheduled visit.

Efficacy data at Week 30/Week 56

The scheduled measurements at the endpoint visit (Week 30 or Week 56) as collected will be used in the efficacy analyses including those obtained after IMP discontinuation and/or introduction of rescue therapy. For participants whose efficacy measurement is not available at the endpoint visit, the measurement at unscheduled visit (including the end of treatment and/or study visit for those prematurely discontinued) will be used if the unscheduled measurement is within +/-30 days (7 days for FPG and SMPG) of the date of the end point visit [targeted study Day 210 for Week 30 (or Day 392 for Week 56)]. If multiple measurements are associated to the same targeted date, the closest to the targeted study day will be used. In case of equality, the last measurement will be used. If there are still no measurement for a given parameter at an endpoint visit, the data is considered missing for efficacy analyses, where multiple imputation would be applied as appropriately as described in Section 2.4.4.1.

Linked adverse events that worsened or became serious

An AE that worsened or became serious will have a separate record in the data from the original event record with a reference identification number that links the new record to the original record. An AE that worsened or became serious will be considered a new recurring AE in the summary of recurrent events or in the summary of events by time intervals.

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will not be included in the by-visit summaries but will be used for computation of Baseline and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Not Applicable.

2.5.7 Statistical technical issues

Not Applicable.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database is planned to be locked approximately 4 to 6 weeks after last participant last visit.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.3 or higher.

6 REFERENCES

1. FDA Draft Guidance for Industry. Pharmacokinetics in patients with impaired renal function - study design, data analysis, and impact on dosing and labeling. Clinical Pharmacology. 2010 Mar (revision 1).

7 LIST OF APPENDICES

Appendix A Efficacy analysis SAS pseudo code

Primary Analysis missing data imputation:

1. Multiple imputations in participants who prematurely discontinued the study treatment before the Week-30 visit:

```
proc mi data= data_IN out=data_OUT_DISC  nimpute=10000 seed=14822;
              where PEOTF30L = "Y";
              by ARM;
              var BASE AVAL_W30;
              monotone regression (AVAL_W30= BASE );
run;
```

2. Multiple imputations in participants who stay on the study treatment until the Week-30 visit

```
proc mi data  =data_IN out=data_OUT_COMPL_MI  nimpute=10000 seed=14822;
              where PEOT30FL='N' and (ARM='Placebo' or (ARM ne 'Placebo' and AVAL_W30 =. ));
              class HbA1c_strata BMI_strata;
              var HbA1c_strata BMI_strata base AVAL_W30;
              monotone regression (AVAL_W30 = HbA1c_strata BMI_strata  BASE );
run;
```

3. Transform dataset of EFPEG participants who are under treatment at Week 30 visit with a collected endpoint to have 10 000 replications.

```
Data  data_OUT_COMPL_EFPEG;
Set   data_IN (where=( PEOT30FL='N' and  ARM ne 'Placebo' and AVAL_W30 ne .));
      n_imput=1;
      %do i = 1 %to 10 000;
      n_imput=n_imput+1;
      %end;
run;
```

4. Combine multiple imputations from the three subsets of participants

```
Data    dataMI;
set     data_OUT_DISC
        data_OUT_COMPL_MI
        data_OUT_COMPL_EFPEG;
run;
```

Back-up plan:

```
Data    data_OUT_COMPL_EFPEG;
Set     data_IN (where=( ARM ne 'Placebo' and AVAL_W30 ne .);
        n_imput=1;
        %do i = 1 %to 10 000;
        n_imput=n_imput+1;
        %end;
run;

proc mi data    =data_IN out=data_OUT_MI  nimpute=10000 seed=14822;
                where ARM='Placebo' or (ARM ne 'Placebo' and AVAL_W30 =.;
                class HbA1c_strata BMI_strata;
                var HbA1c_strata BMI_strata base AVAL_W30;
                monotone regression (AVAL_W30 = HbA1c_strata BMI_strata  BASE );
run;
data    dataMI;
set     data_OUT_MI
        data_OUT_COMPL_EFPEG;
run;
```

Sensitivity analysis (*If more than 10 missing endpoint data impacted by COVID-19*):

```
#3 DATA data_OUT_COMPL;
        Set     data_IN (where = (PEOTF56L='N' and W56_missing = "N"));
                _imputation_=0;
                do i = 1 to 10 000;
                _imputation_=_imputation_+1;
                output;
                end;
run;


#1 Multiple imputations in participants who prematurely discontinued the study treatment before the Week 56 visit:
        proc mi data= data_IN out=data_OUT_DISC  nimpute=10000 seed=14822;
                        where PEOTF56L = "Y";
                        by ARM;
                        var BASE AVAL_W56;
                        monotone regression (AVAL_W56= BASE );
        run;


#2a proc mi data        =data_IN out=data_OUT_MI nimpute=10000 seed=14822;
                where PEOT56FL='N' and ((ARM='Placebo' and W56_missing = "N") or (ARM = 'Placebo' and W56_missing = "Y" and
        COVID = "N") or (ARM ne 'Placebo' and W56_missing = "Y" and COVID = "N"));
                class HbA1c_strata BMI_strata;
                var HbA1c_strata BMI_strata base AVAL_W56;
                monotone regression (AVAL_W56 = HbA1c_strata BMI_strata BASE);
run;
```

```
data data_OUT_MI_MISSING;
        set data_OUT_MI;
        if W56_missing = “Y”;
run;

proc sort data= data_IN out=data_IN_COVID;
        by ARM;
run;

#2b step 1
proc mi data    =data_IN_COVID out= monotone nimpute=10000 seed=14822;
                by ARM;
                where PEOT56FL=’N’ and (W56_missing ne “Y” or (W56_missing = “Y” and COVID=“Y”));
                mcmc chain=multiple impute=monotone
                var BASE AVAL_W12 AVAL_W30 AVAL_W43 AVAL_W56;
                        /* For body weight, include Weeks 4, 8, 12, 24, 30, 43, and 56 */
run;

#2b step2
proc mi data= monotone out= OUT_MI_MISSING_COVID nimpute=1 seed=14822;
        by ARM _imputation_;
        class HbA1c_strata BMI_strata;
         monotone reg (  / details);
        var HbA1c_strata BMI_strata BASE AVAL_W12 AVAL_W30 AVAL_W43 AVAL_W56;
                        /* For body weight, include Weeks 4, 8, 12, 24, 30, 43, and 56 */
 run;
```

```
data data_ OUT_MI_MISSING_COVID;
        set OUT_MI_MISSING_COVID;
        if W56_missing = "Y";
run;


data    dataMI;
set     data_OUT_DISC
        data_OUT_MI_MISSING
        data_ OUT_MI_MISSING_COVID
        data_OUT_COMPL;
run;
```

In this sample SAS® (version 9.4) code:

- DATA_IN is the input dataset including one observation per participant in the ITT population with Baseline HbA1c value and change from baseline at Week 30.
- data_OUT_DISC is the output dataset including observed and imputed data for participants who have prematurely discontinued the treatment.
- data_OUT_COMPL_MI is the output dataset including observed and imputed data for all Placebo participants who have completed the 30-week study treatment period and all Efpeg participants who have completed the 30-week study treatment period without Week 30 endpoint.
- Data_OUT_COMPL_EFPEG is the output dataset included observed data for Efpeg participants who have completed the 30-week study treatment period and have Week 30 endpoint.
- DataMI is the final output containing 10,000 lines by participant with all observed and imputed data used for the ANCOVA.
- PEOT30/56FL is the variable indicating whether the participant prematurely discontinued the study treatment (PEOT30/56FL="Y" if the participants prematurely discontinued the study treatment before Week 30/56 visit and PEOT30/56FL="N" if the participant stay on the study treatment until Week 30/56 visit).
- ARM is the randomized treatment group (Placebo, Efpeglenatide 2mg, Efpeglenatide 4mg, Efpeglenatide 6mg).

- HbA1c_strata is the randomization stratum of screening Hb1Ac (<8%, ≥8%)
- BMI_strata is the randomization stratum of BMI at Visit 3(<30, ≥30)
- BASE is the baseline HbA1c.
- AVAL_W30/56 is the change from baseline in HbA1c at Week 30/56.
- W56_missing = “Y” if the Week 56 value is missing, otherwise W56_missing = “N”.
- COVID = “Y” if the missing data is impacted by COVID-19, otherwise COVID = “N”.
- The seed (14822) has been chosen arbitrarily and is based on the study code (EFC14822).

Appendix B Criteria for potentially significant abnormalities - for Phase 2/3 studies (oncology excepted)

Parameter	PCSA	Comments
Clinical Chemistry		
ALT	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
AST	By distribution analysis: >3 ULN >5 ULN >10 ULN >20 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.
Alkaline Phosphatase	>1.5 ULN	Enzymes activities must be expressed in ULN, not in IU/L. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Total Bilirubin	>1.5 ULN >2 ULN	Must be expressed in ULN, not in µmol/L or mg/L. Categories are cumulative. Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008.
Conjugated Bilirubin	>35% Total Bilirubin and TBILI >1.5 ULN	Conjugated bilirubin dosed on a case-by-case basis.
ALT and Total Bilirubin	ALT >3 ULN and TBILI >2 ULN	Concept paper on DILI – FDA draft Guidance Oct 2007. Internal DILI WG Oct 2008. To be counted within a same treatment phase, whatever the interval between measurement.

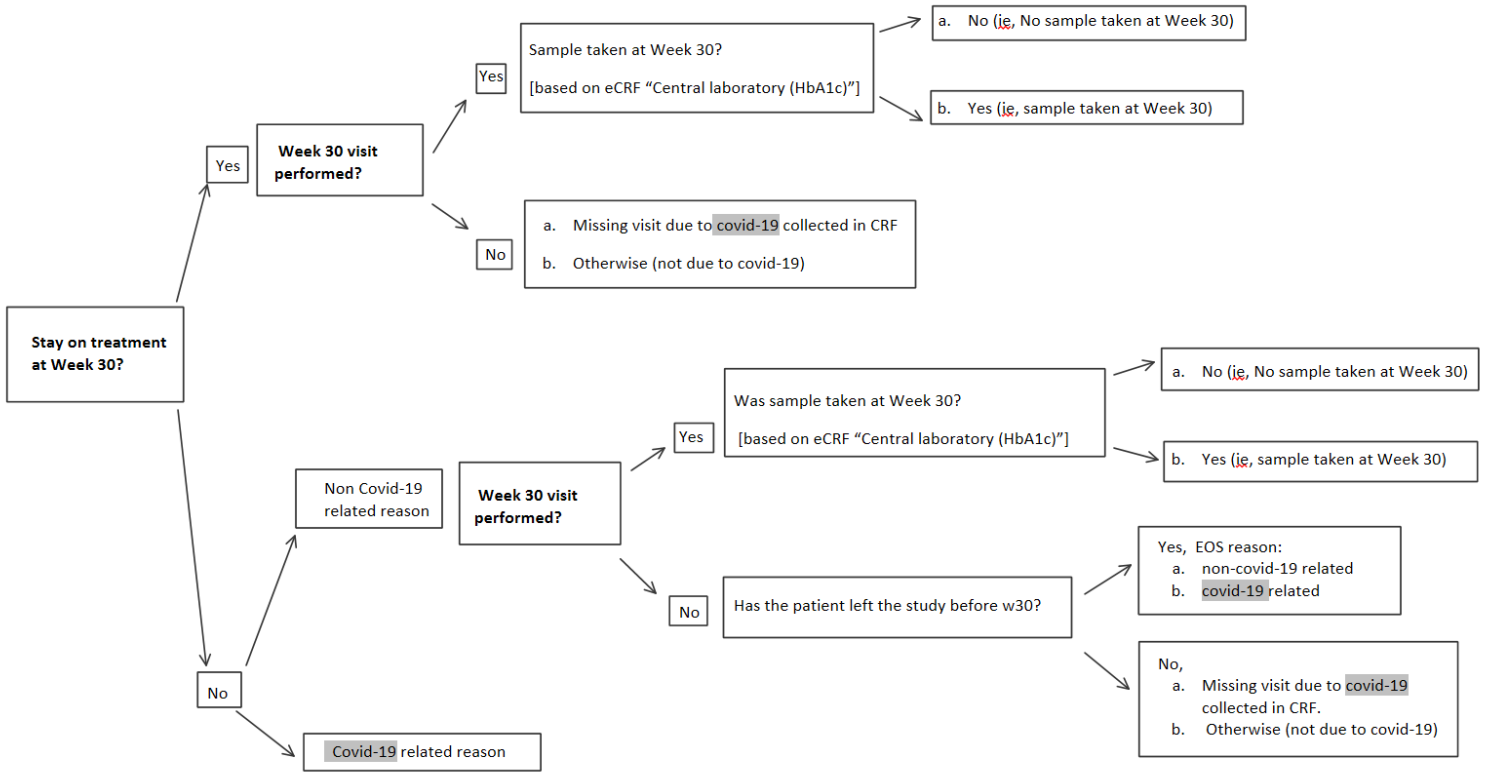
Parameter	PCSA	Comments
CPK	>3 ULN	FDA Feb 2005.
	>10 ULN	Am J Cardiol April 2006.
		Categories are cumulative.
		First row is mandatory. Rows following one mentioning zero can be deleted.
CLcr (mL/min)	<15 (end stage renal disease)	FDA draft Guidance 2010
(Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR)	Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥30 - < 60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥ 90 (normal GFR)	
eGFR (mL/min/1.73m2)	<15 (end stage renal disease)	FDA draft Guidance 2010
(Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR)	Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥30 - < 60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥ 90 (normal GFR)	
Creatinine	≥150 µmol/L (Adults)	Benichou C., 1994.
	≥30% change from baseline	
	≥100% change from baseline	
Uric Acid		Harrison- Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L	
	>115 mmol/L	
Sodium	≤129 mmol/L	
	≥160 mmol/L	
Potassium	<3 mmol/L	FDA Feb 2005.
	≥5.5 mmol/L	
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.

Parameter	PCSA	Comments
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black) ≥16.0 Giga/L	Increase in WBC: not relevant. To be interpreted only if no differential count available.
Lymphocytes	>4.0 Giga/L	
Neutrophils	<1.5 Giga/L (Non-Black);<1.0 Giga/L (Black)	International Consensus meeting on drug-induced blood cytopenias, 1991. FDA criteria.
Monocytes	>0.7 Giga/L	
Basophils	>0.1 Giga/L	
Eosinophils	>0.5 Giga/L or >ULN (if ULN ≥0.5 Giga/L)	Harrison- Principles of internal Medicine 17th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 g/L (Female) Decrease from Baseline ≥20 g/L	Criteria based upon decrease from baseline are more relevant than based on absolute value. Other categories for decrease from baseline can be used (≥30 g/L, ≥40 g/L, ≥50 g/L).
Hematocrit	≤0.37 v/v (Male); ≤0.32 v/v (Female) ≥0.55 v/v (Male); ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb. Otherwise, consider FDA criteria.
Platelets	<100 Giga/L ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
Urinalysis		
pH	≤4.6 ≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.

Parameter	PCSA	Comments
SBP	≤95 mmHg and decrease from baseline ≥20mmHg	To be applied for all positions (including missing) except STANDING.
	≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
	≥110 mmHg and increase from baseline ≥10 mmHg	
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline	FDA Feb 2007.
	≥5% decrease from baseline	
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4): 489-500)
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	

Parameter	PCSA	Comments
PR	>200 ms	Categories are cumulative
	>200 ms and increase from baseline ≥25%	
	> 220 ms	
	>220 ms and increase from baseline ≥25%	
	> 240 ms	
	> 240 ms and increase from baseline ≥25%	
QRS	>110 ms	Categories are cumulative
	>110 msec and increase from baseline ≥25%	
	>120 ms	
	>120 ms and increase from baseline ≥25%	
QT	>500 ms	
QTc	Absolute values (ms)	To be applied to any kind of QT correction formula.
	>450 ms	Absolute values categories are cumulative
	>480 ms	
	>500 ms	QTc >480 ms and QTc>60 ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix C Diagram for identifying missing data due to COVID-19



Note: the diagram could be adapted to secondary efficacy endpoints as appropriate.

Appendix D Schedule of activities (SoA)

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

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
Acceptable range (days)	**-21 (up to)**	**-7 (±3)**	**1**	**14 (3±)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**210 (±3)**	**252 (±5)**	**301 (±5)**	**350 (±5)**	**392 (±5)**	**434 (±7)**	V2 can be done as soon as the Screening eligibility is confirmed and at least 7 days after screening visit (V1). V3 can be done 4 to 10 days after V2. V3 cannot be later than 21 days after V1 (except in case of Holter re-test when an additional 1 week is allowed).
Vital signs	X		X		X	X	X		X	X		X		X	X	BP and HR in sitting position after at least 5 minutes of rest.
Height	X															
Body weight	X		X		X	X	X		X	X		X		X	X	
12-lead ECG			X				X			X				X		The 12-lead ECG recording should be obtained in supine position, prior to IMP dose administration
Injection training at Visit 2, retraining as needed; review of injection sites		X	X		X	X	X		X	X		X		X		
Diary dispensation		X	X		X	X	X		X	X		X		X		
Diary review			X		X	X	X		X	X		X		X	X	
Glucose meter dispensation and training, training for hypoglycemia awareness and management		X														
Diet and lifestyle counseling	X		X		X	X	X		X	X		X		X		As per current practice, to be documented.

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
Acceptable range (days)	**-21 (up to)**	**-7 (±3)**	**1**	**14 (3±)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**210 (±3)**	**252 (±5)**	**301 (±5)**	**350 (±5)**	**392 (±5)**	**434 (±7)**	V2 can be done as soon as the Screening eligibility is confirmed and at least 7 days after screening visit (V1). V3 can be done 4 to 10 days after V2. V3 cannot be later than 21 days after V1 (except in case of Holter re-test when an additional 1 week is allowed).
IRT contact	X	X	X		X	X	X		X	X		X		X	X	
IMP dispensed		X	X		X	X	X		X	X		X				At Visit 2 placebo training kit(s) will be allocated; self-injection will be done at site.
IMP collection and accounting					X	X	X		X	X		X		X		
Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	SMPG, diary, and IMP.
Efficacy																
HbA1c	X		X				X			X		X		X		
FPG			X			X	X			X		X		X		For these visits, participants need to come in fasting condition
7-point SMPG profiles			X				X			X		X		X		Performed on at least 1 day in the week prior to visits indicated.
Fasting (pre-breakfast) SMPG			X	X	X	X	X	X	X	X	X	X	X	X		Recommended daily, mandatory at least 3 days in the week prior to indicated visits with the study glucometer before breakfast and any intake of antihyperglycemic drug(s).

Procedure	Screening Period		Double-blind placebo-controlled Core Treatment Period								Double-blind, placebo-controlled Safety extension Period				Follow-up	Notes
Week	**-3**	**-1**	**0 BL**	**2**	**4**	**8**	**12**	**18**	**24**	**30[a]**	**36**	**43**	**50**	**56**	**Last IMP +6 wks**	
Visit	**1**	**2**	**3 R**	**4 ☎**	**5**	**6**	**7**	**8 ☎**	**9**	**10**	**11 ☎**	**12**	**13 ☎**	**14 EOT**	**15 EOS**	
Acceptable range (days)	**-21 (up to)**	**-7 (±3)**	**1**	**14 (3±)**	**28 (±3)**	**56 (±3)**	**84 (±3)**	**126 (±3)**	**168 (±3)**	**210 (±3)**	**252 (±5)**	**301 (±5)**	**350 (±5)**	**392 (±5)**	**434 (±7)**	V2 can be done as soon as the Screening eligibility is confirmed and at least 7 days after screening visit (V1). V3 can be done 4 to 10 days after V2. V3 cannot be later than 21 days after V1 (except in case of Holter re-test when an additional 1 week is allowed).
Safety																
Rescue therapy assessment				X	X	X	X	X	X	X	X	X	X			Assessed by the Investigator after Randomization via fasting SMPG performed by the participants and/or via the central laboratory alerts received on FPG and on HbA1c (at Week 12 onward).
24-hour ECG (Holter) including diary		X								X				X		For 24-hour ECG (Holter) repeat procedure, Randomization may be delayed up to 7 days if needed.
Hematology	X		X				X			X		X		X	X	
Clinical chemistry	X		X				X			X		X		X	X	
Calcitonin	X		X				X			X				X	X	
Lipid profile			X							X				X		
Urinalysis			X							X				X		
C-peptide (fasting)			X													For this visit, participants need to come in fasting condition

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

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

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

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

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

Signature Page for VV-CLIN-0365210 v3.0
efc14822-16-1-9-sap

Approve & eSign	[redacted]
Approve & eSign	[redacted]