NCT03684642

STATISTICAL ANALYSIS PLAN

A 56-week, Multicenter, Open-label, Active-controlled, Randomized Study to Evaluate the Efficacy and Safety of Efpeglenatide Once Weekly Compared to Dulaglutide Once Weekly in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
AE:	adverse event
AERSM:	adverse event requiring specific monitoring
AESI:	adverse events of special interest
ALT:	alanine aminotransferase
BMI:	body mass index
CMH:	Cochran-Mantel-Haenszel
ECG:	electrocardiogram
EOS:	end of study
EOT:	end of treatment
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
mITT:	modified intent-to-treat
NIMP:	noninvestigational medicinal product
PCSA:	potentially clinically significant abnormality
PRO:	patient reported outcome
PT:	preferred term
R:	randomization
SAE:	serious adverse event
SOC:	system organ class
T2DM:	Type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
UB:	upper bound
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter, 56-week, randomized, open-label for the drug (efpeglenatide and dulaglutide) and double-blind for the doses of efpeglenatide, active-controlled, 3-arm, parallel group study in participants with type 2 diabetes mellitus (T2DM) inadequately controlled with metformin.

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 ratio to 1 of the following 3 treatment groups:

- efpeglenatide 4 mg
- efpeglenatide 6 mg
- dulaglutide 1.5 mg

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

Approximately 900 participants (300 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 noninferiority of once-weekly injection of efpeglenatide 4 or 6 mg in comparison to once-weekly injection of dulaglutide 1.5 mg on HbA1c change from Baseline to Week 56 in participants with T2DM inadequately controlled with metformin.

1.2.2 Secondary objectives

The secondary objectives of this study are:

- To demonstrate the superiority of once-weekly injection of efpeglenatide 4 and 6 mg with once-weekly injection of dulaglutide 1.5 mg on glycemic control.

- To demonstrate the superiority of once-weekly injection of efpeglenatide 4 and 6 mg with once-weekly injection of dulaglutide 1.5 mg on body weight.
- To evaluate the safety of once-weekly injection of efpeglenatide 4 and 6 mg and once-weekly injection of dulaglutide 1.5 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 56.

Assuming a common standard deviation of 1.1%, and the true difference between efpeglenatide and dulaglutide is zero, 300 participants per arm will ensure that the upper bound (UB) of the 2-sided 95% CI of the adjusted mean difference would not exceed 0.3% with 91% power.

Hence, there are 3 parallel dosing arms as follows:

- Efpeglenatide 4 mg, N=300
- Efpeglenatide 6 mg, N=300
- Dulaglutide 1.5 mg, N=300

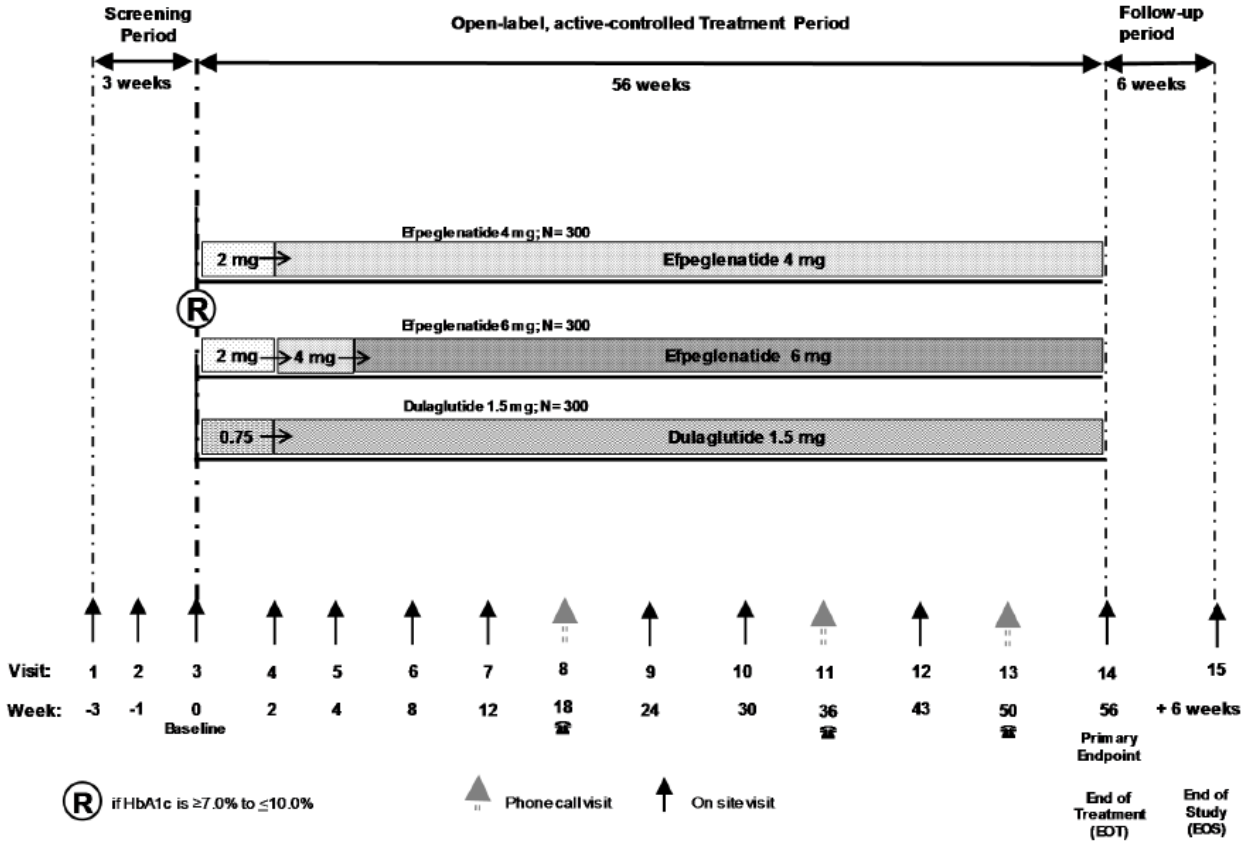
1.4 STUDY PLAN

This is a multicenter, 56-week, randomized, open-label for the drug (efpeglenatide and dulaglutide) and double-blind for the doses of efpeglenatide, active-controlled, 3-arm, parallel group Phase 3 study consisting of 3 study periods:

- An up to 3-week Screening Period (with a minimum of 11 days)
- A 56-week open-label, active-controlled Treatment Period, for efficacy and safety assessments
- A 6-week post-treatment Follow-up Period to collect safety information after last dose of Investigational Medicinal Product (IMP) after treatment is completed or permanent treatment discontinued

The maximum study duration per participant will be 65 weeks with treatment lasting for 56 weeks. 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 statistical section of the protocol was never changed in an amendment.

1.6 STATISTICIAL MODIFICATIONS MADE IN STATISTICAL ANALYSIS PLAN

The statistical analysis plan history table below provides the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan and/or protocol.

Table 1 - Statistical analysis plan Statistical changes

SAP Version Number	Date Approved	Rationale	Description of Statistical Changes
2	02-Oct-2020	Additional analyses provided due to Covid-19 pandemic.	2.2.1 Added analyses for COVID-19 related PDs 2.4.4.4.2 Added HbA1c sensitivity analysis due to COVID-19 at Week 56. COVID-19 impact on disposition data will be presented. Assessment of missing data due to COVID-19 added 2.4.5.1 COVID-19 related AEs have been added Appendix C Added diagram for identifying missing data due to COVID-19
		Clarification on- and post-study periods; Updated definition of actual treatment group for as-treated analysis; clarified AERSM definitions; Added definitions of ADA responses.	2.1.4 Clarified on-study and post-study observation periods 2.3.2 Updated definition of actual treatment group 2.4.5.1 Updated definitions of AERSM 2.1.5.1 Added definitions for Persistent, Transient and indeterminate ADA response
		Since the study was terminated early, the mITT was added and defined; Added additional sensitivity analysis using retrieved-dropout multiple imputation method and back-up multiple imputation method on the primary endpoint; Removed model-based analyses for the change from baseline in mean 24-hour SMPG and time to initiation of rescue medication; Clarified analysis window for efficacy endpoints.	2.3.1. Added mITT population 2.4.4.1 Added sensitivity analyses using the retrieved-dropout multiple imputation method and the back-up multiple imputation method (in case of insufficient retrieved dropouts). 2.4.4.1 descriptively summarized HbA1c at Week 56 by ADA status only 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. 2.5.4 Clarified analysis window for efficacy endpoints at Weeks 30 and 56 in case of missing scheduled visits

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and Baseline characteristics

The Baseline value (except for serum creatinine and eGFR) is defined as the last available value prior to the first dose administration of open-label IMP or the last available value on or before the date of randomization if not treated with the open-label IMP. Note: any assessment undertaken on the day of first dose administration of open-label 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 the open-label IMP for those randomized and exposed or before randomization for those who were randomized but never exposed to open-label 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, Eastern Europe (including Hungary and Poland)), and randomization strata (Baseline BMI (quantitative and qualitative variable: <30, ≥30 and <40, ≥40 kg/m^2), HbA1c at screening (<8.0, ≥8.0%)).

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) (neuropathy, nephropathy, retinopathy) and retinopathy history (Proliferative, Non-proliferative, Macular Edema);
- Use of anti-diabetic medication, duration of Metformin (years), and daily dose of Metformin (mg) at screening;
- Estimated Glomerular Filtration Rate (eGFR) at baseline (ml/min/1.73m^2);
- Estimated glomerular filtration rate (eGFR) categories at baseline (<15 ml/min/1.73m^2 [End stage renal Disease], ≥15 to <30 ml/min/1.73m^2 [Severe decrease in glomerular filtration rate (GFR)], ≥30 to <60 ml/min/1.73m^2 [Moderate decrease in GFR], ≥60 to <90 ml/min/1.73m^2 [Mild decrease in GFR], and ≥90 ml/min/1.73m^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);
- Waist Circumference (cm)
- 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 open-label IMP administration. Prior medications can be discontinued before first open-label 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.

Background medication

Metformin tablets, administered as per Principal Investigator prescription and in accordance with local labeling, and rescue medication(s) that will be used to treat hyperglycemia if a participant's glycemic values reach the applicable rescue threshold.

The doses of metformin at randomization should be maintained throughout the study unless down-titration is required for safety reasons.

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

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 and 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 56

2.1.3.2 Secondary efficacy endpoints

- Number of participants with HbA1c < 7.0% at Week 56 (yes/no)
- Change in FPG from Baseline to Week 56
- Changes in body weight from Baseline to Week 56

2.1.3.3 Exploratory efficacy endpoint(s)

- Participant perspective on benefit/risk of the drug using the Patient qualitative assessment of treatment version 2 (PQAT v2) at Weeks 30 and 56
- Number of participants with HbA1c < 7.0% at Week 30 (yes/no)

- Change in HbA1c from Baseline to Week 30
- Change in FPG from Baseline to Week 30
- 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
- Number of participants with rescue therapy used during the treatment period until Weeks 30 and 56 (yes/no)
- Time to initiation of rescue therapy (weeks)
- Change from baseline to week 30 in body weight
- Number of participants with change in body weight ≥ 5% from Baseline to Week 56 (yes/no)
- Number of participants with change in body weight ≥ 10% from Baseline to Week 56 (yes/no)
- Change in waist circumference from Baseline to Weeks 30 and 56

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 open-label IMP
- The **on-treatment** period is defined as the time from the first injection of the open-label IMP up to 30 days (7 days for hypoglycemia) after the last injection of the IMP
- The **post-treatment** period is defined as the period from the end of the on-treatment period.

The **on-study observation period** is defined as the time from first injection of open-label IMP up to either the last protocol-planned visit or the date of last available information if participants discontinue the study prematurely, whichever is later.

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 SAE, AESI, and AERSM, up to database lock.

2.1.4.1 Adverse events variables

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.

2.1.4.2 Deaths

The death observation periods are per the observation periods defined below.

- 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

2.1.4.3 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 D). 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 patients will be analyzed.
  - Calcitonin

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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

2.1.4.5 Electrocardiogram variables

ECG variables will include 12-lead ECG interpretation (normal/abnormal) provided by the investigator. 12-lead ECG recording will be performed locally at Randomization, Week 12 and Week 56. Investigator's interpretation of normal and abnormal will be reported in the eCRF.

2.1.4.6 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.

2.1.4.7 Gastrointestinal (GI) symptoms from the participant perspective

The evolution of GI symptoms will be evaluated from the participant perspective using 3 PROMIS GI Symptom scales version 1.0 (nausea and vomiting, diarrhea, and belly pain) at Day 1, Weeks 1, 2, 3, 4, 5, 6, 7, 8, 12, 18, 30, 43, and 56.

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 is defined as: (1) Only the last sampling time point is positive; or (2) the last two samples, separated by a period less than 16 weeks are positive.

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 concentration (C_{trough}) of efpeglenatide at pre-dose (Weeks 4, 12, 24, 30)
- Serum concentration of efpeglenatide at least 1 additional postdose (3 days [±1 day] after administration of efpeglenatide, preferably between Week 8 and Week 12, but other weeks are also acceptable [eg, after 1st dose, 4th dose, or 12th dose]) in a subset of participants. All valid efpeglenatide 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 an open-label kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used or not.

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 56-week study treatment period as per protocol
- Participants who did not complete the 56-week study treatment period, and main reasons for permanently treatment discontinuation
- Participants who completed the study as per protocol

- Participants who discontinued the study by main reasons 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. This summary will be provided by treatment group.

List of participants who discontinued treatment and/or study will be provided with reasons for discontinuation (including each specific reason categorized as 'OTHER'), including reasons related to COVID-19.

Kaplan-Meier cumulative incidence of early IMP withdrawal, 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, modified ITT (mITT) population
- Safety population
- ADA population
- Pharmacokinetics (PK) 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 or not.

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.

2.3.1.2 Modified Intent–to-treat population

Due to the study terminated early by sponsor on September 9, 2020 (hereinafter referred to as "early termination"), the efficacy analyses will be performed in mITT population instead of ITT population originally planned. The mITT population is defined as,

- Participants who have completed the study treatment, or
- Participants who discontinued the study treatment AND completed/discontinued the study before the early termination, or
- Participants who discontinued treatment before early termination and discontinued the study due to early termination within 30 days of the target Week 56 visit (Day 392), or
- Participants who discontinued treatment due to early termination within 30 days of the target Week 56 visit (Day 392).

Participants will not be included in mITT if they discontinued study due to termination and discontinued study treatment (before or due to early termination) and had visits performed more than 30 days before the target Week 56 visit (Day 392).

By-visit summary will be provided for ITT population in addition for mITT population.

2.3.2 Safety population

The safety population is defined as:

- Randomized population who 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 during the trial, the treatment group allocation for as-treated analysis will be included in the treatment group that they are exposed for longer duration. In case of tie, highest dose group of efpeglenatide will be used. When calculating the Dulaglutide treatment duration, the Dulaglutide 0.75 mg duration will be combined with Dulaglutide 1.5 mg
- 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 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 efpeglenatide 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). 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 open-label IMP exposure will be assessed by cumulative exposure (patient years), duration (days), and category (weeks).

Duration of open-label 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 open-label 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 study duration is defined as date of completion or discontinuation – date of first open-label IMP + 1. If the date of first open-label IMP is missing, then the date of randomization will be used.

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 on-treatment period will be summarized separately by time of day (morning, afternoon, evening, night) and location of injection (Abdomen, Arm, Thigh, 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.

2.4.4.1 Analysis of primary efficacy endpoint

Hypothesis Testing of the Primary Endpoint:

For the primary efficacy variable of change from Baseline to Week 56 in HbA1c, the following statistical null hypothesis and alternative will be tested as:

- H0: efpeglenatide - dulaglutide ≥ 0.3%
- H1: efpeglenatide - dulaglutide < 0.3%

The null hypothesis will be tested at a 1-sided alpha level of 0.025 using a non-inferiority margin of 0.3%.

Primary Analysis:

The statistical analysis for the primary endpoint is described below.

The Baseline value is defined in Section 2.1.1.

Analysis of the primary efficacy endpoint (change from Baseline to Week 56 in HbA1c) will be performed using the ITT population, using HbA1c measurements obtained during the study, including those obtained after IMP discontinuation or introduction of rescue therapy.

The primary efficacy endpoint of change in HbA1c from Baseline to Week 56 will be analyzed with missing values imputed by BOCF-like MI method for both efpeglenatide and dulaglutide groups, under the MNAR framework:

- For participants with missing HbA1c values at Week 56, the missing values will be imputed using a random draw from a normal distribution with mean equal to their Baseline HbA1c and the standard deviation equal to the pooled standard deviation calculated from the square root of the mean square error estimated from a regression model with Baseline HbA1c as the dependent variable and randomization strata and treatment as the covariates.

In this analysis, missing endpoint values will be imputed 10 000 times to generate 10 000 data sets with complete data. Each of the complete datasets after the imputation will be analyzed by the ANCOVA model with the treatment groups (efpeglenatide 4 or 6 mg, dulaglutide 1.5 mg), randomization stratum of screening HbA1c (<8.0, ≥8.0%), Visit 3 (Day 1) BMI (<30 and

≥30 kg/m^2), and geographical region (North America, Eastern Europe (including Hungary and Poland)) as fixed effects, and baseline HbA1c value as a covariate.

In case a baseline value needed for multiple imputations is missing, it will be imputed by the population mean at Baseline.

SAS pseudo-codes are provided in Appendix A.

Results from each complete dataset will be combined to provide the adjusted mean change in HbA1c from baseline to Week 56 (regardless of treatment discontinuation or initiation of rescue therapy) for each treatment group, as well as the between-group difference (comparing each efpeglenatide group versus dulaglutide group) and the 95% CI for the difference. This will be implemented using MIANALYZE procedure in SAS. If the UB of the 2-sided 95% CI for the adjusted mean difference (efpeglenatide versus dulaglutide) in HbA1c change from baseline to Week 56 is ≤0.3%, the noninferiority will be declared.

If noninferiority is demonstrated on the primary endpoint for both efpeglenatide groups, ie, the UB of the 2-sided 95% CI ≤0.3%, the superiority of each efpeglenatide group versus dulaglutide for the primary endpoint will be tested in a hierarchical fashion, with efpeglenatide 6 mg tested first and then efpeglenatide 4 mg.

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

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 added to participants in efpeglenatide groups (4 or 6 mg) who have no HbA1c data at Week 56. The penalty will be gradually increased to evaluate at which level the conclusion of the analyses in terms of non-inferiority 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 56 creates a shift in the treatment effect of efpeglenatide from the demonstration of non-inferiority to the failure of non-inferiority. The penalty δ will start at 0 and increase by 0.1 (unit: %) at each imputation until UB of the 2-sided 95% CI for the adjusted mean difference is > 0.3%. Least square mean difference between each efpeglenatide dose and dulaglutide and their associated 95% CI will be provided for each penalty level.

SAS pseudo-codes are provided in Appendix A.

Retrieved-dropout multiple imputation method:

The retrieved-dropout multiple imputation sensitivity analysis will have 2 separates parts as follows:

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 baseline measurements are included as the predictor. Each treatment group will have their own imputation model.
2. Missing endpoint data in all participants who stay on the study treatment until 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 stay on the study treatment until Week-56 visit and have the endpoint measurement, where randomization strata and Hb1Ac baseline measurements are included as the predictors.

In both parts, the missing data will be imputed using the regression method. After imputation, the completed data sets will be analyzed using an ANCOVA model similar to the primary analysis.

If there are no sufficient data to support the imputation approach in item 1 described above (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 method will be used. In particular, missing endpoint data in all participants, regardless of staying on the study treatment or not, will be imputed using a model built separately in each arm and estimated from participants in the same treatment arm with endpoint data, where randomization strata and corresponding baseline values are included as the predictors.

SAS pseudo-codes are provided in Appendix A.

Analysis on completers:

For participants in ITT population who completed the 56-week 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.

2.4.4.1.1 Sensitivity analysis due to COVID-19 at Week 56 (HbA1c)

Sensitivity analysis will be performed using ANCOVA (as specified in Section 2.4.4.1) with missing values imputed based upon BOCF-like MI method 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.

- For participants with missing HbA1c values at Week 56 not due to Covid-19, the missing values will be imputed using a random draw from a normal distribution with mean equal to their Baseline HbA1c and the standard deviation equal to the pooled standard deviation calculated from the square root of the mean square error estimated from a regression model with Baseline HbA1c as the dependent variable and randomization strata and treatment as the covariates.

- For participants with missing HbA1c values at Week 56 due to Covid-19 in each group, the missing values 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%), Visit 3 (Day 1) BMI (<30, ≥30 kg/m²), corresponding baseline values and preceding scheduled postbaseline values.

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.

Assessment of missing data:

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

Patients without data at the endpoint visit be summarized by treatment status (discontinued, completed) and by impact of Covid-19 on participants (yes, no) for each treatment group. Reasons for missing primary efficacy endpoint (ie, HbA1c at Week 56) will be listed.

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, Eastern Europe (including Hungary and Poland))
- Baseline estimated GFR categories (mL/min/1.73m²): (<60; ≥60 to <90, ≥90)

The treatment effects (efpeglenatide 4, or 6 mg, versus dulaglutide 1.5 mg) across the subgroups defined for each of these factors will be estimated for the change from Baseline to Week 56 in HbA1c in the ITT population, and using a similar imputation approach (ie, BOCF-like MI method under MNAR framework) as applied to the analysis of the primary efficacy endpoint. The ANCOVA model will include treatment groups (efpeglenatide 4, or 6 mg, dulaglutide 1.5 mg) 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 dulaglutide) 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. In case that the subgroup factor is country, the region will not be included in the model.

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

- ADA status (positive, negative) at Baseline, if ≥ 5% of patients 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 versus dulaglutide will be performed at the alpha level of 0.05.

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

Proportions of participants achieving the HbA1c target value of <7.0% at Week 56 will be compared between each efpeglenatide dose versus dulaglutide 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. For categorial secondary endpoint in which HbA1c is assessed at Week 56, all HbA1c values at Week 56 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 56 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 in FPG from Baseline to Week 56 and in body weight from baseline to Week 56

Changes in FPG from baseline to Week 56 and in body weight to Week 56 will each be analyzed using the same ANCOVA model with missing values imputed by MI analysis method as the method used for the primary efficacy endpoint analysis. Differences between treatment groups and CIs will be estimated by this method. 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 4, 6 mg and 1.5 mg dulaglutide 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.

2.4.4.3 Multiplicity issues

After noninferiority for the primary endpoint of change in HbA1c from Baseline to Week 56 has been established for both efpeglenatide 4 and 6 mg, the secondary endpoints will be tested in the prioritized order as follows:

1. Change from baseline to Week 56 in HbA1c for efpeglenatide 6 mg versus dulaglutide (Superiority)
2. Change from baseline to Week 56 in body weight for efpeglenatide 6 mg versus dulaglutide (Superiority)
3. HbA1c <7.0% at Week 56 for efpeglenatide 6 mg versus dulaglutide (yes/no) (Superiority)
4. Change from baseline to Week 56 in body weight for efpeglenatide 4 mg versus dulaglutide (Superiority)
5. Change from baseline to Week 56 in HbA1c for efpeglenatide 4 mg versus dulaglutide (Superiority)
6. HbA1c <7.0% at Week 56 for efpeglenatide 4 mg versus dulaglutide (yes/no) (Superiority)
7. Change from baseline to Week 56 in FPG for efpeglenatide 6 mg versus dulaglutide (Superiority)

8. Change from baseline to Week 56 in FPG for efpeglenatide 4 mg versus dulaglutide (Superiority)

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 dulaglutide than those mentioned earlier in this section.

2.4.4.4 Exploratory efficacy analysis

The analysis of the exploratory endpoints will be descriptive in general with no formal testing, unless otherwise specified. Summary statistics at scheduled visits using OC will be provided by each treatment group. For the continuous exploratory endpoints, descriptive summary statistics will be provided, including the number of observations, mean, SD, SE, minimum, median, and maximum. Graphical presentations will also be provided as appropriate.

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

Proportions of participants achieving HbA1c target values of <7.0% at Week 30 will be analyzed by same approach described in secondary endpoint: HbA1c < 7.0% at Week 56. Participants with missing HbA1c data at Week 30 will be considered not achieving HbA1c < 7.0%.

2.4.4.4.2 Change in HbA1c/body weight/FPG from baseline to Week 30

Changes from Baseline in HbA1c to Week 30, in body weight to Weeks 30 and in FPG to Week 30 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.

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 graphs will be presented by treatment group at each visit for each time point.

2.4.4.4.4 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.

2.4.4.4.5 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.

2.4.4.4.6 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 until Week 56 respectively will be summarized.

2.4.4.4.7 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.

2.4.4.4.8 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 IMP. 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 open-ended questions will be provided separately and the analyses results will not be included in CSR.

2.4.4.4.9 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.

- Descriptive statistics of change in waist circumference from baseline to Week 30 and 56 will be provided by treatment group.

- Descriptive statistics of change in the ratio C-peptide (nmol/L)/ FPG (mmol/L) from baseline will be provided by scheduled visit and treatment group.

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group on the on-treatment 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 56-week on-treatment period, taking into account all evaluations performed during the 56-week on-treatment period, including nonscheduled or repeated evaluations. The number of all such participants will be the numerator for the 56-week 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 56-week 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 between treatment groups 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, when appropriate, 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 up to 56 weeks, 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 2.1.4.1 and the criteria of AESI and AERSM are in Table 2.

Table 2 - 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 >3ULN	"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)

AE Grouping	Criteria
Pancreatic event	Cases reported in eCRF “Suspected or confirmed Pancreatitis” page or AE Category=”Pancreatic Neoplasm”
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 number of participants, and the percent of participants who experienced TEAEs of special interest and TEAEs requiring specific monitoring will be presented for each AESI and AERSM specified above by PT and treatment group. PTs will be sorted by decreasing frequency in Efpeglenatide 6 mg group.

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 patients with an event positively adjudicated by CEC 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 56-week on study observation period

The following selected AE will also be summarized for the 56-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 patients with at least 1 adverse event)
- SAE (by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 serious adverse event)
- AEs leading to death

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, randomization strata, 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, 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.

Analysis of COVID-19 related adverse events

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

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 2.1.4.6 (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 be counted. Event rates of hypoglycemia per participant year {all reported hypoglycemia, severe, documented symptomatic [<54 mg/dL (<3.0 mmol/L), ≥54 and <70 mg/dL (≥3.0 and <3.9 mmol/L), ≤70 mg/dL(≤3.9 mmol/L) respectively], asymptomatic, probable symptomatic, relative hypoglycemia} will be presented by treatment group during the 56-week 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 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 the following order: severe, documented symptomatic.

2.4.5.3 Deaths

The following summaries of deaths will be generated for the safety population:

- TEAE leading to death (death as an outcome on the AE case report form page as reported by the Investigator) during the 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 the 56-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 period (on-treatment period, post-treatment period), post-study period)
- 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

2.4.5.4 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. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs at any time during the 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 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 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 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.

2.4.5.5 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 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).

2.4.5.6 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.

2.4.5.7 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) 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.

Patient – Reported Outcomes:

Eight Patient-Reported Outcome Measurement Information System (PROMIS) GI symptom scales have been developed and validated to capture the breadth and depth of GI symptoms experienced by people with a wide range of digestive disorders. In this study, only nausea and vomiting (4 items), diarrhea (6 items), and belly pain (5 items) symptom scales will be collected. The participants will be asked to complete the evaluation electronically from home or at site before the start of any procedures or tests, at the timepoints showed in the SoA (Appendix D). In case of early IMP discontinuation, the PROMIS GI symptom scales will be completed by the participant at the time of discontinuation and afterwards as normally planned.

The analysis of PROMIS GI symptoms scales v1 will be descriptive with no formal testing and conducted on the ITT population. Summary statistics of the raw scores and T-scores of GI symptom scales at scheduled visits will be provided by treatment group for each scale (nausea and vomiting, diarrhea, belly pain). The raw score for each scale is calculated as the arithmetic sum of all the individual item scores according to PROMIS GI symptoms scales v1 documentation. In case the participant does not answer every question (has missing data), the raw score can be approximately estimated according to following steps:

- Sum up all scores from the items that were answered
- Multiply the results obtained above by the total number of questions in that scale
- Divide the results obtained above by the number of items answered

The T-score will be calculated using the association table provided in the PROMIS GI symptoms scales v1 documentation between the raw score and T-Score. The T-score has been estimated using an item response theory graded response model (GRM) that includes a slope parameter that differs across items.

Plots will be also presented to illustrate trends over visits by treatment group for mean raw scores and mean T-scores for each scale. The mean raw scores and mean T-scores for each scale will be presented on the y-axis. Schedule visits will be presented on the x-axis.

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 and by visit.

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:

a) year and month are not missing, but day is missing, then day = 01

b) 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 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 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:

a) If year and month are not missing, but day is missing, then day = 15

b) 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 on-treatment period, but the imputed date falls outside of the on-treatment period, then imputed date will be set to the nearest date inside the 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 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 open-label 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 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.

Early Treatment Discontinuation (efficacy parameters)

Subjects who discontinue treatment at or just before a regularly scheduled visit will have the Early Treat Term Visit page completed instead of the scheduled visit in the eCRF, and the scheduled visit will be reported as not done. For analysis purposes, values from Early Treat Term Visits will be mapped directly to 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 measurements 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 9.4 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

Appendix B: Criteria for Potentially Significant Abnormalities

Appendix C Diagram for Identifying Missing Data due to COVID-19

Appendix D Schedule of Activities

Appendix A Efficacy Analysis SAS pseudo code

Primary Analysis missing data imputation:

1) Multiple imputations in participants who have missing HbA1c values at Week 56

Step 1: Perform regression to estimate pooled mean and standard deviation of non-missing baseline HbA1c measures

```
proc glm data=BaseHbA1c;
        class ARM HbA1c_strata BMI_strata;
        model base = ARM HbA1c_strata BMI_strata;
        ods output FitStatistics=basefit;
run;

proc sql noprint;
        select RootMSE, depmean
        into :std, mean
        from basefit;
quit;
```

Step 2: For participants with missing HbA1C values at week 56, simulate week 56 HbA1c 10000 times by random draw (with seed=14829) from a normal distribution with mean equal to baseline HbA1c and STD equal to the pooled STD from the regression model in Step 1. In case baseline HbA1c is missing, pooled mean is used as baseline HbA1c.
For participants with non-missing HbA1C values at week 56, repeat the same record 10000 times (iteration 1 to 10000) to generate 10000 data sets.

```
data HbA1cW56Complete;
  set InputData;
  call streaminit(14829);
   do _imputation_ = 1 to 10000;
    if base = . then newbase = &mean;  /* in case of missing baseline HbA1c measure, pooled mean is used as the
baseline HbA1c*/
    else newbase = base ;

   base_simu = rand ('normal', newbase, &std);

   if aval=. then do ;
     aval=base_simu ;
     msfl = 'Y';   /* Flag missing record for tipping analysis */
    end;

   chg_wk56 = aval - newbase ;

   output ;
end;
run;
```

Step 3: Use ANCOVA and Rubin's formula to obtain the between-group difference and 95% CI.

```
proc mixed data=HbA1cW56Complete;
        class ARM HbA1c_strata BMI_strata region;
        model chg_wk56 = ARM HbA1c_strata BMI_strata region NEWBASE;
        by _Imputation_;
```

```
        lsmeans ARM/ pdiff=control ('Dulaglutide 1.5 mg') cl;
        ods output LSMeans=lsmeans  diffs=lsmeansdiff;
run;

proc mianalyze parms=lsmeansdiff;
        modeleffects ARM;
        by ARM;
        ods output parameterestimates=miparm;
run;
```

In this sample SAS® (version 9.4) code:

- BaseHbA1c contains one observation per participant in the ITT population with Baseline HbA1c value.
- InputData contains one observation per participant in the ITT population with Week 56 HbA1c value
- HbA1cW56Complete is the final output containing 10,000 lines by participant with all observed and simulated data used for the ANCOVA.
- ARM is the randomized treatment group (Dulaglutide 1.5 mg, Efpeglenatide 4mg, Efpeglenatide 6mg).
- HbA1c_strata is the randomization stratum of screening Hb1Ac (<8.0, ≥8.0%)
- BMI_strata is the randomization stratum of BMI at Visit 3(<30, ≥30)
- BASE is the observed baseline HbA1c.
- BASE_simu contains the simulated baseline HbA1c values.
- NEWBASE is the baseline HbA1c including observed (If non-missing) and imputed (If missing, pooled mean) data.
- CHG_WK56 is the change from baseline in HbA1c at Week 56.
- REGION is the geographical region.
- The seed is 14829.

Sensitivity analysis using retrieved-dropout multiple imputation method:

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=14829;
      where PEOT56FL = "Y";
      by ARM;
      var BASE AVAL_W56;
      monotone regression (AVAL_W56= BASE );
run;
```

2. Multiple imputations in participants who stay on the study treatment until the Week-56 visit:

```
proc mi data=data_IN out=data_OUT_COMPL_MI  nimpute=10000 seed=14829;
      where PEOT56FL='N';
      by ARM;
      class HbA1c_strata BMI_strata;
      var HbA1c_strata BMI_strata base AVAL_W56;
      monotone regression (AVAL_W56 = HbA1c_strata BMI_strata  BASE );
run;
```

3. Combine multiple imputations from the step 1 and step 2 above

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

Back-up plan:

```
proc mi data    =data_IN out=data_OUT_MI  nimpute=10000 seed=14829;
                  by ARM;
               class HbA1c_strata BMI_strata;
               var HbA1c_strata BMI_strata base AVAL_W56;
               monotone regression (AVAL_W56 = HbA1c_strata BMI_strata  BASE );
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 56.
- 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 participants who have completed the 56-week study treatment period.
- Data_OUT_MI is the output dataset including observed and imputed data for all participants using backup plan.
- PEOT56FL is the variable indicating whether the participant prematurely discontinued the study treatment (PEOT56FL=”Y” if the participants prematurely discontinued the study treatment before Week 56 visit and PEOT56FL=”N” if the participant stay on the study treatment until Week 56 visit).
- ARM is the randomized treatment group (Dulaglutide 1.5 mg, 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_W56 is the HbA1c at Week 56.
- The seed (14829) has been chosen arbitrarily and is based on the study code (EFC14829).

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

Step 1: Perform regression to estimate pooled mean and standard deviation of non-missing baseline HbA1c measures

```
proc glm data=BaseHbA1c;
        class ARM HbA1c_strata BMI_strata;
        model base = ARM HbA1c_strata BMI_strata;
        ods output FitStatistics=basefit;
run;

proc sql noprint;
        select RootMSE, depmean
        into :std, mean
        from basefit;
quit;

data base_imputed;
  set InputData;
    if base = . then newbase = &mean;  /* in case of missing baseline HbA1c measure, pooled mean is used as the
baseline HbA1c*/
    else newbase = base ;
run;
```

Step 2: Multiple imputations

1) Multiple imputations in participants who have missing HbA1c values at Week 56 not due to Covid-19

   For participants with missing HbA1C values at week 56, simulate week 56 HbA1c 10000 times by random draw (with seed=14829) from a normal distribution with mean equal to baseline HbA1c and STD equal to the pooled STD from the regression model in Step 1. In case baseline HbA1c is missing, pooled mean is used as baseline HbA1c.
   For participants with non-missing HbA1C values at week 56, repeat the same record 10000 times (iteration 1 to 10000) to generate 10000 data sets.

```
data data_OUT_MI_MISSING;
  set base_imputed (where W56_missing = “Y” and COVID = “N”);
  call streaminit(14829);
   do _imputation_ = 1 to 10000;

   base_simu = rand ('normal', newbase, &std);

   if aval_W56=. then do ;
      aval_W56=base_simu ;
    end;

   chg_wk56 = aval_W56 - newbase ;

   output ;
end;
run;
```

2) Multiple imputations in participants who have missing HbA1c values at Week 56 due to Covid-19

```
proc sort data=base_imputed out= data_IN_COVID;
                by ARM;
run;

proc mi data    =data_IN_COVID out= monotone nimpute=10000 seed=14829;
                by ARM;
                where (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;
run;

proc mi data= monotone out= OUT_MI_MISSING_COVID nimpute=1 seed=14829;
        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;
 run;

data data_OUT_MI_MISSING_COVID;
        set OUT_MI_MISSING_COVID;
        if W56_missing = “Y”;
run;
```

3) Identifying observed values

```
data_data_OUT_COMPL_MI;
        Set     base_imputed (where = (AVAL_W56^=.));
                _imputation_=0;
                do i = 1 to 10 000;
                _imputation_=_imputation_+1;
                output;
                end;
        run;
```

4) Combine imputation datasets and use ANCOVA and Rubin's formula to obtain the between-group difference and 95% CI.

```
data    dataMI;
        set     data_OUT_MI_MISSING
                data_OUT_MI_MISSING_COVID
                data_OUT_COMPL_MI;
        run;
```

Step 3: ANCOVA analysis

```
proc mixed data=HbA1cW56Complete;
        class ARM HbA1c_strata BMI_strata region;
        model chg_wk56 = ARM HbA1c_strata BMI_strata region NEWBASE;
        by _Imputation_;
        lsmeans ARM/ pdiff=control ('Dulaglutide 1.5 mg') cl;
        ods output LSMeans=lsmeans  diffs=lsmeansdiff;
run;

proc mianalyze parms=lsmeansdiff;
          modeleffects ARM;
          by ARM;
          ods output parameterestimates=miparm;
run;
```

In this sample SAS® (version 9.4) code:

- BaseHbA1c contains one observation per participant in the ITT population with Baseline HbA1c value.
- InputData contains one observation per participant in the ITT population
- data_OUT_COMPL_MI is the output dataset including observed values 10,000 times by participant
- data_OUT_MI_MISSING is the output dataset containing 10,000 lines per participant with missing endpoint data not due to COVID-19
- data OUT_MI_MISSING_COVID is the output dataset containing 10,000 lines per participant with missing endpoint data due to COVID-19
- dataMI is the final output containing 10,000 lines by participant with all observed and simulated data used for the ANCOVA.

- ARM is the randomized treatment group (Dulaglutide 1.5 mg, Efpeglenatide 4mg, Efpeglenatide 6mg).
- HbA1c_strata is the randomization stratum of screening Hb1Ac (<8.0, ≥8.0%)
- BMI_strata is the randomization stratum of BMI at Visit 3(<30, ≥30)
- BASE is the observed baseline HbA1c.
- BASE_simu contains the simulated baseline HbA1c values.
- NEWBASE is the baseline HbA1c including observed (If non-missing) and imputed (If missing, pooled mean) data.
- CHG_WK56 is the change from baseline in HbA1c at Week 56.

- W56_missing = for each patient, “Y” if the Week 56 value is missing, otherwise W56_missing = “N”.
- COVID = for each patient, “Y” if the missing data at Week 56 is impacted by COVID-19, otherwise COVID = “N”.
  - REGION is the geographical region.
  - The seed is 14829.

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.

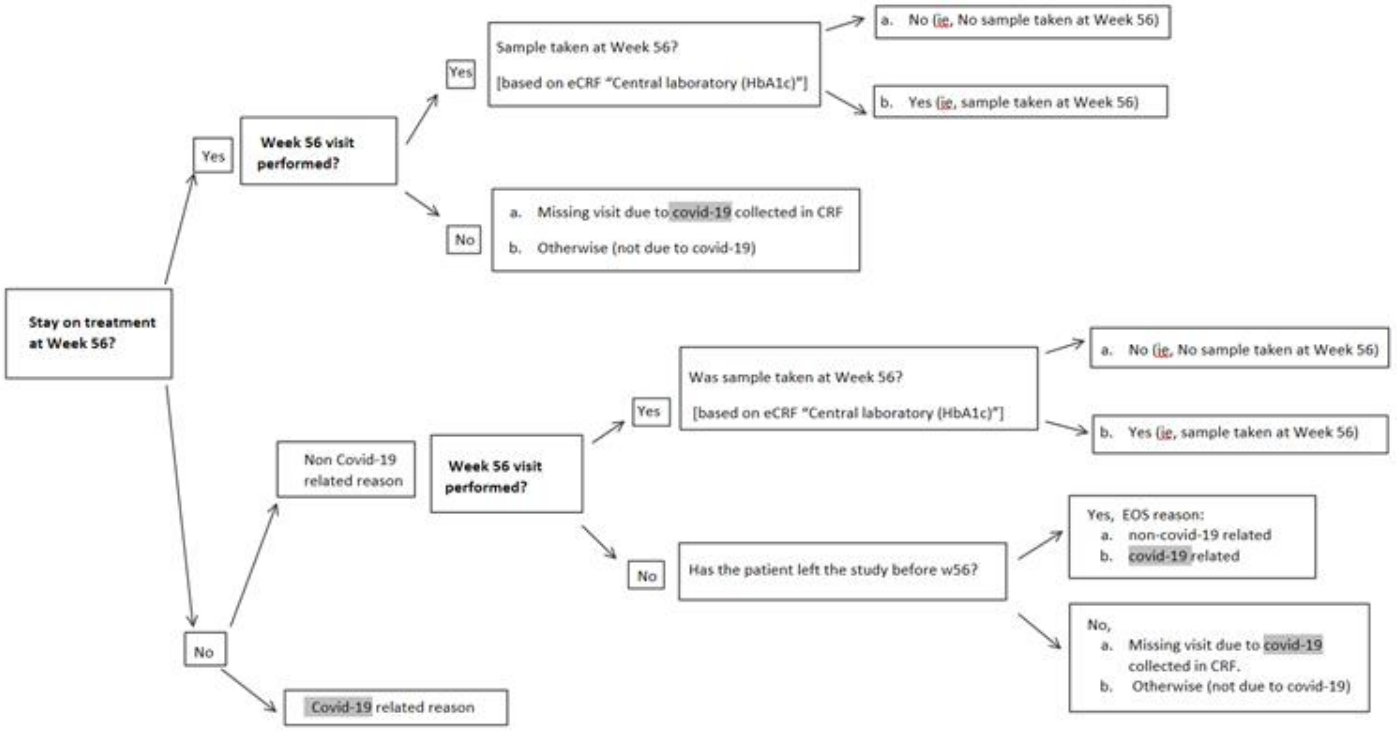
Parameter	PCSA	Comments
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >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)	

Parameter	PCSA	Comments
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.
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg	To be applied for all positions (including missing) except STANDING.
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline ≥5% decrease from baseline	FDA Feb 2007.
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)

Parameter	PCSA	Comments
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	
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	

Parameter	PCSA	Comments
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 (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Injection of weekly dose on the day of visit			X	X	X		X		X	X						Participants will self-administer the injection only after blood samples (if any) 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		See Table 2 in the protocol 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 V2 and before randomization
Demography, medical/surgical history	X															Includes diabetes complications, CV and allergy history, alcohol and smoking habits.

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Physical examination	X		X				X			X		X		X		
Vital signs	X		X		X	X	X		X	X		X		X	X	BP and HR in sitting position after at least 5 minutes of rest.
Height	X															
Body weight	X		X	X	X	X	X		X	X		X		X	X	
Waist circumference			X							X				X		See Section 8.1.4 in the protocol
12-lead ECG			X				X							X		The 12-lead ECG recording should be obtained in supine position prior to IMP dose administration. See Section 8.2.3 in the protocol.
IMP injection training/retraining as needed		X	X	X	X	X	X		X	X		X				See Section 6.1.1 in the protocol.
Inspection of injections sites			X	X	X	X	X		X	X		X		X	X	

Procedure	**Screening (up to 3 weeks)**		**Treatment Period (56 Weeks)**												**Post treatment Follow-up (6 wks)**	**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** base-line	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Diary dispensation		X	X	X	X	X	X		X	X		X		X		
Diary review and collection			X	X	X	X	X		X	X		X		X	X	
Glucose meter dispensation and training		X														Will include training for hypoglycemia awareness and management.
Diet and life style counseling	X		X	X	X	X	X		X	X		X		X		As per current practice, to be documented. See Section 5.3.1 in the protocol
IRT contact	X	X	X	X	X	X	X		X	X		X		X	X	
IMP dispensation		X	X	X	X	X	X		X	X		X				At V2, training kit(s) will be allocated; self-injection will be done at site.
IMP collection and accounting		X		X	X	X	X		X	X		X		X		Training kit(s) will be collected and accounted at V2.
Compliance			X	X	X	X	X	X	X	X	X	X	X	X	X	SMPG, IMP, diary
Efficacy:																
HbA1c	X		X				X			X		X		X		

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** base-line	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
FPG			X			X	X			X		X		X		For these visits, participants need to come in fasting condition as described in Section 5.3.1 in the protocol
C-peptide (fasting)			X											X		For these visits, participants need to come in fasting condition as described Section 5.3.1 in the protocol
7-point SMPG			X				X			X		X		X		Performed on at least 1 day in the week prior to visits indicated. See Section 8.1.5 in the protocol for details.
Fasting (prebreakfast) SMPG			X	X	X	X	X	X	X	X	X	X	X	X	X	Daily within the first 8 weeks after randomization and at least 3 days in the weeks prior to other visits indicated. See Section 8.1.2 in the protocol for details.

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Safety:																
Hematology	X		X				X			X		X		X	X	See Appendix 2 (Section 10.2) in the protocol.
Clinical chemistry	X		X				X			X		X		X	X	See Appendix 2 (Section 10.2) in the protocol.
Calcitonin	X		X				X			X				X	X	See Appendix 2 (Section 10.2) in the protocol.
Lipid profile			X							X				X		See Appendix 2 (Section 10.2) in the protocol.
Urinalysis			X							X				X		See Appendix 2 (Section 10.2) in the protocol.

Procedure	**Screening (up to 3 weeks)**		**Treatment Period (56 Weeks)**												**Post treatment Follow-up (6 wks)**	**Notes**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** base-line	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Pregnancy test (WOCBP)	X		X		X	X	X		X	X		X		X	X	Serum pregnancy testing (β-HCG) at screening for WOCBP (Appendix 4 [Section 10.4] in the protocol), urine pregnancy testing subsequently (at on-site visits and monthly at home in between visits). If the urine test is positive, serum β-HCG should be tested for confirmation of the pregnancy.
Serum FSH and estradiol	X															For women of non-childbearing potential. In case the definition of postmenopausal or premenopausal cannot be satisfied (see Appendix 4 [Section 10.4] in the protocol).

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** base-line	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Antidrug antibody (ADA) sampling			X		X		X			X				X	X	Participants positive for ADA at EOS, and who experienced severe injection site or hypersensitivity reaction at any time during the study, will be asked to provide sample for anti-efpeglenatide antibodies assessments 4 and 6 months after the end of the treatment. Blood samples are to be collected to assess the efpeglenatide ADA status (positive or negative) and level (titer) applicable for the participants assigned to efpeglenatide.

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
IMP concentration (PK) sampling					X		X		X	X						All participants assigned to efpeglenatide will have 1 blood sample collected just before their weekly injection (and at least 6 days after last dose administration) for the predose serum concentration (Ctrough) of efpeglenatide at selected clinical visits. See Section 8.5 in the protocol. For efpeglenatide participants who consent, at least 1 additional postdose sample will be taken 3 days (±1 day) after administration of efpeglenatide, preferably between Week 8 and Week 12, but other weeks are also acceptable (eg, after the 1st dose, 4th dose, or 12th dose). Participant will need to provide separate consent. See Section 8.5 in the protocol.

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Patient-reported Outcomes																
PQATv2										X				X		PQATv2 should be completed by participants as far as possible at home before on-site visits. See Section 8.1.7 in the protocol.
PROMIS GI symptoms scale, version 1			X	X	X	X	X	X		X		X		X		This questionnaire will have to be completed by participants as far as possible at home before on-site visits after randomization and additionally at Weeks 1, 3, 5, 6, 7, and 18.

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Rescue therapy assessment			Continuous assessment and recording during treatment periods													After randomization, the need of rescue treatment should be assessed by the Investigators via fasting SMPG performed by the participants and/or the central laboratory alerts received on FPG and on HbA1c (from Week 12 [Visit 7] onwards). Participants must have an unscheduled in-person visit prior to rescue therapy initiation, with the assessments normally planned for the EOT visit. See Section 6.1.2.2 in the protocol

Procedure	Screening (up to 3 weeks)		Treatment Period (56 Weeks)												Post treatment Follow-up (6 wks)	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	
			R					☎			☎		☎	**EOT**	**EOS**	
Week	**–3**	**–1**	**0** baseline	**2**	**4**	**8**	**12**	**18**	**24**	**30**	**36**	**43**	**50**	**56** [a]	**Last IMP+6 weeks**	
Acceptable range (days)	-21 to -11	-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 V3 can be done 4 to 10 days after V2 V3 should be done at least 11 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Concomitant medication recording	Continuous assessment and recording throughout the study															
AE/SAE recording																
Reporting hypoglycemia (symptoms, SMPG)																Hypoglycemia eCRF page must be filled in for all SMPG values ≤3.9 mmol/L (≤70 mg/dL) 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 after last IMP administration with the assessments normally planned for EOT visit (including a PK sample if the visit can be scheduled 7 days after the permanent IMP discontinuation). 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. Every effort should be made to have the participant complete the Week 56 Visit assessments (primary and main secondary endpoints) as the minimum.
For safety reasons, participants who do not want to continue to be followed in the study after IMP discontinuation, should be assessed 6 weeks (±1 week) from the last IMP dose (at the minimum) using the procedure normally planned for the post-treatment follow-up visit at EOS. At the time corresponding to their Week 56 Visit, all attempts will be made to contact the participants to inquire about safety/vital status.

Abbreviations: ADA: antidrug antibody, AE: adverse event, β-HCG: beta-human chorionic gonadotropin, BP: blood pressure, CV: cardiovascular, ECG: electrocardiogram, EOS: end of study, EOT: end of treatment, FPG: fasting plasma glucose, FSH: follicle-stimulating hormone, HbA1c: hemoglobin A1c, GI: gastrointestinal, HR: heart rate, IMP: investigational medicinal product, IRT: interactive response technology, PK: pharmacokinetics, PQATv2: Patient´s Qualitative Assessment of Treatment version 2; PROMIS: Patient-Reported Outcomes Measurement Information System; R: Randomization; SAE: serious adverse event, SMPG: self-monitored plasma glucose, WOCBP: women of childbearing potential

Signature Page for VV-CLIN-0365236 v2.0
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Approve & eSign	[redacted]
Approve & eSign	[redacted]