NCT03770728

STATISTICAL ANALYSIS PLAN

A 30-week, Multicenter, Double-blind, Placebo-controlled, Randomized Study to Evaluate the Efficacy and Safety of Efpeglenatide Once Weekly in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Metformin Alone or in Combination with Sulfonylurea

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADA:	anti-drug antibody
AERSM:	adverse events requiring specific monitoring
AESI:	adverse events of special interest
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BMI:	body mass index
CEC:	Clinical Endpoint Committee
CSR:	clinical study report
CV:	cardiovascular
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
ITT:	intent-to-treat
LLT:	lower-level term
MedDRA:	Medical Dictionary for Regulatory Activities
MI:	myocardial infarction
NIMP:	noninvestigational medicinal product
OAD:	oral antidiabetic drug
OC:	observed cases
PCSA:	potentially clinically significant abnormality
PT:	preferred term
R:	randomization
SAE:	serious adverse event
SAP:	statistical analysis plan
SOC:	system organ class
SU:	sulfonylurea
T2DM:	Type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
TIA:	transient ischemic attack
ULN:	upper limit normal
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, 4-arm, parallel group study in participants with type 2 diabetes mellitus (T2DM) inadequately controlled with Metformin alone or in combination with sulfonylurea (SU).

After a Screening phase of up to 3 weeks (with a minimum of 10 days), participants will be centrally randomized (using permuted block randomization schedule) via Interactive Response Technology (IRT) in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:

- Efpeglenatide 2 mg
- Efpeglenatide 4 mg
- Efpeglenatide 6 mg
- Efpeglenatide placebo

Randomization will be stratified by Screening hemoglobin A1c (HbA1c) (<8%, ≥8%) and SU use at screening (Yes/No). Participants will receive double-blinded treatment for 30 weeks. Additional details on the study design and plan is in Section 1.4.

Approximately 640 participants (160 participants per treatment group) [details in Section 1.3] will be randomized.

The study was terminated early by the Sponsor on September 9, 2020 (hereinafter referred to as "early termination").

1.2 OBJECTIVES

1.2.1 Primary objectives

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

1.2.2 Secondary objectives

Secondary objectives of this study include:

- To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on glycemic control

- To demonstrate the superiority of once-weekly injection of efpeglenatide 2, 4, and 6 mg in comparison to placebo on body weight
- To evaluate the safety of once-weekly injection of efpeglenatide 2, 4, and 6 mg.

1.2.3 Tertiary/exploratory

- To compare the effects of once weekly injection of efpeglenatide 2, 4, and 6 mg with placebo on glycemic control
- To characterize the pharmacokinetics (PK) of efpeglenatide
- To evaluate the immunogenicity of once weekly injection of efpeglenatide 2, 4, and 6 mg

1.3 DETERMINATION OF SAMPLE SIZE

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

A sample size of 160 per arm (ie, 160 participants for each of the efpeglenatide dose groups and 160 for the placebo group) has >99% power to detect a treatment difference of -0.6% between each dose of efpeglenatide and placebo in HbA1c change from baseline to Week 30, assuming a common SD of 1.1% (2-sided, α=0.05) for each comparison. Furthermore, with approximately 50% of participants being on metformin alone (ie, 80 per arm) and approximately 50% on Metformin + SU (ie, 80 per arm), there will be 92% (81%) power to detect a treatment difference of -0.6% (-0.5%) between each efpeglenatide dose and placebo within the subgroup of participants on metformin alone or subgroup of participants on metformin + SU.

Hence, there are 4 parallel dosing arms:

- Efpeglenatide 2 mg, N=160
- Efpeglenatide 4 mg, N=160
- Efpeglenatide 6 mg, N=160
- Efpeglenatide placebo, N=160

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

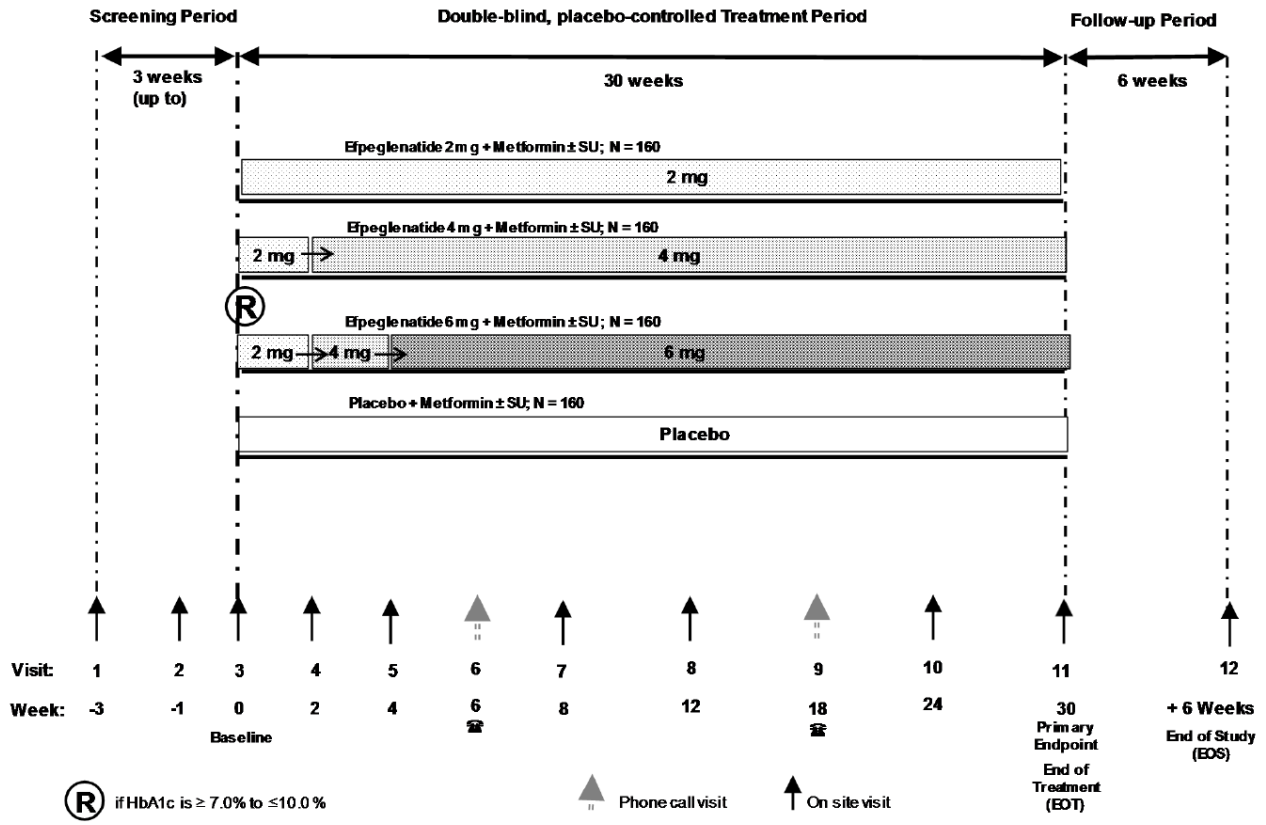
1.4 STUDY PLAN

This is a multicenter, 30-week, randomized, double-blind, placebo-controlled Phase 3 study consisting of 3 study periods:

- An up to 3-week screening period (with a minimum of 10 days)
- A 30-week double-blind, placebo-controlled treatment period, for efficacy and safety assessment
- A 6-week posttreatment follow-up period to collect safety information after last dose of IMP

The maximum study duration per participant will be 39 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; SU, sulfonylurea.
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

Not applicable.

1.6 STATISTICAL MODIFICATIONS MADE IN STATISTICAL ANALYSIS PLAN

Due to study early termination, the efficacy evaluations originally planned in the protocol were no longer considered to be relevant and were not performed. PK and ADA samples were not analyzed thus no analyses were planned. This is a simplified statistical analysis plan (SAP) for the purpose of synopsized clinical study report (CSR).

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The Baseline value (with the exception of serum creatinine and eGFR) is defined as the last available value prior to the first dose administration of IMP or the last available value on or before the date of randomization if not treated with the study treatment.

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

All Baseline safety parameters (apart from those listed below) are presented along with the on-treatment summary statistics in the safety sections (Section 2.4.4).

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

Demographic characteristics

Demographic variables are gender (Male, Female), race (Asian, Black or African American, White, Multiple, other), age in years (quantitative and qualitative variable: <50, ≥50 and <65, ≥65 and <75, and ≥75 years), ethnicity (Hispanic or Latino, not Hispanic or Latino, Unknown, and Not reported), country, Baseline body mass index (BMI) (quantitative and qualitative variable: <30, ≥30 and <40, ≥40kg/m^2), randomization strata [HbA1c at screening (<8.0%, ≥8.0%); SU use at screening (Yes/No)].

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

Medical history

Medical history includes medical or surgical history.

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

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 years, ≥10 years)

- Age at diagnosis of diabetes (years) derived as: Year of diagnosis of diabetes – Year of birth
- eGFR (mL/min/1.73 m^2) at baseline
- Categories of eGFR at baseline (in ml/min/1.73 m^2) (≥90 (normal), ≥60 and <90 (mild decrease in GFR), ≥30 and <60 (moderate decrease in GFR), ≥15 and <30 (severe decrease in GFR), <15 (end stage renal disease)
- Antidiabetic medication at the time of screening (Metformin, Metformin and Sulfonylurea)
- Duration of Metformin and Sulfonylurea (years) at screening
- Daily dose of Metformin (mg) at screening

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

2.1.2 Prior or concomitant medications

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or during the study must be recorded in the corresponding case report form page.

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

Medications will be classified into the following 3 groups:

- Prior medications are those the participant used prior to first IMP administration. Prior medications can be discontinued before first IMP administration or can be ongoing during the 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 includes metformin alone or in combination with SU. Background metformin and SU are considered as Non-IMPs (NIMP). Metformin and SU (commercial formulations) will be administered orally according to the locally approved label.

Rescue medication(s) is considered Non-IMP treatment. Except for GLP-1 RA and DPP-4 inhibitors, any approved medications (including increase of prior metformin or SU dose) can be prescribed to treat the hyperglycemia. Increasing the SU dose up to the Screening dose level is not

considered as rescue therapy in participants whose SU dose was temporarily decreased for HbA1c <8.0% at Week -1 or for hypoglycemia.

Prohibited medication

The following treatments are prohibited during the study (including during the screening period and the 30 weeks of treatment period).

- Initiation of any antidiabetic agents, other than the IMP, or increase in dose of preexisting oral antidiabetic drugs (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, dulaglutide, or semaglutide) and DPP-4 inhibitors (eg, sitagliptin, saxagliptin, vildagliptin, or linagliptin)
- Initiation of any prescription weight loss drugs (eg, phentermine, lorcaserin, or orlistat)
- Gastric surgery or other gastric procedures for weight loss
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, nasal spray, and inhaled or intra-articular applications are allowed)
- Any investigational drug other than IMP for this study

Similar to concomitant medications, summary table for prohibited mediations will be provided as well.

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

2.1.3 Efficacy endpoints

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

Efficacy endpoints will be summarized in conventional units for HbA1c (%) and weight (kg), and standard international units for FPG (mmol/L).

2.1.3.1 Primary efficacy endpoint

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

2.1.3.2 Secondary efficacy endpoints

- Number of participants with HbA1c <7.0% at Week 30
- Change in FPG from Baseline at Week 30
- Change in body weight from Baseline at Week 30

2.1.3.3 Exploratory efficacy endpoint(s)

- Changes in 7-point SMPG profiles (mmol/L, mg/dL: mean 24-hour SMPG) from Baseline to Week 30
- 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
- Number of participants with rescue therapy used until Week 30
- Time to initiation of rescue therapy (weeks)

2.1.4 Safety endpoints

The safety analysis will be based on the reported AEs, hypoglycemia and other safety information, such as, vital signs.

Observation period

The observation period will be divided into 3 main segments:

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

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

2.1.4.1 Adverse events observation period

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

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

All AEs (including serious adverse events (SAE), AESIs, 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 (AESI) include the following terms:

- 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 non-serious) with IMP/NIMP
- Increase in alanine aminotransferase (ALT) >3 x upper limit normal (ULN)

Adverse events requiring specific monitoring (AERSM) 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) will review, assess, and/or adjudicate all events of death, selected CV events and pancreatic events.

2.1.4.2 Deaths

Deaths will be categorized according to 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 (end of on-study observation period)

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 B). 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: ALT, Aspartate aminotransferase (AST), Alkaline phosphatase (ALP), Total bilirubin
  - Lipid profile: Triglyceride, Total cholesterol, Low-density lipoprotein cholesterol, High-density lipoprotein cholesterol (For triglycerides, only values assessed in fasted participants will be analyzed)
  - Calcitonin

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

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

2.1.4.5 Electrocardiogram variables

The 12-lead ECG recording will be performed locally at Randomization, Week 12, and Week 30. 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 hypoglycemia with a measured plasma glucose concentration ≥3.0 - <3.9 mmol/L (≥54 - <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.

2.1.5 Immunogenicity endpoints

2.1.5.1 Antidrug (efpeglenatide) antibody

Anti-drug antibody (ADA) is sampled at Visit 3/Week 0, Visit 5/Week 4, Visit 8/Week 12, at the end of treatment visit, and 6 weeks post-treatment follow up visit.

2.1.6 Pharmacokinetic endpoints

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

- Serum C_{trough} of efpeglenatide at predose (Weeks 4, 12, 24, 30)
- Serum concentration of efpeglenatide at postdose (either 4 days [±1 day] after first IMP dose [Week 1], 4 days [±1 day] after 4th dose [Week 4], or 4 days [±1 day] after 12th dose [Week 12] in a subset of participants, approximately 10% of total: [N=16 per group]).

2.1.7 Pharmacodynamic/genomics endpoints

Pharmacodynamic parameters are not evaluated in this study.

2.2 DISPOSITION OF PARTICIPANTS

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

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

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

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

- Screened participants
- Nonrandomized but treated participants
- Randomized participants
- Randomized but not treated participants
- Randomized and treated participants
- Participants who have completed the 30-week treatment period as per protocol
- Participants who did not complete the 30-week treatment period, and main reasons for permanently treatment discontinuation
- Participants who completed the study as per protocol

- Participants who discontinued the study by main reason for permanent study discontinuation
- Status at last study contact

For all categories of participants (except for the screened, 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. A summary of participants who discontinued treatment and/or study will be provided with reasons for discontinuation, including reasons related to COVID-19.

2.2.1 Protocol Deviations

All significant deviations, potentially impacting efficacy analyses, randomization, drug-dispensing irregularities, and other selected significant deviations will be recorded.

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 intent-to-treat (ITT) population.

2.3.1.1 Intent-to-treat population

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

2.3.2 Safety population

The safety population is defined as:

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

In addition:

- Nonrandomized but treated participants will not be part of the safety population; however, their safety data will be presented separately
- Randomized participants for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For participants receiving 1 or more injections of efpeglenatide during the trial, regardless of being assigned to the efpeglenatide groups or not, the treatment group allocation for as treated analysis will be included in the efpeglenatide dose group that they are exposed for longer duration. In case of a tie, the highest dose group will be used. Participants, who premature discontinued study treatment during the titration phase, will be summarized in their planned treatment group for as-treated analysis too.
- Randomized participants will be excluded from the safety population only if there is documented evidence (ie, all study dates recorded as no medication taken) that participants have not taken the study treatment. If a participant is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the participant will be considered exposed.

2.4 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.

Due to study early termination, the analyses specified in this document focus on demographics, disease characteristics at baseline, exposure, participant disposition, and safety. Primary and secondary efficacy data will be descriptively summarized.

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, 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.

Technical formulas are described in Section 2.5.1.

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

2.4.2 Extent of investigational medicinal product exposure

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

2.4.2.1 Extent of investigational medicinal product exposure

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

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

Duration of IMP exposure will be summarized descriptively as a quantitative variable (N, mean, SD, median, minimum, and maximum). Duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following 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, >30 weeks. Cumulative duration of treatment exposure will be summarized similarly for ≥1 week, ≥3 weeks, ≥5 weeks, ≥9 weeks, ≥13 weeks, ≥19 weeks, ≥25 weeks, and >30 weeks. The duration of treatment exposure in weeks will be the duration (in days)/7 rounded up to the nearest integer.

2.4.3 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 or introduction of rescue therapy, unless otherwise specified (see Section 2.5.4).

A descriptive summary will be provided at screening, baseline, and Week 30, displaying observed value and change from baseline for efficacy endpoints (HbA1c, FPG, body weight, and % participants achieving 7%).

2.4.4 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 following common rules:

- Safety data in participants who do not belong to the safety population (eg, treated but not randomized) will be listed separately
- 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 21May2014 effective date 24May2014 [Appendix A])

- PCSA criteria will determine which participants had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including nonscheduled or repeated evaluations. The number of all such participants will be the numerator for the 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 on-treatment period and by treatment group on the safety population.

- The analysis of the safety variables will be descriptive, and no systematic testing is planned.

2.4.4.1 Analyses of adverse events

Generalities

The primary focus of AE reporting will be on TEAEs.

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. 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
    - Discontinued per investigator decision

  - Discontinued per participant decision
- Treatment-related TEAE
- TEAEs of special interest (AESI)
- TEAEs requiring specific monitoring (AERSM)

- All TEAE 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, and 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.
- Summary of common TEAEs (eg, PTs with incidence ≥2% in any treatment group) will be presented by primary SOC and PT.

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.

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

- All TEAEs leading to treatment discontinuation per investigator decision, by primary SOC, HLGT, HLT, and PT, showing the number (%) of participants
- All TEAEs leading to treatment discontinuation per investigator and/or participant decision, by primary SOC, HLGT, HLT, and PT, showing the number (%) of participant.

Analysis of adverse events of special interest (AESI) and requiring specific monitoring (AERSM)

TEAEs of special interest (AESI) and requiring specific monitoring (AERSM) include AE defined in Section 2.1.4 and the criteria of AESI and AERSM are in Table 1.

Table 1 - 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 events	AE severity= “severe” using Gastrointestinal disorders CMQ
Severe hypoglycemia	Any hypoglycemia event which required assistance (from hypoglycemia page)
Pancreatic events	Cases reported in eCRF "Suspected or confirmed Pancreatitis" page or AE category = “Pancreatic Neoplasm”

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

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

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

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/or adjudicated by CEC. The events sent for adjudication will be presented in the listings, which will include at least the following information, sorted by treatment, participant identification, and onset date: treatment, participant identification, country, age, gender, race, primary SOC, PT, reported term, onset date, study day (relative day to the start date of IMP), AE duration, duration of exposure, intensity, action taken with IMP, date of treatment discontinuation (if relevant), relationship to

IMP/NIMP/study procedures, outcome, date of death (if any), seriousness, seriousness criteria, and AE status ("Pre" for a pretreatment AE; "T" for a TEAE; and "Post" for a posttreatment AE).

2.4.4.2 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). Documented hypoglycemia (symptomatic or asymptomatic) will be also evaluated for the more stringent plasma glucose threshold of 3.0 mmol/L (<54 mg/dL), as well as for ≥3.0 and <3.9 mmol/L (≥54 and <70 mg/dL), and ≤3.9 mmol/L (≤70 mg/dL). Frequency and percentage of participants with at least 1 hypoglycemia event will be summarized as well.

Event rate of hypoglycemia per participant year will be calculated by treatment using the total number of hypoglycemia events from all participants (denoted as n) divided by the total exposures from all participants expressed in years (ie, participant exposure in days divided by 365.25, denoted as t). Multiple events from an individual participant will all count. Event rates of hypoglycemia per participant year (all reported hypoglycemia, severe, documented symptomatic, asymptomatic, probable symptomatic, relative hypoglycemia, and documented hypoglycemia with plasma glucose <3.0 mmol/L [<54 mg/dL], as well as for ≥3.0 and <3.9 mmol/L [≥54 and <70 mg/dL], and ≤3.9 mmol/L [≤70 mg/dL]) will be presented by treatment group for the on-treatment period.

A listing of participants for all severe hypoglycemia events reported on the specific eCRF "Hypoglycemic Event Information" page will be provided.

2.4.4.3 Deaths

A listing of all deaths for screened participants will be generated.

2.4.4.4 Analyses of vital sign variables

The incidence of PCSAs at any time during the on-treatment period will be summarized for heart rate 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

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, then the duration will be calculated using the following:

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 is imputed to January and the 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 conventions will be used.

2.5.3 Missing data

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

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

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

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

In the definition of the 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 2/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 posttreatment medication.

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 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 potentially clinically significant abnormalities

If baseline is missing, the participant 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.

Handling of missing screening value to derive randomization strata

In case of missing data at screening visit for HbA1c, 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.

Participants who do not have a documented stable daily dose of SU for at least 3 months prior to screening will be considered non-SU users.

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.

2.5.4 Windows for time points

Nominal postbaseline visits will be used for descriptive statistics and time course plots.

Efficacy data at Week 30

The scheduled measurements at the endpoint visit (Week 30) 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) of the date of the end point visit [targeted study Day 210 for Week 30]. If multiple measurements are associated to the same targeted date, the closest to the targeted study day will be used. In case of equality, the last measurement will be used. If there are still no measurement for a given parameter at an endpoint visit, the data is considered missing for efficacy analyses.

2.5.5 Unscheduled visits

Unscheduled visit measurements will be used for computation of Baseline and PCSA.

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 4-6 weeks after the last participant's last visit.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

1. FDA Draft Guidance for Industry: Pharmacokinetics in Patients with Impaired Renal Function - Study Design, Data Analysis, and Impact on Dosing and Labeling. Clinical Pharmacology. March 2010 (revision 1).

7 LIST OF APPENDICES

Appendix A 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 measurements.
CPK	>3 ULN >10 ULN	FDA Feb 2005. Am J Cardiol April 2006. Categories are cumulative. First row is mandatory. Rows following one mentioning zero can be deleted.

Parameter	PCSA	Comments
CLcr (mL/min)	<15 (end stage renal disease)	FDA draft Guidance 2010
(Estimated creatinine clearance based on the Cokcroft-Gault equation)	≥15 - <30 (severe decrease in GFR)	Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥30 - <60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥90 (normal GFR)	
eGFR (mL/min/1.73m2)	<15 (end stage renal disease)	FDA draft Guidance 2010
(Estimate of GFR based on an MDRD equation)	≥15 - <30 (severe decrease in GFR)	Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
	≥30 - <60 (moderate decrease in GFR)	
	≥60 - <90 (mild decrease in GFR)	
	≥90 (normal GFR)	
Creatinine	≥150 µmol/L (Adults)	Benichou C., 1994.
	≥30% change from baseline	
	≥100% change from baseline	
Uric Acid		Harrison- Principles of internal Medicine 17th Ed., 2008.
Hyperuricemia	>408 µmol/L	
Hypouricemia	<120 µmol/L	
Blood Urea Nitrogen	≥17 mmol/L	
Chloride	<80 mmol/L	
	>115 mmol/L	
Sodium	≤129 mmol/L	
	≥160 mmol/L	
Potassium	<3 mmol/L	FDA Feb 2005.
	≥5.5 mmol/L	
Total Cholesterol	≥7.74 mmol/L	Threshold for therapeutic intervention.
Triglycerides	≥4.6 mmol/L	Threshold for therapeutic intervention.
Lipasemia	≥3 ULN	
Amylasemia	≥3 ULN	
Glucose		
Hypoglycaemia	≤3.9 mmol/L and <LLN	ADA May 2005.
Hyperglycaemia	≥11.1 mmol/L (unfasted); ≥7 mmol/L (fasted)	ADA Jan 2008.
HbA1c	>8%	
Albumin	≤25 g/L	
CRP	>2 ULN or >10 mg/L (if ULN not provided)	FDA Sept 2005.

Parameter	PCSA	Comments
Hematology		
WBC	<3.0 Giga/L (Non-Black); <2.0 Giga/L (Black)	Increase in WBC: not relevant.
	≥16.0 Giga/L	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)	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).
	≥185 g/L (Male); ≥165 g/L (Female)	
	Decrease from Baseline ≥20 g/L	
Hematocrit	≤0.37 v/v (Male) ; ≤0.32 v/v (Female)	
	≥0.55 v/v (Male) ; ≥0.5 v/v (Female)	
RBC	≥6 Tera/L	Unless specifically required for particular drug development, the analysis is redundant with that of Hb.
		Otherwise, consider FDA criteria.
Platelets	<100 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.
	≥700 Giga/L	
Urinalysis		
pH	≤4.6	
	≥8	
Vital signs		
HR	≤50 bpm and decrease from baseline ≥20 bpm	To be applied for all positions (including missing) except STANDING.
	≥120 bpm and increase from baseline≥20 bpm	
SBP	≤95 mmHg and decrease from baseline ≥20mmHg	To be applied for all positions (including missing) except STANDING.
	≥160 mmHg and increase from baseline ≥20 mmHg	
DBP	≤45 mmHg and decrease from Baseline ≥10 mmHg	To be applied for all positions (including missing) except STANDING.
	≥110 mmHg and increase from Baseline ≥10 mmHg	

Parameter	PCSA	Comments
Orthostatic Hypotension		
Orthostatic SDB	≤-20 mmHg	
Orthostatic DBP	≤-10 mmHg	
Weight	≥5% increase from baseline	FDA Feb 2007.
	≥5% decrease from baseline	
ECG		Ref.: ICH E14 guidance (2005) and E14 Q&A (2012), and Cardiac Safety Research Consortium White Paper on PR and QRS (Nada et al. Am Heart J. 2013; 165(4) : 489-500)
HR	<50 bpm	Categories are cumulative
	<50 bpm and decrease from baseline ≥20 bpm	
	<40 bpm	
	<40 bpm and decrease from baseline ≥20 bpm	
	<30 bpm	
	<30 bpm and decrease from baseline ≥20 bpm	
	>90 bpm	
	>90 bpm and increase from baseline ≥20bpm	
	>100 bpm	
	>100 bpm and increase from baseline ≥20bpm	
	>120 bpm	
	>120 bpm and increase from baseline ≥20 bpm	
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.
		Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and ΔQTc>60 ms are the 2 PCSA categories to be identified in individual subjects/ patients listings.
	>500 ms	
	Increase from baseline	
	Increase from baseline]30-60] ms	
	Increase from baseline >60 ms	

Appendix B Schedule of Activities (SoA)

	Screening		Double-blind placebo-controlled Treatment period									Post-treatment Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
			R			☎			☎		**EOT**	**EOS**	
Week	**-3**	**-1**	**0** Baseline	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**[a]	Last IMP + 6 weeks	
Acceptable range (days)	-10 to - 21	-7 (±3)	1	14 (±3)	28 (±3)	42 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	259 (±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 10 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		Participant 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				See Table 2 for details of dosing windows
Informed consent	X												Informed consent taken prior to any study-related procedures being performed.
Inclusion and exclusion criteria	X	X	X										Check eligibility before Visit 2 and before randomization
Demography, medical/surgical history	X												Includes diabetes complications, cardiovascular (CV) and allergy history, alcohol and smoking habits
Physical examination	X		X					X			X		
Vital signs	X		X		X		X	X		X	X	X	Blood pressure (BP) and heart rate (HR) in sitting position after at least 5 minutes of rest
Height	X												
Body weight	X		X		X		X	X		X	X	X	
12-lead ECG			X					X			X		The 12-lead ECG recording should be obtained in supine position, prior to IMP dose administration
IMP injection training at V2/retraining as needed		X	X	X	X		X	X		X			See Section 6.1.1

	Screening		Double-blind placebo-controlled Treatment period									Post-treatment Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
			R			☎			☎		**EOT**	**EOS**	
Week	**-3**	**-1**	**0** Baseline	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**[a]	Last IMP + 6 weeks	
Acceptable range (days)	-10 to - 21	-7 (±3)	1	14 (±3)	28 (±3)	42 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	259 (±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 10 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
Review of injection sites			X	X	X		X	X		X	X	X	
Diary dispensation		X	X	X	X		X	X		X	X		
Diary review and collection			X	X	X		X	X		X	X	X	
Review of SMPG and metformin and sulfonylurea doses		X	X	X	X	X	X	X	X	X	X	X	
Glucose meter dispensation and training		X											Will include training for hypoglycemia awareness and management
Diet and life style counselling	X		X	X	X		X	X		X	X		As per current practice, to be documented
IRT contact	X	X	X	X	X		X	X		X	X	X	
IMP dispensation		X	X	X	X		X	X		X			At V2, placebo training kit(s) will be allocated; self-injection will be done at site (see Section 6.1.1)
IMP collection and accounting		X		X	X		X	X		X	X		Training kit will be collected and accounted at V2 (see Section 6.1.1)
Compliance			X	X	X	X	X	X	X	X	X	X	SMPG, IMP, diary
Efficacy:													
HbA1c	X		X					X			X		
FPG			X				X	X			X		For these visits, participants need to come in fasting conditions as described in Section 5.3.1 and Section 8.1.2
C-peptide (fasting)			X										For this visit, participants need to come in fasting conditions as described in Section 5.3.1

	Screening		Double-blind placebo-controlled Treatment period									Post-treatment Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
			R			☎			☎		**EOT**	**EOS**	
Week	**-3**	**-1**	**0** Baseline	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**[a]	Last IMP + 6 weeks	
Acceptable range (days)	-10 to - 21	-7 (±3)	1	14 (±3)	28 (±3)	42 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	259 (±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 10 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
7-point SMPG profiles			X					X			X		Performed on at least 1 day in the week prior to visits indicated. See Section 8.1.4 for details
Fasting (before breakfast) SMPG			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 other weeks, prior to visits indicated. See Section 8.1.2 for details
Safety:													
Hematology	X		X					X			X	X	See Appendix 2 (Section 10.2)
Clinical chemistry	X		X					X			X	X	See Appendix 2 (Section 10.2)
Calcitonin	X		X					X			X	X	See Appendix 2 (Section 10.2)
Lipid profile			X								X		See Appendix 2 (Section 10.2)
Urinalysis			X								X		See Appendix 2 (Section 10.2)
Pregnancy test (for women of childbearing potential)	X		X		X		X	X		X	X	X	Serum pregnancy testing (β-HCG) at screening for women of childbearing potential (WOCBP Appendix 4, Section 10.4), urine pregnancy testing subsequently (at on-site visits and monthly at home in between visits). If the urine test is positive, serum β-HCG should be tested for confirmation of the pregnancy
Serum FSH and estradiol	X												For women of non-childbearing potential. In case the definition of postmenopausal or premenopausal cannot be satisfied (see Appendix 4, Section 10.4)
ADA sampling			X		X			X			X	X	Participants positive for ADAs at the end of study, and who experienced severe injection site or hypersensitivity reaction at any time during the study, will be asked to provide sample for anti-efpeglenatide antibodies assessments 4 and 6 months after the EOT

	Screening		Double-blind placebo-controlled Treatment period									Post-treatment Follow-up	Notes
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
			R			☎			☎		**EOT**	**EOS**	
Week	**-3**	**-1**	**0** Baseline	**2**	**4**	**6**	**8**	**12**	**18**	**24**	**30**[a]	Last IMP + 6 weeks	
Acceptable range (days)	-10 to - 21	-7 (±3)	1	14 (±3)	28 (±3)	42 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	259 (±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 10 days after V1 (to allow IMP to be sent to the site) and no later than 21 days after V1
PK sampling					X			X		X	X		All participants will have 1 blood sample collected just before their weekly injection of the IMP (and at least 6 days after last dosing of the IMP) for the predose IMP serum concentration (C_{trough}) at selected clinical visits. For a subset of participants, 1 additional postdose sample will be taken either 4 days (±1 day) after first IMP dose or 4 days (±1 day) after 4th dose or 4 days (±1 day) after 12th dose. A separate consent will be signed. See Section 8.5
Rescue therapy assessment			Continuous assessment and recording during treatment period										After randomization, the need of rescue treatment should be assessed by the Investigators via fasting SMPG performed by the participants and/or via the central laboratory alerts received on FPG and on HbA1c (from Week 12 onwards). See Section 6.1.2.2
Concomitant medication review	Continuous assessment and recording throughout the study												
AE/SAE recording													
Reporting hypoglycemia (symptoms, SMPG)													Hypoglycemia eCRF page must be filled in for all SMPG ≤70 mg/dL (3.9 mmol/L) and/or in case of symptoms suggesting hypoglycemia (between V1 and V2 SMPGs measured with nonstudy glucometer can be used)

a **In case of premature permanent IMP discontinuation**, the participant should have a visit as soon as possible after the last IMP administration with the assessments normally planned for EOT visit. Afterwards, the participants should continue in the study up to the scheduled date of study completion and be followed according to the study procedures as specified in the protocol. Every effort should be made to have the participant complete the Week 30 Visit´s assessments (primary and main secondary endpoints) as the minimum. For safety reasons, participants who wish to terminate participation in the study, should be assessed 6 weeks (±1 week) from the last IMP dose (at the minimum) using the procedure normally planned for the posttreatment follow-up visit at EOS. At the time corresponding to their Week 30 Visit, all attempts will be made to contact the participant to inquire about safety and/or vital status.

Abbreviations: ADA: antidrug antibody, AE: adverse event, AESI: adverse event of special interest, β-HCG: beta-human chorionic gonadotropin, ECG: electrocardiogram, EOS: end of study, EOT: end of treatment, FPG: fasting plasma glucose, FSH: follicle-stimulating hormone, HbA1c: glycosylated hemoglobin, IMP: investigational medicinal product, IRT: interactive response technology, PK: pharmacokinetics, R: randomization; SAE: serious adverse event, SMPG: self-monitored plasma glucose.

Signature Page

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Approve & eSign	[redacted]
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