



NCT03713684

STATISTICAL ANALYSIS PLAN

A 56-week, Multicenter, Double-blind, Placebo-controlled, Randomized Study to Evaluate the Efficacy and Safety of Efpeglenatide Once Weekly in Patients with Type 2 Diabetes Mellitus Inadequately Controlled with Basal Insulin Alone or in Combination with Oral Antidiabetic Drug(s)

SAR439977-EFC14893

STATISTICIAN: [REDACTED]

Statistical Project Leader: [REDACTED]

DATE OF ISSUE: 11-Nov-2020

Total number of pages: 46

Any and all information presented in this document shall be treated as confidential and shall remain the exclusive property of Sanofi (or any of its affiliated companies). The use of such confidential information must be restricted to the recipient for the agreed purpose and must not be disclosed, published or otherwise communicated to any unauthorized persons, for any reason, in any form whatsoever without the prior written consent of Sanofi (or the concerned affiliated company); 'affiliated company' means any corporation, partnership or other entity which at the date of communication or afterwards (i) controls directly or indirectly Sanofi, (ii) is directly or indirectly controlled by Sanofi, with 'control' meaning direct or indirect ownership of more than 50% of the capital stock or the voting rights in such corporation, partnership or other entity

TABLE OF CONTENTS

STATISTICAL ANALYSIS PLAN	1
TABLE OF CONTENTS.....	2
LIST OF ABBREVIATIONS AND DEFINITION OF TERMS.....	4
1 OVERVIEW AND INVESTIGATIONAL PLAN	5
1.1 STUDY DESIGN AND RANDOMIZATION	5
1.2 OBJECTIVES.....	5
1.2.1 Primary objectives.....	5
1.2.2 Secondary objectives	5
1.2.3 Tertiary/exploratory	6
1.3 DETERMINATION OF SAMPLE SIZE.....	6
1.4 STUDY PLAN.....	6
1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL.....	7
1.6 STATISTICAL MODIFICATIONS MADE IN STATISTICAL ANALYSIS PLAN	8
2 STATISTICAL AND ANALYTICAL PROCEDURES	9
2.1 ANALYSIS ENDPOINTS	9
2.1.1 Demographic and baseline characteristics	9
2.1.2 Prior or concomitant medications.....	10
2.1.3 Efficacy endpoints.....	11
2.1.3.1 Primary efficacy endpoint.....	12
2.1.3.2 Secondary efficacy endpoints	12
2.1.3.3 Exploratory efficacy endpoint(s).....	12
2.1.4 Safety endpoints	12
2.1.4.1 Adverse event observation period	13
2.1.4.2 Deaths	14
2.1.4.3 Laboratory safety variables	14
2.1.4.4 Vital signs variables	15
2.1.4.5 Electrocardiogram variables	15
2.1.4.6 Hypoglycemia.....	15
2.1.5 Immunogenicity endpoints	16
2.1.5.1 Anti-drug (efpeglenatide) antibody.....	16
2.1.6 Pharmacokinetic endpoints	16

2.1.7	Pharmacodynamic/genomics endpoints	17
2.2	DISPOSITION OF PARTICIPANTS.....	17
2.2.1	Protocol Deviations	18
2.3	ANALYSIS POPULATIONS.....	18
2.3.1	Efficacy populations	18
2.3.1.1	Intent-to-treat population.....	18
2.3.2	Safety population	18
2.4	STATISTICAL METHODS	19
2.4.1	Demographics and baseline characteristics	19
2.4.2	Extent of investigational medicinal product exposure	19
2.4.2.1	Extent of investigational medicinal product exposure	19
2.4.3	Analyses of efficacy endpoints.....	20
2.4.4	Analyses of safety data	20
2.4.4.1	Analyses of adverse events	21
2.4.4.2	Analysis of Hypoglycemia	25
2.4.4.3	Deaths	25
2.4.4.4	Analyses of vital sign variables	26
2.5	DATA HANDLING CONVENTIONS	26
2.5.1	General conventions	26
2.5.2	Data handling conventions for secondary efficacy variables	26
2.5.3	Missing data	26
2.5.4	Windows for time points	28
2.5.5	Unscheduled visits	28
2.5.6	Pooling of centers for statistical analyses	28
2.5.7	Statistical technical issues	28
3	INTERIM ANALYSIS	29
4	DATABASE LOCK	30
5	SOFTWARE DOCUMENTATION	31
6	REFERENCES.....	32
7	LIST OF APPENDICES	33
	APPENDIX A CRITERIA FOR POTENTIALLY SIGNIFICANT ABNORMALITIES – FOR PHASE 2/3 STUDIES (ONCOLOGY EXCEPTED).....	34
	APPENDIX B SCHEDULE OF ACTIVITIES (SOA)	41

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE:	adverse event
ALP:	alkaline phosphatase
ALT:	alanine aminotransferase
AST:	aspartate aminotransferase
BMI:	body mass index
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
LLT:	lower-level term
MI:	myocardial infarction
NIMP:	noninvestigational medicinal product
OAD:	oral antidiabetic drug
OC:	observed cases, standard deviation
PCSA:	potentially clinically significant abnormality
PT:	preferred term
R:	randomization
SC:	subcutaneous
SOC:	system organ class
SU:	sulfonylurea
T2DM:	Type 2 diabetes mellitus
TEAE:	treatment-emergent adverse event
TIA:	transient ischemic attack
WHO-DD:	World Health Organization-Drug Dictionary

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

Protocol EFC14893, is a multicenter, 30-week, double-blind, randomized, placebo-controlled Phase 3 study with an additional 26-week Treatment Extension Period evaluating the efficacy and safety of efpeglenatide addition in participants with type 2 diabetes mellitus (T2DM) inadequately controlled with basal insulin alone or in combination with Oral Antidiabetic Drug (OAD)(s).

After a Screening phase of 2 weeks, participants will be centrally randomized (using permuted block randomization schedule) via Interactive Response Technology (IRT) in a 1:1:1:1 ratio to 1 of the following 4 treatment groups:

- efpeglenatide 2 mg
- efpeglenatide 4 mg
- efpeglenatide 6 mg
- efpeglenatide placebo

Randomization will be stratified by Screening hemoglobin A1c (HbA1c) (<8.0, \geq 8.0%) and sulfonylurea (SU) use at Screening (Yes/No). Participants will receive double-blinded treatment for 56 weeks. Additional details on the study design and plan are located in [Section 1.4](#).

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

The study was early terminated by the Sponsor on 09 September 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 basal insulin alone or in combination with OAD(s).

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 additional 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 characterize the pharmacokinetics (PK) of efpeglenatide in dose regimen of once weekly injection of 2, 4, and 6 mg
- To evaluate the immunogenicity of once weekly injection of efpeglenatide 2, 4, and 6 mg
- To compare the effects on once weekly injection of efpeglenatide 2, 4 and 6 mg with placebo on additional parameters of glycemic control
- To compare the effects on once weekly injection of efpeglenatide 2, 3 and 6 mg with placebo on waist circumference
- To compare the effect of once weekly injection of efpeglenatide 2, 4, and 6 mg with placebo on insulin dose

1.3 DETERMINATION OF SAMPLE SIZE

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

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

Hence, there are 4 parallel dosing arms:

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

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

1.4 STUDY PLAN

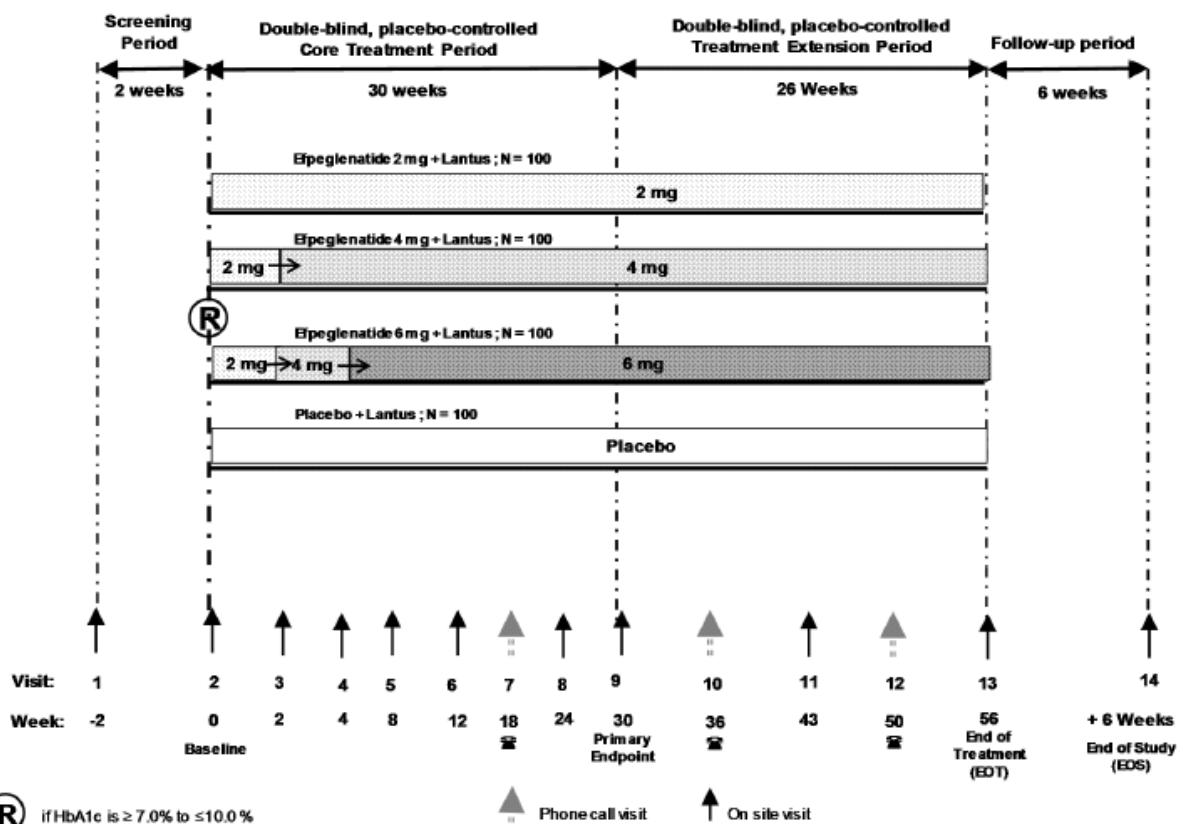
This is a multicenter, 56-week, randomized, double-blind, placebo-controlled Phase 3 study consisting of 4 study periods:

- A 2-week Screening Period (11 to 14 days)

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

The maximum study duration per participant will be 64 weeks with treatment lasting for 56 weeks (a 30-week core treatment period and a 26-week extension period). The graphical study design is shown in [Figure 1](#).

Figure 1 - Study Design Overview



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. Note: any assessment undertaken on the day of first dose administration of IMP with missing assessment time will be considered as baseline.

For serum creatinine and eGFR, baseline is defined as the average of all values before the first dose of double-blind IMP for those randomized and exposed to IMP or before randomization for those randomized but not 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 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), country (US, China and Korea), HbA1c (%) at screening, randomization strata HbA1c (%) at screening ($<8\%$, $\geq 8\%$), randomization strata SU use at screening (Yes, No), baseline weight (kg), baseline body mass index (BMI) (quantitative and qualitative variable: <30 , ≥ 30 and <40 , ≥ 40 kg/m^2), and baseline waist circumference.

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

Medical history

Medical history includes medical or surgical history.

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.

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, \geq 10 years);
- Age at diagnosis of diabetes (years) derived as: Year of diagnosis of diabetes – Year of birth;
- Antidiabetic drugs at the time of screening (basal insulin, basal insulin + SU, basal insulin + OAD other than SU);
- Basal insulin dose at Screening (U, U/kg);
- Basal insulin dose at Baseline (U, U/kg);
- Duration of treatment with (any) basal insulin;
- Estimated Glomerular Filtration Rate (eGFR) at baseline (ml/min/1.73m²);
- Estimated glomerular filtration rate (eGFR) categories at baseline (<15 ml/min/1.73 m² [End stage renal Disease], \geq 15 to $<$ 30 ml/min/1.73 m² [Severe decrease in glomerular filtration rate (GFR)], \geq 30 to $<$ 60 ml/min/1.73 m² [Moderate decrease in GFR], \geq 60 to $<$ 90 ml/min/1.73 m² [Mild decrease in GFR], and \geq 90 ml/min/1.73 m² [Normal])

Any technical details related to computation, dates, and imputation for missing dates are described in [Section 2.5](#).

2.1.2 Prior or concomitant medications

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

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

Medications will be classified into the following 3 groups:

- Prior medications are those the participant used prior to first IMP administration. Prior medications can be discontinued before first IMP administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the participant concomitantly to the IMP(s), from first dose to the end of treatment + 30 days (+ 7 days for antidiabetic

drugs). A given medication can be classified both as a prior medication and as a concomitant medication. Concomitant medications do not include medications started during the posttreatment period (as defined in the observation period in [Section 2.1.4](#)).

- Posttreatment 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 Lantus for SC injections, and OAD(s) administered as per Investigator prescription and in accordance with local labeling.

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

Prohibited medication(s)

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

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

- Initiation of any GLP-1 RAs (eg, exenatide, liraglutide, dulaglutide, or semaglutide) and DPP-4 inhibitors (eg, sitagliptin, saxagliptin, vildagliptin, or linagliptin)

The following treatments are prohibited during the on-treatment treatment period from 1st intake up to the last intake of investigational product.

- Initiation of any antidiabetic agents including oral or injectable antihyperglycemic agents other than IMP and Lantus or a change in dose or preexisting OAD(s) before pre-rescue assessments and initiation of rescue therapy.

Note: Short-term use (<10 consecutive days) of short-acting insulin for treatment of acute illness or surgery is allowed

- Initiation of any prescription weight loss drugs (eg, phentermine, lorcaserin, or orlistat)
- Gastric surgery or other gastric procedures for weight loss
- Systemic use of glucocorticoids for more than 10 consecutive days (topical, nasal spray, and inhaled or intra-articular applications are allowed)
- Any investigational drug other than IMP for this study

Any technical details related to computation, dates, imputation for missing dates are described in [Section 2.5](#).

2.1.3 Efficacy endpoints

Efficacy endpoints are defined in [Section 2.1.3.1](#), [Section 2.1.3.2](#) and [Section 2.1.3.3](#).

Efficacy variables HbA1c (%) and weight (kg) will be summarized in conventional units and FPG (mmol/L) will be summarized in SI units.

2.1.3.1 Primary efficacy endpoint

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

2.1.3.2 Secondary efficacy endpoints

- Number of participants with HbA1c <7.0% at Weeks 30 and 56 (yes/no)
- Change in FPG from Baseline at Weeks 30 and 56
- Change in HbA1c (%) from Baseline at Week 56
- Changes in body weight from Baseline at Weeks 30 and 56

2.1.3.3 Exploratory efficacy endpoint(s)

- HbA1c <7.0% at Week 30 and Week 56 without weight gain
- Change in waist circumference from Baseline to Week 30 and 56
- Changes in mean 24-hour SMPG (7-point SMPG profile) 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
- Change in daily basal insulin dose from Baseline to Week 30 and 56
- Time to initiation of rescue therapy (weeks)
- Number of participants with rescue therapy used during the treatment period until Weeks 30 and 56

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

- The **pre-treatment** period is defined as the time from informed consent up to the time of first injection of IMP
- The whole **on-treatment** period is defined as the time from the first injection of the IMP up to 30 days (7 days for hypoglycemia) after the last injection of the IMP
 - The 30-week core on-treatment period is defined as the time from the first injection of IMP up to Visit 9 (Week 30) (or Day 210 if Visit 9 [Week 30] visit is missing) or up to 30 days (7 days for hypoglycemia) after the last injection of IMP, whichever comes earlier
- The **post-treatment** period is defined as the period from the end of the whole on-treatment period.

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

2.1.4.1 Adverse event observation period

- **Pretreatment 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
- **Posttreatment 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) $>3 \times$ 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

Deaths will be categorized according to the following observation periods:

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

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

Technical formulas are described in [Section 2.5](#).

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 include 12-lead ECG interpretation (normal/abnormal) provided by the investigator. 12-lead ECG recording will be performed locally at Randomization, Week 12, Week 30 and Week 56. Investigator's interpretation of normal and abnormal will be reported in the eCRF.

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 - < 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 Anti-drug (efpeglenatide) antibody

Blood samples are taken to assess the Anti-drug antibody (ADA) status (positive/negative) and level (titer) at Visit 2/Week 0, Visit 4/Week 4, Visit 6/Week 12, Visit 9/Week 30, 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 pre-dose (Weeks 4, 12, 24, 30);
- Serum concentration of efpeglenatide at post-dose (either 4 days [± 1 day] after first IMP dose, 4 days [± 1 day] after 4th dose, or 4 days [± 1 day] after 12th dose in a subset of

participants). All valid samples collected will be sent to the laboratory to be analyzed, even if out of the specified window.

2.1.7 Pharmacodynamic/genomics endpoints

Pharmacodynamic parameters are not evaluated in this study.

2.2 DISPOSITION OF PARTICIPANTS

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

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

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

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

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

For all categories of participants (except for the screened, 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.

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, and 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.

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

2.3.2 Safety population

The safety population is defined as:

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

In addition:

- Nonrandomized but treated participants will not be part of the safety population; however, their safety data will be presented separately.
- Randomized participants for whom it is unclear whether they took the IMP will be included in the safety population as randomized according to their planned treatment.

- For participants receiving 1 or more injections of efpeglenatide during the trial, regardless of being assigned to the efpeglenatide groups or not, the treatment group allocation for as-treated analysis will be included in the efpeglenatide dose group that they are exposed for longer duration. In case of 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 participants is dispensed double-blind IMP and is lost to follow-up without any documented evidence, the participants 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, participants 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, 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.

Technical formulas are described in [Section 2.5](#).

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 (participants years), duration (days), and category (weeks).

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

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories: 1 to 2 weeks, 3 to 4 weeks, 5 to 8 weeks, 9 to 12 weeks, 13 to 18 weeks, 19 to 24 weeks, 25 to 30 weeks, 31 to 43 weeks, 44 to 56 weeks, and >56 weeks; cumulative duration of treatment by category (weeks) will also be summarized. The duration of treatment exposure in weeks will be the duration (in days)/7 rounded 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](#)).

Descriptive summary will be provided at screening, baseline, Week 30 and Week 56 displaying observed value and change from baseline for efficacy endpoints (HbA1c, FPG, body weight and % participants achieving 7%).

In summary by visits, Week 56 data will be presented respectively:

1. Including all Week 56 visits performed per protocol as well as premature end of treatment/study visit recorded as Week 56 due to early termination.
2. Including Week 56 visits for participants who completed treatment and/or study.

2.4.4 Analyses of safety data

The summary of safety results will be presented by treatment group on the “whole 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 21 May 2014 effective date 24 May 2014 [[Appendix A](#)])
 - PCSA criteria will determine which participants had at least 1 PCSA during the whole on-treatment period, taking into account all evaluations performed during the whole on-treatment period, including nonscheduled or repeated evaluations. The number of all such participants will be the numerator for the whole on-treatment period PCSA percentage.
 - The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of participants assessed for that given parameter in the whole on-treatment period 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, HLT, and PT, sorted in SOC internationally agreed order and 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 TEAEs by primary SOC, HLT, HLT, and PT, showing number (%) of participants with at least 1 TEAE sorted by the SOC internationally agreed order. The other levels (HLT, HLT, PT) will be presented in alphabetical order. This sorting order will be applied to all other tables by SOC, HLT, HLT, and PT, unless otherwise specified.
- Summary of common TEAEs (eg, PTs with incidence $\geq 2\%$ 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, HLT, 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, HLT, HLT, and PT, showing the number (%) of participants
- All TEAEs leading to treatment discontinuation per investigator and/or participant decision, by primary SOC, HLT, HLT, and PT, showing the number (%) of participants

Analysis of adverse events of special interest and requiring specific monitoring

Adverse events of special interest (AESI) and adverse events requiring specific monitoring (AERSM) include AE defined in [Section 2.1.4](#) and the criteria of AESI and AERSM are in [Table 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 event	AE severity = “severe” using CMQ
Severe hypoglycemia	Any hypoglycemia event which required assistance (from hypoglycemia page)
Pancreatic event	Cases reported in pancreatic specific eCRF 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 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 adjudicated by CEC.

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

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 2.1.4.5](#) (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 whole 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

Listing of all Deaths (Screened participants) will be generated.

2.4.4.4 Analyses of vital sign variables

The incidence of PCSAs at any time during the whole on-treatment period will be summarized only 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:

- 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):

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

2.5.2 Data handling conventions for secondary efficacy variables

No special data handling.

2.5.3 Missing data

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

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

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

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

In the definition of the whole on-treatment period, the date of the last dose of IMP is equal to the date of the last administration reported on the treatment status case report form page. If this date is missing, the date of the last IMP injection in the exposure page will be used for participants with at least 1 injection or the date of visit 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 whole on-treatment period, the AE/hypoglycemia will be classified as treatment-emergent. No imputation of AE end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of AE resolution.

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

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

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

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) of the date of the endpoint visit [targeted study Day 210 for Week 30 (or Day 392 for Week 56)]. If multiple measurements are associated to the same targeted date, the closest to the targeted study day will be used. In case of equality, the last measurement will be used. If there are still no measurement for a given parameter at an endpoint visit, the data is considered missing for efficacy analyses.

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 last participant last visit.

5 SOFTWARE DOCUMENTATION

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

6 REFERENCES

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

7 LIST OF APPENDICES

[Appendix A](#) Criteria for Potentially Significant Abnormalities

[Appendix B](#) Schedule of Activities

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 μ mol/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.

Parameter	PCSA	Comments
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.
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) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
eGFR (mL/min/1.73m ²)	<15 (end stage renal disease) ≥15 - <30 (severe decrease in GFR) ≥30 - <60 (moderate decrease in GFR) ≥60 - <90 (mild decrease in GFR) ≥90 (normal GFR)	FDA draft Guidance 2010 Pharmacokinetics in patients with impaired renal function-study design, data analysis, and impact on dosing and labeling
Creatinine	≥150 µmol/L (Adults) ≥30% change from baseline ≥100% change from baseline	Benichou C., 1994.

Parameter	PCSA	Comments
Uric Acid		Harrison- Principles of internal Medicine 17 th 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 ≥5.5 mmol/L	FDA Feb 2005.
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) ≥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 $ULN \geq 0.5$ Giga/L)	Harrison- Principles of internal Medicine 17 th Ed., 2008.
Hemoglobin	≤115 g/L (Male); ≤95 g/L (Female) ≥185 g/L (Male); ≥165 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).
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 ≥700 Giga/L	International Consensus meeting on drug-induced blood cytopenias, 1991.

Parameter	PCSA	Comments
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)
HR	<50 bpm <50 bpm and decrease from baseline ≥20 bpm	Categories are cumulative

Parameter	PCSA	Comments
	<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 ≥ 20 bpm >100 bpm >100 bpm and increase from baseline ≥ 20 bpm >120 bpm >120 bpm and increase from baseline ≥ 20 bpm	
PR	>200 ms >200 ms and increase from baseline $\geq 25\%$ >220 ms >220 ms and increase from baseline $\geq 25\%$ >240 ms >240 ms and increase from baseline $\geq 25\%$	Categories are cumulative
QRS	>110 ms >110 msec and increase from baseline $\geq 25\%$ >120 ms >120 ms and increase from baseline $\geq 25\%$	Categories are cumulative

Parameter	PCSA	Comments
QT	<u>>500 ms</u>	
QTc	<u>Absolute values (ms)</u>	To be applied to any kind of QT correction formula. Absolute values categories are cumulative
	>450 ms	
	>480 ms	QTc >480 ms and $\Delta QTc > 60$ ms are the 2 PCSA categories to be identified in individual subjects/patients listings.
	>500 ms	
<hr/>		
<u>Increase from baseline</u>		
Increase from baseline]30-60] ms		
Increase from baseline >60 ms		

Appendix B Schedule of Activities (SoA)

Procedure	Screening (2 weeks)		Double-blind placebo-controlled Core Treatment Period (30 weeks)									Double-blind, placebo-controlled Extension Period (26 weeks)				Post-treatment Follow-up (6 weeks)		Notes
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	EOT	EOS		
	R						📞			📞		📞						
Week	-2	0 BL	2	4	8	12	18	24	30 ^a	36	43	50	56	Last IMP +6 wks				
Acceptable range (days)	-14 to -11	1	14 (3±)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	252 (±5)	301 (±5)	350 (±5)	392 (±5)	434 (±7)				
Injection of weekly dose at day of visit		X	X	X	X	X		X	X						Participant will self-administer the injection only after blood samples have been drawn at the respective visit.			
Injection of weekly dose may be on a different day than visit		X					X			X	X	X	X	X	See Table 2 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												Check eligibility before Randomization.			
Demography, medical/surgical history		X													Includes diabetes complications, cardiovascular (CV) and allergy history. Includes alcohol and smoking habits.			
Physical examination	X	X			X			X		X		X						
Vital signs	X	X		X	X	X		X	X		X		X	X	BP and HR in sitting position after at least 5 minutes of rest.			
Height	X																	
Body weight	X	X		X	X	X		X	X		X		X	X				
Waist circumference		X						X					X		See Section 8.1.4 in the protocol			

Procedure	Screening (2 weeks)	Double-blind placebo-controlled Core Treatment Period (30 weeks)									Double-blind, placebo-controlled Extension Period (26 weeks)			Post-treatment Follow-up (6 weeks)	Notes	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Visit	R														EOT	EOS
	Week	-2	0 BL	2	4	8	12	18	24	30 ^a	36	43	50	56	Last IMP +6 wks	
Acceptable range (days)	-14 to -11	1	14 (3±)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	252 (±5)	301 (±5)	350 (±5)	392 (±5)	434 (±7)		
12-lead ECG		X				X			X				X		The 12-lead ECG recording should be obtained in supine position prior to IMP dose administration (see Section 8.2.3 in the protocol)	
Transition from prestudy insulin glargine 100 U/mL to Lantus		X													See Section 6.1.2.1 in the protocol of NIMPs	
IMP injection training/retaining with prefilled syringe if needed	X	X	X	X	X	X		X	X		X				See Section 6.1.1 in the protocol	
Review of injection sites		X	X	X	X	X		X	X		X		X	X		
Diary dispensation	X	X	X	X	X	X		X	X		X		X			
Diary collection		X	X	X	X	X		X	X		X		X	X		
Review of SMPG and Lantus dose adjustments		X	X	X	X	X	X	X	X	X	X	X	X	X		
Glucose meter dispensation and training	X														Will include training for hypoglycemia awareness and management	
Diet and lifestyle counseling		X	X	X	X	X		X	X		X		X		As per current practice, to be documented (Section 5.3.1 in the protocol)	
IRT contact	X	X	X	X	X	X		X	X		X		X	X		
Lantus dispensation		X	X	X	X	X		X	X		X					

Procedure	Screening (2 weeks)		Double-blind placebo-controlled Core Treatment Period (30 weeks)									Double-blind, placebo-controlled Extension Period (26 weeks)				Post-treatment Follow-up (6 weeks)	Notes
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	EOT	EOS	
	R						📞			📞		📞					
Week	-2	0 BL	2	4	8	12	18	24	30 ^a	36	43	50	56	Last IMP +6 wks			
Acceptable range (days)	-14 to -11	1	14 (3±)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	252 (±5)	301 (±5)	350 (±5)	392 (±5)	434 (±7)			
Lantus collection and accounting			X	X	X	X		X	X		X		X				
IMP dispensed		X	X	X	X	X		X	X		X						
IMP collection and accounting			X	X	X	X		X	X		X		X				
Compliance		X	X	X	X	X	X	X	X	X	X	X	X		SMPG, IMP, Lantus, diary		
Efficacy																	
HbA1c	X	X				X			X		X		X				
FPG		X			X	X			X		X		X			For these visits, participants need to come in fasting conditions as described in Section 5.3.1 and Section 8.1.2 in the protocol	
C-peptide (fasting)		X														For these visits, participants need to come in fasting conditions as described in Section 5.3.1 in protocol	
7-point SMPG profiles (on at least 1 day in the week prior to the visit)		X			X			X				X				Performed on at least 1 day in the week prior to clinical visits indicated. See Section 8.1.5 in protocol for complete details.	
Fasting (prebreakfast) SMPG		X	X	X	X	X	X	X	X	X	X	X	X	X		Daily within first 8 weeks after randomization and at least 3 days in the other weeks, prior to visits indicated. See Section 8.1.5 in protocol	

Procedure	Screening (2 weeks)	Double-blind placebo-controlled Core Treatment Period (30 weeks)									Double-blind, placebo-controlled Extension Period (26 weeks)			Post-treatment Follow-up (6 weeks)	Notes	
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	
Visit	R													EOT	EOS	
Week	-2	0 BL	2	4	8	12	18	24	30 ^a	36	43	50	56	Last IMP +6 wks		
Acceptable range (days)	-14 to -11	1	14 (3±)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	252 (±5)	301 (±5)	350 (±5)	392 (±5)	434 (±7)		
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	
Pregnancy test (for women of childbearing potential)	X	X		X	X	X		X	X		X		X	X	Serum pregnancy testing (β-HCG) at screening for WOCBP (Appendix 4 [Section 10.4] in 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	
ADA		X		X		X			X				X	X	Participants with positive ADA at the end of study, and who experienced severe injection site or hypersensitivity reaction at any time during the study, will be asked to provide samples for anti-efpeglenatide antibodies assessments 4 and 6 months after the end of the treatment or as soon as possible after study database lock whichever comes later	

Procedure	Screening (2 weeks)	Double-blind placebo-controlled Core Treatment Period (30 weeks)									Double-blind, placebo-controlled Extension Period (26 weeks)				Post-treatment Follow-up (6 weeks)	Notes
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
	R						📞			📞		📞	EOT	EOS		
Week	-2	0 BL	2	4	8	12	18	24	30 ^a	36	43	50	56	Last IMP +6 wks		
Acceptable range (days)	-14 to -11	1	14 (3±)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	252 (±5)	301 (±5)	350 (±5)	392 (±5)	434 (±7)		
IMP concentration (PK) sampling				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 IMP dose administration) for the predose serum concentration (Ctrough) of efpeglenatide at selected clinical visits. For participants who consent, at least 1 additional postdose sample will be taken 3 days (±1 day) after administration of IMP, preferably between Week 8 and Week 12. See Section 8.5 in the protocol	
Rescue therapy assessment		Continuous assessment and recording during treatment periods													After randomization, the need of rescue therapy should be assessed by the Investigator via fasting SMPG performed by the participants and the central laboratory alerts received on FPG and on HbA1c (from Week 12 onwards). Participants must have an unscheduled in-person visit prior to rescue therapy initiation, with the assessments normally planned for EOT visit. See Section 6.1.2.2. in protocol	

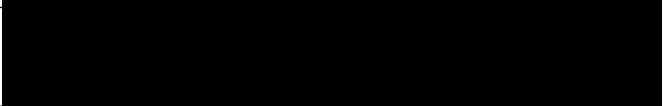
Procedure	Screening (2 weeks)	Double-blind placebo-controlled Core Treatment Period (30 weeks)									Double-blind, placebo-controlled Extension Period (26 weeks)				Post-treatment Follow-up (6 weeks)	Notes
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
	R						📞			📞		📞	EOT	EOS		
Week	-2	0 BL	2	4	8	12	18	24	30 ^a	36	43	50	56	Last IMP +6 wks		
Acceptable range (days)	-14 to -11	1	14 (3±)	28 (±3)	56 (±3)	84 (±3)	126 (±3)	168 (±3)	210 (±3)	252 (±5)	301 (±5)	350 (±5)	392 (±5)	434 (±7)		
Concomitant medication review	Continuous assessment and recording throughout the study															
AE/SAE recording																
Reporting hypoglycemia (symptoms, SMPG)															Hypoglycemia eCRF page must be filled in for all SMPG ≤70 mg/dL (3.9 mmol/L) and/or in case of symptoms suggesting hypoglycemia	

^a In case of premature permanent IMP discontinuation, the participant should have a visit as soon as possible after the last IMP administration with the assessments normally planned for EOT visit. Afterwards, the participant should continue in the study up to the scheduled date of study completion and be followed according to the study procedures as specified in the protocol. Every effort should be made to have the participant complete the Week 30 and Week 56 visits' assessments (primary and main secondary endpoints) as the minimum. For safety reasons, participant who wish to terminate participation in the study, should be assessed 6 weeks (±1 week) from the last IMP dose (at the minimum) using the procedure normally planned for the posttreatment follow-up visit at EOS. At the time corresponding to their Week 56 visit, all attempts will be made to contact the participant to inquire about safety and/or vital status.

Abbreviations: ADA: antidrug antibody, AE: adverse event, β-HCG: beta-human chorionic gonadotropin, BP: blood pressure, CV: cardiovascular, ECG: electrocardiogram, eCRF: electronic Case Report Form, EOS: end of study, EOT: end of treatment, FPG: fasting plasma glucose, FSH: follicle stimulating hormone, HbA1c: hemoglobin A1c, HR: heart rate, IMP: investigational medicinal product, IRT: interactive response technology, NIMP: noninvestigational medicinal product, PK: pharmacokinetic, R: Randomization, SAE: serious adverse event, SMPG: self-monitored plasma glucose, WOCBP: women of childbearing potential.

Signature Page for VV-CLIN-0591286 v1.0
efc14893-16-1-9-sap

Approve & eSign



Approve & eSign

