AstraZeneca

Statistical Analysis Plan

Study Code	D5551C00002
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A Phase 3, Double-Blind, Placebo-Controlled, Randomized, Multicenter Study to Assess the Safety and Efficacy of Exenatide Once Weekly in Adolescents with Type 2 Diabetes

LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BMI	Body mass index
CAP	Controlled assessment period
CEA	Carcinoembryonic antigen
CMH	Cochran-Mantel-Haenszel test
CSP	Clinical study protocol
CSR	Clinical Study Report
CV	Coefficient of variation
DAE	Adverse event leading to discontinuation
DBL	Database lock
DHEAS	Dehydroepiandrosterone
eCRF	Electronic case report form
EP	Extension period
EQW	Exenatide once weekly
FPG	Fasting plasma glucose
Free T4	Thyroxine
FSH	Follicle-stimulating hormone
GCV	Geometric coefficient of variation
GSD	Geometric standard deviation factor
HbA1c	Glycated hemoglobin A1c
HDL	High-density lipoprotein
HOMA	Homeostasis Model Assessment
HOMA-B	Homeostasis Model Assessment -Beta-cell function
HOMA-S	Homeostasis Model Assessment- Insulin sensitivity
ICH	International Conference on Harmonization
IE	Intercurrent events
IGF-1	Insulin-like growth factor 1
ITT	Intent-to-treat
LDL	Low-density lipoprotein
LH	Luteinizing hormone
LS	Least squares
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MNAR	Missing not at random
PBO	Placebo

PD	Protocol Deviation
PK	Pharmacokinetic
PP	Per-protocol
PT	Preferred term
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SC	Subcutaneous
SD	Standard deviation
SE	Standard error
SI	Standardized international
SHBG	Sex hormone binding globulin
SMBG	Self-monitored blood glucose
SOC	System Organ Class
SU	Sulfonylurea
TB	Total bilirubin
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UN	Unstructured
US	United States
WHODD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Date	Brief description of change
	N/A first version
05MAR2020	Section 3.2: C-peptide secondary endpoint removed due to collection at study visits not aligning for analysis.
	Section 3.6.3: Wording aligned for inclusion of data surrounding rescue medication.
	Section 3.6.4.3: Definition of treatment completion added as per AZ request.
	Section 3.6.4.4: Definition of controlled assessment period completion added to clarify difference from treatment completion.
	Section 3.6.5: Total daily insulin dosing clarification added to define how to derive dosing occurring throughout study, records to be used and handling of missed doses.
	Section 3.6.6: Derivation added for calculating free testosterone using total testosterone.
	Section 4.1.2: Number of decimal places clarified for presentation of p-value, in line with presentation guidelines for summary statistics.
	Section 4.1.3.2: Display of missing data in baseline and demographic outputs updated to be presented as a count outside of total count.
	Section 4.2.1: Removed text surrounding missing/unknown values for study disposition and baseline demographics to avoid inconsistency with Section 4.1.3.2.
	Section 4.2.1.2: Removal of Evaluable analysis set presentations for baseline, patient and demographic outputs after request at BDR1.
	Section 4.2.1.4: Details provided for summarizing background insulin therapy by visit and medication classification. Also, which data to be excluded from the summary.
	Section 4.2.2: Overall compliance analysis set changed from ITT to Safety as per request and change from CSP.
	Section 4.2.3.2: C-peptide removed from hierarchical testing due to removal from secondary endpoints.
	Section 4.2.3.3: Wording updated to add clarity to analysis being performed and default procedures in SAS programming. Aligned wording for inclusion of data surrounding rescue medication and efficacy endpoints. Updated baseline BMI percentiles for consistency of parameter throughout.
	Section 4.2.3.4: Revised wording for the sensitivity analysis to clarify the procedure to be used and the steps involved with implementing.

Date	Brief description of change
	Section 4.2.3.5: Text surrounding addition of Kaplan-Meier output and handling of censoring. Also reference for windowing rescue medication for glycemic control added.
	Section 4.2.4.1: Analysis for AEs off-treatment added by as per BDR1 request to capture all AEs occurring during the study.
	Section 4.2.4.4: Change from worst value for laboratory parameters to maximum or minimum value.
	Section 4.2.4.7: Clarity added for patients to be considered using medication at baseline.
	Table 3.1: Rescue medication added to the target windowing.
	Sections 4.3.1 and 4.3.3: Update to visit window tables to add analysis visit associated with protocol visit and target day's surrounding assessments close to the CAP (Week 24 and 28) and EP (Week 52). Visit windows for total daily insulin added.
	Section 5: More information provided on changes from protocol to SAP.
	Section 6: Reference for free testosterone added.
	Updated derivation for rescue medication from data to be included or excluded 'on or after' to 'after' first administration, throughout.

Date	Brief description of change
04MAY2020	Updated throughout the addition of the HbA1c goal <6.5% in line with other Exenatide projects. Section 3.6.1: Study baseline derivation adapted to be 'on or prior to' first dose of study medication, to be consistent with programming. Section 3.6.4.1: Addition of text surrounding the Extension Period to be consistent with the outlined approach in the protocol deviation plan. Section 3.6.4.2: Window of 90 days after last dose of study medication for serious adverse events added to definition, in line with CSP. Section 4.1.1: Removed wording for descriptive statistics not presented on the log-transformed outputs. Section 4.1.4: Updated approach for handling of systolic blood pressure to exclude data collected after the first administration of rescue medication, in line with diastolic blood pressure and other secondary endpoints. Section 4.2.1.2: Calculation for duration of diabetes to take the earliest date i.e. changed to use date of informed consent rather than screening. Section 4.2.1.4: Prior medication definition updated for clarity and consistency with outputs. Section 4.2.3.1: Removal of systolic blood pressure using a different approach to rescue medications than the other secondary endpoints, as outlined in update to Section 4.1.4. Section 4.2.3.3: Addition of baseline HbA1c by visit interaction to MMRM model. Removal of text surrounding unscheduled and early termination visits since windowing in Section 4.3 already outlines how to handle the data. Section 4.2.3.4: Aligned model fixed effects with primary analysis. Sections 4.2.3.5 and 4.2.4.4: Aligned modelling approach with primary with the addition of baseline dependent variable by visit interaction. Section 4.2.4: Noted for summary tables the 10-week follow-up will be included where applicable in safety outputs. Section 4.2.4.1: Approach to off-treatment adverse events updated to separate those which occurred for patients completing treatment and those prematurely discontinuing treatment. Section 4.2.4.2: Addition of injection site reactions to be summarized by injection device type. Section 4.2.4.6: Wording updated to align with outputs. Section 4.2.4.7: Addition of text from the CSP outlining mild, moderate and severe hypoglycemic events. Section 4.2.5: Text added surrounding new summary table for the mixed meal sub-study.

Date	Brief description of change
20MAY2020	Section 3.6.1: Text added regarding handling of multiple measurements that could be used for study baseline. Section 3.6.3: Information on the early termination visit added from the CSP. Section 3.6.4: Time element clarified about handling of HbA1c data surrounding rescue therapy. Section 3.6.5.2: Hypoglycemic events brought in line with handling within periods similar to AEs. Windows for capturing data in the controlled assessment and extension periods clarified so patients prematurely discontinuing IP and completing IP have consistent approaches. Section 3.6.5.3-6: Additional text added to define completers in the controlled assessment and extension periods for completing treatment or the period itself. Section 3.6.6: Wording revised to clearly state that 7 days are being used for average calculations. Section 4.2.1.4: Windows for capturing data for new concomitant medications in the controlled assessment and extension periods clarified so patients prematurely discontinuing IP and completing IP have consistent approaches around last dose of study medication. Section 4.2.3.1: The eGFR estimands were added to Table 2 to describe approach to handling intercurrent events. Section 4.2.3.5: Change from baseline HbA1c to screening HbA1c strata to be used in the MMRM modelling of secondary endpoints. Section 4.2.4.1: Windows for capturing treatment-emergent adverse events in the controlled assessment and extension periods, as well as off-treatment adverse events clarified so patients prematurely discontinuing IP and completing IP have consistent approaches around last dose of study medication. Text surrounding AEs to be considered as leading to study discontinuation added. Section 4.2.4.2: Date of device dispensing change added. Section 4.2.4.4: Change from baseline HbA1c to screening HbA1c strata to be used in the MMRM modelling of secondary endpoints. Section 4.3.3: Table 3.4, target day for Week 52 updated. Clarity also provided on how patients discontinuing study medication should be handled when deriving total daily insulin. Section 4.3.4.2: Removed phrasing around handling of selecting adverse events by intensity. Section 5: More information provided on changes from protocol to SAP. Section 7 (Appendix B1): Text surrounding imputing of completely missing end dates added.

1. STUDY DETAILS

The scope of this statistical analysis plan (SAP) is to describe the planned summaries and analyses of data collected during the double-blind controlled assessment period (Week 0 to Week 24), open-label extension period (Week 24 to Week 52), follow-up period (Week 52 to Week 62) and the mixed meal sub-study. The presentation of data collected during the long-term safety extension period is not within the scope of this SAP.

1.1 Study objectives

1.1.1 Primary objective

The primary objectives of the study are:

- To assess the effect on glycemic control, as measured by glycated hemoglobin A1c (HbA1c), of exenatide once weekly (EQW) following 24 weeks of treatment compared to placebo (PBO) in children and adolescents with type 2 diabetes mellitus
- To evaluate the safety and tolerability of EQW compared to PBO following 24 weeks of treatment in children and adolescents with type 2 diabetes mellitus

1.1.2 Secondary objective

The secondary objectives are:

- To compare the effects of EQW following 24 weeks of treatment to those achieved by PBO in children and adolescents with type 2 diabetes mellitus on the following:
  - Fasting plasma glucose concentration
  - Proportion of patients achieving HbA1c goals
  - Body weight and Tanner pubertal stage
  - Blood pressure and lipids
- To assess the effects of long-term EQW therapy (~1 year) in children and adolescents with type 2 diabetes mellitus on the following:
  - Long-term safety and tolerability
  - Parameters related to glycemic control, including HbA1c, fasting plasma glucose concentration, and proportion of patients achieving HbA1c goals
  - Body weight and Tanner pubertal stage
  - Blood pressure and lipids (total cholesterol, HDL, LDL, triglycerides)
- To examine the effect of EQW on beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostasis model assessment (HOMA) in children and adolescents with type 2 diabetes who are not taking insulin.
- To assess the pharmacokinetics (PK) of EQW in children and adolescents with type 2 diabetes.

1.2 Study design

This Phase 3, double-blind (controlled assessment period), randomized, multicenter, placebo-controlled parallel study is designed to examine the efficacy and safety of EQW compared to PBO in adolescents with type 2 diabetes for 24 weeks.

This study will assess safety and efficacy of EQW (as monotherapy and adjunctive therapy to oral antidiabetic agents and/or insulin). A schematic overview of the study design is shown in Figure 1. See D5551C00002 Clinical Study Protocol version 4.0, dated 14th December 2017 (CSP) Table 1 for the schedule of activities planned.

The study includes a 24-week, controlled assessment period, during which patients will receive study medication in accordance to their randomized treatment group, followed by a 28-week, open-label, uncontrolled extension period in which all patients will receive EQW.

At least 40% and not more than 60% of the randomized patients must be females. At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states.

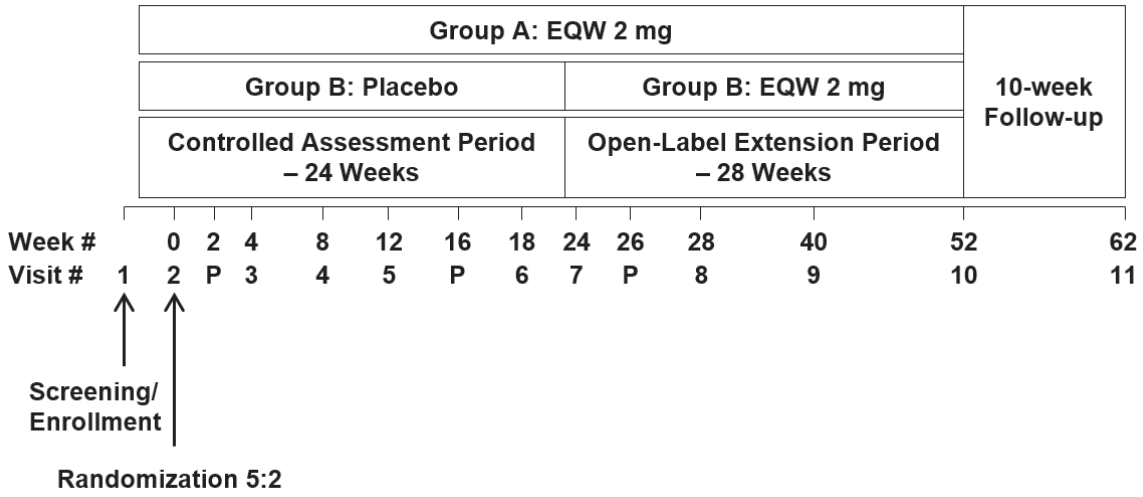
Approximately 77 patients will be randomly assigned across 2 treatment groups in a 5:2 ratio to receive either subcutaneous (SC) administration of EQW 2 mg (Group A) or PBO (Group B), respectively, with at least 50 evaluable patients in the EQW and at least 20 evaluable patients in the PBO group.

In addition to receiving study medications, all patients will participate in a lifestyle intervention program encompassing diet and physical activity modifications from Visit 1 (Week -2) to Visit 10 (Week 52). If patients are taking concomitant antidiabetic medication, they should administer their usual concomitant antidiabetic medication therapy at approximately the same time each day throughout the study.

Following the 24-week controlled assessment period, all patients will enter the 28-week extension period. During the 28-week extension period, all patients will receive EQW 2 mg for 28 weeks up to Visit 10 (Week 52/End of Treatment). The patients will return to the study site at 4- or 12-week intervals for safety, efficacy, Pharmacodynamics, and PK assessments and will complete study termination procedures at Visit 11 (Week 62/Study Termination).

All patients will complete study termination procedures Visit 11 (Week 62/Study Termination) which is a follow-up visit occurring 10 weeks after administration of the last dose of EQW at Visit 10 (Week 52).

Figure 1: Study Design



Abbreviations: EQW, exenatide once weekly; P, phone call

Note: All visits scheduled during the controlled assessment period and during the open-label extension period should occur within ±2 days of the scheduled date, relative to Visit 2 (Week 0).

Visit 11 must occur at least 10 weeks from final dose of study medication but no more than 12 weeks.

The Investigator and/or qualified study-site personnel will contact patients by phone at Week 2, Week 16, and Week 26 to discuss study compliance, address any questions related to study medication, and review adverse events.

Note: The first dose of open-label EQW during the extension period will be given at the Week 24 visit.

1.3 Number of patients

Assuming the following conditions, a sample size of 70 patients meeting all study requirements was calculated:

- True treatment difference of -0.7% between EQW and PBO in changes from baseline for HbA1c (%).
- Standard deviation (SD) of 1.0%
- Two-sided level of significance of 0.05
- 74% power to detect treatment difference

With an estimated 10% dropout rate, approximately 77 patients who have met all study requirements will be randomized in a ratio of 5:2 to the EQW or PBO treatment group on Visit 2 (Week 0) and will be carried out with stratification to achieve a balanced distribution of patients across treatment groups with regard to the screening HbA1c strata (<9.0% or ≥9.0%).

At least 40% and not more than 60% of the randomized patients must be females. At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states. The restriction on gender in the study population and also on the ethnicity and lifestyle will be enforced through putting caps on enrollment of patients with different genders and from different regions (Europe, United States [US], and others).

1.4 Mixed meal sub-study

1.4.1 Sub-study objectives

The primary objective of this exploratory sub-study is:

- To evaluate the effect of EQW on postprandial beta-cell function as assessed by C-peptide secretion during a mixed-meal test, following approximately 28 weeks of EQW treatment and at approximately 10 to 12 weeks following cessation of drug therapy.

The secondary objective of this exploratory sub-study is:

- To assess postprandial glucose and glucagon responses during a mixed-meal test following approximately 28 weeks of EQW treatment and at approximately 10 to 12 weeks following cessation of drug therapy.

1.4.2 Sub-study design

At baseline Visit 2 (Week 0), the study procedures to be assessed are outlined in the CSP. Study medication will be administered after all study procedures outlined in the main CSP are completed.

At Visit 10 (Week 52), the study procedures to be assessed are outlined in the CSP. Ten to twelve weeks following the discontinuation of study medication administration, patients will return to the study site for Visit 11 (Week 62/Study Termination). At this visit, the study procedures to be assessed are outlined in the CSP and in addition, patients will receive the standardized mixed-meal test and have blood drawn for additional postprandial pharmacodynamic assessments for the sub-study. Sub-study procedures to be performed at this visit are outlined in Section 9.1.3 of the CSP Appendix F.

1.4.3 Number of patients in sub-study

Approximately 20 patients participating in Protocol BCB114 who have volunteered to participate will be included in the sub-study. Based on a paired t-test, assuming a standard deviation of 110 for the change in the incremental area under the curve from 0 to 240 minutes (AUC(0-240)) of C-peptide, a sample size of 20 patients will be adequate to provide about 93% power to detect a change of 90 in the incremental AUC(0-240) from baseline. Power calculations to support the number of patients to participate in this assessment are provided in Table 1 of the CSP.

1.4.4 Pharmacodynamic assessments: Plasma Glucose, Serum Insulin, C-Peptide, and Glucagon

Blood will be drawn for the measurement of glucose, insulin, C-peptide, and glucagon concentrations according to the schedules presented in Sections 9.1.1, 9.1.2, and 9.1.3 of Appendix F of the CSP. For each assessment specified in those sections, one fasting blood sample will be taken anytime within the 30 min prior to the start of the standardized meal at baseline Visit 2 (Week 0), Visit 10 (Week 52), and Visit 11 (Week 62/Study Termination).

Subsequent blood samples will be taken at 15 min, 30 min, 60 min, 120 min, 180 min, and 240 min, relative to the start of the standardized meal.

1.4.5 Pharmacokinetic assessments

Blood samples for pharmacokinetic measurements of plasma exenatide concentrations for potential future analysis will be collected within the 30 min prior to the start of the standardized meal, according to the schedule presented in Section 9.1.2 and Section 9.1.3 of Appendix F of the CSP.

2. ANALYSIS SETS

2.1 Definition of analysis sets

2.1.1 All patients analysis set

The All patients analysis set will include all patients who provided written informed consent/assent, as relevant.

2.1.2 Randomized analysis set

The Randomized analysis set will include all randomized patients. Randomized patients will be analyzed in accordance to their planned treatment group.

2.1.3 Intent-to-treat (ITT) analysis set

The ITT analysis set will consist of all randomized patients who receive at least 1 dose of randomized study medication. ITT patients will be analyzed in accordance to their planned treatment group.

2.1.4 Evaluable analysis set

The Evaluable analysis set will consist of all randomized patients who receive at least 1 dose of randomized study medication and have at least 1 baseline and post-baseline HbA1c assessment. Evaluable patients will be analyzed in accordance to their planned treatment group.

2.1.5 Safety analysis set

The Safety analysis set will consist of all patients who received at least one dose of study medication.

All safety analyses on adverse events (AEs), clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide will be based on the safety

analysis set. Patients will be analyzed and presented in accordance to the actual treatment received, regardless of planned treatment assignment. If a patient randomized to the placebo arm receives at least one dose of EQW during the controlled assessment period, their actual arm will be derived as EQW.

2.1.6 Pharmacokinetic (PK) analysis set

The PK analysis set will consist of all patients who receive at least 1 dose of EQW, for whom at least 1 post-dose PK concentration assessment is available, and do not deviate from the CSP in ways that would significantly affect the PK analyses, as determined at the final protocol deviations meeting prior to unblinding of this study. Patients will be presented in accordance to the actual treatment received.

2.1.7 Standardized mixed meal test evaluable analysis set

The analysis set will consist of all ITT patients who provide informed consent/assent, as relevant, for the sub-study and participate in the Standardized Mixed-Meal Test, complete study procedures in compliance with the main CSP and the sub-study and have valid and adequate pharmacodynamic measurements (see CSP Appendix F, Section 10) for data analysis. Patients will be presented in accordance to their planned treatment group.

2.2 Violations and deviations

AstraZeneca use International Conference on Harmonization (ICH) E3 terminology for protocol deviations (PD), which are all important deviations related to study inclusion or exclusion criteria, conduct of the trial, patient management or patient assessment. Deviations and/or other factors that may greatly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being include, at a minimum, the following categories:

- Patients who do not meet the inclusion criteria and/or who meet one or more of the exclusion criteria (eligibility and entry criteria) but enter the study and are potentially randomized and treated.
- Patients who receive the incorrect randomized study medication at any time during the 24-week double-blind treatment period. In addition, patients assigned to the incorrect IVRS randomization stratification factor as compared to HbA1c test result at screening: Screening HbA1c strata (<9.0% or ≥9.0%)
- Patients who are not compliant with study medication administration requirements (dose, frequency and minimum exposure etc.). This criterion includes concomitant oral antidiabetic medication (SoC). Defined as:
    - Stable dose of an oral antidiabetic agent (metformin and/or sulfonylurea [SU]) and/or insulin for at least 2 months prior to screening for the subset of patients who are not treatment naïve.
- Patients taking concomitant medications not complying with:
    - Either is not treated with or has been on a stable treatment regimen with any of the following medications for a minimum of 1 month prior to Visit 1

(Screening):

- (a) Oral contraceptives (female patients)
- (b) Antihypertensive agents
- (c) Lipid-lowering agents
- (d) Thyroid replacement therapy
- (e) Antidepressant agents

- Patients who develop withdrawal criteria during the study but were not discontinued from study medication/study.
- Patients who do not comply with the protocol-specified assessments criteria (efficacy + safety).
- Patients who do not adhere to the protocol-specified visit schedule.
- Other factors, for example GCP violations, fraudulent data which will exclude patients at that level.
- Emergency unblinding during the 24-week double-blind treatment period.
- Discrepancies in IVRS versus electronic case report form (eCRF) randomization stratification factors.

Important protocol deviations (PDs or other underlying factors), as detailed in a separate PD plan, will be identified and documented by the study physicians and statisticians prior to unblinding of the data.

3. PRIMARY AND SECONDARY VARIABLES

3.1 Primary efficacy variable

The primary efficacy endpoint is change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24).

3.2 Secondary efficacy variables

The following are the secondary efficacy endpoints:

- Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in fasting plasma glucose concentration from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Proportions of patients achieving HbA1c goals of <6.5%, ≤6.5% and <7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit as applicable
- Change in body weight from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

- Change in fasting insulin from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments in EQW patients not taking insulin from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in lipids (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL] and triglycerides) from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in blood pressure (systolic and diastolic) from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Plasma exenatide concentrations at baseline Visit 2 (Week 0), Visit 7 (Week 24), Visit 10 (Week 52), and each intermediate visit, as applicable
- Proportions of patients discontinuing the study and the proportion of patients needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit as applicable

3.3 Exploratory efficacy variables

The exploratory efficacy endpoints are:

- Change in Body Mass Index (BMI) from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in body weight percentile and height percentile from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable. The height and weight percentile will be determined based on the standardized growth chart for boys and girls (developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion).

3.4 Safety variables

- Corresponding to the primary safety objective, safety and tolerability endpoints including the incidence of treatment emergent AEs (TEAEs; see section 4.2.4.1), antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Proportions of patients reporting different injection site reactions at Visit 3 (Week 4) through Visit 10 (Week 52) (see Section 4.2.4.2 for details of injection site reaction reporting)
- Change in calcitonin, pancreatic amylase, and lipase from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52)

- Change in Thyroid-stimulating hormone (TSH), thyroxine (free T4), prolactin, cortisol, insulin-like growth factor 1 (IGF-1), and Dehydroepiandrosterone (DHEAS) from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)
- Tanner pubertal stage at baseline Visit 2 (Week 0), Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52)

3.5 Exploratory safety variables

- Change in carcinoembryonic antigen (CEA) from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52)
- Change in bone specific alkaline phosphatase and N-telopeptide from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24) and Visit 10 (Week 52)
- Change in follicle-stimulating hormone (FSH), luteinizing hormone (LH), FSH/LH, total testosterone, sex hormone binding globulin (SHBG), and estradiol from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)
- Change in total testosterone and SHBG also at Visit 9 (Week 40). Free testosterone will be calculated from total testosterone and SHBG values at Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52).

3.6 Definition of study variables

Refer to Section 4.3 for details on conventions such as visit windowing and handling of duplicate efficacy assessments.

3.6.1 Study baseline

The baseline measurement is defined as the last non-missing (either numerical or character) value, including values from unscheduled visits, collected on or prior to the first dose of study medication in the double-blind treatment period. Assessments carried out on the date of first dose are assumed to have been done pre-dose unless time information indicates otherwise. In case of multiple measurements for a given variable with tied collection date or date/time, the mean of the values will be calculated for baseline. If the baseline value is missing for a given variable, change from baseline will be missing.

For change from baseline summaries of data collected during the extension period, the baseline value will not be rederived.

3.6.2 Change and percent change from baseline

Change from baseline to any randomized treatment period Week t is defined as follows:

$$C_{Week\ t} = M_{Week\ t} - M_{baseline},$$

Where:

- $C_{Week\ t}$ is the change from baseline at Week t,
- $M_{Week\ t}$ is the measurement at Week t,

- $M_{baseline}$ is the baseline measurement.

Percent change from baseline to any randomized treatment period Week t is defined as follows:

$P_{Week\ t} = 100 \times (M_{Week\ t} - M_{baseline}) / M_{baseline}$.

If the baseline value is zero, the percent change will be missing.

3.6.3 Early Termination visit

If a patient discontinues after randomization but prior to completion of the study treatment period, the patient will be invited to return as soon as possible to the study site for an early termination (ET) visit. Patients will be invited to return to the study site for an ET visit to collect HbA1c, fasting plasma glucose, body weight, and clinical safety laboratory measures. Patients who discontinue study medication prior to Visit 11 (Week 62/Study Termination) will also participate in the Extended Safety Follow-up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study-site visits prior to discontinuation of study medication.

3.6.4 Rescue therapy

Rescue therapy is defined as any new concomitant medication (see Section 4.2.1.4 for detail) with therapy reason given as “Protocol defined exacerbation of disease under study”.

A rescue episode will be defined as the first unique rescue therapy entry on the CM eCRF. If a patient has multiple entries on the CM form flagged as a rescue therapy, the first will be considered the point at which the patient was rescued.

Increases in insulin from baseline in patients receiving insulin at baseline will be programmatically derived from the CM CRF and reviewed by the clinical team prior to unblinding. Increases identified as potential rescue episodes will be queried at the site-level and therapy reason may be updated to “Protocol defined exacerbation of disease under study”.

For patients who require initiation of rescue therapy and continue study treatment, only data before initiation of rescue therapy will be included in the primary efficacy analysis. If HbA1c is measured before rescue therapy, then we will include the HbA1c measurement. If HbA1c is measured on the date of first rescue therapy but no time information is available to indicate if it was taken before rescue therapy, then HbA1c will be assumed to be prior and included in the primary efficacy analysis. Sensitivity analyses including data after initiation of rescue therapy will be carried out to test the robustness of the missing data assumption.

3.6.5 Study periods

The following definitions will be used to assign data to the correct study period. For details on which data will be presented in outputs for each endpoint, refer to Section 4.2.

3.6.5.1 Efficacy

Controlled assessment period: For efficacy parameters, the controlled assessment period will be defined as date of first dose of randomized study medication to date of the Week 24 visit, or the Early Termination visit for patients who discontinue the study prior to Week 24.

Extension period: For efficacy parameters, the start date of the extension period will be defined as date of first dose of open-label EQW + 1 day, in order to ensure assessments done on the Week 24 visit date are assigned to the controlled assessment period. The end date of the extension period will be defined as the Week 52 visit, or the Early Termination visit for patients who discontinue the study prior to Week 52. The extension period will only be defined for patients who enter the extension period and receive at least one dose of open-label EQW.

Treatment period: The treatment period for efficacy parameters will be defined as the controlled assessment period and extension period combined i.e. date of first dose of randomized study medication to date of Week 52 visit or Early Termination visit for patients who discontinue the study prior to Week 52.

See Section 4.1.3 for details on missing data handling.

3.6.5.2 Safety and concomitant medications

Adverse events, hypoglycemic events and concomitant medications on the date of first dose of open-label EQW (Week 24 visit) will be assigned to the extension period as this is considered a conservative approach. Other safety assessments at the Week 24 visit will be considered to have been carried out pre-dose and will therefore be assigned to the controlled assessment period. This is reflected in the definitions below.

Controlled assessment period:

- For patients who do not enter the extension period, the controlled assessment period will be defined as date of first dose of randomized study medication to date of last dose of randomized study medication + 7 days (or + 90 days after last dose of study medication for reporting of serious adverse events (SAEs) and other clinically significant or related AEs).

- For patients who go on to enter the extension period, the controlled assessment period for all safety parameters except AEs, hypoglycemic events and concomitant medications will be defined as date of first dose of randomized study medication to date of first dose of open-label EQW. For AEs, hypoglycemic events and concomitant medications, the controlled assessment period will be defined as date of first dose of randomized study medication to date of the first dose of open-label EQW – 1 day, in order for AEs, hypoglycemic events and medications recorded on the date of first dose of open-label EQW to be assigned to the extension period.

Extension period: For all safety parameters, except AEs, hypoglycemic events and concomitant medications, the extension period will be defined as date of first dose of open-

label EQW + 1 to date of last dose of open-label EQW + 7 days. For AEs, hypoglycemic events and concomitant medications, the extension period will be defined as date of first dose of open-label EQW to date of last dose of open-label EQW + 7 days (or + 90 days for SAEs and other clinically significant or related AEs). The extension period will only be defined for patients who enter the extension period and receive at least one dose of open-label EQW.

Treatment period: The treatment period for safety parameters will be defined as the controlled assessment period and the extension period combined i.e. date of first randomized study dose to the date of last dose of study medication + 7 days (randomized study medication for patients who do not enter the extension period or last dose of open-label EQW for patients who enter the extension period). For SAEs and other clinically significant or related AEs, the last dose of study medication + 90 days will be used for reporting.

See Section 4.1.3 for details on missing data handling.

3.6.5.3 Controlled assessment period treatment completion

A treatment completer for the controlled assessment period is defined as a patient who has a Week 24 assessment without discontinuing study medication for the controlled assessment period prior to the visit.

3.6.5.4 Controlled assessment period completion

A completer of the controlled assessment period is defined as a patient who has a Week 24 assessment regardless of study medication status at the visit.

3.6.5.5 Extension period treatment completion

A treatment completer for the extension period is defined as a patient who has a Week 52 assessment without discontinuing open-label EQW for the extension period prior to the visit.

3.6.5.6 Extension period completion

A completer of the extension period is defined as a patient who has a Week 52 assessment regardless of open-label EQW status at the visit.

3.6.6 Total daily insulin dose

Baseline total daily insulin dose will be calculated as the sum of available insulin doses taken in the 7 days prior to date of first dose of randomized study treatment, divided by 7. This is because it is not possible to ascertain whether insulin taken on date of first study treatment was pre or post dose.

Total daily dose for all post-baseline visits to Week 52 will be calculated as the sum of available insulin doses taken 6 days before and additionally including the target day of each visit (e.g. Week 4 total daily dose will be based on insulin taken on study day 29, plus the 6 days prior), divided by 7. If a subject is missing days with insulin records within the range, total daily dose will be set to zero for that day (i.e. absence of insulin implies the patient was

not taking insulin). For the Week 24 visit only, total daily dose will be calculated as 7 days prior to the Week 24 visit, divided by 7.

Overlapping records for short-acting insulin medications (i.e. multiple insulin records known to be received on the same day) will be summed to obtain the total daily dose on that day. Overlapping records for long-acting insulin medications will be queried to site. Where overlapping records of one day still occur, it will be assumed the new long-acting insulin dose started the day after the current long-acting insulin dose.

Only records with dose in units (IU) will be included in the derivation of total daily dose. Any medications identified as "Intermediate" will be classified under short-acting insulin medications.

For the purposes of derivation of total daily insulin dose, insulin records with completely missing start dates will have start date imputed as 7 days prior to first dose of randomized study treatment, except in the case where stop date of the medication is earlier than 7 days before first dose. Completely missing end dates will be imputed as date of last contact. Partial start and end dates will be imputed using the rules in Section 7.2.

3.6.7 Free testosterone

Free testosterone will be derived at each visit using the following equations steps:

N = 1 + Kalb*ALB/69000
a = N*Kshbg
b = N + Kshbg*(SHBG - TT)/10^9
c = -TT/10^9
FT = (-b + sqrt(b^2 - 4*a*c))/(2*a)*10^9

Where,

- Kalb is constant for albumin, defined as 3.6×10^4
- Kshbg is constant for SHBG, defined as 10^9
- ALB is albumin in g/L
- SHBG is sex hormone binding globulin in nmol/L
- TT is total testosterone in nmol/L
- FT is free testosterone

4. ANALYSIS METHODS

4.1 General principles

All statistical evaluations as well as summaries and tabulations will be done by qualified personnel at IQVIA. Before breaking the treatment codes, following clean file declaration (database lock), all decisions on the evaluability of the data for each individual patient will be made and documented, and each patient will be assigned to the appropriate analysis set.

Statistical analysis software (SAS) version 9.4 or later will be used to generate all statistical analyses, data summaries and listing.

4.1.1 Statistical notations and presentations

In general, all efficacy and safety variables will be summarized using descriptive statistics as appropriate. Continuous variables will be summarized by descriptive statistics (sample size (n), mean, SD, minimum, median and maximum). Quartiles 1 and 3 may be included for some parameters where appropriate. The mean and median will be presented with one more decimal place than the original data. Standard deviation with two more decimal places than the original data. Minimum and maximum values with the same number of decimal places than the original data. Categorical variables will be summarized using frequency tables (frequencies and percentages). Percentages will be rounded to 1 decimal place.

For log-transformed data, the following descriptive statistics will be presented: n, geometric mean, geometric coefficient of variation (GCV%), geometric standard deviation factor (GSD), arithmetic mean, standard deviation, coefficient of variation (CV%), median, minimum and maximum.

GCV (%) will be calculated as

$$100 \cdot \sqrt{\left(\exp\left(s^2\right)-1\right)}$$

where s is the SD of the data on a log scale.

Individual data will be presented in patient listings. All patient data listings will be sorted by treatment and patient ID.

In outputs, the following treatment labels will be used, except where data from the extension period are displayed:

Treatment group	**Label**
Exenatide 2mg	EQW
Placebo	Placebo

Summaries including data from the extension period will be presented by the controlled assessment period treatment group. The following treatment labels will be used:

Treatment group during controlled assessment period	**Label**
Exenatide 2mg	EQW
Placebo	Placebo -> EQW

4.1.2 Hypothesis testing significance level

All statistical tests will be conducted at a 2-sided significance level of 5% unless otherwise specified. Where appropriate, model-based point estimates, together with their 95% confidence intervals will be presented along with the 2-sided p-values for the tests. P-values will be rounded to 3 decimal places.

A hierarchy of the primary and selected secondary endpoints is defined in Section 4.2.3.2.

4.1.3 Handling of missing data

4.1.3.1 Missing efficacy data

Missing data in this study may result from patients discontinuing from the study prematurely or missing intermediate visits or selected assessments while remaining on study. Every effort will be made to obtain the CSP-required data for all study assessments that are scheduled for all patients who have been enrolled. Data collected after initiation of rescue therapy will be excluded from most efficacy analyses (see Section 4.2.3 for details) and therefore these data will effectively be handled as missing in analyses. For efficacy analyses, in general missing observations will not be imputed, except those inherited from the mixed model repeated measures (MMRM) which implicitly assumes that data are missing at random (MAR). A sensitivity for the primary analysis will be performed using pattern mixture model imputation for missing values and details of this imputation is provided in Section 4.2.3.4.

Missing at Random (MAR) refers to missingness that is independent of missing responses, conditionally on observed responses and covariates. As the imputation strategy should always consider the dropout patterns and the time-course of the efficacy measurements by treatment, the pre- and post- withdrawal values will be assessed to understand the impact of dropouts on the efficacy results. The primary efficacy endpoint of HbA1c data will be visually examined to explore the missingness patterns by (1) plotting each individual patient's HbA1c change trajectory in completers side-by-side with those who have prematurely discontinued study medication, and by (2) plotting the last HbA1c change from baseline for those who discontinue study medication prematurely, overlaid with the box plot of change from baseline in HbA1c by visit for completers.

For categorical endpoints HbA1c goals of <6.5%, ≤6.5% and < 7% at 24 weeks, any patient with missing HbA1c value at 24 weeks will be considered as failed to meet HbA1c <6.5%, ≤6.5% and < 7%, respectively, at endpoint (24 Weeks). The same will apply for these endpoints at 52 weeks endpoint.

4.1.3.2 Missing baseline and demographic data

For demographic and baseline characteristics, each variable will be analyzed and/or summarized using the available data. For continuous variables, missing data will be indicated in the "n" count and for categorical variables, unless indicated otherwise, percentages will be calculated out of the total number of patients with data available. A count of patients with missing data will be tabulated.

4.1.3.3 Missing safety data

Safety analyses will be conducted on the observed data only.

However, imputation of missing or partial AE and concomitant medication onset/start and end/stop dates will be used to determine the status of each AE and the previous/concomitant status of each medication. Refer to Appendix B1 and B2 for the method of imputation of missing/partial AE/concomitant onset/start and end/stop dates. Missing/partial start/stop dates will appear as is (i.e., without imputation) in the patient data listings, but will be imputed to permit the proper tabulation of AE and concomitant medications data.

4.1.3.4 Premature discontinuation

Patients who discontinue study medication prior to Visit 11 (Week 62/Study Termination) should enter the Extended Safety Follow-up Period, unless they have a height difference of less than 5 mm over a 6-month interval at study-site visits prior to discontinuation of study medication. Efficacy data are not collected during the Extended Safety Follow-up Period and this period will be reported separately to the primary clinical study report (CSR), so data beyond discontinuation of study medication will not be included in analyses.

Patients who discontinue the study prematurely should have all early termination visit procedures done at the time of study discontinuation.

4.1.4 Handling of data post rescue medication

Instances of patients meeting rescue criteria and subsequently receiving rescue medication will be recorded by sites as defined in Section 3.6.3.

A loss of glycemic control observed by either 1) an increase from baseline in HbA1c values by 1.0% or more that is confirmed at a subsequent clinic visit scheduled at the Investigator's discretion, or 2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home self-monitored blood glucose (SMBG), and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, will result in initiation of rescue medication. A clinic visit to confirm the values obtained by home SMBG or fasting/random glucose tests must take place within 2 weeks following the aforementioned self-measurements.

Patients meeting rescue criteria will be treated with antihyperglycemic therapy (e.g., insulin) by the Investigator or referred to their treating physician to seek conventional antihyperglycemic intervention. Patients meeting these criteria should remain in the study and continue to receive study medication, at the discretion of the Investigator. Acute decompensation due to an intercurrent illness treated briefly with insulin will be allowed for 2 weeks, if longer this should be considered as rescue medication.

Derivation of variables at initiation of rescue medication

Efficacy

In general, efficacy data are to be continuously collected during the glycemic rescue therapy. For all efficacy endpoints, except the plasma exenatide concentration endpoint, data collected after the first administration of rescue therapy will be excluded from the descriptive statistical summary and inferential statistical analyses.

However, data collected after initiation of rescue medication will be included in several sensitivity and supportive analyses for the primary analysis to provide a comprehensive view of the treatment effect (see more details in Section 4.2.3.4).

Safety

Because patients can continuously receive study medication concurrent with the rescue therapy, all safety data collected during the rescue medication treatment period will be summarized and analyzed together with those collected prior to the rescue therapy.

4.1.5 Statistical modelling

In general, continuous variables will be analyzed using a MMRM if multiple post-baseline measurements are required by CSP. The MMRM analysis will be treated as the primary analysis method for continuous efficacy endpoints. The statistical analysis of categorical variables will be done using a stratified Cochran-Mantel-Haenszel (CMH) test.

Standard diagnostic approaches will be used to verify that the key statistical assumptions of the MMRM and CMH test hold.

If the distributional assumptions of the MMRM for the primary analysis do not hold, alternative models will be explored using appropriate transformed data.

4.2 Analysis methods

4.2.1 Study disposition and baseline demographics

4.2.1.1 Patient disposition

Patient disposition information for all patients who provided informed consent, including counts and percentages of patients who completed the controlled assessment period and extension period will be summarized. Patients who discontinue study medication early and patients who discontinue the study early (including reasons for early discontinuation) during the controlled assessment and extension periods, will be summarized overall and by region and country for each treatment group, for all patients. The denominator for percentages will be the total number of patients in the randomized analysis set, overall and by treatment group. No percentage will be displayed for number of patients enrolled. A listing of patient disposition will be provided, including reasons for early discontinuation and reasons for IP discontinuation. A flow diagram of patient disposition will be presented.

The number and percentage of patients in each analysis set will also be reported overall and by treatment group. The denominator for percentages will be the total number of patients in the randomized analysis set, overall and by treatment group.

4.2.1.2 Demographics and baseline characteristics

Demographic and baseline characteristics will be summarized for the ITT and safety analysis sets overall and by treatment group as per below table.

Table 1 Analysis for demographics, baseline patient and disease characteristics

Demographic and baseline characteristics	Categories
Age (years), (continuous)	

Table 1 Analysis for demographics, baseline patient and disease characteristics

Demographic and baseline characteristics	Categories
Age group 1 (years), (categorical)	<10
	10 to 17
	>17
Age group 2 (years), (categorical)	<10
	10 to 12
	13 to 16
	> 16
Sex	Male
	Female
Race	White
	Black or African American
	Asian
	Native Hawaiian or Other Pacific Islander
	American Indian or Alaska Native
	Other
Ethnic Group	Hispanic or Latino
	Not Hispanic or Latino
Region	Europe
	Middle East
	North America
	South America
Country	Bulgaria
	Hungary
	Israel
	Mexico
	Ukraine
	USA
	Kuwait
Height (cm), (continuous)	

Table 1 Analysis for demographics, baseline patient and disease characteristics

Demographic and baseline characteristics	Categories
Weight (kg), (continuous)	
Body Mass Index (BMI) (kg/m2), (continuous)	
Height population percentile group (categorical)	<3
	3 to < 85
	85 to < 97
	> = 97
Weight population percentile group (categorical)	<3
	3 to < 85
	85 to < 97
	> = 97
BMI population percentile group (categorical)	<3
	3 to < 85
	85 to < 97
	> = 97
Baseline HbA1c (%), (continuous)	
HbA1c stratum (%), (categorical)	<9.0
	≥9.0
Duration of Diabetes (years), (continuous)	
Duration of Diabetes (years), (categorical)	< 1
	≥ 1 to ≤5
	>5
Baseline FPG (fasting plasma glucose), mg/dL, (continuous)	
Baseline FPG (fasting plasma glucose), mmol/L, (continuous)	
Baseline eGFR (mL/min/1.73^2) (continuous)	
Baseline eGFR (mL/min/1.73^2)	≥125
	<125

Table 1 Analysis for demographics, baseline patient and disease characteristics

Demographic and baseline characteristics	Categories
Baseline Tanner Stage	Stage 1
	Stage 2
	Stage 3
	Stage 4
	Stage 5

Patient's age (years) will be presented as collected on the DM eCRF at screening.

BMI will be calculated as the ratio of patient's baseline weight (in kilograms) to the square of the patient's height (in meters): BMI = kg/m². The Investigator-calculated BMI will not be summarized or listed. Height is collected in cm and will be converted to meters (by dividing by 100) before calculating BMI.

Percentile of body weight and percentile of height will be determined based on the standardized growth chart for boys and girls (developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (Center for Disease Control and Prevention, 2000).

Duration of diabetes (years) will be calculated using the informed consent date and the date of diabetes diagnosis (see below).

If date of diabetes diagnosis is…	Then duration of diabetes (years) is…
Complete date	(Date of informed consent – Date of diabetes diagnosis + 1) / 365.25
Partial date	
(a) Year and month are not missing, but day is missing	(a) Impute missing day 1st of the month, then use complete date rule
(b) Year is not missing, but month and date are both missing	
(b1) Year of diabetes diagnosis is different from the year of informed consent (b2) Year of diabetes diagnosis is the same as year of informed consent	(b1) Difference between year of diabetes diagnosis and year of informed consent (b2) 2/12 (2 months)

4.2.1.3 Medical/Surgical history

All medical/surgical history by each system organ class (SOC) and preferred term (PT) will be summarized by treatment group for the safety analysis set in accordance with the terminology

of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at database lock (DBL).

Percentages will be calculated out of the total number of patients in the analysis set displayed in the output, overall and by treatment group.

4.2.1.4 Concomitant medications

All medications will be coded using the latest version of WHO Drug Dictionary (WHODD) available at DBL.

Medications will be classified as:

- Pre-treatment medication: Medications stopped prior to first randomized dose of study medication.
- Prior concomitant medication:
    - Controlled assessment period: Medications started prior to and that continue past the first randomized dose of study medication.
    - Extension period: Medications started prior to the first EQW dose at Visit 7 (Week 24), that either stop or are ongoing in the extension period, continuing past Visit 7 (Week 24). Note, for patients receiving EQW during the controlled assessment period, this definition includes medications started during the controlled assessment period, prior to the first EQW dose at Visit 7 (Week 24) and continuing past Visit 7 (Week 24). These medications will be considered as "new concomitant' for the controlled assessment period in the tabulation of new concomitant medications (see below).
- New concomitant medication:
    - Controlled assessment period: Medications with a start date on or after the first randomized dose up to but not including Visit 7 (Week 24) for patients who enter the extension period. For patients who do not enter the extension period, medications initiated with a start date on or after the first randomized dose up to and including last dose of randomized study medication + 7 days. Hence, for patients who go into the extension period, any medications started on the date of the first open-label EQW dose will be assigned to the extension period.
    - Extension period: Medications with start date on or after Visit 7 (Week 24) up to and including last dose of open-label EQW + 7 days.
- Post-treatment medications: Medications that started the day after the last dose of study medication + 7 days. If the patient discontinues prior to Week 24, the last dose is the last dose of randomized study medication. If the patient discontinues during the extension period, the last dose is the last dose of open-label EQW.

The number and percentage of patients receiving prior concomitant and new concomitant medications will be summarized by treatment and Anatomical Therapeutic Chemical (ATC)

classification (level 4) for the ITT analysis set. The summary will be presented by study period (controlled assessment period and extension period).

Antidiabetic concomitant medications will be summarized separately by chemical/pharmacological/therapeutic subgroup (ATC level 4) and generic term in the same manner.

Background insulin therapy use during the study will be summarized as outlined in Section 3.6.5 for long-acting, short-acting and overall total daily insulin dose. Data collected after discontinuation of study medication will be excluded.

Rescue medications will be summarized during the controlled assessment period for the ITT analysis set and separately during the extension period separately for the subset of ITT patients who received open-label EQW.

A listing for rescue medications will be provided.

Pre-treatment medications and post-treatment medications will be summarized separately by treatment and ATC classification for the ITT analysis set.

Medications with start/stop dates that are partially/completely missing will be imputed as described in Appendix B2.

4.2.2 Overall compliance and extent of exposure

Treatment compliance (number of doses received relative to doses planned) will be summarized by treatment for the safety analysis set.

For the calculation of the compliance, the number of planned doses is defined as the duration of treatment exposure (in days) / 7, rounded to the highest integer.

Compliance will be presented for patients in the controlled assessment period (Week 0 to Week 24) for the Safety analysis set. It will also be presented for the Treatment period (see Section 4.1.1) in the subset of Safety patients who received open-label EQW. For this summary, PBO compliance will be calculated based on EQW exposure. Treatment compliance for controlled assessment period of 24 weeks will be calculated for each patient using the total number of doses received divided by the number of planned doses. Treatment compliance for the Treatment period will be calculated for each patient using the total number of EQW doses received divided by the number of planned EQW doses. Percent compliance will then be categorized to <80%, 80% to <120%, and ≥120% and summarized by treatment group.

The total number of doses received will be calculated as the total number of used/ partially used vials returned, based on returned used/unused study medication data collected in the eCRF page at each visit.

The total number of medication packets dispensed will be calculated from the study medication dispensation information collected on the DA eCRF.

Exposure will be presented for patients in the controlled assessment period (Week 0 to Week 24) for the Safety analysis set. Separately, it will be summarized for the subset of Safety patients who received open-label EQW for the Treatment period based on EQW exposure.

The following will be used to calculate the duration of exposure, in days:

- Duration of EQW exposure for EQW patients during the Treatment period = Date of Last Injection of Study Medication - Date of First Injection of Study Medication + 7;
- Duration of EQW exposure for PBO patients who enter the extension period = Date of Last Injection of EQW - Date of First Injection of EQW + 7;
- Duration of PBO/EQW exposure during the controlled assessment period = Date of Last Injection of Study Medication during the controlled assessment period - Date of First Injection of Study Medication during the controlled assessment period + 7

Dose interruptions will not be taken into consideration for calculation of duration of exposure.

The mean, SD, median, minimum, and maximum duration of exposure will be provided by treatment group. Extent of exposure will also be categorized into fixed intervals as follows, with number of patients and percentage summarized by treatment group:

- For the summary of exposure during the controlled assessment period, intervals are defined: 1-13, 14-27, 28-55, 56-83, 84-111, 112-139, 140-167, ≥168 days
- For the summary of exposure during the treatment period, intervals are defined: 1-13, 14-27, 28-55, 56-83, 84-111, 112-139, 140-167, 168-195, 196–223, 224-251, 252-279, 280-307, 308-335, 336-363, ≥364 days

In addition, the extent of exposure will also be summarized by country for both the controlled assessment period and the Treatment period.

4.2.3 Efficacy analysis

4.2.3.1 Estimands

Estimands for the study are defined in Table 2. Intercurrent events (IE) that may occur during the study are receipt of rescue therapy, IP discontinuation and study withdrawal.

Table 2 Estimand framework

	Attributes			
Estimand	Population	Variable	Intercurrent event strategy	Population-level summary
Primary	Evaluable	Change in HbA1c from baseline to Week 24	Rescue and IP discontinuation: Data after event excluded. Hypothetical approach due to missing at random (MAR) assumption of MMRM analysis. Withdrawal from study prior to Week 24: Hypothetical approach due to MAR assumption of MMRM analysis.	Least squares mean difference in CFBL at W24 between EQW and PBO
Sensitivity to primary	Evaluable	Change in HbA1c from baseline to Week 24	All IEs: Data after event excluded. Hypothetical approach using multiple imputation (MI) pattern mixture model imputation.	Least squares mean difference in CFBL at W24 between EQW and PBO

Supplementary to primary	Evaluable	Change in HbA1c from baseline to Week 24	Rescue and IP discontinuation: Data after event included. Treatment policy approach. Withdrawal from study prior to Week 24: Hypothetical approach due to MAR assumption of MMRM analysis.	Least squares mean difference in CFBL at W24 between EQW and PBO
Sensitivity to supplementary of primary	Evaluable	Change in HbA1c from baseline to Week 24	Rescue and IP discontinuation: Data after event included. Treatment policy approach. Withdrawal from study prior to Week 24: Hypothetical approach using MI pattern mixture model imputation.	Least squares mean difference in CFBL at W24 between EQW and PBO
Secondary 1	Evaluable	Change in HbA1c from baseline to Week 24 and each intermediate visit	Rescue and IP discontinuation: Data after event excluded. Hypothetical approach due to MAR assumption of MMRM analysis. Withdrawal from study prior to Week 24: Hypothetical approach due to MAR	Least squares mean difference in CFBL at Week 24 and each intermediate visit.

			assumption of MMRM analysis.	
Secondary 2	Evaluable	Proportions of patients having HbA1c goals of <6.5%, ≤6.5% and <7.0% at Week 24 and at each intermediate visit	Rescue and IP discontinuation: Data after event excluded. Composite approach used, with patients with missing data at endpoint treated as non-responders. Withdrawal from study prior to Week 24: Composite approach used, with patients with missing data at endpoint treated as non-responders.	Difference in proportion of responders at Week 24 and each intermediate visit between EQW and PBO
Sensitivity to secondary 2	Evaluable	Proportions of patients having HbA1c goals of <6.5%, ≤6.5% and <7.0% at Week 24 and at each intermediate visit	Rescue and IP discontinuation: Data after event excluded. Hypothetical approach using MI pattern mixture model imputation. Withdrawal from study prior to Week 24: Hypothetical approach using MI pattern mixture model imputation.	Difference in proportion of responders at Week 24 and each intermediate visit between EQW and PBO
Other continuous secondary endpoints	ITT	Change in X from baseline to Week 24 and each intermediate visit	Rescue and IP discontinuation: Data after event excluded. Hypothetical approach due to MAR	Least squares mean difference in CFBL at Week 24 and each intermediate visit, as applicable.

			assumption of MMRM analysis. Withdrawal from study prior to Week 24: Hypothetical approach due to MAR assumption of MMRM analysis.	
Exploratory	Safety	Change in eGFR from baseline to Week 24 and each intermediate visit by baseline eGFR category	Rescue and IP discontinuation: Data after event excluded. Hypothetical approach due to MAR assumption of MMRM analysis. Withdrawal from study prior to Week 24: Hypothetical approach due to MAR assumption of MMRM analysis.	Least squares mean difference in CFBL at Week 24 and each intermediate visit.
Sensitivity to exploratory	Safety	Change in eGFR from baseline to Week 24 and each intermediate visit by baseline eGFR category	Rescue: Data after event included. Treatment policy approach. IP discontinuation: Data after event excluded. Hypothetical approach due to MAR assumption of MMRM analysis.	Least squares mean difference in CFBL at Week 24 and each intermediate visit.

			Withdrawal from study prior to Week 24: Hypothetical approach due to MAR assumption of MMRM analysis.	

4.2.3.2 Hierarchical testing strategy

To protect the family-wise error rate for the primary endpoint and secondary endpoints, a fixed sequence procedure hierarchical testing strategy will be followed i.e., only if superiority for the primary endpoint is established at the significance level $\alpha = 0.05$ two-sided, the superiority test for the selected secondary endpoints will be tested in the order specified, also at the significance level $\alpha = 0.05$ two-sided. Endpoints will be tested in the following order:

1. Change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24).
2. Change in fasting plasma glucose concentration from baseline Visit 2 (Week 0) to Visit 7 (Week 24)
3. Change in body weight from baseline Visit 2 (Week 0) to Visit 7 (Week 24)
4. Change in fasting insulin from baseline Visit 2 (Week 0) to Visit 7 (Week 24)

If the null hypothesis is not rejected for any of the first four tests in the hierarchy, for remaining endpoints a p-value will be presented in outputs but will be considered exploratory and inferences will not be drawn.

For all other secondary and exploratory endpoints, p-values will be presented but these will be considered exploratory in nature with no multiplicity adjustment applied. A nominal level of $\alpha = 0.05$ will be used for inference.

4.2.3.3 Analysis of primary variable

The MMRM analysis of the primary endpoint in the Evaluable population will be considered the primary analysis.

The primary efficacy analysis will compare treatment groups (EQW vs. PBO) with respect to change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 7 (Week 24) by using the MMRM approach. The model will include change in HbA1c as the dependent variable and treatment group, visit, interaction between visit and treatment, region, baseline HbA1c and interaction between visit and baseline HbA1c as the fixed effects. The variance - covariance structure to be used for this modelling will be unstructured (UN); if the model does not converge with unstructured variance – covariance matrix, then autoregressive order 1 (AR [1]) and heterogeneous autoregressive order 1 (ARH [1]) structures will be tried and the covariance structure will be decided based on model convergence status and the Akaike information criterion. The restricted maximum likelihood (REML) method will be used for parameter estimation, and the Kenward-Roget adjustment will be applied (ddfm=KR option in SAS PROC MIXED model statement. The least squares (LS) mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between the EQW and PBO groups at Visit 7 (Week 24) will be provided. The mean (SD) observed HbA1c at baseline and Week 24 will also be given by treatment group.

HbA1c data from post-baseline visits (including Early Termination) will be included in the MMRM analysis. See Section 4.1.3 for details on missing data handling.

For patients who initiate rescue medication or discontinue IP and continue study participation, only data before initiation of rescue medication or up to and including date of discontinuation from IP will be included in the MMRM analysis. If there is evidence that a measurement was taken prior to initiation of rescue medication, then this data will be included. If the measurement was taken on the date of initiation of rescue medication but time information is not available, then the measurement will be included. Namely, the data after initiation of rescue medication or after premature IP discontinuation will be excluded from the primary analysis.

Summaries and descriptive analysis of the primary endpoint will be performed using the Evaluable analysis set.

Subgroup analyses of primary endpoint

The primary endpoint, change from baseline in HbA1c at week 24, will be summarized descriptively for subgroups of interest listed below. Observed and change from baseline in HbA1c by visit will be presented. No statistical analyses will be conducted.

- HbA1c baseline strata (<9.0% or ≥9.0%)
- Age group: <10, 10 to 17, and >17.
- Country
- Region (North America (USA), South America (Mexico), Europe (Israel, Hungary, Bulgaria, Ukraine), Middle East (Kuwait))
- Sex –Male/Female
- Race
- Baseline BMI Percentile <3, 3-<85, 85-<97, >=97

BMI percentile will be calculated using height and weight data collected on the CRF. The SAS macro from CDC website listed below will be used to calculate BMI percentile and the method provided on the website will be followed for analysis.
https://www.cdc.gov/nccdphp/dnpao/growthcharts/resources/sas.htm.

4.2.3.4 Sensitivity and supplementary analyses for primary endpoint

To further support the primary endpoint analysis and to examine the influence of missing data due to drop-out and/or receiving rescue therapy, sensitivity and supplementary estimands described in Section 4.2.3.1 are defined and will be addressed using an MMRM analysis at Week 24.

The MMRM model that will be used for analyzing the change in HbA1c will include treatment group, visit, interaction between visit and treatment, region, baseline HbA1c and interaction between visit and baseline HbA1c as the fixed effects. The variance - covariance structure to be used for this modelling will be the same as used for the primary analysis. The LS mean in each treatment group at Week 24, the standard error (SE), and the corresponding 95% CI, as well as the LS mean difference between treatment groups, the SE, the 95% CI, and

the p-value, will all be derived and presented from the MMRM model. The mean (SD) observed HbA1c at baseline and Week 24 will also be given by treatment group.

In addition, an imputation sensitivity analysis will test the assumption of MAR that is made by the MMRM analysis. For this purpose, a model that assumes missing not at random (MNAR) will be used, whereby assumptions for the missing data "stress test" the MAR assumptions of the primary analysis, by positing outcomes that, while clinically plausible, are likely to be worse for the EQW group than the outcomes assumed by MAR. A plausible stress test could assume that the outcome for the EQW treatment is somewhat worse than would be predicted by MMRM from the study data. Such a stress test would appropriately disadvantage the estimate of treatment effect, compared to the estimate of the primary analysis. In this way the MAR assumption of the primary analysis could be stress tested.

The proposed MNAR sensitivity analysis assumes that the trajectory after the intercurrent event from the EQW group, regardless of the type of event, can be modelled by that of PBO patients. This assumption will tend to result in smaller estimates of difference between the treatment groups, compared to those under the MAR assumption, and as such constitutes a reasonable stress test of the MAR assumption. Note that this approach constitutes a pattern mixture model as defined by Molenberghs and Kenward[4]. The patterns here are defined by the time of the intercurrent event, with the imputed values for both treatment groups modeled by observed outcomes from the placebo group only. Specifically, for a patient with missing/excluded observations after visit t, imputed value for the change from baseline at visit t+n will be based on a model estimated from all in the control group who have an outcome observed at visit t+n conditioning on that patient's outcomes up to and including visit t. Then, the overall estimate of treatment effect is obtained by using Rubin's rules to combine the imputed outcomes. Note that in this analysis, PBO missing/excluded observations are imputed assuming MAR and here follows the pattern of observed PBO observations, while missing/excluded observations for the EQW group are assumed MNAR. This strategy for imputation is commonly referred to as the Copy-Reference approach.

In summary, the pattern mixture models will be implemented by multiple imputation via the following steps;

Step 1: Non-monotone missing data (usually relatively infrequent) will be imputed using the MCMC statement of SAS PROC MI under the MAR assumption. The following variables will be included in the imputation model: treatment, region and HbA1c measurements from baseline to Week 24. Note: Dummy variables will be used for treatment and region. This will create a monotone missing pattern in the dataset within each treatment group. This step will create 1000 imputed datasets.

Step 2: Then the values for each pattern will be imputed via the sequential regression method, using SAS PROC MI statement MONOTONE REG. The imputation model will be estimated from the observed data in the PBO group and it will be used to impute missing/excluded observations in both treatment groups using the MNAR statement of SAS PROC MI. The following variables will be included in the imputation model: region and HbA1c measurements from baseline to Week 24.

Step 3: The imputed data from Step 1 and Step 2, along with observed data will be analyzed using the same MMRM model for the outcome of week 24 change from baseline as for the primary analysis. The estimates from multiple imputed datasets will be combined using Rubin's combination rules for statistical inference[5] (using PROC MI ANALYZE).

The seed used will be 88281 for both steps 1 and 2.

4.2.3.5 Analysis of secondary variables

Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment for the ITT analysis set during the controlled assessment period and separately for the subset of ITT patients who received open-label EQW during the extension period for the Treatment period (see Section 3.6.5 for Treatment period definition), unless otherwise stated.

Similar to the primary analysis, data including the Early Termination visit where applicable will be included in the MMRM and CMH analysis for secondary analysis variables. Data collected from an Early Termination visit will be mapped to the next closest scheduled visit. For patients who initiate rescue medication and continue study participation, data collected after the initiation of rescue medication will be excluded from analyses. Data collected after discontinuation of IP will be excluded from analyses for all secondary efficacy endpoints.

Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each intermediate visit as applicable

The MMRM method for change in HbA1c will be used until Week 24 and to each intermediate visit, using the Evaluable analysis set, which is the same approach as stated in Section 4.2.3.3.

The least squares mean (LSM) change from baseline and SE bar by visit will be presented in a figure by treatment group. The p-value for the difference between treatment groups by visit will also be provided in the figure.

The observed values and change from baseline will be summarized by visit using descriptive statistics (mean, median, standard deviation, minimum, maximum). This will be provided separately for both the Evaluable analysis set during the controlled assessment period and for the subset of Evaluable patients who received open-label EQW during the extension period analysis set for the Treatment period.

HbA1c measures will be listed.

Change in fasting plasma glucose concentration, body weight, fasting insulin, lipids, blood pressure from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

The same MMRM approach will be used to analyze the change in body weight, blood pressure, fasting plasma glucose, and fasting insulin from baseline (Week 0) to Week 24, and each intermediate visit.

The least squares mean (LSM) change from baseline and SE bar by visit will be presented in a figure by treatment group. The p-value for the difference between treatment groups by visit will also be provided in the figure.

The observed values and change from baseline will be summarized by visit using descriptive statistics (mean, median, standard deviation, minimum, maximum) for body weight, blood pressure, fasting plasma glucose, fasting insulin and lipids. This will be provided separately for both the ITT analysis set during the controlled assessment period and for the subset of ITT patients who received open-label EQW during the extension period for the Treatment period.

The models for changes in body weight, blood pressure, fasting plasma glucose, and fasting insulin will include treatment group, visit, interaction between visit and treatment, region, baseline of the dependent variable, interaction between visit and baseline of the dependent variable and screening HbA1c strata (<9.0%, ≥9.0%) as the fixed effects. The REML method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be provided.

FPG, body weight, fasting insulin, lipids and blood pressure (systolic and diastolic) will be presented in listings.

Proportions of patients achieving HbA1c goals at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit

Proportions of patients having HbA1c goals of <6.5%, ≤6.5% and <7.0% at Week 24 and at each intermediate visit will be compared between treatments using the Evaluable analysis set via the CMH procedure, in which screening HbA1c strata (<9.0%, ≥9.0%) will serve as the stratification factors.

A bar chart of the percentage of patients achieving HbA1c goals of <6.5%, ≤6.5% and <7.0% by visit and treatment group will be provided along with p-values.

Any Evaluable patient without HbA1c value at the endpoint will be considered as not achieving HbA1c goal at endpoint. The denominator will be the total number of Evaluable patients in a treatment group, and the numerator will be the number of patients achieving HbA1c <6.5%, ≤6.5% and <7.0%.

As a sensitivity analysis also in the Evaluable analysis set, the probabilities of patients reaching HbA1c targets of <6.5%, ≤6.5% and <7.0% will be analyzed to Week 24 using the CMH procedure, with missing data imputed using MI pattern mixture model imputation. HbA1c strata (<9.0%, ≥9.0%) will serve as the stratification factors. The imputed HbA1c data for the sensitivity analysis of the primary endpoint (Section 4.2.3.4) will be used for this analysis.

The number and percentage of patients having HbA1c target values of <6.5%, ≤6.5% and <7.0% will be summarized by visit and treatment group. This will be provided separately for both the Evaluable analysis set during the controlled assessment period and for the subset of Evaluable patients who received open-label EQW during the extension period for the Treatment period.

Proportions of patients discontinuing the study, needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit

A Kaplan-Meier table and corresponding figure of time to rescue will be provided. Patients who are not rescued will be censored at Week 24 visit or last dose of study medication for those who discontinue study treatment for reasons unrelated to lack of glycemic control, as indicated by an adverse event withdrawal that required rescue medication prior to Week 24 visit.

The number and percentage of patients needing rescue due to failure to maintain glycemic control will be summarized by visit according to the windows defined in Section 4.3.1. This will be provided separately for both the ITT analysis set during the controlled assessment period and for the subset of ITT patients who received open-label EQW during the extension period for the Treatment period. The number of patients included at each analysis visit will be derived by including patients in the counts at every visit up to study completion date or date of last dose of study medication for patients who prematurely discontinue study medication.

Data collected after study treatment discontinuation will be excluded from summaries.

The proportion of patients discontinuing the study will be presented in the disposition table, by study period.

Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments in patients not taking insulin from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

The same MMRM approach will be used to analyze the change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments in patients not taking insulin from baseline Visit 2 (Week 0) to Week 24, and each intermediate visit.

The least squares mean (LSM) change from baseline and SE bar by visit will be presented in a figure by treatment group. The p-value for the difference between treatment groups by visit will also be provided in the figure.

The observed values and change from baseline for these parameters will be summarized by visit using descriptive statistics (mean, median, standard deviation, minimum, maximum). This will be provided separately for both the ITT analysis set during the controlled assessment period and for the subset of ITT patients who received open-label EQW during the extension period for the Treatment period.

The effects of the study medications on HOMA will be examined. The pancreatic beta-cell function (HOMA-B) and peripheral and hepatic insulin sensitivity (HOMA-S) will be computed from a computerized HOMA model, which can predict the plasma glucose, insulin, c-peptide, and proinsulin concentrations for any possible combination of these 2 parameters in the fasting state in patients not taking insulin.

HOMA-B and HOMA-S will be computed from a computerized HOMA model, the HOMA Calculator[2]. The HOMA Calculator, developed by Diabetes Trials Unit at the Oxford Center for Diabetes, Endocrinology, and Metabolism, is a computer algorithm that that takes account of variations in hepatic and peripheral glucose resistance, increases in the insulin secretion curve for plasma glucose concentrations above 10 mmol/L (180 mg/dL), and the contribution of circulating proinsulin (e.g., C-peptide) to estimate the steady state beta-cell function and insulin sensitivity, as percentages of a normal reference population. The model assumes %HOMA-B and %HOMA-S values of 100% in normal young adults as a recalibration.

All HOMA parameters will be analyzed on a logarithmic scale (natural logarithmic transformation), and then back-transformed to the original scale for result presentation using the following formulae:

Geometric Mean= exp(mean(log (X)))

SE of Geometric Mean = Geometric Mean* SE of Mean (log (X))

LS means will be back-transformed in the same way.

Separate tables of back-transformed and non-transformed results will be provided.

Homeostasis results will be listed.

Plasma exenatide concentrations at baseline Visit 2 (Week 0), Visit 7 (Week 24), Visit 10 (Week 52), and each intermediate visit, as applicable.

Descriptive statistics (geometric mean, geometric coefficient of variation: GCV %, geometric standard deviation factor: GSD, arithmetic mean, standard deviation, coefficient of variation: CV %, median, minimum, maximum) will be presented by visit and controlled assessment period treatment group for the PK analysis set.

The geometric mean plasma exenatide concentration with GSD bars will be plotted over time by treatment group.

Plasma exenatide concentrations will be listed.

4.2.3.6 Analysis of exploratory variables

Analysis of all exploratory endpoints will be performed in the ITT analysis set unless otherwise specified. Baseline values, the values at each visit, and changes from baseline values will be summarized for percentiles of body weight, percentile of height, and BMI by treatment.

Change in BMI from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit

A similar MMRM modeling approach will be implemented to compare changes in BMI between treatment groups from Visit 2 (Week 0) to Week 24, and each intermediate visit.

The least squares mean (LSM) change from baseline and SE bar by visit will be presented in a figure by treatment group. The p-value for the difference between treatment groups by visit will also be provided in the figure.

The observed values and change from baseline will be summarized by visit using descriptive statistics (mean, median, standard deviation, minimum, maximum). This will be provided separately for both the ITT analysis set during the controlled assessment period and for the subset of ITT patients who received open-label EQW during the extension period for the Treatment period.

Change in BMI percentile from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit

Observed and change from baseline in BMI percentile will be summarized by visit using descriptive statistics (mean, median, standard deviation, minimum, maximum). This will be provided separately for both the ITT analysis set during the controlled assessment period and for the subset of ITT patients who received open-label EQW during the extension period for the Treatment period.

Change in body weight percentile and height percentile from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit

The height and weight percentile will be determined based on the standardized growth chart for boys and girls (developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion). For this purpose, the percentile values for weight and height will be calculated using the growth chart tables on CDC[3] using the raw data available for weight and height. The growth chart tables for boys' and girls' population will be used separately for 3rd to 97th percentile.

A MMRM modeling approach will be implemented to compare changes in body weight percentile, and height percentile between treatment groups from Visit 2 (Week 0) to Week 24, and each intermediate visit.

The least squares mean (LSM) change from baseline and SE bar by visit will be presented in figures by treatment group. The p-value for the difference between treatment groups by visit will also be provided in the figure.

The observed values and change from baseline for body weight percentile and height percentile will be summarized by visit using descriptive statistics (mean, median, standard deviation, minimum, maximum). This will be provided separately for both the Evaluable analysis set during the controlled assessment period and for the subset of Evaluable patients who received open-label EQW during the extension period for the Treatment period.

4.2.4 Safety and tolerability analysis

Analysis of safety data will be performed using the Safety analysis set. All safety and tolerability variables such as examination of AEs, clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide will be summarized descriptively by treatment groups. Observations post-rescue will be included for safety analyses.

For all safety endpoints summary tables will be presented by visit to Week 52, and where applicable also for the 10-week follow-up, for each treatment group. Continuous variables (observed, change from baseline, laboratory and vital signs parameters) will be summarized by visit using number, mean, median, standard deviation, minimum and maximum for each

treatment group. Categorical variables (incidence of AEs, antibodies, physical examination, Tanner pubertal stage) will be summarized by visit in the form of number and percentage (%) for each treatment group.

A listing of Tanner pubertal stage data will also be provided.

4.2.4.1 Adverse event analysis

Adverse events (AE) will be classified in accordance to the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. All adverse events will be coded using the latest available version of MedDRA by the database lock.

Treatment-emergent AEs (TEAE) are defined as AEs occurring after the first dose of study medication through the end of the treatment plus 7 days (or + 90 days for SAEs and other clinically significant or related AEs), including AEs collected after patients initiate glycemic rescue therapy.

AEs occurring after Study Termination but considered by the Investigator as clinically significant and as related to study medication or study procedure, and SAEs occurring within 90 days of the last administration of study medication or EQW if in the extension phase will be recorded on the AE eCRF and reported in the AE listing.

Any AE that is recorded as the reason for study discontinuation will be considered an adverse event leading to discontinuation (DAE) regardless of the date recorded. All DAEs will be reported regardless of when they occurred. Note, any AE that is a DAE under these rules will also count as an AE when reporting.

Off-treatment AEs will be defined for the following:

- Treatment completers to Week 52: An AE that occurs between Week 52 to Week 62 and starts the day after last dose of open-label EQW + 7 days (or + 90 days for SAEs and other clinically significant or related AEs). Only patients completing study medication to Week 52 will be considered. Patients completing study medication to Week 52 but who withdraw prior to Week 62 will also be included.

- Premature discontinuation: An AE that starts the day after last dose of study medication + 7 days (or + 90 days for SAEs and other clinically significant or related AEs), for patients who discontinue study medication before Week 24 or Week 52.

AEs for the combined periods are those that occur during the Treatment period or post-treatment.

AEs with a start date prior to the first administration of study medication will be classified as pre-treatment (non-treatment emergent).

AEs with a stop date prior to the date of the first administration of study medication will be classified as pre-treatment (non-treatment emergent) AEs.

In case of missing AE severity, AE causality, or AE seriousness, a worst-case approach will be used. For AE missing severity, the AE will be considered severe; for missing causality, the

AE will be considered as possibly-related to study medication; for missing seriousness, the AE will be considered serious.

On-treatment AEs (TEAEs) will be summarized for 24-week controlled assessment period and 28-week extension period as defined below. Off-treatment AEs for treatment completers to Week 52 will be tabulated where required. Off-treatment AEs for patients who prematurely discontinued will be listed only.

An overall summary of number and percentage of patients experiencing at least 1 TEAE will be presented for EQW and PBO. The summary will be presented by study period (controlled assessment period and extension period). A summary of AEs during the Treatment period for patients with actual treatment EQW during the controlled assessment period will be provided. The AE summary will include the number and percentage of patients experiencing any AE, any SAE, any AE related to treatment per Investigator's discretion, any AE leading to treatment discontinuation, any AE leading to study withdrawal, and any fatal AE.

Additionally, all TEAEs will be summarized for each treatment group as follows:

- AEs summarized by SOC, PT, maximum intensity (Mild, Moderate, Severe), causality (Not related, Related), action taken, and outcome.
- SAEs summarized by SOC and PT, maximum intensity (Mild, Moderate, and severe), causality (Not related, Related).
- AEs leading to treatment discontinuation summarized by SOC and PT.
- Frequent AEs (AE with at least 5% incidence in any treatment) summarized by preferred term.
- Non-serious frequent AEs summarized by SOC and PT.
- Potentially immune-related AEs summarized by antibody status (positive versus negative), SOC and PT.
- Potentially immune-related AEs summarized by antibody titer (higher: ≥625 versus low: <625), SOC and PT.
- Potentially immune-related injection site-related AEs summarized by SOC and PT.

Summaries by maximum intensity will be presented separately for the controlled assessment period (Safety analysis set) and extension period (subset of Safety patients who received open-label EQW during the extension period). All other AE summary tables will be presented by study period in a single table.

Potentially immune-related AEs will be identified using the PTs given in Appendix B4.

Injection site-related AEs will be identified using AEs within higher-level term "Injection site reactions".

Tables of key patient information for SAEs and AEs leading to discontinuation of study medication will be provided. Adverse events will be listed.

The number of AEs and number of SAEs will be summarized for the controlled assessment period and extension period.

The denominator for summaries will be the number of patients included in the analysis set by treatment group and total. Where the controlled assessment period and extension period are presented side-by-side in the same summary, the denominator for the controlled assessment period will be the number of patients in the Safety analysis set by treatment group and total; the denominator for the extension period will be the number of patients in the subset of Safety patients who received open-label EQW during the extension period by treatment group and total.

4.2.4.2 Injection-site reactions

Proportions of patients reporting different injection site reactions at Visit 3 (Week 4) through Visit 10 (Week 52).

Injection-site reactions will be identified from the AE dataset using the higher-level term (HLT) "Injection site reactions". Injection-site reactions reported on the INJECT eCRF will not be included in summaries as this eCRF was introduced part-way through the study and therefore does not provide a complete picture of the number of injection-site reactions. Data reported on the INJECT form will be listed only.

The number and percentage of patients reporting different injection site reactions, per the AE dataset, will be summarized by visit (see Section 4.3.3 for details on visit windows for injection site reactions). This will be provided separately for both the Safety analysis set during the controlled assessment period and for the subset of Safety patients who received open-label EQW during the extension period for the Treatment period. The injection site reactions will be additionally repeated by injection device type i.e. pre-filled syringe or dual-chamber pen. All patients randomized to the study on or after 12th August 2018 are dispensed dual chamber pen devices.

4.2.4.3 Drug-induced liver injury

Number and percentage of patients meeting potential Hy's laws criteria (aspartate aminotransferase [AST] or alanine aminotransferase [ALT] ≥3x upper limit of normal [ULN] and total bilirubin [TB] ≥2x ULN) at any point during the Treatment period or follow-up period will be presented in a summary table by visit and treatment group for Safety analysis set. Similarly, a table with key patient data for patients with combined ALT or AST, and TB, elevations will be presented.

4.2.4.4 Clinical laboratory

Continuous clinical laboratory parameters will be summarized in standardized international (SI) and US conventional units.

For quantitative measurements, observed values and changes from baseline to each post-baseline visit will be determined by visit windows described in Section 4.3.1 and 4.3.3.

All hematology, clinical chemistry, growth and development hormones and urinalysis results will be listed by treatment group, patient, and visit, including scheduled and unscheduled/repeat measurements. Laboratory assessments that are outside of normal ranges will be flagged.

Baseline values, the observed values at each visit to Week 52 and including the 10-week follow-up, as well as change from baseline values will be summarized for each of the quantitative laboratory assessments by treatment group. Additionally, listings by individual patients' data will be reported as appropriate.

Clinical laboratory results (chemistry, hematology, growth and development hormones and urinalysis) will be summarized using descriptive statistics for each visit. Shift from baseline to the minimum/maximum value during treatment will be presented for the controlled assessment period and extension period, separately, based on high/low/normal findings for clinical laboratory parameters if normal ranges are available (for quantitative measurements and categorical measurements). For the categorical Urine-Blood parameters, a shift table from baseline to every planned visit will be performed. For the categorical measurements Urine Glucose, Ketones and Urine Total Protein, results will be presented under the following categories: 0, trace, +1, +2, +3.

Number and percentage of laboratory results that are potentially clinically significant (see Appendix B3) will be summarized by analyte name and criteria for each treatment group.

Estimated glomerular filtration rate will be derived based on the Bedside Schwartz formula:

eGFR = 41.3 * (Height in meters / Serum creatinine in mg/dL)

A table of observed and change from baseline in eGFR values will be provided. This will be provided both overall and by baseline eGFR, hyperfiltrating versus non-hyperfiltrating, where hyperfiltration is defined as an eGFR ≥125 ml/min/1.73m^2).

A MMRM analysis of change in eGFR from baseline to Week 24 and each intermediate visit by baseline eGFR (hyperfiltrating: ≥125 ml/min/1.73m^2 versus non-hyperfiltrating: <125 ml/min/1.73m^2) will be provided. The same approach as stated in Section 4.2.3.3 will be used. The model will include treatment group, visit, interaction between visit and treatment, region, screening HbA1c strata (<9.0%, ≥9.0%), baseline eGFR, and interaction between visit and baseline eGFR as the fixed effects. The REML method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be presented. This analysis will be done both excluding data after initiation of rescue therapy and separately including data after initiation of rescue therapy.

A shift table from baseline UACR category to highest post-baseline UACR category will be provided for the controlled assessment period and extension period, separately. Categories are defined as follows:

- <30 mg/g (Normal)
- ≥30 mg/g and ≤300 mg/g (Micro or moderately increased albuminuria)
- >300 mg/g (Macro or severely increased albuminuria)
- Unknown

Strip Sign for Selected Laboratory Data

For selected laboratory test values that have been received with a qualifier as a part of the result (>, ≥, <, or ≤), a process to strip the qualifier will be applied and the resulting numeric

values will be used for data analysis. The raw value with operator will remain as such in the database and will be used when listed.

4.2.4.5 Vital signs

Vital signs (systolic and diastolic blood pressure and heart rate) will be summarized by visit and treatment group. Observed and change from baseline values will be summarized for each visit where appropriate. This summary will be repeated by age group (<12 years, ≥12 years).

Number and percentage of vital signs that are potentially clinically significant (see Appendix B3) will be summarized by parameter, category treatment group and age group (<12 years, ≥12 years). Individual patient data for patients with marked abnormality criteria will be summarized.

Vital signs parameters will be listed.

4.2.4.6 Antibodies to exenatide

A patient is said to have treatment emergent antibodies to exenatide at a visit if the antibody test is positive after the first injection of study medication following a negative or missing antibody measurement prior to the first injection of study medication, or the titer is increased by at least 3 dilutions from a detectable measurement prior to the first injection of study medication.

Number and percentage of patients incidence of antibodies to Exenatide for the categories negative, any positive, low positive, and high positive will be summarized descriptively by visit for the safety analysis set, for the treatment period.

The primary efficacy endpoint HbA1c will be summarized by antibody status (negative, any positive, low positive, higher positive) and by visit to evaluate the effect of antibody formation on efficacy.

Descriptions of planned summaries of AEs by antibody status can be found in Section 4.2.4.1. Antibodies to exenatide will be defined based on the highest antibody titer in each patient at any time during the on-treatment period.

4.2.4.7 Hypoglycemia

All summaries of hypoglycemic events will be presented for both the controlled assessment period (Safety analysis set) and the extension period (subset of Safety patients who received open-label EQW during the extension period). Hypoglycemic events will be presented as events occurring after the first dose of study medication through the end of the treatment plus 7 days.

The number and percentage of patients with hypoglycemic events, per the HYAEBO eCRF, along with the number of events will be summarized by severity (mild, moderate, severe or unknown) defined as follows,

Mild: Usually transient, requires no special treatment, and does not interfere with the patient's daily activities.

Moderate: Usually causes a low level of inconvenience or concern to the patient and may interfere with daily activities but is usually ameliorated by simple therapeutic measures.

Severe: Requires the assistance of another person to obtain treatment (e.g., intravenous glucose, intramuscular glucagon, or oral carbohydrate) for the event.

Additionally, hypoglycemia will be programmatically classified as major, minor, or other hypoglycemia as follows,

- Major hypoglycemia is defined as:

An event that results in loss of consciousness, seizure, or coma (or other mental status change consistent with neuroglycopenia in the judgment of the Investigator or physician), and which resolves after administration of glucagon or glucose

Or

An event that requires third party assistance to resolve because of severe impairment in consciousness or behavior (whether or not symptoms of hypoglycemia are detected by the patient) and is associated with a plasma or capillary glucose concentration of <3 mmol/L (54 mg/dL)

- Minor hypoglycemia is a non-major hypoglycemia event that has symptoms consistent with hypoglycemia and had a glucose value of <3 mmol/L (54 mg/dL) prior to treating the episode.

- If a hypoglycemia event does not meet the criteria for a major or minor event described above, it will be classified as other.

The number and percentage of patients with hypoglycemic events, along with the number of events will be summarized by major/minor classification.

Hypoglycemic events will also be programmatically classified into three levels[6] according to severity:

- Level 1: A glucose alert value of 3.9 mmol/L (70 mg/dL) or less.
- Level 2: A glucose level of <3.0 mmol/L (<54 mg/dL) is sufficiently low to indicate serious, clinically important hypoglycemia
- Level 3: Severe hypoglycemia, as defined by the ADA[7, 8], denotes severe cognitive impairment requiring external assistance for recovery

The number and percentage of patients with hypoglycemic events based on the aforementioned classification, along with the number of events will be summarized by level.

The number and percentage of patients with any hypoglycemic event by baseline insulin and sulfonylurea use will be summarized according to the following categories:

- Any (includes patients with and without insulin/sulfonylurea use at baseline)
- Insulin and sulfonylurea use at baseline
- Insulin only
- Sulfonylurea only

- No insulin or sulfonylurea

Key patient information for hypoglycemic events will be presented.

4.2.5 Mixed meal sub-study

Baseline values, the observed values and change from baseline values will be summarized for C-peptide, glucose, glucagon and insulin results, over timepoints for the Standardized mixed meal test evaluable analysis set. A listing by individual patients' data will also be reported.

4.3 Conventions

4.3.1 Visit assignments for efficacy variables

All visits scheduled during the 24-week controlled assessment and 28-week extension period should occur within ± 2 days of the scheduled date relative to Visit 2 (Week 0) per the CSP.

Patients do not always adhere strictly to the visit timing in the CSP. Therefore, the designation of visits during the treatment period will be based on the day of evaluation relative to the start of the controlled assessment period (day of study medication = Day 1) rather than the nominal visit recorded in the eCRF.

To assign a measurement to a Week t during the study, the first step is to select all measurements falling within the study period. Mutually exclusive relative day windows are used to determine the Week t measurement. These relative day windows are defined to provide derived visits that correspond to the post-baseline time points specified in the CSP. Some restrictions may exist on some laboratory assessments to be included in efficacy analyses. These restrictions will be reflected in the relative day ranges. Visit windows for efficacy variables are listed below.

Visit windows will not be used for Visit 11 (Week 62) and data will be presented per the visit label.

Table 3.1 Visit Windows: HbA1c, Body weight, BMI, Rescue medication (based on start date of medication) and blood pressure

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline
3	1	4	CAP	29	2-42
4	2	8	CAP	57	43-70
5	3	12	CAP	85	71-105
6	4	18	CAP	127	106-147
7	5	24	CAP	minimum (last day of CAP or 169)	148 to last day of CAP

Visit	Analysis Visit	Week	Period	Target Day	Day range
8	6	28	EP	maximum (last day of CAP+1 or 197)	last day of CAP +1 to 238
9	7	40	EP	281	239-322
10	8	52	EP	minimum (last day of EP or 365)	323 to last day of EP

CAP: Controlled assessment period. EP: Extension period.

Table 3.2 Visit Windows: Fasting plasma glucose, Fasting Insulin, Plasma Exenatide

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline
3	1	4	CAP	29	2-42
4	2	8	CAP	57	43-70
5	3	12	CAP	85	71-126
7	5	24	CAP	minimum (last day of CAP or 169)	127 to last day of CAP
10	8	52	EP	minimum (last day of EP or 365)	last day of CAP +1 to last day of EP

CAP: Controlled assessment period. EP: Extension period.

Table 3.3 Visit Windows: Fasting Lipids

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline
5	3	12	CAP	85	2-126
7	5	24	CAP	minimum (last day of CAP or 169)	127 to last day of CAP
10	8	52	EP	minimum (last day of EP or 365)	last day of CAP +1 to last day of EP

CAP: Controlled assessment period. EP: Extension period.

Table 3.4 Visit Windows: Total daily insulin

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline: -7 to -1
3	1	4	CAP	29	23 to 29
4	2	8	CAP	57	51 to 57
5	3	12	CAP	85	79 to 85
6	4	18	CAP	127	121 to 127
7	5	24	CAP	minimum (last day of CAP or 169)	[min (last day of CAP, 169) – 7] to [min (last day of CAP, 169) - 1]
8	6	28	EP	maximum (last day of CAP+1 or 197)	[max (last day of CAP +1, 197) – 6] to [max (last day of CAP +1, 197)]
9	7	40	EP	281	275-281
10	8	52	EP	last day of EP	(last day of EP – 6) to (last day of EP)

CAP: Controlled assessment period. EP: Extension period.

If a patient discontinues study medication prior to the upper day range specified in the Table 3.4 window, the average total daily insulin will not be calculated for that visit.

4.3.2 Duplicate efficacy assessments

The assessments for laboratory parameters will be based only on central laboratory values. For laboratory efficacy parameters, if a patient has more than one measurement (scheduled or unscheduled) included within a relative day window, the assessment closest to the target day and time (the target time is always assumed to be 8:00 am) will be used. In case of ties between observations located on different sides of the target day and time, the later assessment will be used. In case of ties located on the same side of the target day and time (i.e. more than 1 value for the same day and time), the mean of the values will be used.

For non-laboratory efficacy parameters, if a patient has more than one measurement (scheduled or unscheduled) included within a relative day window, the assessment closest to the target day will be used. In case of ties between observations located on different sides of the target day, the later assessment will be used. In case of ties located on the same side of the target day (i.e., more than 1 value for the same day), the mean of the values will be used.

4.3.3 Visit assignment for safety variables

Below tables provide day windows for vital signs, safety lab parameters (clinical chemistry/hematology), and growth and development hormones.

Table 3.5 Visit Windows: Vital signs

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline
3	1	4	CAP	29	2-42
4	2	8	CAP	57	43-70
5	3	12	CAP	85	71-105
6	4	18	CAP	127	106-147
7	5	24	CAP	minimum (last day of CAP or 169)	148 to last day of CAP
8	6	28	EP	maximum (last day of CAP+1 or 197)	last day of CAP +1 to 238
9	7	40	EP	281	239-322
10	8	52	EP	minimum (last day of EP or 365)	323 to last day of EP

CAP: Controlled assessment period. EP: Extension period.

Table 3.6 Visit Windows: Injection site reaction

Visit	Analysis Visit	Week	Period	Day range
3	1	4	CAP	1-42
4	2	8	CAP	43-70
5	3	12	CAP	71-105
6	4	18	CAP	106-147
7	5	24	CAP	Subjects not entering EP: 148 to last day of CAP Subjects entering EP: 148 to last day of CAP -1
8	6	28	EP	Subjects not entering EP: last day of CAP +1 to 238 Subjects entering EP: last day of CAP to 238
9	7	40	EP	239-322
10	8	52	EP	323 to last day of EP

CAP: Controlled assessment period. EP: Extension period.

Table 3.7 Visit Windows: Total testosterone, SHBG, Tanner Pubertal Stage

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline
5	3	12	CAP	85	2-126
7	5	24	CAP	minimum (last day of CAP or 169)	127 to last day of CAP
9	7	40	EP	maximum (last day of CAP+1 or 281)	last day of CAP +1 to 322
10	8	52	EP	minimum (last day of EP or 365)	323- last day of EP

CAP: Controlled assessment period. EP: Extension period.

Table 3.8 Visit Windows: Laboratory (hematology, clinical chemistry, urinalysis), Growth and development hormones such as TSH, FSH etc., Bone specific Alkaline phosphatase and N-telopeptide.

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline
5	3	12	CAP	85	71-126
7	5	24	CAP	minimum (last day of CAP or 169)	127 to last day of CAP
10	8	52	EP	minimum (last day of EP or 365)	last day of CAP +1 to last day of EP

CAP: Controlled assessment period. EP: Extension period.

Table 3.9 Visit Windows: calcitonin, pancreatic amylase, lipase, CEA

Visit	Analysis Visit	Week	Period	Target Day	Day range
2	0	0	CAP	1	Baseline
5	3	12	CAP	minimum (last day of CAP or 85)	71 to last day of CAP
10	8	52	EP	minimum (last day of EP or 365)	last day of CAP +1 to last day of EP

CAP: Controlled assessment period. EP: Extension period.

4.3.4 Rules for safety observations

4.3.4.1 Multiple safety assessments

For tabulations of visit summaries, changes from baseline or shift analyses, if multiple measurements are included within a relative day window, the measurement closest to the target day will be used; in the case of a tie, the measurement obtained on the earlier day will be used in the analyses. In case of ties located on the same side of the target day (i.e., more than 1 value for the same day), the mean of the values will be used.

4.3.4.2 Adverse events at patient level

When a patient has the same adverse event, based on SOC/PT, reported multiple times in a single analysis period, the patient will only be counted once at the SOC/PT level in adverse event frequency tables.

When a patient has the same adverse event, based on preferred terminology, reported multiple times in a single analysis period, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

1. Relationship to study medication
2. Intensity of event
3. Onset date and time

When assessing relationship to study medication, relationship is reported by the Investigator into 2 categories - related and not related. Related events will take precedence over not related events in determining the event to include in summary tables.

More intense events will take precedence over less intense events in determining the event to include in summary tables.

Earlier onset date-time events will take precedence over late onset date-time events in determining the onset to include in summary tables.

4.3.4.3 Adverse event at event level

At event level, each unique AE record will be counted. Unique AE record can be obtained by collapsing all AE records following a standard algorithm described below.

To ensure that multiple events for the same patient are counted accurately in the summaries, a methodology for collapsing AE records and reporting for the analysis will be followed as below. For each patient and PT, AE records will be collapsed into a single record (unique AE) when:

1. Multiple AE records have the same onset date,
2. The onset date of an event record is either the same day or 1 day later than the resolution date of a preceding event record (contiguous events),
3. The onset date of an event record is after the onset date and prior to or on the resolution date of a preceding event record (overlapping events).

The unique AE record will contain the earliest onset date, latest resolution date (if available), highest intensity, relationship (yes/no), and highest action taken in the following order (highest to lowest): drug discontinued, drug interrupted, none. In addition, the unique AE record will be classified as a SAE if at least 1 AE record was classified as a SAE and the unique AE record will be classified as requiring treatment if at least 1 AE record required treatment.

5. CHANGES OF ANALYSIS FROM PROTOCOL

Section 3.1 of the CSP states that patients return to clinical study site at "6-, 10-, and 12-week intervals but in accordance to the study plan, patients return at 6- and 12-week intervals, with a follow-up visit at Week 62. Section 1.2 of the SAP reflects this.

Per CSP Section 12.1, a Per-Protocol (PP) analysis set is defined. However, given the limitations of PP analyses in that they lead to lack of preservation of the randomization and given the CSP states that efficacy analyses will be carried out on the Evaluable Population "and/or" the Per-Protocol population, i.e. allowing some flexibility, the team agrees to not define a PP analysis set. Additionally, an All Patients analysis set, Randomized analysis set and PK analysis set.

CSP Section 12.1 states that safety will be assessed using the ITT population, however, the team decided a safety analysis set should be defined instead. Patients would be analyzed in accordance to actual treatment received.

CSP Section 12.1 states the Evaluable population will consist of all ITT patients who receive at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment. It was decided that this definition should be modified to include at least 1 baseline and post-baseline HbA1c assessment.

CSP Section 12.2 has change in C-peptide from baseline to each study week as a secondary endpoint but this was only collected at screening and then for patients in the mixed meal sub-study at Week 52 and Week 62. Therefore this endpoint has been omitted from the SAP.

CSP section 12.2 lists the proportion of patients achieving HbA1c goals of ≤6.5% and <7.0% as a secondary endpoint. To align with other exenatide studies the addition of goal <6.5% has been added.

CSP Section 12.3 states that demographic and baseline characteristics will be summarized for the ITT and Evaluable analysis sets, however the study team requested these be summarized for the ITT and Safety analysis sets.

CSP Section 12.4 states that treatment compliance will be summarized for the ITT analysis set, however, this will be summarized for the Safety analysis set.

A hierarchical testing strategy was not defined in the CSP but has been included in the SAP to protect the family-wise error rate for the primary and secondary endpoints.

CSP Section 12.6.1 states that last observation carried forward will be used for missing data at endpoint for proportion of patients meeting HbA1c goals of ≤6.5% and <7.0%, however, patients with missing HbA1c at endpoint will be considered as non-responders. Additionally, the logistic regression sensitivity analysis described in the CSP has been replaced with a more appropriate CMH analysis using MI pattern mixture model imputation (Sections 4.2.3.4 and 4.2.3.5), as this tests the robustness of the results from the main analysis by altering the missing data assumption.

CSP Section 12.6.1 stipulates 'The analyses of all other efficacy endpoints will be performed in ITT population.' Upon review of the endpoints it was agreed that all endpoints related to HbA1c should be evaluated using the Evaluable analysis set.

CSP Section 12.6.1 outlines a MMRM method will be implemented for the secondary efficacy endpoint, lipids. It was agreed after blinded data review that the data could be sufficiently reviewed as summary statistics.

CSP Section 12.6.2 specifies that both baseline HbA1c and HbA1c strata will be included in the MMRM model for the primary analysis. However, these variables will be highly correlated resulting in multicollinearity in the statistical model. Therefore, HbA1c strata will not be included in the primary model. For secondary and exploratory MMRM analyses, screening HbA1c strata will be used in the model instead of continuous baseline HbA1c.

The sensitivity and supportive analyses in Section 4.2.3.4 were not specified in the CSP and have been added to further support the primary analysis and to examine the influence of missing data due to drop-out and/or receiving rescue therapy.

Section 12.6.3 of the CSP states that the proportion of patients discontinuing the study will be analyzed using a CMH test and logistic regression by visit. However, the team agreed it would be sufficient to summarize withdrawals during the study, which is presented in the disposition summary table. Hence no statistical analyses were planned for this endpoint. In the same section of the CSP, it is stated that the proportion of patients rescued due to failure to maintain glycemic control will be analyzed using a CMH test and logistic regression by visit. However, based on the observed number of patients rescued at Week 24 being low, the team agreed summaries of this endpoint would suffice. By way of a clarification to the CSP, the team also agreed that “number of rescue episodes” should be interpreted as “number of patients rescued”, given a patient is considered rescued after initiation of rescue therapy. Therefore, a summary of the cumulative proportion of patients rescued by visit will be considered sufficient to address this endpoint.

Section 12.6.3 of the CSP states that for MMRM analyses, country will be included as a covariate. However, to align to the approach for the primary endpoint, region will be used instead.

The CSP does not specify BMI percentile as an endpoint, however the study team requested this be included and therefore summaries of observed and change from baseline in BMI percentile will be provided as specified in Section 4.2.3.6 of this SAP.

The CSP does not specify eGFR as an endpoint, nor is it provided by the laboratory. However, the team felt it would provide important information for this study so it will be derived and analyzed as stated in Section 4.2.4.4 of this SAP.

Hypoglycemia analyses are not defined in the CSP. However, the team requested events be classified and summaries be included as defined in Section 4.2.4.7 of this SAP.

Free testosterone in the CSP has been outlined as calculated at Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40) and Visit 10 (Week 52). Since this endpoint is calculated using Albumin, total testosterone and SHBG and these parameters are not collected at Week 40, this visit will not be presented in the outputs.

Appendix F of the CSP (Mixed Meal Substudy) lists statistical analyses and summaries will be presented. However, due to an insufficient amount of data being collected for the study, the study team decided no formal analysis will be presented, only summary tables and listings.

6. REFERENCES

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7. APPENDIX

7.1 Appendix B1 Partial date conventions for AEs

Missing type	Action
If only the **day part** of the AE **onset date** is missing	If the month and year are the same as that of first dose of study medication, the date of first dose of study medication will be used as the onset date of the AE. Otherwise, the first day of the month will be used to complete the onset date of the AE
If the **day and month parts** of the AE **onset date** are missing	If the year is the same as that of the first dose of study medication, the date of the first dose of study medication will be used as the onset date of the AE. Otherwise, January 1st will be used to complete the onset date of the AE.
If the AE **onset date** is **completely** missing	The date of the first dose of study medication will be used as the onset date of the AE.
If only the **day part** of the AE **end date** is missing	The last day of the month will be used to complete the end date of the AE.
If the **day and month parts** of the AE **end date** are missing	December 31st will be used to complete the end date of the AE.
If the end date of the AE is completely missing and the AE is not ongoing, and the onset date of the AE occurs after the date of the first dose of study medication,	Then the onset date of the AE will be used as the AE end date. Otherwise, the date of the first dose of study medication will be used as the AE end date.

7.2 Appendix B2 Algorithm for prior /concomitant medications

START DATE	STOP DATE	Action
Known	Known	If stop date < study med start date, assign as pre-treatment If stop date ≥ study med start date and start date < study med start date, assign as prior concomitant If stop date ≥ study med start date and start date ≥study med start date, assign as new concomitant
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: Follow the same algorithm above for a known start date and known stop date.
	Missing	If stop date is missing could never be assumed a prior medication If start date < study med start date, assign as prior concomitant If start date ≥ study med start date, assign as new concomitant
Partial	Known	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown), then: Follow the same algorithm above for a known start date and known stop date.
	Partial	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: Follow the same algorithm above for a known start date and known stop date.

START DATE	STOP DATE	Action
Missing	Missing	Impute start date as earliest possible date (ie, first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication Follow the same algorithm above for a known start date and missing stop date.
	Known	If stop date < study med start date, assign as pre-treatment If stop date ≥ study med start date, assign as prior concomitant
	Partial	Impute stop date as latest possible date (ie, last day of month if day unknown or 31st December if day and month are unknown), then: Follow the same algorithm above for a missing start date and known stop date.
	Missing	Assign as prior concomitant

7.3 Appendix B3 Units and marked abnormality criteria for safety laboratory variables and vital sign parameters

Clinical laboratory variables will be summarized using the reference ranges in the lab manual.

Potentially clinically significant changes are assessed with the following marked abnormality criteria for vital signs[9]:

Age: 6 - <12 years

		Marked abnormality criteria	
Vital signs variables	**Units**	**Low**	**High**
Heart Rate			
Value	bpm	< 60	> 95
Value - Baseline	bpm		> 20
Baseline - Value	bpm		>10
Systolic Blood Pressure			
Value	mmHg	< 100	> 120
Value - Baseline	mmHg		> 10
Baseline - Value	mmHg		>10
Diastolic Blood Pressure			
Value	mmHg	< 60	> 75
Value - Baseline	mmHg		> 10
Baseline - Value	mmHg		>10

Age: ≥12 years

		Marked abnormality criteria	
Vital signs variables	**Units**	**Low**	**High**
Heart Rate			
Value	bpm	< 55	> 85
Value - Baseline	bpm		> 20
Baseline - Value	bpm		>10
Systolic Blood Pressure			

		Marked abnormality criteria	
Vital signs variables	**Units**	**Low**	**High**
Heart Rate			
Value	mmHg	< 110	> 135
Value - Baseline	mmHg		> 10
Baseline - Value	mmHg		>10
Diastolic Blood Pressure			
Value	mmHg	< 65	> 85
Value - Baseline	mmHg		> 10
Baseline - Value	mmHg		>10

7.4 Appendix B4 Preferred terms for potentially immune-related adverse events

Allergic bronchitis	Immediate post-injection reaction	Rash
Allergic colitis	Injection site dermatitis	Rash erythematous
Allergic cough	Injection site eczema	Rash follicular
Allergic cystitis	Injection site erythema	Rash macular
Allergic keratitis	Injection site hypersensitivity	Rash maculo-papular
Allergic oedema	Injection site induration	Rash maculovesicular
Allergic otitis media	Injection site inflammation	Rash papular
Allergic pharyngitis	Injection site macule	Rash pruritic
Allergic respiratory symptom	Injection site nodule	Rash pustular
Hypersensitivity pneumonitis	Injection site oedema	Rash vesicular
Anaphylactic reaction	Injection site papule	Reaction to excipient
Anaphylactic shock	Injection site photosensitivity reaction	Reaction to preservatives
Anaphylactoid reaction	Injection site pruritus	Reversible airways obstruction
Anaphylactoid shock	Injection site pustule	Scleral oedema
Angioedema	Injection site rash	Scleritis allergic
Arthralgia	Injection site reaction	Skin oedema

Arthritis	Injection site recall reaction	Intestinal angioedema
Arthritis allergic	Injection site streaking	Stevens-Johnson syndrome
Asthma	Injection site swelling	Stridor
Auricular swelling	Injection site urticaria	Suffocation feeling
Bronchial hyperreactivity	Injection site vesicles	Swelling face
Bronchial oedema	Joint effusion	Swollen tongue
Bronchospasm	Joint swelling	Throat tightness
Circumoral oedema	Laryngeal obstruction	Tongue oedema
Conjunctival oedema	Laryngeal oedema	Tongue pruritus
Corneal oedema	Laryngitis allergic	Toxic epidermal necrolysis
Dermatitis	Laryngotracheal oedema	Toxic skin eruption
Dermatitis allergic	Lip oedema	Tracheal obstruction
Diffuse cutaneous mastocytosis	Swelling	Tracheal oedema
Drug eruption	Local swelling	Type I hypersensitivity
Drug hypersensitivity	Localised oedema	Type II hypersensitivity
Drug reaction with eosinophilia and systemic symptoms	Mechanical urticaria	Type III immune complex mediated reaction
Encephalopathy allergic	Nasal oedema	Type IV hypersensitivity reaction
Eosinophilia	Nephritis allergic	Urticaria
Eosinophilic oesophagitis	Oculorespiratory syndrome	Urticaria cholinergic
Epiglottic oedema	Oedema mouth	Urticaria chronic
Erythema multiforme	Oedema mucosal	Urticaria contact
Erythema nodosum	Oesophageal oedema	Urticaria papular
Eye oedema	Orbital oedema	Urticaria physical
Eye swelling	Oropharyngeal swelling	Urticaria pigmentosa
Eyelid oedema	Palatal oedema	Urticaria pressure
Face oedema	Periarthritis	Urticaria thermal
Gastrointestinal oedema	Periorbital oedema	Urticaria vesiculosa
Gingival oedema	Pharyngeal oedema	Urticaria vibratory
Gingival swelling	Photosensitivity reaction	Visceral oedema
Haemorrhagic urticaria	Pruritus	Wheezing
Hereditary angioedema	Pruritus allergic	
Hypersensitivity		
Idiopathic urticaria		

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