Statistical Analysis Plan

Study Code	H8O-MC-GWBQ
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Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

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LIST OF ABBREVIATIONS

Abbreviation or special term	Explanation
AE	Adverse events
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CCT	Concomitant Therapy
CDE	Certified diabetes educator
CEA	Carcinoembryonic antigen
CFBL	Change from baseline
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CSP	Clinical study protocol
CSR	Clinical study report
CTMS	Clinical trial management system
CV	Coefficient of variation
DAE	AE Leading to Treatment Discontinuation
DBL	Database lock
DMC	Data Monitoring Committee
DRM	Data Review Meeting
EBID	Exenatide twice daily
ECG	Electrocardiogram
ED	Early discontinuation
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
FSG	Fasting serum glucose
FSI	Fasting serum insulin
GCV	Geometric coefficient of variation
GSD	Geometric standard deviation
HbA1c	Glycated hemoglobin A1c
HOMA-B	Homeostasis model assessments – beta-cell functions

Abbreviation or special term	Explanation
HOMA-S	Homeostasis model assessments – insulin sensitivity
ICH	International Conference on Harmonisation
ITT	Intent-to-Treat
LLN	Lower limit of normal range
LMP	Lifestyle modification program
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MMRM	Mixed model repeated measures
MNAR	Missing not at random
OAM	Oral anti-diabetic medication
OC	Observed case
PBO	Placebo
PD	Protocol deviations
PK	Pharmacokinetic
PT	Preferred term
QD	Once daily
QW	Once weekly
RD	Registered dietitian
SAP	Statistical Analysis Plan
SD	Standard deviation
SI	Standard International (Unit)
SMBG	Self-monitored blood glucose
SOC	System organ class
SU	Sulfonylurea
TEAE	Treatment emergent adverse events
ULN	Upper limit of normal range
WHODD	World Health Organization Drug Dictionary

AMENDMENT HISTORY

Date	Brief description of change
22th April 2020	Due to change of company for the analysis of this study from Amylin Pharmaceuticals, LLC to IQVIA, the Statistical Analysis Plan has been fully rewritten from Version 1.0. Rewritten to be consistent with Study D5551C00002 where appropriate. Summaries and analysis of long-term safety follow-up period included. Due to power considerations, efficacy analysis comparisons will be between both exenatide treatment arms combined versus placebo.
	Updated to allow for possibility of analysis of treatment period data and safety follow-up period data separately
	Important Protocol Deviation #1 has been amended to consider screening time, rather than enrolment. Baseline definition and end of study treatment measurement have been updated. Columns for the EBID treatment groups have been swapped. Updated to only consider informed consent, and not assent. Race and Region has been updated. Ethnic group has been deleted. Country has been sorted in alphabetical order. Medications will be presented for ITT and safety follow-up analysis set. MI definition has been extended and additional table for primary analysis has been added. Post-treatment AE definition has been updated to account for the overlap between TEAEs and previous post-treatment AE definition. Shift from baseline to the worst value for lab parameters has been deleted. Total bilirubin upper limit updated. PK and antibodies data will only be listed.

1 STUDY DETAILS

The scope of this statistical analysis plan (SAP) is to describe the planned summaries and analyses of data collected during this study. The study comprises a treatment period (Week 0 to Week 28) and a long-term safety follow-up period (after completion/early discontinuation (ED) of the treatment period, for 3 years or until the difference between 2 consecutive height measurements at 6-month intervals is less than 5 mm if earlier).

On entry to this study, patients will have inadequate glycemic control and will be either antidiabetic drug-naïve, defined as treatment with diet and exercise alone, or receiving treatment with oral antidiabetic agent(s), either metformin, a sulfonylurea (SU), or a combination of metformin and an SU (with or without diet and exercise).

Refer to Appendices 1 and 2 for schedules for both periods. Reporting of treatment period data may be performed before reporting of safety follow-up period data.

1.1 Study objectives

1.1.1 Primary objective

The primary objective of the treatment period is to test the hypothesis that glycemic control, as measured by change in glycated hemoglobin A1c (HbA1c) from baseline to endpoint, with exenatide 5 µg twice daily or 10 µg twice daily (Total EBID) is superior to that of placebo (PBO), after up to 28 weeks of study drug treatment, in adolescent patients with type 2 diabetes.

The primary objective of the safety follow-up period is to assess ongoing development and growth following up to 28 weeks of study drug treatment in adolescent patients with type 2 diabetes and to document the following:

- Adverse events of special interest
- Prescription medications
- Body weight, height and Tanner pubertal stage
- Carcinoembryonic antigen (CEA) concentration
- Calcitonin concentration

1.1.2 Secondary objectives

The secondary objectives are:

- To compare the effects of EBID to those of PBO, after up to 28 weeks of study drug treatment, in adolescents with type 2 diabetes, on the following:
  - Proportion of patients achieving HbA1c goals
  - Body weight

  - Fasting serum glucose (FSG) concentrations
  - Fasting serum insulin (FSI) concentrations
  - Self-monitored blood glucose (SMBG) measurements before and 2 hours after the two main meals of the day
  - Beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments (HOMA)
  - Proportion of patients discontinuing the study due to failure to maintain glycemic control
- To assess the safety and tolerability of up to 28 weeks of EBID treatment, in adolescents with type 2 diabetes, on the following:
  - Adverse events
  - Incidence and rate of hypoglycemia
  - Antibodies to exenatide
  - Laboratory measurements (including CEA and calcitonin concentrations)
  - Vital signs and physical examination including Tanner pubertal stage
  - Electrocardiograms (ECGs)

1.1.3 Exploratory objectives

- To assess the pharmacokinetics (PK) of EBID treatment, in adolescents with type 2 diabetes who participated in the PK sub-study

1.2 Study design

This is a multicenter, double-blind, placebo-controlled, randomized, parallel, 3-arm trial. Approximately 195 adolescents, ages 10 to 17 years inclusive, with type 2 diabetes will be enrolled. The number of patients aged 17 years of age will be limited to no more than 10% of patients in each treatment arm. Patients will be naïve to antidiabetic agents, or they will be receiving oral treatment with metformin, an SU, or a combination of metformin and an SU at the time of enrolment. Randomization will be stratified by the patient's background diabetes therapy and screening HbA1c. The study will commence with a 1-week, single-blind, injectable placebo lead-in period before patients are randomly assigned to add injectable exenatide or injectable placebo to their existing diabetes treatment. Patients will be randomly assigned to 1 of 3 treatment arms: exenatide 5 µg twice daily, exenatide 10 µg twice daily, or placebo twice daily (volume of injection equivalent to exenatide 5 µg or exenatide 10 µg). During the first 4 weeks after randomization, all patients assigned to treatment will receive exenatide 5 µg twice daily or equivalent placebo volume twice daily. A starting dose of exenatide 5 µg twice daily and titration to exenatide 10 µg twice daily has been shown to mitigate the incidence of nausea. At the end of 4 weeks post-randomization, patients assigned to the exenatide 10 µg twice daily treatment arm, or equivalent placebo volume, are then to increase their dose from 5 µg twice daily to 10 µg twice daily, or equivalent placebo volume. Study drug will be administered

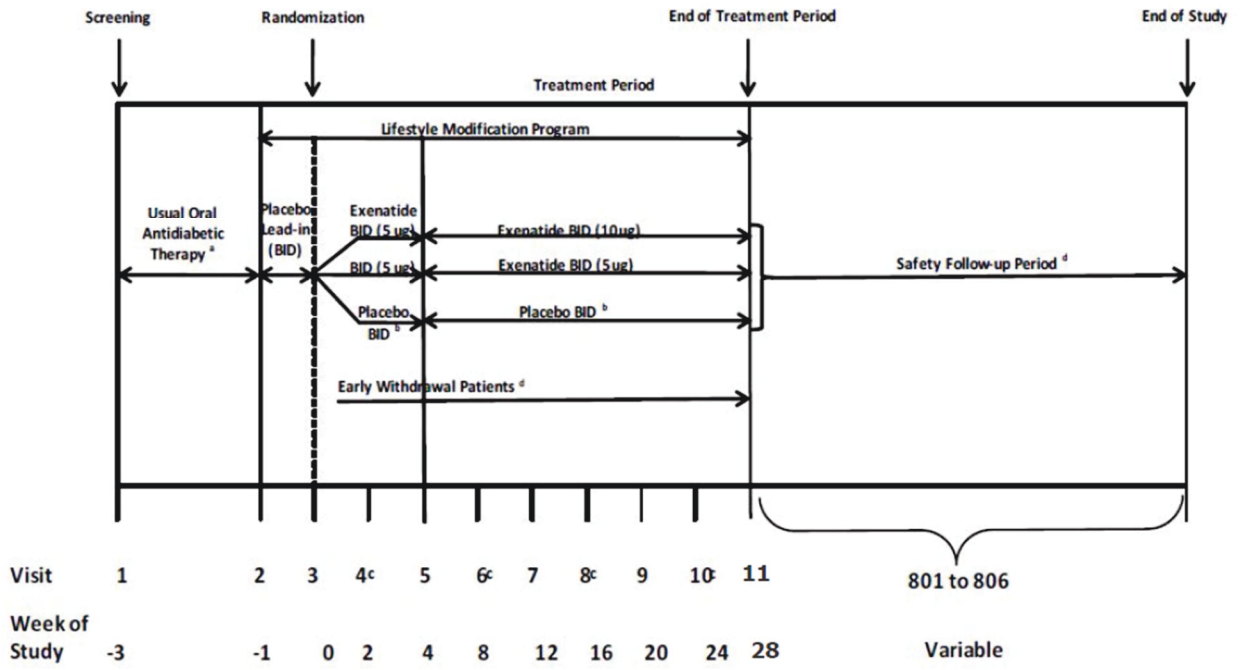
within 60 minutes before morning and evening meals (or the 2 main meals of the day, approximately 6 hours or more apart) for 28 weeks.

All patients will be expected to participate in a simplified lifestyle modification program (LMP) throughout this study. The simplified lifestyle modification program will include both dietary education and physical activity components. At the clinic visits, the patients will meet with a registered dietitian (RD) or certified diabetes educator (CDE) who will review the patient's dietary history and physical activity record. The LMP will be reinforced at each visit.

Patients who have discontinued the study due to loss of glycemic control will be offered alternative antidiabetic therapy at the discretion of the investigator.

In response to a request from the European Medicines Agency Pediatric Committee, patients will be observed in a long-term safety follow-up period following discontinuation of study drug administration. Patients will return to the clinic every 6 months for evaluation of safety measures. Patients will be followed for up to 3 years after the completion of the treatment period, or until the difference between 2 consecutive height measurements at 6-month intervals is less than 5mm (whichever occurs first). Patients who have achieved the final height requirement of a change of less than 5mm between Visit 3 (Week 0) and Visit 11 (Week 28/Early Discontinuation) of the treatment period will be excluded from the safety-follow up period. Patients who do not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication will enter the safety follow-up period.

Figure 1 Study Design



Abbreviations: BID = twice a day

[a] Metformin (MET) or sulfonylurea (SU) or combination of Met and SU, with or without diet and exercise, or naïve to antidiabetic agents defined as being treated with diet and exercise alone.

[b] The volume of placebo is equivalent to 5 µg or 10 µg exenatide.

[c] Scheduled telephone visit.

[d] Patients will return to the study site at approximately 6-month intervals for a period of up to 3 years or until the difference between 2 height measurements over a 6-month interval is less than 5 mm (whichever comes first). Patients who have a height change of less than 5 mm over a 6-month interval during the treatment period will not enter the safety follow up period. Patients who do not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication will enter the safety follow-up period. Patients will not receive any study drug but may be treated with a diabetes treatment regimen deemed appropriate by the investigator or healthcare provider.

1.3 Number of patients

Approximately 195 patients diagnosed with type 2 diabetes were planned to be enrolled. Approximately 65 patients were to be randomized to receive placebo and 130 patients were to be randomized to receive exenatide (65 per exenatide treatment arm). A sample of 65 patients per treatment arm would provide >95% power to reject the null hypothesis of no difference among treatments assuming true mean changes in HbA1c of -0.7, -0.5, and 0 for patients receiving exenatide 10 µg twice daily, exenatide 5 µg twice daily, and placebo twice daily, respectively (based on results of previous Studies 2993-112, CCI [redacted], H8O-MC-GWAA, H8O-MC-GWAD). This power computation also assumes a common standard deviation of 1.0% and a two-sided significance level of 0.05. Assuming the same true mean changes in HbA1c, common standard deviation, and two-sided significance level, 65 patients per treatment arm would also provide >95% power to detect a difference between 10 µg exenatide twice daily and placebo

treatments, and 80% power to detect a difference between 5 µg exenatide twice daily and placebo with a Fisher Protected Testing procedure (Hayter 1986).

Due to an approximate 23% discontinuation rate in the exenatide arms (based on results from 2993-112), 65 patients randomized per treatment arm would be enough to observe 50 completers per treatment arm. Patients will be eligible to participate if they are not achieving adequate glycemic control (i.e. HbA1c at screening is 6.5% to 10.5%, inclusive) with metformin, an SU, or metformin and an SU, or diet and exercise only. Patients will be stratified to treatment assignment based on diabetes therapy at enrolment and screening HbA1c. The three-arm design was intended to allow comparison of exenatide at doses of 5 µg twice daily and 10 µg twice daily with placebo twice daily.

Due to the availability of other more conveniently administered therapies e.g. oral, once daily (QD), or once weekly (QW), recruitment to this study has been slow/difficult despite extensive efforts by the sponsor. The planned number of patients will take unreasonably long to recruit so a decision was made with agreement by the European Medicines Agency and Food and Drug Administation to stop recruitment and to pool patients from both exenatide arms and compare the pooled arm with placebo. With a total of 122 patients randomized (Total EBID:Placebo 2:1), the study should have approximately 87% power to detect a difference between Total EBID and placebo assuming the true mean changes in HbA1c are -0.7, -0.5, and 0 for patients receiving exenatide 10 µg BID, exenatide 5 µg BID, and placebo BID, respectively. The combined effect of the Total EBID doses compared to placebo (mean difference) is assumed to be -0.6 with a common standard deviation of 1% at the 5% significance level without consideration of patient discontinuation and impact on effect size. An assumed effect size of -0.455 was considered in power calculation.

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. This set will be used for listings and summaries of patient disposition and pre-randomized treatment adverse events.

2.1.2 Intent-to-Treat analysis set

The Intent-to-Treat (ITT) analysis set will include all randomized patients. ITT patients will be analyzed in accordance to their planned treatment group. This set will be used for listings and summaries of demographic and baseline characteristics.

2.1.3 Full analysis set

The Full analysis set (FAS) will consist of all randomized patients who receive at least one dose of randomized study medication. Full analysis set patients will be analyzed in accordance to

their planned treatment group. This set will be used for listings and summaries of non-HbA1c efficacy data.

2.1.4 Evaluable analysis set

The Evaluable analysis set will consist of all randomized patients who received at least 1 dose of randomized study medication and have a baseline and at least 1 post-baseline HbA1c assessment. Evaluable patients will be analyzed in accordance to their planned treatment group. This set will be used for listings and summaries of HbA1c efficacy data.

2.1.5 Safety analysis set

The Safety analysis set consists of all patients who received at least 1 dose of randomized study medication.

Patients will be analyzed and presented in accordance to the actual treatment received, regardless of planned treatment assignment. If a patient receives at least one dose of exenatide treatment during the assessment period, they will be analyzed and presented in accordance with the actual exenatide treatment received no matter what arm they were randomized to. If a patient randomized to the placebo arm receives exenatide at doses of both 5 μg twice daily and 10 μg twice daily, they will be analyzed and presented in the 10 μg twice daily treatment group.

This set will be used for listings and summaries of safety data during the treatment period.

2.1.6 Safety follow-up analysis set

The safety follow-up (SFU) analysis set consists of all patients who have at least 1 safety follow-up period assessment Visit 801 (6 months after Week 28/ED) to Visit 806 (3 years after Week 28/ED).

This set will be used for listings and summaries of safety data during the safety follow-up period.

2.1.7 Pharmacokinetic (PK) analysis set

The PK analysis set will consist of all patients who receive at least 1 dose of EBID, for whom at least 1 evaluable post-dose PK concentration assessment is available, and do not deviate from the clinical study protocol (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.

This set will be used for listing of PK data.

2.2 Violations and deviations

AstraZeneca use 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.

Important deviations may include deviations pertaining (but not limited) to those presented in Table 1.

These protocol deviations will be programmatically derived (where possible) and presented in a listing. In addition, protocol deviations attributed to these criteria reported in the IQVIA Clinical Trial Management System (CTMS) for all patients randomized by IQVIA in this study will be reported in the Clinical Study Report (CSR). No additional per protocol analyses are planned.

Table 1 Important Protocol Deviations

Number	Important protocol deviations criteria
1	Randomized patients without type 2 diabetes or central laboratory HbA1c obtained at screening not within ± 0.2% of the protocol-specified HbA1c range
2	Randomized patients not satisfying the target population baseline antihyperglycemic therapy requirement
3	Randomized patients who were treated with any systemic corticosteroid therapy for ≥5 consecutive days during randomized treatment
4	Randomized patients who received no (or incorrect) study medication at any time during the 28-week treatment period (*).
5	Patients assigned to the incorrect IVRS randomization stratification factor as compared to the HbA1c test result at screening (≤8.0% or >8.0%) or background diabetes therapy (drug naïve, metformin only, SU only and metformin + SU)
6	Missed the background anti-diabetic medication for ≥10 consecutive days in the last three months of the study (*)
7	No valid baseline HbA1c
8	No single valid on-treatment HbA1c
9	Randomized patients who are not compliant with study medication administration requirements (dose, frequency) (*)

(*) PD will only be presented from the CTMS as not possible to fully identify programmatically.

This list is not intended to be all-inclusive. Other protocol deviations may be identified by the study team during on-going review of the study conduct prior to treatment unblinding.

3 PRIMARY AND SECONDARY VARIABLES

3.1 Primary efficacy variable

The primary efficacy endpoint for the treatment period is the change in HbA1c from baseline Visit 3 (Week 0) to Visit 11 (Week 28).

3.2 Secondary efficacy variables

The following are the secondary efficacy endpoints:

- Change in HbA1c from baseline Visit 3 (Week 0) to each intermediate visit as applicable

- Proportion of patient achieving HbA1c goals of <7%, ≤6.5%, and <6.5% at Visit 11 (Week 28) and each intermediate visit as applicable

- Change in body weight from baseline Visit 3 (Week 0) to Visit 11 (Week 28), and to each intermediate visit as applicable

- Change in FSG from baseline Visit 3 (Week 0) to Visit 11 (Week 28)

- Change in FSI from baseline Visit 3 (Week 0) to Visit 11 (Week 28)

- Change in SMBG measurements before and 2 hours after the 2 main meals of the day on 3 days during the week before Visit 3 (Week 0) and Visit 11 (Week 28)

- Change in HOMA-B and HOMA-S as measured by homeostasis model assessment from baseline Visit 3 (Week 0) to Visit 11 (Week 28)

- Proportions of patients discontinuing the study, due to failure to maintain glycemic control at Visit 11 (Week 28), and to each intermediate visit as applicable

3.3 Exploratory efficacy variables

The exploratory efficacy endpoints are:

- Change in body mass index (BMI) from baseline Visit 3 (Week 0) to Visit 11 (Week 28), and to each intermediate visit as applicable
- Change in body weight and BMI percentile from baseline Visit 3 (Week 0) to Visit 11 (Week 28), and to each intermediate visit as applicable. The body weight and BMI percentiles will be determined based on the standardized growth chart for boys and girls (2000 CDC Growth Charts)
- Change in hip and waist circumference from baseline Visit 3 (Week 0) to Visit 11 (Week 28)

3.4 Safety variables

Safety endpoints during the treatment period are:

- Incidence of treatment-emergent adverse events (TEAEs; see section 4.2.5.1) and hypoglycemic events (see section 4.2.5.2) over the treatment period

- Antibodies to exenatide, physical examination (height), laboratory measurements (clinical chemistry, hematology and urinalysis including calcitonin and CEA concentrations), vital signs (blood pressure and heart rate) and ECGs (overall assessment) from screening Visit 1 (Week -3) or baseline Visit 3 (Week 0) to Visit 11 (Week 28), and to each intermediate visit as applicable

- Tanner pubertal stage at baseline Visit 3 (Week 0), Visit 5 (Week 4), Visit 7 (Week 12), Visit 9 (Week 20) and Visit 11 (Week 28)

Safety endpoints during the follow-up period are:

- Adverse events of special interest
- CEA and calcitonin concentrations
- Prescription medications
- Body weight, height and Tanner pubertal stage

3.5 Exploratory safety variables

The exploratory safety endpoint is change in estimated glomerular filtration rate (eGFR) from baseline Visit 3 (Week 0) to Visit 11 (Week 28).

3.6 Definition of study variables

Refer to Section 4.3 for details on conventions such as visit windowing and handling of duplicate 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 on/at Visit 3 (Week 0). Assessments carried out on the date of the first dose are assumed to have been done pre-dose unless time information indicates otherwise.

The baseline measurement for demographic and baseline characteristic data in patients who do not get treated is defined as the last non-missing value collected on or prior to Visit 3 (Week 0).

If the last non-missing value ties with another non-missing value happening at the same day and time (or same day, if time is not collected) then the mean of the values will be used.

If the baseline value is missing for a given variable, change from baseline will be missing.

Baseline for BMI will be calculated from last non-missing values for height and weight, even if they were at separate dates.

3.6.2 End of study treatment measurement

For completers, end of study treatment measurement is the last non-missing post-baseline measurement obtained at or prior to Visit 11 (Week 28).

If patient discontinues prior to Week 28 (Visit 11), then the end of study treatment measurement is the last non-missing post-baseline measurement obtained at or prior to ED visit.

If patient discontinues prior to Week 28 (Visit 11) and there is no ED visit, then the end of study treatment measurement is the last dose date +1 (or + 30 days if discontinued due to SAEs and other clinically significant or related AEs).

3.6.3 Change and percent change from baseline

Change from baseline to any post-baseline 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 post-baseline 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.

3.6.4 Rescue therapy

Rescue therapy is defined as any new antidiabetic concomitant medication or changes to background oral-diabetic medication, for exacerbation of diabetes.

Treatment with insulin may be given for emergency reasons during the treatment period. If the period of insulin use exceeds 10 days during a 3-month period, then a decision to discontinue study treatment will be made after consultation between the investigator and the Sponsor's clinical research physician.

Background oral antidiabetic medication (metformin and SU) were to be continued throughout the study at the same dose and schedule as before study entry. However, metformin dosage could be adjusted for up to 10 consecutive days or 10 days in a 30-day period and the SU dosage could be decreased in response to hypoglycemia.

Changes in background metformin and SU will be programmatically derived from the concomitant therapy (CCT) oral anti-diabetic medication (OAM) CRFs and reviewed by the clinical team prior to unblinding. Increases identified as potential rescue episodes will be queried at the site-level to determine whether rescue therapy or not.

New antidiabetic medication will be programmatically identified from the CCT OAM CRFs where the Anatomical Therapeutic Chemical (ATC) code begins with "A10".

A rescue episode will be defined as the first unique rescue therapy entry on the CCT OAM CRFs as derived as above. If a patient has multiple entries, the first will be considered the point at which the patient was rescued.

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, then HbA1c will be 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 Early discontinuation visit

If a patient discontinues after randomization but prior to completion of the study treatment period, the patient will be asked to return as soon as possible to the study site for an early discontinuation (ED) visit. The patients will not receive exenatide or placebo; however, a treatment regimen, as deemed clinically appropriate, should be initiated. Investigative staff

should complete a study summary page for each patient. Patients who discontinue early from the study treatment period should continue into the safety follow-up addendum unless the patient is lost to follow-up, withdraws consent, or achieved final height criteria of a change of less than 5 mm during the treatment period.

3.6.6 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.

Pre-treatment period: defined as the period prior to the date of the first dose of randomized study medication. All data for patients who do not receive randomized study medication will be considered pre-treatment.

Treatment period: defined as the date of first dose of randomized study medication to date of the Week 28 visit, or the ED visit for patients who discontinue the study prior to Week 28.

Safety follow-up period: defined as the day after the Visit 11 (Week 28) visit, or the day after the ED visit for patients who discontinue the study prior to Visit 11 to the date of completion of the Safety follow-up study (typically after 3 years or once the patient has a height difference of less than 5 mm between two 6-month interval visits). The safety follow-up period will only be defined for patients who enter the safety follow-up period.

See Section 4.1.3 for details on missing data handling.

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 unblinding, 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

Although patients randomly assigned to placebo will be assigned to take the volume equivalent to 5 µg exenatide twice daily or to take the volume equivalent to 10 µg exenatide twice daily, all patients assigned to placebo will be combined into 1 group for analysis purposes. Descriptive summaries will present treatment groups separately, as follows:

5 µg EBID	10 µg EBID	Total EBID	Placebo	Total

EBID Exenatide twice daily

Total EBID is the pool of the 10 µg and 5 µg EBID doses. Total (over all treatments) will not be included in efficacy and safety endpoint outputs.

Summaries including data from the safety follow-up period will be presented by the actual treatment group during the randomized period.

All efficacy and safety variables will be summarized using descriptive statistics as appropriate. Continuous variables will be summarized by descriptive statistics including n (number of patients with available data), arithmetic mean, standard deviation (SD), median, minimum value and maximum value. The mean and median will be presented with one more decimal place than the original data; the standard deviation with two more decimal places than the original data; and minimum and maximum values with the same number of decimal places as the original data. Categorical variables will be summarized using frequency tables (number of patients and percentage of patients in each category). Unless otherwise stated, percentages will be calculated out of the analysis set total for the treatment group. Percentages will be rounded to one decimal place.

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

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 identifier ID. The first 3 digits of the patient ID denotes the center number and the next 4 digits denotes the individual patient number.

4.1.2 Hypothesis testing significance level

Statistical tests, where performed, will be conducted at a 2-sided significance level of 5%. 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.

No adjustments for multiplicity (including hierarchical testing) will be made for the primary, secondary and exploratory variables.

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 4.2.4 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). Sensitivity of the primary analysis will be performed using pattern mixture model imputation for missing values and details of this imputation is provided in Section 4.2.4.3.

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 from the early study drug withdrawal, and by (2) plotting the early study drug withdrawal's last HbA1c change data, overlaid with the box plot by visit from completer population.

For categorical endpoints HbA1c goals of <6.5%, ≤6.5% and <7% at 28 weeks, any patient with missing HbA1c value at 28 weeks will be considered as failed to meet HbA1c <6%, ≤6.5% and <7%, respectively, at endpoint (28 Weeks).

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, patients with missing data will be included in the "Total" count and denominator for percentages.

4.1.3.3 Missing safety data

Safety analyses will be conducted on the observed case (OC) 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. See Appendices 3 and 4 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.

In addition, in case of missing AE severity, AE causality, or AE seriousness, a worst-case approach will be used. For missing severity, the AE will be considered severe; for missing causality, the AE will be considered as possibly-related to study drug; for missing seriousness, the AE will be considered serious.

4.1.3.4 Premature discontinuation

Patients who discontinue study medication prior to Visit 11 (Week 28) should enter the 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.

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 receiving rescue medication is defined in Section 3.6.4.

Efficacy

For all efficacy endpoints 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 4.2.4.3).

Safety

Because patients can continuously receive study medication concurrent with the rescue therapy, all safety data (except eGFR) collected during the rescue medication use will be summarized together with data collected prior to the rescue therapy. The exploratory analysis of eGFR will be repeated twice (once including data after rescue therapy and once excluding data after rescue therapy).

4.1.5 Statistical modelling

In general, continuous variables will be analyzed using a MMRM if multiple post-baseline measurements are collected. If only an endpoint measurement is collected, analysis of covariance (ANCOVA) will be used. The MMRM/ANCOVA 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/ANCOVA 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

Unless otherwise stated, for patient disposition and baseline demographics outputs, percentages will be calculated out of the total number of patients in the analysis set displayed in the output, overall and by treatment group (i.e., each denominator will also include the number of patients with missing/unknown values for the endpoint).

4.2.1.1 Patient disposition

Patient disposition information for all patients who provided informed consent, including counts and percentages of patients who entered placebo lead-in, were randomized, received randomized treatment, completed the treatment period, entered the safety follow-up period and completed the safety follow-up period, will be summarized. Patients who were not randomized (including reasons for non-randomization), patients who did not receive randomized treatment, patients who discontinued the randomized treatment period early (including reasons for early discontinuation), patients who did not enter the safety follow-up period (including reasons for not entering) and patients who discontinued the safety follow-up period early (including reasons for early discontinuation), will be summarized overall and for each treatment group.

No percentage will be displayed for number of patients who provided informed consent. The denominator for percentages for the patients entered placebo lead-in will be the number of patients who provided informed consent. The denominator for other percentages will be the total number of patients in the ITT analysis set, overall and by treatment group. A listing of patient

disposition will be provided, including reasons for early discontinuation and reasons for not entering safety follow-up.

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 ITT 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, FAS, evaluable, safety and SFU analysis sets overall and by treatment as per below table.

Table 2 Demographics and baseline characteristics

Demographic and baseline characteristics	Categories
Age years (continuous)	
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
	Hispanic
	Other

Demographic and baseline characteristics	Categories
Region	Africa
	Asia
	Europe
	Latin America
	USA
Country	Brazil
	India
	Mexico
	Republic of Korea
	Russia
	South Africa
	USA
Height (cm), (continuous)	
Weight (kg), (continuous)	
Body Mass Index (BMI) (kg/m^2), (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

Demographic and baseline characteristics	Categories
	3 to <85
	85 to <97
	≥97
Waist Circumference (cm), (continuous)	
Hip Circumference (cm), (continuous)	
Baseline HbA1c %, (continuous)	
HbA1c stratum	≤8.0%
	>8.0%
Background Diabetes therapy	Naïve
	Metformin
	SU
	Metformin + SU
Duration of Diabetes (years), (continuous)	
Duration of Diabetes (years), (categorical)	<1
	≥1 to ≤5
	>5
Baseline FPG (fasting serum glucose), mg/dL, (continuous)	
Baseline FPG (fasting serum glucose), mmol/L, (continuous)	
ECG	Abnormal
	Clinically significant
	Not clinically significant
	Normal
Baseline eGFR (mL/min/1.73^2) (continuous) (Bedside Schwartz equation)	

Demographic and baseline characteristics	Categories
Baseline eGFR (mL/min/1.73^2) (Bedside Schwartz equation)	≥125 <125
Baseline eGFR (mL/min/1.73^2) (continuous) (CKD-Epi equation)	
Baseline Tanner Stage (repeat for each of Pubic hair-female, breast-female, pubic hair-male, genitals-male, overall)	Stage 1 Stage 2 Stage 3 Stage 4 Stage 5

Patient's age (years) and ECG will be taken from the Case Report Form (CRF) at screening.

If a patient switches to a different site during the study, the patient will be summarized at the site he/she originally enrolled in, regardless of when the patient switched sites.

Region will be categorized as following:

Africa - South Africa

Europe - Russia

Asia - India, Republic of Korea

Latin America - Brazil, Mexico

USA - USA.

BMI will be calculated as the ratio of patient's 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 before calculating BMI by dividing by 100.

Percentile of body weight, height and BMI percentile will be determined based on the standardized growth chart for boys and girls.

Values and percentiles will be listed for height, body weight and BMI.

Duration of diabetes (years) will be calculated using the screening visit 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 screening – Date of diabetes diagnosis + 1) / 365.25
Partial date (a) Year and month are not missing, but day is missing (b) Year is not missing, but month and date are both missing (b1) Year of diabetes diagnosis is different from the year of screening (b2) Year of diabetes diagnosis is the same as year of screening	 (a) Impute missing day 1st of the month, then use complete date rule (b1) Difference between year of diabetes diagnosis and year of screening (b2) 2/12 (2 months)

4.2.1.3 Medical/surgical history

All medical/surgical history (pre-existing conditions) by each system organ class (SOC) and preferred term (PT) will be summarized by treatment group for the safety analysis set in accordance to the terminology of the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) available at database lock (DBL).

Conditions will be defined as pre-existing if the start date is on or before the date of informed consent.

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 Prior and 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 dose of randomized study medication (or all medications recorded for patients who did not receive randomized study medication)
- Prior concomitant medication: Medications started prior to and that continue past the first dose of randomized study medication.
- New concomitant medication: Medications with a start date on or after the first dose of randomized study medication up to but not including Visit 11 (Week 28/ED)
- Post-treatment medications: Medications with a start date on or after last dose of study medication

A listing of all medications will be produced.

The number and percentage of patients receiving prior concomitant and new concomitant medications will be summarized by treatment and ATC classification (level 4) for the ITT analysis set. Prior concomitant and new concomitant medications will be combined for summary tables. This will be repeated for the safety follow-up analysis set.

Prior antidiabetic concomitant medications will be summarized separately by reported term for the ITT and safety follow-up analysis sets.

Rescue therapy will be summarized by ATC classification (level 4) and generic term for the ITT and safety follow-up analysis set.

A listing of rescue medications will be provided.

Pre-treatment medications and post-treatment medications will be summarized separately by treatment and ATC classification (level 4) for the ITT analysis set. Post-treatment prescription medications will also be summarized by actual treatment during the randomized period, ATC classification (level 4) and generic term for the safety follow-up analysis set.

Medications with start/stop dates that are partially/completely missing will be imputed as described in Appendix 4.

Review of unique combinations of ATC code classifications and generic terms captured will be performed by a physician prior to database lock to confirm prohibited medication use including the following:

- alpha-glucosidase inhibitors, meglitinide or pramlintide
- inhaled steroids at a dose equal to or above 1000 µg Flovent ® (fluticasone propionate) daily
- oral steroids
- thiazolidinedione

Prohibited medications will be listed.

4.2.2 Treatment compliance

No specific study data was collected for analysis of study medication treatment compliance.

4.2.3 Exposure

Exposure to study medication will be presented for the treatment period (Week 0 to Week 28) for the safety analysis set and for the safety follow-up analysis set.

Duration of exposure in days will be calculated as the date on the last dose CRF form (STR_LD) minus the date on the first dose CRF form (STR_FD) + 1.

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. Duration of exposure will also be categorized into fixed intervals as follows, with number of patients and percentage summarized by treatment group:

- 1-13, 14-27, 28-55, 56-83, 84-111, 112-139, 140-167, 168-195, ≥196 days

In addition, duration of exposure will also be summarized by country and treatment group.

4.2.4 Efficacy analysis

4.2.4.1 Estimands

Estimands for the study are defined in Table 3. Intercurrent events (IE) that may occur during the study are receipt of rescue therapy, IP discontinuation and study withdrawal.

Table 3 Estimand framework

	Attributes			
Estimand	**Population**	**Variable**	**Intercurrent event (IE) strategy**	**Population-level summary**
Primary	Evaluable	Change in HbA1c from baseline to Week 28	All IEs: Data after event excluded. Hypothetical approach due to missing at random (MAR) assumption of MMRM analysis.	Least squares mean difference in CFBL at Week 28 between Total EBID and PBO
Sensitivity to primary	Evaluable	Change in HbA1c from baseline to Week 28	All IEs: Data after event excluded. Hypothetical approach using multiple imputation (MI) pattern mixture modelling.	Least squares mean difference in CFBL at Week 28 between Total EBID and PBO
Supplementary to primary	Evaluable	Change in HbA1c from baseline to Week 28	Rescue and IP discontinuation: Data after event included. Treatment policy approach Withdrawal from study prior to Week 28: Hypothetical approach due to MAR assumption of MMRM analysis	Least squares mean difference in CFBL at Week 28 between Total EBID and PBO

	Attributes			
Estimand	**Population**	**Variable**	**Intercurrent event (IE) strategy**	**Population-level summary**
Sensitivity to supplementary of primary	Evaluable	Change in HbA1c from baseline to Week 28	Rescue and IP discontinuation: Data after event included. Treatment policy approach Withdrawal from study prior to Week 28: Hypothetical approach using MI pattern mixture modelling	Least squares mean difference in CFBL at Week 28 between Total EBID and PBO
Secondary 1	Evaluable	Proportions of patients having HbA1c goals of <7%, ≤6.5%, and <6.5% at Week 28	All IEs: Data after event excluded. Composite approach used, with patients with missing data at endpoint treated as non-responders	Difference in proportion of responders at Week 28 between Total EBID and PBO
Sensitivity to secondary 1	Evaluable	Proportions of patients having HbA1c goals of <7%, ≤6.5%, and <6.5% at Week 28	All IEs: Data after event excluded. Hypothetical approach using MI pattern mixture modelling	Difference in proportion of responders at Week 28 between Total EBID and PBO
Secondary 2	Evaluable	Change in HbA1c from baseline to Week 28 and each intermediate visit	All IEs: Data after event excluded. Hypothetical approach due to missing at random (MAR) assumption of MMRM analysis	Least squares mean difference in CFBL at Week 28 and each intermediate visit between Total EBID and PBO

	Attributes			
Estimand	**Population**	**Variable**	**Intercurrent event (IE) strategy**	**Population-level summary**
Sensitivity to secondary 2	Evaluable	Change in HbA1c from baseline to Week 28 and each intermediate visit	All IEs: Data after event excluded. Hypothetical approach using multiple imputation (MI) pattern mixture modelling	Least squares mean difference in CFBL at Week 28 and each intermediate visit between Total EBID and PBO
Continuous secondary and exploratory efficacy endpoints measured post-baseline at a single endpoint	Full analysis set	Change in XX* from baseline to Week 28	All IEs: Data after event excluded. Hypothetical approach due to missing at random (MAR) using MI ANCOVA analysis	Least squares mean difference in CFBL at Week 28 between Total EBID and PBO
Other continuous secondary and exploratory efficacy endpoints	Full analysis set	Change in HbA1c from baseline to Week 28 and each intermediate visit	All IEs: Data after event excluded. Hypothetical approach due to missing at random (MAR) assumption of MMRM analysis.	Least squares mean difference in CFBL at Week 28 and each intermediate visit between Total EBID and PBO
Exploratory	Safety	Change in eGFR from baseline to Week 28 by baseline eGFR category	All IEs: Data after event excluded. Hypothetical approach due to MAR assumption of MMRM analysis.	Least squares mean difference in CFBL at Week 28 between Total EBID and PBO
Sensitivity to exploratory	Safety	Change in eGFR from baseline to Week 28 by baseline eGFR category	Rescue and IP discontinuation: Data after event included. Treatment policy approach.	Least squares mean difference in CFBL at Week 28 between Total EBID and PBO

	Attributes			
Estimand	**Population**	**Variable**	**Intercurrent event (IE) strategy**	**Population-level summary**
			Withdrawal from study prior to Week 28: Hypothetical approach due to MAR assumption of MMRM analysis.	

*where XX are FSG, FSI, SMBG, HOMA-B, HOMA-S, hip and waist circumference.

4.2.4.2 Analysis of primary variable

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

The primary efficacy analysis will compare treatment groups (Total EBID vs. PBO) with respect to change in HbA1c from baseline Visit 3 (Week 0) to Visit 11 (Week 28) using the MMRM approach. The model will include change in HbA1c as the dependent variable and treatment, baseline HbA1c, background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin + SU), week of visit, baseline HbA1c-by-week interaction and treatment-by-week interaction 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. The least squares (LS) mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between the Total EBID and PBO groups at Visit 11 (Week 28) will be provided. The mean (SD) observed HbA1c at baseline and Week 28 will also be given by treatment group.

HbA1c data from post-baseline visits (including ED) will potentially be included in the MMRM analysis. In addition, if a patient's last available measurement during the 28-week assessment period is from an unscheduled visit or ED visit, the value will be programmatically mapped to the next closest scheduled visit and potentially included in the MMRM analysis. See Section 4.1.3 for details on missing data handling and Section 4.2.4.1 for details on handling of data after IEs.

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/ANCOVA 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. Data collected after discontinuation of IP will be excluded from analyses for all secondary efficacy endpoints.

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

Assessment of homogeneity of treatment effect:

The homogeneity of treatment effect will be assessed by adding treatment by baseline interaction and treatment by strata interaction to the primary MMRM model as described in Section 4.2.4.2. The same covariance structure as used for the primary analysis will be used for this model. The p-value for the interaction effects will be explored to identify the potential trend for non-homogeneity.

Descriptive summary of primary efficacy variable by visit

Actual, change and percent change from baseline values of HbA1c will be summarized using descriptive statistics by visit and treatment group. Plots of mean ± standard error of mean for the change from baseline in HbA1c by visit and treatment group will be provided. Only OC summaries will be provided.

Subgroup analysis

The primary endpoint, change from baseline in HbA1c at week 28, will be summarized descriptively for subgroups of interest listed below. No statistical analyses will be conducted.

- Sex
- Age group: two different definitions.
  - Age (years) <10, 10 to 12, 13 to 16, >16
  - Age (years) <10, 10 to 17, and >17
- Race

Actual, change and percent change from baseline values of HbA1c will be summarized using descriptive statistics by visit and treatment group for each subgroup of the Evaluable analysis set. OC summaries will be provided.

4.2.4.3 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 4.2.4.1 are defined and will be addressed using an MMRM analysis at Week 28.

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 Total EBID group than the outcomes assumed by MAR. A plausible stress test could assume that the outcome for the Total EBID 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.

If this is so, the proposed MNAR sensitivity analysis, which assumes that the trajectory of withdrawals from the Total EBID group, regardless of reason for withdrawal, is as bad as that of PBO patients, is quite conservative and a reasonable stress test of the already somewhat conservative MAR assumption of a common trajectory for withdrawals. Note that this approach constitutes a pattern mixture model (Molenberghs and Kenward, 2007). The patterns here are

defined by the time of withdrawal combined with the treatment group. The time of withdrawal is used in the definition of the pattern to allow the estimate to take account of the improvement over time that tends to be observed in all patients. By the end of the study earlier withdrawals are likely to have improved somewhat more from their last observation, than late withdrawals. Specifically, for patients who drop out after visit t, the change from baseline at visit t + n will be assumed to be the mean for visit t plus the difference in the means of the PBO group at visits t and t + n, given the study data. Then, the overall estimate of treatment effect is obtained by averaging the estimates across the dropout patterns, according to the proportions of dropouts occurring at each visit. Note that in this analysis, PBO missing observations are imputed assuming MAR and follow the pattern of observed PBO observations, and missings for the Total EBID group are assumed MNAR.

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 option of SAS PROC MI with treatment, baseline HbA1c, background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin +SU) and value of the endpoint at each visit. This will create a monotone missing pattern in the dataset within each treatment group. This step will create 1000 imputed datasets.

Step 2: The values for each pattern will be imputed via the chained equation method, using SAS PROC MI option MONOTONE REG (). The MNAR imputation is achieved by using only appropriate study data for each pattern. For example, to impute for time t if the EBID missing data has the trajectory of PBO, include only PBO observations up to and including time t, plus only observations from patients in the EBID group that have observations up to but not beyond time t-1. First, all missings for the first post-baseline visit are imputed, then missings for the next visit are imputed using observed data plus the missings just imputed; and so on to the final visit. The covariates used in the model will be baseline HbA1c, background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin +SU) and HbA1c measured at time t-1.

Step 3: The imputed data from Step 1 and Step 2, along with observed data will be analyzed using an MMRM model for the outcome of change from baseline with treatment, baseline HbA1c, background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin +SU), week of visit, baseline HbA1c-by-week interaction and treatment-by-week interaction as the fixed effects. The variance - covariance structure to be used for this modelling will be unstructured (UN). The estimates from multiple imputed datasets will be combined using Rubin's combination rules for statistical inference (Rubin, 1987) using PROC MI ANALYZE.

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

At Step 1, if a categorical covariate has more than 2 levels, then dummy coding has to be performed to present it as either 0/1 or 1/2. If categorical variable has X categories (X>2) then we would create X-1 dummy variables, using the rule described in the table below.

Table 4 Dummy variables

Category	Dummy variable 1	Dummy variable 2	…	Dummy variable X-1
A	1	0		0
B	0	1		0
…	0	0		0
X-1	0	0		1
X	0	0		0

A supplemental to the primary analysis and a sensitivity to the supplemental of the primary analysis will also be performed. In these analyses, data after rescue medication use or date of IP discontinuation will be included in the MMRM analysis and MI pattern mixture modelling.

Further sensitivity analysis will be as described in section 4.2.4.2, where it will compare active treatment group doses vs Placebo (EBID vs. PBO).

4.2.4.4 Analysis of secondary variables

Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment for the Full analysis set during the treatment period (see Section 3.6.5 for treatment period definition), unless otherwise stated.

As for the primary analysis, data including the ED visit where applicable will be included in the MMRM/ANCOVA and CMH analysis for secondary analysis variables. Data collected from an ED 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 other secondary efficacy endpoints.

Change in HbA1c from baseline Visit 3 (Week 0) to each intermediate visit

The MMRM method for change in HbA1c will be used until Week 28 and to each intermediate visit, using the Evaluable analysis set, which is the same approach as stated in Section 4.2.4.2.

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.

Actual, change and percent change from baseline values of HbA1c will be summarized using descriptive statistics by visit and treatment group for the Evaluable analysis set. OC summaries will be provided.

HbA1c measures will be listed.

Proportions of patients achieving HbA1c goals

Proportions of patients having HbA1c goals of <7%, ≤6.5%, and <6.5% at Week 28 will be compared between treatments (Total EBID vs. PBO) using the Evaluable analysis set via the CMH procedure, in which screening HbA1c strata and background diabetes therapy strata will serve as the stratification factors.

A bar chart of the percentage of patients achieving HbA1c goals of <7%, ≤6.5%, and <6.5% by treatment group will be provided along with p-values.

The number and percentage of patients having HbA1c goals of <7%, ≤6.5%, and <6.5% will be summarized by visit and treatment group for the Evaluable analysis set.

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 the treatment group, and the numerator will be the number of patients achieving HbA1c <7%, ≤6.5%, and <6.5%.

As a sensitivity analysis, also in the Evaluable analysis set, the probabilities of patients reaching HbA1c targets of <7%, ≤6.5%, and <6.5% will be analyzed to Week 28 using the CMH procedure, with missing data imputed using MI pattern mixture model imputation. HbA1c and background diabetes therapy strata will serve as the stratification factors. The imputed HbA1c data for the sensitivity analysis of the primary endpoint will be used for this analysis.

Similar outputs (bar chart including p-values and summary of the numbers and percentage of patients having HbA1c goals by visit and treatment group) will be produced for the Evaluable analysis set for this sensitivity analysis.

Change in body weight, FSG and FSI from baseline Visit 3 (Week 0)

The same MMRM approach (as used for the primary analysis) will be used to analyze the change in body weight from baseline Visit 3 (Week 0) to Week 28, and each intermediate visit. Baseline body weight will replace baseline HbA1c and screening HbA1c strata will be included in these models.

Since only baseline and endpoint FSG and FSI measurements are collected, these endpoints will be analyzed by multiple imputation based on the assumption that missing data are MAR via the following steps:

Step 1: Non-monotone missing data (expected to be infrequent) will be imputed using the MCMC option of SAS PROC MI with treatment, baseline FSG/FSI, screening HbA1c strata (≤8% and >8%) and background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin +SU) and value of the endpoint at each visit. This will create a monotone missing pattern in the dataset within each treatment group. This step will create 1000 imputed datasets.

Step 2: After a monotone missing pattern is created for the data, PROC MI using MONOTONE REGRESSION will be used to impute missing post-baseline values. The covariates used in the model will be treatment, baseline FSG/FSI, screening HbA1c strata (≤8% and >8%) and background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin +SU) and value of the endpoint at each visit. This is MAR imputation.

Step 3: The imputed data from Step 1 and Step 2, along with observed data will be analyzed using separate ANCOVA models for each imputed dataset with change from baseline in FSG/FSI as the dependent variable and treatment, baseline FSG/FSI, screening HbA1c strata (≤8% and >8%) and background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin +SU) as fixed effects. Parameter estimates (LS means and standard errors) and variance/covariance matrix will be obtained for each of the multiple imputed datasets.

Step4: The estimates from multiple imputed datasets will be combined using Rubin's combination rules for statistical inference (Rubin, 1987) using PROC MI ANALYZE.

The seed used will be 88281 for both steps 1 and 2. The number of imputed datasets may be reduced depending on the extent of missing data.

The residuals from the ANCOVA model will be plotted against the quartiles from standard Normal distribution for each of the imputed datasets. A Kolmogorov–Smirnov normality test will be conducted for the residuals. If deviation from normality is noted in the ANCOVA model or imputation diagnostics including trace and autocorrelation plots indicate issues with the multiple imputation then alternative approaches will be discussed e.g. analysis of variance (ANOVA), number of imputed datasets etc.

Actual values and change from baseline will be summarized using descriptive statistics by visit and treatment group for the Full analysis set. OC summaries will be provided where appropriate.

Body weight, FSG and FSI measures will be listed.

Change in SMBG measurements from baseline Visit 3 (Week 0)

In both the seven days prior to Visit 3 (Week 0) and the seven days prior to Visit 11 (Week 28), patients will be asked to perform 4-point SMBG profiles (pre- and 2-hour post-prandial measurements at the 2 main meals of the day) on 3 separate days. SMBG profiles will be summarized as follows.

Only complete pairs of pre-prandial and post-prandial SMBG concentrations will be used. If measurements are taken for more than 2 main meals of the day, then the latest 2 meals of the day will be used that have both a pre-prandial and post-prandial measurement. If measurements were taken on more than 3 separate days in a period, then the latest 3 days of measurements that have both a pre-prandial and post-prandial measurement prior to the visit will be used. If data are missing for a meal, then the remaining available data will be used. Thus, summary measures will be calculated provided the patient had a least one complete pair of measurements in the period.

Mean SMBG will be calculated as the mean of SMBG concentrations (pre- and post-prandial) over the 2 main meals over 3 separate days, where complete pairs of both pre-prandial and post-prandial measurements for a given meal are present. Mean SMBG at baseline Visit 3 (Week 0) and Visit 11 (Week 28) as well as the change in overall daily mean from baseline Visit 3 (Week 0) to Visit 11 (Week 28) will be summarized using descriptive statistics by treatment group for the Full analysis set.

Post-prandial excursions will be calculated as the difference between the pre-prandial and post-prandial blood glucose concentrations (post-prandial – pre-prandial) and averaged (mean) over the 2 main meals over the 3 separate days in each period. Mean post-prandial excursions at

baseline Visit 3 (Week 0) and Visit 11 (Week 28) as well as the change from baseline values will be summarized using descriptive statistics by treatment group.

The mean pre-prandial (post-prandial) SMBG concentration will be defined as the average (mean) measurement over the 2 main meals over 3 separate days in each period. Mean pre-prandial (post-prandial) SMBG concentrations at baseline Visit 3 (Week 0) and Visit 11 (Week 28) as well as the change from baseline values will be summarized using descriptive statistics by treatment group.

The same multiple imputation ANCOVA approach (as used for the analysis of FSG and FSI) will be used to analyze change from baseline Visit 3 (Week 0) to Visit 11 (Week 28) for each of the 4 SMBG summary measures (overall, pre-prandial, post-prandial, post-prandial excursions).

Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) from baseline Visit 3 (Week 0) to Visit 11 (Week 28)

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, the HOMA Calculator (Matthews et al 1985). The HOMA Calculator, developed by Diabetes Trials Unit at the Oxford Center for Diabetes, Endocrinology, and Metabolism, is a computer algorithm 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.

HOMA parameters will be log transformed (natural logarithmic transformation). The observed values and change from baseline for these parameters will be summarized by visit using descriptive statistics (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 value) for the Full analysis set.

The same multiple imputation ANCOVA approach (as used for the analysis of FSG and FSI) will be used to analyze change from baseline Visit 3 (Week 0) to Visit 11 (Week 28) for HOMA-B and HOMA-S.

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.

Proportions of patients discontinuing the study due to failure to maintain glycemic control at Visit 11 (Week 28), and at each intermediate visit

Patients should be discontinued from the study if the patient experiences a loss of glycemic control, as evidenced by:

- Increase in absolute HbA1c ≥0.5% from baseline at 2 consecutive scheduled visits which are at least 1 month apart, prior to study completion

and/or

- Fasting blood glucose >250 mg/dL (13.9 mmol/L) or non-fasting glucose >300 mg/dL (16.7 mmol/L) for 4 days in a 7-day period as measured by SMBG. The patient will return to the clinic for a confirmatory fasting glucose, if possible, or a non-fasting glucose. If by local laboratory measurement a fasting glucose is >250 mg/dL (13.9 mmol/L) or a non-fasting glucose is >300 mg/dL (16.7 mmol/L), the patient will be discontinued from the study.

A patient who discontinues because of loss of glycemic control should have discontinuation reason "Loss of Glucose Control" on their Disposition form. In addition, early patients in the study may have also discontinued due to glycemic control but only stated this on the Adverse Event form.

For the purposes of this analysis a patient will be deemed as having discontinued due to loss of glycemic control if they satisfy at least one of the following criteria:

(a) They have discontinuation reason "Loss of glucose control" on SUM CRF form.

(b) They have an adverse event with lower level MedDRA terms "Loss of glucose control" or "Hyperglycaemia" leading to study drug discontinuation.

The proportion of patients who discontinue the study due to failure to maintain glycemic control will be summarized using frequencies and percentages by visit for the Full analysis set. OC summaries will be provided.

A listing of patients with loss of glycemic control will be produced.

4.2.4.5 Analysis of exploratory efficacy variables

Analysis of all exploratory endpoints will be performed for the Full analysis set unless otherwise specified.

The same MMRM approach (as used for the primary analysis) will be used to analyze the change in BMI, body weight percentiles and BMI percentiles from baseline Visit 3 (Week 0) to Week 28, and each intermediate visit.

The same multiple imputation ANCOVA approach (as used for the analysis of FSG and FSI) will be used to analyze change from baseline Visit 3 (Week 0) to Visit 11 (Week 28) for waist and hip circumference.

Baseline values, the values at each visit, and changes from baseline values will be summarized for BMI, percentiles of body weight, percentiles of BMI, hip circumference and waist circumference by treatment. OC summaries will be provided.

Exploratory efficacy variables will be listed.

4.2.5 Safety analyses

4.2.5.1 Adverse events

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

AEs starting (or worsening) after Week 28/ED but considered by the Investigator as clinically significant and as related to study medication or study procedure, and serious adverse events (SAE) occurring within 30 days of the last administration of study medication will be recorded on the AE CRF and reported in the AE listing.

Treatment-emergent AEs (TEAE) are defined as AEs starting (or worsening) after the first dose of study medication through the end of the treatment + 1 day (or + 30 days for SAEs and other clinically significant or related AEs), including AEs collected after patients initiate glycemic rescue therapy. For patients who discontinue study medication before Week 28, the end of the treatment refers to the date of the ED visit even if last study medication was before this date.

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

Post-treatment AEs are defined as AEs that start (or worsen) during the off-treatment period (safety follow-up period) defined as the day after the Visit 11 (Week 28/ED) + 1 day (or + 30 days for SAEs and other clinically significant or related AEs) to the date of completion of the safety follow-up period. As per protocol only adverse events of special interest (AESIs) will be collected in long term extension.

On-treatment AEs (TEAEs) will be summarized for 28-week treatment period as defined below.

An overall summary of number and percentage of patients experiencing at least 1 TEAE will be presented for EBID and PBO. The AE summary will include the number and percentage of patients experiencing any AE, any SAE, any AE possibly related to study drug, study procedure or study device as judged by the investigator, any AE leading to treatment discontinuation, and any fatal AE.

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

- AEs summarized by SOC, PT, intensity (Mild, Moderate, Severe), possibly related to study drug (No, Yes) and outcome
- SAEs summarized by SOC and PT, intensity (Mild, Moderate, Severe), possibly related to study drug (No, Yes)
- AEs leading to treatment discontinuation (DAE) 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
- Adverse events of special interest by SOC and PT

Summaries will be presented for the treatment period (Safety analysis set).

Any AE that is recorded as the reason for study discontinuation will be considered a DAE regardless of the date recorded.

Potentially immune-related AEs will be listed and identified using the PTs given in Appendix 5.

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 treatment period.

The denominator for summaries will be the number of patients included in the analysis set by treatment group and total.

Selected AEs have been identified as AESIs. During the safety follow-up period, only AESIs will be recorded in the CRF.

The AESIs recorded are as follows:

- Hematological malignancies
- Thyroid neoplasms
- Pancreas neoplasms
- Aplastic anemia
- Pancreatitis
- Pregnancy and pregnancy outcomes (including congenital anomalies)

This list may be updated if additional AESIs are identified. All AESIs will be listed.

AESIs will be summarized by system organ class (SOC), PT, intensity (Mild, Moderate, Severe), seriousness and outcome by the actual treatment during the randomized period for the Safety follow-up analysis set.

4.2.5.2 Hypoglycemic episodes

Confirmed hypoglycemic episodes will be defined as follows:

Minor hypoglycemia:

- Any time a patient feels that he or she is experiencing a sign or symptom associated with hypoglycemia that is either self-treated by the patient or resolves on its own

and

- Has a concurrent fingerstick blood glucose <3.0 mmol/L (54 mg/dL).

Major hypoglycemia:

- any episode with symptoms consistent with hypoglycemia resulting in loss of consciousness or seizure that shows prompt recovery in response to administration of glucagon or glucose

or

- documented hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL]) requiring the assistance of another person because of severe impairment in consciousness or behavior (regardless of whether symptoms of hypoglycemia are detected by the patient).

Episodes will be categorized into major or minor following medical review of the hypoglycemic data by an AstraZeneca or IQVIA physician.

Incidence of hypoglycemic episodes will be summarized by whether they are major or minor and by when the episodes occurred (night-time will be defined to be between 11pm and 5 am) using frequencies and percentages of patients with at least one episode of hypoglycemia occurring during the study. The number of episodes per patient will be classified into categories (0, 1 to 2, 3 to 4, ≥5), and summarized using frequencies by treatment group and visit for the Safety analysis set.

Similar analyses will be performed for confirmed hypoglycemic episodes (those with a blood glucose record) and unconfirmed hypoglycemic episodes (those reported into study database without corroborating blood glucose record).

Minor and Major hypoglycemia rate (adjusted for duration of exposure to study drug therapy = the date of last dose of IP – date of first dose of IP +1) will be summarized by treatment.

The number and percentage of patients with any confirmed and unconfirmed hypoglycemic episodes will also be summarized by baseline sulfonylurea use (yes/no) and treatment.

Hypoglycemic events will be listed.

4.2.5.3 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.

Patients with antibodies to exenatide during the treatment, as well as incidence of negative, any positive, low positive (<625), and high positive (≥625) will also be summarized descriptively by visit.

4.2.5.4 Laboratory data (including CEA and calcitonin concentrations)

Continuous laboratory parameters will be summarized in standardized international (SI) and US units. The visit windows described in Section 4.3.2 will be used. There will be no imputation for missing values.

All hematology, clinical chemistry 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. Separate listings of laboratory values above/below the upper/lower limit of the reference range will be produced. The central laboratory or local laboratory (for assessments measured at a local laboratory) reference ranges will be used. The observed values at each visit to Visit 11 (Week 28) and change from baseline values will be summarized for each of the quantitative laboratory assessments by treatment group for the Safety analysis set. For categorical parameters, shift tables from baseline to each visit to Visit 11 (Week 28) will be produced by treatment group for the Safety analysis set. Tumor marker CEA and calcitonin levels will also be summarized by visit for the Safety follow-

up analysis set. These summaries will include observed values at each visit from Visit 3 (Week 0) through Visit 11 (Week 28) to end of the safety follow-up period and change from baseline by actual treatment group during the randomized period and overall.

Number and percentage of laboratory results that are potentially clinically significant (see Appendix 6) will be listed and summarized by analyte name and criteria for each treatment group for the safety analysis set. A listing of calcitonin values >100 ng/L will be produced.

Estimated glomerular filtration rate (eGFR) will be derived based using the Bedside Schwartz formula (Schwartz, 2009):

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.

An ANCOVA analysis of change in eGFR from baseline to Week 28 by baseline eGFR (hyperfiltrating: ≥125 ml/min/1.73m^2 versus non-hyperfiltrating: <125 ml/min/1.73m^2) will be provided. The same multiple imputation approach as stated in Section 4.2.4.4 will be used. The model will include treatment, screening HbA1c strata (≤8%, >8%), background diabetes therapy strata (drug naïve, metformin only, SU only, and metformin + SU), baseline eGFR as the fixed effects. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between Total EBID 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.

eGFR will also be calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al, 2009):

$eGFR = 141 \times \min(Scr/\kappa, 1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times$ [1.018 if female, x 1.159

if black]

where Scr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1.

eGFR using the CKD-EPI equation will be summarized at baseline and may be analyzed as a sensitivity analysis.

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.

4.2.5.5 Vital signs

Vital signs (systolic and diastolic blood pressure and heart rate) will be summarized by visit and treatment group for the safety analysis set. 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 7) 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 listed.

Vital signs parameters will be listed.

4.2.5.6 ECG

A shift table from screening Visit 1 (Week -3) to Visit 11 (Week 28/ED) will be produced showing the number and percentage of patients in each overall interpretation category (normal, abnormal not clinically significant, abnormal clinically significant) by treatment for the safety analysis set.

A listing of clinically significant abnormal ECGs will be produced.

4.2.5.7 Height

Baseline values (and percentiles), the values (and percentiles) at each visit and changes from baseline values (and percentiles) will be summarized by actual treatment during the randomized period for both the Safety analysis set and for Safety follow-up analysis set.

Height at all visits will be listed.

4.2.5.8 Tanner pubertal assessment

A shift table of change in pubertal stage from baseline Visit 3 (Week 0) will be produced for the safety analysis set (to Week 28, and each intermediate visit) and for the safety follow-up set (to up to 3-years, and each intermediate visit).

Each pubertal assessment category (pubic hair – females, breasts – females, pubic hair – males genitals – males and overall) will be summarized separately.

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

4.2.6 Pharmacokinetic analyses

The PK analysis set is defined in Section 2.1.6.

The exclusion of any patients from the PK analysis will be agreed by the study physician, statistician and PK Scientist during the data review meeting (DRM). The exclusion of concentration data from the PK analysis for an individual time point will be documented by the PK Scientist including the reason(s) for exclusion. These individual concentration data will be listed.

Plasma exenatide concentrations will be listed.

4.3 Conventions

All visits scheduled during the 28-week treatment period should occur within ± 7 days of the scheduled date relative to Visit 3 (Week 0) per the CSP. All visits during the safety follow-up period should occur within 6 months ± 2 weeks of the previous visit.

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 treatment period (day of study medication = Day 1) rather than the nominal visit recorded in the CRF. Designation of visits during the safety follow-up period will be based on the day of evaluation relative to the last date of the treatment period (Visit 11/ED).

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. Visit windows are listed below.

4.3.1 Visit assignments for efficacy variables

Selection of SMBG measurements is discussed in section 4.2.4.4.

Table 5 Visit Windows: HbA1c

Visit	Week	Period	Target Day	Day range
3	0	TP	1	Baseline
5	4	TP	29	2-56
7	12	TP	85	57-112
9	20	TP	141	113-168
11	28	TP	197	169-last day of TP

TP: Treatment period.

Table 5 Visit Windows: FSG, FSI, HOMA-B and HOMA-S

Visit	Week	Period	Target Day	Day range
3	0	TP	1	Baseline
11	28	TP	197	2-last day of TP

TP: Treatment period.

Table 6 Visit Windows: Failure to maintain glycemic control

Visit	Week	Period	Target Day	Day range
3	0	TP	1	Baseline
4	2	TP	15	2-21
5	4	TP	29	22-42

Visit	Week	Period	Target Day	Day range
6	8	TP	57	43-70
7	12	TP	85	71-98
8	16	TP	113	99-126
9	20	TP	141	127-154
10	24	TP	169	155-182
11	28	TP	197	183-last day of TP

TP: Treatment period.

4.3.2 Visit assignment for safety variables

Table 7 Visit Windows: Antibodies to exenatide and vital signs

Visit	Week	Period	Target Day	Day range
3	0	TP	1	Baseline
5	4	TP	29	2-56
7	12	TP	85	57-112
9	20	TP	141	113-168
11	28	TP	197	169-last day of TP

TP: Treatment period.

Table 8 Visit Windows: Body weight, height, BMI and Tanner pubertal assessment

Visit	Week	Period	Target Day	Day range
3	0	TP	1	Baseline
5	4	TP	29	2-56
7	12	TP	85	57-112
9	20	TP	141	113-168
11	28	TP	197	169-last day of TP
801	+26	SFU	+183	last day of TP+1-273
802	+52	SFU	+365	274-454
803	+78	SFU	+546	455-636
804	+104	SFU	+729	637-820
805	+130	SFU	+911	821-l001
806/ED	+156	SFU	+1093	1002-last day of SFU

TP: Treatment period. SFU: Safety follow-up period (+ denotes relative to Visit 11/ED)

Table 9 Visit Windows: Laboratory data, ECG, waist circumference and hip circumference

Visit	Week	Period	Target Day	Day range
3	0	TP	1	Baseline
11	28	TP	197	2-last day of TP
801	+26	SFU	+183	last day of TP+1-273
802	+52	SFU	+365	274-454
803	+78	SFU	+546	455-636
804	+104	SFU	+729	637-820
805	+130	SFU	+911	821-l001
806/ED	+156	SFU	+1093	1002-last day of SFU

TP: Treatment period. SFU: Safety follow-up period (+ denotes relative to Visit 11/ED). Only CEA and calcitonin measured during SFU

Table 10 Visit windows: Hypoglycemic episodes

Visit	Week	Period	Target Day	Day range
3	0	TP	1	Baseline
4	2	TP	15	2-21
5	4	TP	29	22-42
6	8	TP	57	43-70
7	12	TP	85	71-98
8	16	TP	113	99-126
9	20	TP	141	127-154
10	24	TP	169	155-182
11	28	TP	197	183-last day of TP

TP: Treatment period.

Collected at clinic visits but discussed during telephone visits

4.3.3 Rules for safety observations

4.3.3.1 Multiple safety assessments

The assessments for laboratory parameters will be based only on central laboratory values if results for both local and central labs exist.

For the baseline visit window see section 3.6.1. For other visit windows rules below apply.

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.

4.3.3.2 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.

When reporting adverse events by intensity, in addition to providing a summary table based on the event selection criteria detailed above, summary tables will also be provided based on the most intense event during the analysis period - independent of relationship to study medication. For these tables, the following criteria, in order of precedence, will be used to select the event to be included in summary tables:

1. Intensity of event

2. Onset date and time

4.3.3.3 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 INTERIM ANALYSES

Three safety analyses were planned for this trial beginning when at least 25% of the patients have been randomized. To minimize the operational and statistical bias that result from performing a safety assessment, the assessment for this study were to be conducted under the auspices of a Data Monitoring Committee (DMC). The purpose of the DMC was to advise the Sponsor regarding the continuing safety of study participants and the continuing validity and scientific merit of the trial. Details regarding the safety updates are given in the Data Monitoring Committee Charter. No interim safety analyses were in fact performed.

6 CHANGES OF ANALYSIS FROM PROTOCOL

The CSP does not specify eGFR as an endpoint, nor is it provided by the laboratory. However, since eGFR could provide important information it will be derived and analyzed as stated in Section 4.2.4.5 of this SAP.

In addition to the protocol-specified analysis, hypoglycemia will be summarized by baseline sulfonylurea use (yes/no) and treatment.

No Generalized Linear Mixed Model (GLMM) analysis will be done using the binary HbA1c outcome (achieved vs. not achieved HbA1c goal) as the dependent variable.

No per-protocol analysis for supportive analyses will be done.

Due to the lack of data and extent of missing data, efficacy analyses will be pooled across the 5 µg and 10 µg twice daily exenatide doses for statistical testing (Total EBID). Thus, the Fisher Protected Testing produced for the primary analysis will not be required.

For the analysis of SMBG, pre and post measurement for the same meal (lunch/dinner) is changed to be generically 2 main meals (i.e. allowing breakfast) and changed to allow data from consecutive days to be used (as many patients had only consecutive days data recorded).

Due to lack of data, plasma exenatide concentrations and antibodies will only be listed.

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2000 CDC Growth Charts

2000 CDC Growth Charts for the United States: Methods and Development

http://www.cdc.gov/growthcharts/cdc_charts.htm

8 APPENDIX

Appendix 1 Study schedule – treatment period

LY2148568
Study Schedule, Protocol H8O-MC-GWBQ

Visit	1[¥]	2	3	4[‡]	5	6[‡]	7	8[‡]	9	10[‡]	11	UV[†]	ED
Time relative to Visit 3 (weeks)	-3	-1	0	2	4	8	12	16	20	24	28		
Visit Interval (± weeks)*	1	1	0	1	1	1	1	1	1	1	1		
Informed consent/assent**	X												
Patient number assigned	X												
Randomization			X										
Dispense study drug/injection pen		X	X		X		X		X				
Collect study drug			X		X		X		X		X		X
Collect injection pen			X								X		X
Dispense glucose meter/supplies		X											
Instruct on glucose meter		X											
Instruct on hypoglycemia		X											
Instruct on/reinforce lifestyle modification plan[a]		X	X	X	X	X	X	X	X	X	X		X
Placebo injection demonstration under staff supervision[b]		X											
Telephone contact				X		X		X		X			
Injection/pen training		X											
Clinical assessments:													
ECG (12-lead)[c]	X										X		X
Medical history	X												
Height[d]	X	X	X		X		X		X		X		X
Waist/Hip circumference[e]	X		X								X		X
Weight/SBP/DBP/HR	X	X	X		X		X		X		X		X
Physical examination	X										X		X
Pubertal Assessments	X	X	X		X		X		X		X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X		X

(continued)

Study Schedule, Protocol H8O-MC-GWBQ (Continued)

Visit	1[‡]	2	3	4[‡]	5	6[‡]	7	8[‡]	9	10[‡]	11	UV[†]	ED
Time relative to Visit 3 (weeks)	-3	-1	0	2	4	8	12	16	20	24	28		
Visit Interval (± weeks)[*]	1	1	0	1	1	1	1	1	1	1	1		
Clinical assessments (continued):													
Adverse events/Pre-existing conditions[f]	X		X	X	X	X	X	X	X	X	X		X
Distribute study diaries/food and exercise worksheets		X	X		X		X		X				
Collect study diaries/food and exercise worksheets			X		X		X		X		X		X
Transfer diary information to eCRF:													
Pre- and 2-hr post-prandial glucose[g]			X								X		
Hypoglycemic episodes [h]			X		X		X		X		X		X
Injectable therapy dose (day prior to visit)[i]											X		X[j]
OAD dose (day prior to visit)			X		X		X		X		X		X
Date of first dose of study drug recorded			X										
Date of final dose of study drug recorded											X		X
Remind patient to fast prior to next clinic visit		X								X			
Laboratory assessments[k]:													
Hematology			X								X		X
Chemistry	X		X								X		X
Stored Samples			X								X		X
Pregnancy test[l]	X	X	X		X		X		X		X		X
Fasting C-peptide	X												
Fasting insulin			X								X		X

(continued)

LY2148568

Study Schedule, Protocol H8O-MC-GWBQ (Continued)

Visit	1[‡]	2	3	4[‡]	5	6[‡]	7	8[‡]	9	10[‡]	11	UV[†]	ED
Time relative to Visit 3 (weeks)	-3	-1	0	2	4	8	12	16	20	24	28		
Visit Interval (± weeks)[*]	1	1	0	1	1	1	1	1	1	1	1		
Laboratory Assessments[k] (continued):													
Fasting glucose	X		X								X	X[†]	X
Random (non-fasting) glucose												X[†]	
Urinalysis	X		X								X		X
Hemoglobin A_{1c}	X		X		X		X		X		X		X
Calcitonin			X								X		X
CEA			X								X		X
Glutamic acid decarboxylase (GAD65) antibodies[m]	X												
Islet cell antigen (ICA512) antibodies[m]	X												
Antibodies to exenatide[n]			X		X		X		X		X		X
Patient Summary											X		X

Perform procedure as indicated unless time interval is shaded.

Abbreviations: CEA= carcinoembryonic antigen; eCRF = electronic case report form; DBP = diastolic blood pressure; ECG = electrocardiogram; ED = early discontinuation visit; HR = heart rate; OAD = oral antidiabetic drug; SBP = systolic blood pressure; UV= unscheduled visit due to loss of glycemic control; X = performed at this visit.

a A qualified person (i.e. registered dietitian (RD) or certified diabetes educator (CDE)) will introduce and reinforce the lifestyle modification program to the patient on an individual basis beginning at visit 2. At Visit 2 patients will receive 3 food and exercise worksheets that are to be completed and returned at Visit 3. At each subsequent clinic visit, the patients will be given new diaries and worksheets. Beginning at Visit 3, and continuing at each subsequent clinic or telephone visit, the RD/CDE will reinforce the lifestyle modification program with each patient until the study is complete.

b Patient (or parent or guardian) will administer a single placebo dose using the study device under the supervision of study site staff for instruction purposes only.

(continued)

c ECGs will be performed locally.
d Patient's height will be measured without shoes, with a wall mounted stadiometer.
e The patient should be standing with their feet 25-30 cm apart, with their arms hanging naturally at the sides. The measurer should stand to the side of the patient, and fit the tape snugly around the waist on bare skin. Take the measurement at end-expiration with the measuring tape positioned in a horizontal plane (horizontal to the floor) at the level of the top of the bony iliac crest (minimum waist). The hip circumference should be measured at the widest area of the buttocks.
f At visit 1, only pre-existing conditions will be collected. Pre-existing conditions will not be collected at any other visit.
g Patient should complete and record self monitored blood glucose testing on 3 days in the week prior to clinic Visits 3 and 11.
h Hypoglycemic episodes will be collected at all clinic visits (beginning at Visit 3). They will be discussed during the telephone visits
i Patients should not administer injectable therapy (exenatide or placebo) prior to visiting the study site on the day of visit.
j Only applies if the early discontinuation occurs at or after Visit 4 or any subsequent visit.
k Patients should fast about 8 hours prior to visiting the study site on the day of visit 3 and visit 11.
l Pregnancy test to be administered to females of childbearing potential. The pregnancy test performed at Visit 1 will be a serum pregnancy test. All tests performed at subsequent clinic visits will be urine pregnancy tests performed locally.
m A positive result will be reconfirmed by a second test at screening, as false positives have occurred.
n Blood samples will be collected for antibodies to exenatide analysis. Samples that test positive for antibodies to exenatide may be subjected to further immunologic characterization.
* All procedures are to be completed prior to next visit.
** Patients who are17 years of age at the time of screening that reach age of majority (as applicable in their country) during the study will be asked to re-consent.
¥ Visit 1 may take place in 2 different dates to accommodate the fasting procedure. If a patient comes for visit 1 non-fasting then the site will request the patient return in a fasting state within a week to draw the fasting blood glucose and c-peptide.
‡ Visits 4, 6, 8, and 10 are telephone visits where the LMP is reinforced and all adverse events and concomitant medications will be documented.
† At the unscheduled visit (UV) associated with loss of glycemic control, fasting or non-fasting glucose testing will be done locally, at which time the investigator will decide whether the patient will begin early discontinuation procedures or continue in the trial.

Appendix 2 Study schedule – long-term safety follow-up period

Study Schedule, Protocol Addendum H8O-MC-GWBQ(4) – Safety Follow-Up Period

Visit (at intervals of approximately 6 months ± 2 weeks)[a]	801	802	803	804	805	806	ED
Informed consent/assent[b]	X						
Clinical Assessments:							
Height[c,d]	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Tanner pubertal assessment	X	X	X	X	X	X	X
AESIs	X	X	X	X	X	X	X
Ongoing prescription medications	X	X	X	X	X	X	X
Laboratory Assessments[e]:							
Calcitonin	X	X	X	X	X	X	X
CEA	X	X	X	X	X	X	X
Patient Summary[f]						X	X

Abbreviations: AESIs = adverse events of special interest; CEA = carcinoembryonic antigen; ED = early discontinuation.

a All procedures are to be completed prior to next visit.
b Required only for patients previously completing the protocol who have returned to the clinic for evaluation.
c Patients will continue to return to the clinic at 6-month intervals for safety evaluation for up to 3 years or until the difference between 2 consecutive height measurements is less than 5 mm (whichever occurs first).
d Patient's height will be measured without shoes, with a wall-mounted stadiometer.
e Assayed by Sponsor-designated laboratory.
f Patient Summary will be completed at the visit where the difference between 2 consecutive height measurements is less than 5 mm if this criterion occurs before the 3-year period ends.

Appendix 3 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 onse 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 and end date missing, or after first dose of study medication	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 en 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.

Appendix 4 Partial date conventions for CMs

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 stop date and start date ≥ study med start date, assign as new concomitant
		If start date ≥ study med stop date, assign as post-treatment
	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 pre-treatment medication
		If start date < study med start date, assign as prior concomitant
		If start date ≥ study med start date and start date < study med stop date, assign as new concomitant
		If start date ≥ study med stop date, assign as post-treatment
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	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 pre-treatment medication Follow the same algorithm above for a known start date and missing stop date.
Missing	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

Appendix 5 Preferred terms for potentially immune-related AEs

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 generalised
Allergic keratitis	Injection site hypersensitivity	Rash macular
Allergic oedema	Injection site induration	Rash maculo-papular
Allergic otitis media	Injection site inflammation	Rash maculovesicular
Allergic pharyngitis	Injection site macule	Rash papular
Allergic respiratory symptom	Injection site nodule	Rash pruritic
Alveolitis allergic	Injection site oedema	Rash pustular
Anaphylactic reaction	Injection site papule	Rash vesicular
Anaphylactic shock	Injection site photosensitivity reaction	Reaction to excipient
Anaphylactoid reaction	Injection site pruritus	Reaction to preservatives
Anaphylactoid shock	Injection site pustule	Reversible airways obstruction
Angioedema	Injection site rash	Scleral oedema
Arthralgia	Injection site reaction	Scleritis allergic
Arthritis	Injection site recall reaction	Skin oedema
Arthritis allergic	Injection site streaking	Intestinal angioedema
Asthma	Injection site swelling	Stevens-Johnson syndrome
Auricular swelling	Injection site urticaria	Stridor
Bronchial hyperreactivity	Injection site vesicles	Suffocation feeling
Bronchial oedema	Joint effusion	Swelling face
Bronchospasm	Joint swelling	Swollen tongue
Circumoral oedema	Laryngeal obstruction	Throat tightness
Conjunctival oedema	Laryngeal oedema	Tongue oedema
Corneal oedema	Laryngitis allergic	Tongue pruritus
Dermatitis	Laryngotracheal oedema	Toxic epidermal necrolysis

Dermatitis allergic	Lip oedema	Toxic skin eruption
Diffuse cutaneous mastocytosis	Lip swelling	Tracheal obstruction
Drug eruption	Local swelling	Tracheal oedema
Drug hypersensitivity	Localised oedema	Type I hypersensitivity
Drug reaction with eosinophilia and systemic symptoms	Mechanical urticaria	Type II hypersensitivity
Encephalopathy allergic	Nasal oedema	Type III immune complex mediated reaction
Eosinophilia	Nephritis allergic	Type IV hypersensitivity reaction
Eosinophilic oesophagitis	Oculorespiratory syndrome	Urticaria
Epiglottic oedema	Oedema mouth	Urticaria cholinergic
Erythema multiforme	Oedema mucosal	Urticaria chronic
Erythema nodosum	Oesophageal oedema	Urticaria contact
Eye oedema	Orbital oedema	Urticaria papular
Eye swelling	Oropharyngeal swelling	Urticaria physical
Eyelid oedema	Palatal oedema	Urticaria pigmentosa
Face oedema	Periarthritis	Urticaria pressure
Gastrointestinal oedema	Periorbital oedema	Urticaria thermal
Gingival oedema	Pharyngeal oedema	Urticaria vesiculosa
Gingival swelling	Photosensitivity allergic reaction	Urticaria vibratory
Haemorrhagic urticaria	Photosensitivity reaction	Visceral oedema
Hereditary angioedema	Pruritus	Wheezing
Hypersensitivity	Pruritus allergic	
Idiopathic urticaria	Pruritus generalised	

Appendix 6 Criteria for potentially clinically significant laboratory tests

	Parameter	Lower Limit	Upper Limit	Percent Decrease from Baseline	Percent Increase from Baseline
Hematology	Hemoglobin	<0.6 x LLN	>1.3 x ULN	> 25%	>30%
	Leukocytes (WBC)	<0.5 x LLN	>2.0 x ULN	> 60%	>100%
Chemistry	Alanine aminotransferase (ALT)	N/A	>3.0 x ULN	N/A	>300%
	Aspartate aminotransferase (AST)	N/A	>3.0 x ULN	N/A	>300%
	Creatinine	N/A	>2.0 × ULN	N/A	>100%
	Total bilirubin	N/A	>2.0 x ULN	N/A	>300%

LLN: Lower limit of normal value provided by the central laboratory

ULN: Upper limit of normal value provided by the central laboratory

Appendix 7 Criteria for potentially significant vital signs

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			
Value	mmHg	<110	>135
Value – Baseline	mmHg		>10
Baseline – Value	mmHg		>10
Diastolic Blood Pressure			
Value	mmHg	<65	>85
Value – Baseline	mmHg		>10

		Marked abnormality criteria	
Vital signs variables	**Units**	**Low**	**High**
Heart Rate			
Baseline - Value	mmHg		>10

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