Revised Clinical Study Protocol	
Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	4
Date	14 December 2017

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

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden.

The following Amendments and Administrative Changes have been made to this protocol since the date of preparation (28 February 2011):

Amendment No.	Date of Amendment	Local Amendment No:	Date of Local Amendment
01	10 May 2011	NA	NA
02	20 June 2012	NA	NA
03	09 April 2015	NA	NA
04	14 December 2017	NA	NA

Administrative Change No.	Date of Administrative Change	Local Administrative Change No.	Date of Local Administrative Change

Note: The protocol text has been adapted from Amylin Pharmaceuticals template to AstraZeneca template.

VERSION HISTORY

Version 5.0, 14 December 2017

Changes to the protocol are summarized below.

Table 1 (Study Plan) was modified to include injection site reaction assessments to study visits during the Treatment Period, and a new secondary endpoint was added (Section 12.2.2): "Proportion of patients reporting different injection site reactions at Visit 3 (Week 4) through Visit 10 (Week 52)".

Section 6.4.10 (Injection site reaction assessment) was added to describe the injection site reaction assessment and the procedure for classification of injection site reactions as AEs. This assessment was added at the request of the European Medicines Agency Paediatric Committee.

Section 1.3.1 (Ethical Safety Considerations): The statement "Nodule formation should not be categorized as an adverse event (AE) unless accompanied by symptoms such as pain, induration, redness, bleeding, or inflammation" was replaced with an alternative description of reporting of injection site reactions in Section 6.4.10.

Section 5.5 (Treatments) was updated to include a new dual chamber pen formulation of the IP. This update was made due to the anticipated expiry of the current IP formulation prior to completion of the study. The new dual chamber pen formulation is intended for all subjects recruited starting August 2018. Additionally, instructions for study medication administration were clarified to ensure that after Visit 2 (Week 0), caregivers will administer study medication to the patient, and patients will self-administer the study medication only if deemed appropriate by a medically qualitified site staff member, based on the patient's capabilities and characteristics. This change will help to minimize the risk that a patient is allowed to self-administer in cases when the capabilities and characteristics of the patient may make self-administration inappropriate.

Section 13.3.2 (Paternal Exposure) was removed from the protocol: "Pregnancy of the patient's partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should if possible be followed up and documented." This text was removed as no effects of exenatide on the male reproductive tract or in fertility studies with treated males have been observed in nonclinical studies.

Safety assessments related to markers of bone turnover were updated throughout the protocol from deoxypyridinoline to N-telopeptide, replacing an out-of-date assessment with a more informative marker of bone turnover. The related exploratory safety endpoint has been updated as follows: "Change in bone specific alkaline phosphatase and N-telopeptide from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24) and Visit 10 (Week 52)".

Minor clarifications and corrections were made throughout the protocol.

Version 4.0, 09 April 2015
Refer to Appendix I for a summary of changes for this amendment.

Version 3.0, 20 June 2012
Refer to Appendix H for a summary of changes for this amendment.

Version 2.0, 10 May 2011
Refer to Appendix G for a summary of changes for this amendment.

Version 1.0, 28 February 2011
Initial creation.

CLINICAL STUDY PROTOCOL SYNOPSIS

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

International Co-ordinating Investigator

Name: PPD

Address of the Center: PPD

USA

Study centers and number of patients planned

A planned total of 77 patients will be randomized at approximately 20 centers in the United States (US) and in other countries.

Study period		Phase of development
Estimated date of first patient enrolled	Q3 2015	3
Estimated date of last patient completed	Q2 2021	3

Objectives

Primary Objectives

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

- To evaluate the safety and tolerability of EQW compared to placebo following 24 weeks of treatment in children and adolescents with type 2 diabetes mellitus.

Secondary Objectives

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

Study Design and Methods

- Study BCB114 is a Phase 3, double-blind (controlled assessment period), placebo-controlled, randomized, parallel study conducted at multiple clinical study sites.
- This study will assess safety and efficacy of EQW (as monotherapy and adjunctive therapy to oral antidiabetic agents and/or insulin).
- At least 40% and not more than 60% of the randomized patients must be females. At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states.
- Approximately 77 patients will be randomly assigned across 2 treatment groups in a 5:2 ratio to receive either subcutaneous (SC) administration of EQW 2 mg or placebo

(PBO), respectively, with at least 50 patients in the exenatide and at least 20 patients in the PBO group.

  - Group A: EQW 2 mg (52 weeks)

  - Group B: PBO (24 weeks), EQW 2 mg (28 weeks)

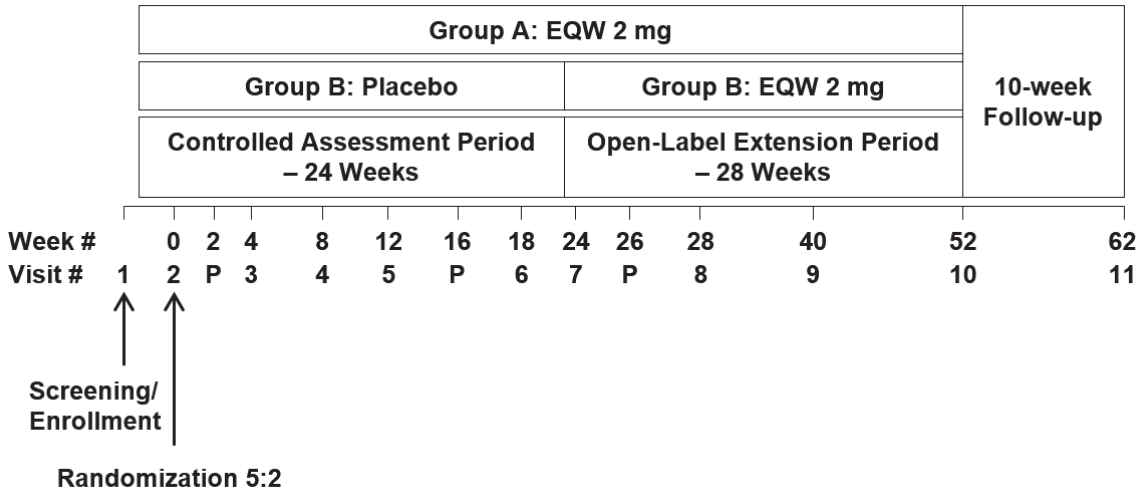
- The study includes a 24-week, controlled assessment period, during which patients will receive study medication according to their randomized treatment group, followed by a 28-week, open-label, uncontrolled extension period in which all patients will receive EQW.

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

- At Visit 1 (Screening), patients will complete eligibility evaluations and screening procedures. Patients who meet eligibility requirements will be randomly assigned to a treatment group (Group A: EQW 2 mg, Group B: PBO) at Visit 2 (Week 0). At Visit 2 (Week 0), patients will complete baseline safety, efficacy, pharmacodynamic (PD), and pharmacokinetic (PK) assessments. Following baseline assessments, patients and parents/caretaker will be trained on study medication administration and the first dose of study medication will be administered. During the controlled assessment period, patients or parent/caretaker will administer study medication. Patients will return to the study site at 4- or 6-week intervals for safety, efficacy, PD, and PK assessments. On weeks with no scheduled study-site visits, patients may opt to return to the study site to have the injection procedure monitored or provided by study-site personnel.

- Following the 24-week controlled assessment period, all patients will enter the 28-week extension period. During the 28-week extension period, all patients will receive EQW 2 mg for 28 weeks up to Visit 10 (Week 52/End of Treatment). The patients will return to the study site at 6- or 12-week intervals for safety, efficacy, PD, and PK assessments and will complete study termination procedures at Visit 11 (Week 62/Study Termination).

The overall study design is shown below.



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

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

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

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

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

- Following Visit 11 (Week 62/Study Termination), patients whose height increase is at least 5 mm between Visit 8 (Week 28) and Visit 11 (Week 62/Study Termination) will participate in an Extended Safety Follow-up Period. Patients who discontinue study medication prior to Visit 11 (Week 62) will also participate in the Extended Safety Follow-up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study-site visits prior to discontinuation of study medication. 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 Extended Safety Follow-up Period.

- The Extended Safety Follow-up Period will continue for up to 3 years or until the increase in height between two 6 month interval visits is less than 5 mm (whichever comes first). No study medication will be administered during the Extended Safety Follow-up Period.

Target Patient Population

A total of 77 male or female children and adolescents of 10 to <18 years of age, diagnosed with type 2 diabetes mellitus and treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (metformin and/or sulfonylurea [SU]) and/or insulin

for at least 2 months prior to screening, will be randomized into this study to yield 70 evaluable patients.

Key Inclusion Criteria

Each patient must meet the following criteria to be enrolled in this study.

1. Is a child or an adolescent of 10 to <18 years old, at Visit 1 (Screening)

2. Has been diagnosed with type 2 diabetes mellitus per American Diabetes Association diagnostic criteria

3. HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/SU, and of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at Visit 1 (Screening)

4. Has a C-peptide of >0.6 ng/mL at Visit 1 (Screening)

5. Has been treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (eg, metformin and/or SU) and/or insulin for their type 2 diabetes for at least 2 months prior to Visit 1 (Screening)

6. Has a fasting plasma glucose concentration <280 mg/dL (15.5 mmol/L) at Visit 1 (Screening).

Key Exclusion Criteria

Patients who meet any of the following criteria will be excluded from the study.

1. Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the Investigator, including but not limited to the following conditions:

(a) Hepatic disease (defined by aspartate or alanine transaminase >3.0 times the upper limit of normal (ULN)

(b) Renal disease or serum creatinine >1.5 mg/dL (132.6 μmol/L) (males) or 1.4 mg/dL (123.8 μmol/L) (females)

(c) Gastrointestinal disease deemed significant by the Investigator

(d) Organ transplantation

(e) Chronic infection (eg, tuberculosis, human immunodeficiency virus, hepatitis B virus, or hepatitis C virus)

(f) Clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of Visit 1 (Screening).

2. Has positive antibody titers to glutamic acid decarboxylase (GAD65) or islet cell antigen (ICA512) at Visit 1 (Screening)

3. Has a personal or family history of elevated calcitonin, calcitonin >100 ng/L, medullary thyroid carcinoma, or multiple endocrine neoplasia-2

4. Has ever used exenatide (exenatide once weekly [exenatide LAR], exenatide BID, BYETTA, or any other formulation) or any glucagon-like peptide-1 (GLP-1) receptor agonist (eg, liraglutide [Victoza®])

5. Is pregnant.

Investigational product, dosage and mode of administration

Exenatide once weekly (EQW) (2 mg) is an extended-release, self-administered, injectable formulation of exenatide containing 5% exenatide sucrose, and 50:50 poly D, L lactic-co-glycolic acid. Weekly doses of EQW will be injected into SC tissue.

Comparator, dosage and mode of administration

Placebo injection will be the same formulation as EQW without the active ingredient injected into SC tissue.

Duration of treatment

The total study duration will be approximately 67 weeks (excluding the Extended Safety Follow-up Period), including up to a 5-week screening period, a 24-week controlled assessment period, a 28-week extension period, and a 10-week post-treatment follow-up period. The beginning of the treatment period should occur within 35 days following screening.

The duration of the Extended Safety Follow-up Period for selected patients is up to 3 years or until the difference between height measurements between two 6-month interval visits is less than a 5 mm increase (whichever comes first).

Outcome variables:

Efficacy Assessments

- HbA1c

Pharmacokinetic Assessments

- Plasma exenatide concentrations

Pharmacodynamic Assessments

- Body weight
- Fasting plasma glucose concentration
- Fasting serum insulin concentration

- C-peptide
- Lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides).

Safety Assessments

- Adverse event (AE) review
- Concomitant medication review
- Physical examinations
- Vital signs
- Pregnancy testing
- Tanner pubertal stage
- Clinical chemistry, hematology, and urinalysis
- Thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, sex hormone-binding globulin (SHBG), estradiol, free T4 (thyroxine), prolactin, cortisol, dehydroepiandrosterone (DHEAS), insulin-like growth factor 1 (IGF-1), bone specific alkaline phosphatase, and N-telopeptide
- Carcinoembryonic antigen (CEA)
- Calcitonin
- Pancreatic amylase and lipase
- Antibodies to exenatide.

Statistical methods

Analysis Populations

Efficacy analyses will be performed in the Intent-to-Treat (ITT) Population or in a set of evaluable patients coming from the ITT Population, ie, the Evaluable Population and/or the Per-Protocol (PP) population. The Evaluable Population will be used for the primary analysis. Safety analyses will be performed for the ITT Population unless stated otherwise.

The following populations will be used for the summaries and analyses of the study data. The populations are defined as follows:

- Intent-to-Treat (ITT): The ITT Population will consist of all randomized patients who receive at least 1 dose of randomized study medication.

- Evaluable Population: The Evaluable Population will consist of all ITT patients who receive at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment.
- Per-Protocol (PP): The per protocol analysis set will be a subset of the ITT population through the exclusion of those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis. Detailed exclusion criteria for the PP population will be specified in the Statistical Analysis Plan (SAP). Patients excluded from the PP analysis will be identified before database lock.

Primary Endpoint:

- Change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24)

Secondary Endpoints:

- Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in fasting plasma glucose concentration from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to intermediate visit as applicable
- Proportions of patients achieving HbA1c goals of ≤6.5% and <7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit
- Change in body weight from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in fasting insulin and C-peptide from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to intermediate visit as applicable
- Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by HOMA in EQW patients not taking insulin from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Change in lipids from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), Visit 10 (Week 52) as applicable
- Change in blood pressure from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable
- Plasma exenatide concentrations at baseline Visit 2 (Week 0), Visit 7 (Week 24), Visit 10 (Week 52) and intermediate visit, as applicable

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

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

Exploratory Endpoints:

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

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

Safety Endpoints:

- Safety and tolerability endpoints including incidence of treatment emergent AEs, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit, as applicable

- Change in calcitonin, pancreatic amylase, and lipase from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52)

- Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)

- Tanner pubertal stage at baseline Visit 2 (Week 0), Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52).

Exploratory Safety Endpoints:

- Change in CEA from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52)

- Change in bone specific alkaline phosphatase and N-telopeptide from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)

- Change in FSH, LH, FSH/LH total testosterone*, SHBG*, and estradiol from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)

- *Change in total testosterone and SHBG will be measured also at Visit 9 (Week 40). Free testosterone will be calculated from total testosterone and SHBG values at Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52).

Statistical analysis methods

Statistical Analyses of Primary Endpoint:

The mixed models repeated measures (MMRM) approach will be used to analyze the change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24). The model will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and region as the fixed effects, baseline HbA1c as the covariate, and patients as the random effects. The variance - covariance structure to be used for this modeling 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.

Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the SAP.

Statistical Analyses of Secondary Endpoints:

Analysis of all secondary endpoints will be performed in the ITT population. Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment.

Proportions of patients having HbA1c target values of ≤6.5% and <7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit will be compared between treatments using the Cochran-Mantel-Haenszel (CMH) procedure, in which baseline HbA1c strata will serve as the stratification factors. Any ITT patient who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint.

As a supportive analysis, the probabilities of patients reaching HbA1c targets of ≤6.5% and <7.0% will also be analyzed using a logistic regression model. The independent variables will include treatment group, HbA1c baseline strata (<9.0% or ≥9.0%), and country as factors, and baseline HbA1c as a continuous covariate.

The same CMH procedure and logistic regression as described above will be used to analyze data on proportion of patients discontinuing the study, needing rescue due to failure to maintain glycemic control. However, the number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit will be analyzed using descriptive statistics only.

The proportions of patients (N [%]) reporting different injection site reactions will be summarized at Visit 3 (Week 4) through Visit 10 (Week 52) using descriptive statistics.

Statistical Analyses of Exploratory Endpoints:

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

Statistical Analyses of Safety Endpoints:

The proportion of patients discontinuing the study, the proportion of patients needing rescue treatment due to failure to maintain glycemic control, and the number of rescue episodes will be evaluated. Absolute and change in calcitonin, pancreatic amylase, and lipase, TSH, free T4, prolactin, cortisol, IGF 1, DHEAS, Tanner pubertal stages, FSH, LH, FSH/LH, total testosterone, estradiol, CEA, and bone specific alkaline phosphatase and N-telopeptide will be summarized by visit. Antibody to exenatide data will be listed and summarized. On treatment AEs will be summarized by treatment, system organ class, and preferred term defined by Medical Dictionary for Regulatory Activities (MedDRA). Standard laboratory measures and vital signs measurements will be listed and summarized by treatment arm.

Interim Analysis

One interim analysis is planned when 40 patients will have completed 24 weeks of treatment, including early withdrawal. This interim analysis will be performed by the independent Data Monitoring Committee (DMC) that does not directly involve with the study design, conduct, and data analysis. No study personnel will have access to the unblinded clinical data to maintain the integrity of the double-blind study design.

Purpose of the interim analysis is to ensure safety of the patient population. Hence, the DMC will only look at the safety data collected in this study. The DMC will review the safety data first in a blinded fashion and then, if needed, will look at the unblinded data to assess the risk of the paediatric patients being exposed to the active drug compared to placebo, using the AE and/or safety laboratory data of the study population.

Analysis of Extended Safety Follow-up Period

Details are provided in Appendix E.

Stratification during randomization

Randomization will be stratified by screening HbA1c (%) <9.0% and ≥9.0%. The restriction on gender in the study population (female patients between 40% and 60%) and also on the ethnicity and lifestyle (40% to 60% patients with European ethnicity and lifestyle) will be enforced through putting caps on enrollment of patients with different genders and from different regions (Europe, US, and others).

Sample Size

Approximately 77 patients who have met all study requirements will be randomized in a ratio of 5:2 to the exenatide or placebo treatment group on Visit 2 (Week 0) and will be carried out with stratification to achieve a balanced distribution of patients across treatment groups with regard to the screening HbA1c strata (<9.0% or ≥9.0%).

The analysis will be performed in the set of evaluable patients coming from the ITT population. Assuming a 10% drop-out rate, approximately 70 patients will complete the 24-week controlled treatment period of study. Based on calculation done using the software NQuery Advisor Version 7, an overall power of 74% will be provided to reject the null hypothesis of no difference between the 2 treatment arms assuming a true treatment difference of -0.7% between exenatide and placebo in changes from baseline for HbA1c (%). This

power computation also assumes a common standard deviation of 1.0% and a two-sided significance level of 0.05.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AE	adverse event
ALT	alanine aminotransferase
AR (1)	autoregressive order 1
ARH (1)	heterogeneous autoregressive order 1
AST	aspartate aminotransferase
ATC	Anatomic Therapeutic Chemical
βhCG	human chorionic gonadotropin, beta subunit
BID	twice daily
BMI	body mass index
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CK-MB	Creatinine kinase MB
CMH	Cochran-Mantel-Haenszel
CPK	creatine phosphokinase
CRF	case report form
CRO	contract research organization
CSR	Clinical Study Report
DAE	adverse event leading to discontinuation
DHEAS	dehydroepiandrosterone
DMC	Data Monitoring Committee
DPP-4	dipeptidyl peptidase-4
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EQW	exenatide once weekly
EU	European
FDA	Food and Drug Administration
Free T4	thyroxine

Abbreviation or special term	Explanation
FSH	follicle-stimulating hormone
GAD65	glutamic acid decarboxylase
GCP	Good Clinical Practice
GLP-1	glucagon-like peptide-1
GMP	Good Manufacturing Practice
HbA1c	glycosylated hemoglobin
HDL-C	high-density lipoprotein cholesterol
HIPAA	Health Insurance Portability and Accountability Act
HOMA	homeostatic model assessment
HOMA B	homeostatic model assessment of beta-cell function
HOMA S	homeostatic model assessment of insulin sensitivity
IB	Investigator's Brochure
ICA512	islet cell antigen
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IGF-1	insulin-like growth factor 1
IRB	Institutional Review Board
ITT	intent-to-treat
IVRS	interactive voice response system
IWRS	interactive web response system
LDL-C	low-density lipoprotein cholesterol
LH	luteinizing hormone
MedDRA	Medical Dictionary for Regulatory Activities
ML	maximum likelihood
MMRM	Mixed Models Repeated Measures
MTC	medullary thyroid cancer
NDA	new drug application
OAE	other significant adverse event
PBO	placebo
PD	pharmacodynamic
PK	pharmacokinetic

Abbreviation or special term	Explanation
PLG	poly D,L-lactide-co-glycolide
PP	per protocol
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous
SHBG	sex hormone binding globulin
SMBG	self-monitored blood glucose
SU	sulfonylurea
SUSAR	Suspected Unexpected Serious Adverse Reaction
TC	total cholesterol
TG	triglycerides
TSH	thyroid stimulating hormone
TZD	thiazolidinedione
ULN	upper limit of normal
UN	unstructured
US	United States
WBDC	Web Based Data Capture

1 INTRODUCTION

1.1 Background

Exenatide (BYETTA® [exenatide] injection) is a glucagon-like peptide-1 (GLP-1) receptor agonist approved by the United States (US) Food and Drug Administration (FDA) as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (new drug application [NDA] 021-773) (Amylin Pharmaceuticals Inc., 2008). BYETTA has also been approved by the European Commission as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of metformin and an SU or metformin and a TZD, or insulin glargine but have not achieved glycemic control.

Exenatide exhibits many of the same glucoregulatory or glucose-lowering actions of GLP-1, a naturally occurring incretin hormone, but exenatide is not substantially degraded by dipeptidyl peptidase-4 (DPP-4), which efficiently degrades glucagon-like peptide-1 (GLP-1) *in vivo* (Kendall et al, 2006; Riley et al, 1997). Nonclinical studies have shown that exenatide has several glucose-lowering actions. These include amplification of insulin secretion (insulinotropic effect), suppression of postprandial glucagon secretion (glucagonostatic effect), reduction in food intake, and modulation of nutrient delivery. In clinical studies, exenatide administered twice daily (BID) improves glycemic control by restoring beta-cell function, decreasing fasting and postprandial glucose concentrations, and producing progressive weight loss in patients with type 2 diabetes.

Exenatide once weekly (EQW; BYDUREON™ [powder and solvent for prolonged release suspension for injection]) is an extended release formulation of BYETTA that is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (NDA 022-200) and by the European Commission (EU Marketing Authorization EU/1/11/696/001) for treatment of type 2 diabetes in combination with oral therapy. The EQW formulation prolongs systemic exposure within the known therapeutic range of BYETTA by slow release from the site of injection to the systemic circulation and provides patients with the option of a weekly dosing regimen. The drug delivery technology uses biodegradable polymeric microspheres, which entrap exenatide and provide extended release of medication over days to months (Riley et al, 1997). The microspheres are composed of exenatide incorporated into a matrix of poly D,L-lactide-co-glycolide (PLG). PLG is a common, biodegradable medical polymer with a history of safe use in humans. Once injected into the subcutaneous (SC) space, the polymer biodegrades over time, providing continuous release of exenatide into the circulation. Regular dosing with EQW 2 mg results in a gradual increase in mean plasma exenatide concentrations over approximately 6 to 8 weeks. The 19 completed and ongoing studies of the EQW development program have evaluated the efficacy, pharmacokinetics, and safety of the once weekly formulation of exenatide in healthy volunteers and in patients with type 2 diabetes. The EQW has demonstrated robust glucose-lowering effects in the fasting, preprandial, and postprandial states, resulting in improvement in 24-hour glucose control in patients with type 2 diabetes.

EQW has also been demonstrated to be well tolerated, with a safety profile generally consistent with that of exenatide BID, although with less nausea and vomiting.

Approximately 90% of individuals with diabetes have type 2 diabetes. Until recently, type 2 diabetes has been regarded as a disease of the middle-aged and elderly (Alberti et al, 2004; Bloomgarden, 2004a). While still a relatively rare diagnosis in children and adolescents, the incidence of type 2 diabetes is increasing worldwide commensurate the global obesity epidemic. It is anticipated that type 2 diabetes will become the primary type affecting children of certain ethnic groups in the next decade (International Diabetes Federation, 2004). Current estimates of several ethnic groups worldwide indicate that the prevalence of type 2 diabetes has already surpassed the incidence of type 1 diabetes in this population (World Health Organization, 2011;Centers for Disease Control and Prevention, 2010).

In the US, a diagnosis of type 2 diabetes in children and adolescents (<19 years of age) has increased significantly over the last twenty years (World Health Organization, 2011). In the young, 8% to 46% of new diabetes cases are presented as type 2 diabetes and there are approximately 176500 documented children and adolescents <20 years of age with this disease (Centers for Disease Control and Prevention, 2010; Von Karla and Hewett, 2007). Analyses of the SEARCH database, the largest database of children registered with diabetes in the US, indicates a greater incidence of type 2 diabetes in children >10 years of age compared to children <10 years of age and a higher frequency of type 2 diabetes in US minority populations compared to non-Hispanic whites (Dabelea et al, 2007). The majority (85%) of children and adolescents diagnosed with type 2 diabetes are obese at the time of diagnosis and often have a family history of diabetes (American Diabetes Association, 2000).

Although substantial data on the incidence of pediatric type 2 diabetes in European communities are not yet available, a significant rise in the incidence of childhood obesity has been observed, suggesting an increase in the prevalence of type 2 diabetes will follow shortly (Erhardt, 2004). The pattern of prevalence of this disease is anticipated to mirror that observed in the US in that the majority of cases are expected to be found in ethnic communities and in families with a history of diabetes.

While multiple medications are available for the treatment of diabetes in the adult population, only metformin has been approved for use in children and adolescents with type 2 diabetes (American Diabetes Association, 2000) and just a few studies have investigated the safety and efficacy of diabetic agents in the pediatric population (Gemmill et al, 2010). The current treatment recommendation in asymptomatic children following the failure of diet and exercise is the initiation of metformin monotherapy (Von Karla and Hewett, 2007; Bloomgarden, 2004b). If metformin monotherapy fails to achieve American Diabetes Association recommended glycosylated hemoglobin (HbA1c) levels, physicians often rely on SUs or insulin (American Diabetes Association, 2000).

Therefore, additional research examining new or existing therapies for type 2 diabetes in children and adolescents is necessary to determine optimal treatment in this population.

1.2 Rationale for Conducting this Study

The incidence of type 2 diabetes in children and adolescents is increasing worldwide commensurate with the global obesity epidemic. It is anticipated that type 2 diabetes will become the primary form of diabetes affecting children in the next decade (International Diabetes Federation, 2004). Evidence has shown that a diagnosis of type 2 diabetes in childhood coupled with inadequate glycemic control, increases the risk of early end organ damage and mortality (Cavallo, 2006).

Exenatide exhibits many desirable antidiabetic properties. Clinical studies conducted in adults have demonstrated that exenatide administered BID (BYETTA) improves glycemic control by restoring first-phase and improving second phase beta-cell function, thus decreasing postprandial and also fasting glucose concentrations. In addition, long-term exenatide therapy has been demonstrated to produce modest progressive weight loss in patients with type 2 diabetes.

The purpose of this study is to examine the effects of 2 mg EQW in children and adolescent patients with type 2 diabetes with respect to glycemic control, safety, and tolerability.

1.3 Benefit/risk and ethical assessment

Details regarding potential risks associated with administration of EQW are provided in the Investigator's Brochure.

The study will provide efficacy and safety information for EQW, with or without metformin, SU, and/or insulin, in children and adolescent patients with type 2 diabetes mellitus. Patients in the placebo group will receive EQW-matching placebo, with or without metformin, SU, and/or insulin. All patients will be monitored throughout the study to ensure adequate glycemic control.

1.3.1 Ethical safety considerations

Based on safety data from previous clinical studies of EQW (where the majority of patients had type 2 diabetes), development of small, asymptomatic, subcutaneous injection site nodules is expected. These nodules are usually transient and resolve without intervention. Injection site reactions were typically mild, transient, and did not interfere with therapy. Other risks with exenatide treatment include mild to moderate nausea, vomiting, and diarrhea.

Exenatide is a peptide and thus has the potential to elicit an allergic response. The Investigator will instruct patients to be aware of signs and symptoms that are consistent with an allergic response and to contact the Investigator immediately if such a response is suspected.

In patients using exenatide BID (BYETTA), there have been rare postmarketing reports of altered renal function, including increased serum creatinine, renal impairment, worsened chronic renal failure, and acute renal failure, sometimes requiring hemodialysis. Some of these events occurred in patients receiving 1 or more pharmacologic agents known to affect renal function/hydration status and/or in patients experiencing nausea, vomiting, and/or diarrhea, with or without dehydration.

Postmarketing cases of acute pancreatitis, including fatal and non-fatal hemorrhagic or necrotizing forms, have been reported in patients treated with BYETTA. In controlled clinical trials where exenatide (BID or once weekly) was studied in comparison to placebo or insulin, no differences in event rates for pancreatitis have been observed. Patients will be instructed to contact the Investigator or other healthcare provider if they experience persistent severe abdominal pain, with or without vomiting, because this is the hallmark symptom of acute pancreatitis. If pancreatitis is suspected, study medication should be discontinued. If pancreatitis is confirmed, appropriate treatment should be initiated and the patient should be carefully monitored until recovery. The Sponsor and Medical Monitor or Global Safety Physician should be contacted to discuss patient disposition.

Results from a 2-year carcinogenicity study performed in rats indicated that administration of exenatide once weekly was associated with a statistically significant increase in thyroid C-cell cancer incidence in both males and females. C-cell cancers are an age-related tumor in rats although this kind of cancer is rare in humans. No other relevant drug-related effect on survival or tumor incidence in any other tissues (including other types of thyroid tumors) was found in the rat study. Exenatide (BID or once weekly) is not mutagenic or genotoxic in in-vitro assays. There was no evidence of any proliferative lesions in any tissue in primates in a toxicology study with up to 11 months of exposure to exenatide once weekly. The clinical significance of these findings in rats and the relevance to humans is not known. At the time this protocol was written, there were no reported cases of medullary thyroid cancer (MTC) in clinical trials with exenatide (BID or once weekly), but have been 2 cases of MTC in the global postmarketing pharmacovigilance database for exenatide BID (BYETTA), and no cases for EQW (BYDUREON), which includes an estimated 3.5 million patient-years of patient exenatide exposure from product launch to 30 September 2014. These 2 cases are assessed as not related to exenatide.

If AEs are severe, the Investigator should contact the Sponsor to discuss appropriate clinical management as well as the continued participation of patients experiencing these events. Investigators will make frequent safety and tolerability assessments throughout study conduct. If a patient's hemoglobin decreases below 11 g/dL, the patient will be withdrawn from the study medication at the Investigator's discretion. The Investigator may also perform physical examinations, electrocardiograms (ECGs), or laboratory tests as deemed necessary according to his/her clinical judgment. Specific instructions for handling hypoglycemia episodes are provided in Section 6.4.3.3.

If patients experience a loss of glucose control, defined as 1) an increase from baseline in HbA1c values by 1.0% or more at 2 consecutive clinic visits that are at least 1 month apart, or

2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home self-monitored blood glucose (SMBG), and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, rescue treatment will be initiated (See Section 5.6). A clinic visit to confirm the values obtained by home SMBG or fasting/random glucose tests must take place within 2 weeks following the aforementioned self-measurements.

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

2 STUDY OBJECTIVES

2.1 Primary objectives

The primary objectives of the study are:

- To assess the effect on glycemic control, as measured by HbA1c, of EQW following 24 weeks of treatment compared to placebo in children and adolescents with type 2 diabetes mellitus
- To evaluate the safety and tolerability of EQW compared to placebo following 24 weeks of treatment in children and adolescents with type 2 diabetes mellitus

2.2 Secondary objectives

The secondary objectives of this study are:

- To compare the effects of EQW following 24 weeks of treatment to those achieved by placebo in children and adolescents with type 2 diabetes mellitus on the following:
  - Fasting plasma glucose concentration
  - Proportion of patients achieving HbA1c goals
  - Body weight and Tanner pubertal stage
  - Blood pressure and lipids
- To assess the effects of long-term exenatide once weekly therapy (~1 year) in children and adolescents with type 2 diabetes mellitus on the following:
  - Long-term safety and tolerability
  - Parameters related to glycemic control, including HbA1c, fasting plasma glucose concentration, and proportion of patients achieving HbA1c goals

  - Body weight and Tanner pubertal stage
  - Blood pressure and lipids

- To examine the effect of exenatide once weekly on beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostatic model assessment (HOMA) in children and adolescents with type 2 diabetes who are not taking insulin
- To assess the pharmacokinetics of exenatide once weekly in children and adolescents with type 2 diabetes

3 STUDY PLAN AND PROCEDURES

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca standard procedures.

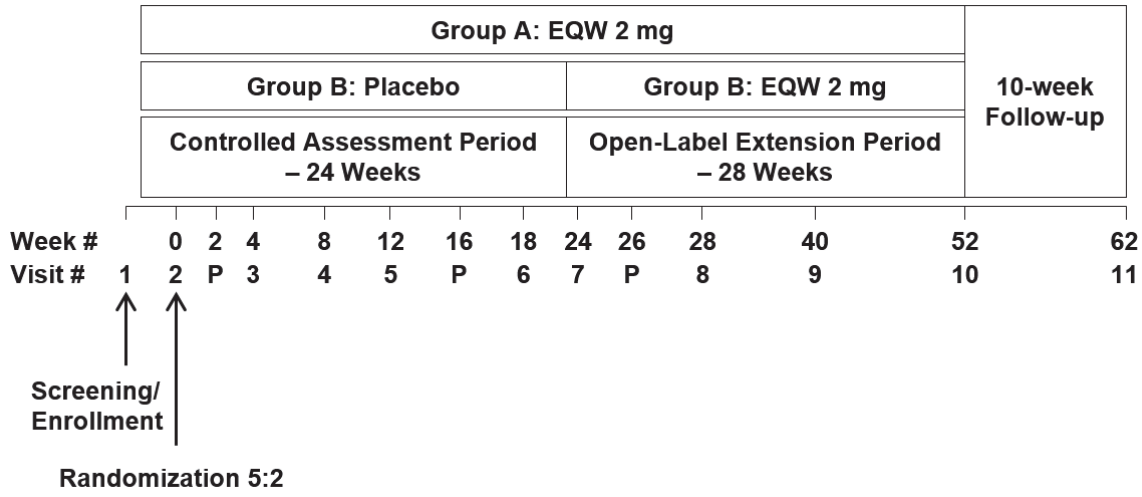
3.1 Overall study design and flow chart

- This Phase 3, double-blind (controlled assessment period), randomized, multicenter, placebo-controlled parallel study is designed to examine the efficacy and safety of EQW compared to placebo (PBO) in adolescents with type 2 diabetes for 24 weeks.
- This study will assess safety and efficacy of EQW (as monotherapy and adjunctive thrapy to oral antidiabetic agents and/or insulin).
- At least 40% and not more than 60% of the randomized patients must be females. At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states.
- Long-term safety and efficacy of EQW will subsequently be monitored for 28 weeks in the open-label, uncontrolled extension period (through Week 52).
- The study will be terminated at Visit 11 (Week 62/Study Termination) which will be a follow-up visit occurring 10 weeks after the last dose administration at Visit 10 (Week 52).
- This study will be conducted in 77 patients with type 2 diabetes treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin for at least 2 months prior to screening. A schematic overview of the study design is presented in Figure 1. During the controlled assessment period, approximately 77 patients will be randomly assigned in a 5:2 ratio to receive either EQW 2 mg (Group A) or PBO (Group B), to yield at least 70 evaluable patients: at least 50 patients in the exenatide and at least 20 patients in the PBO group.

- Following the 24-week controlled assessment period, patients assigned to the EQW 2 mg treatment (Group A) will continue to be treated with EQW 2 mg during the extension period (through Week 52). Patients randomized to PBO (Group B) will receive EQW 2 mg beginning at the start of the extension period, Week 25 through Week 52.

- In addition to receiving study medications, all patients will participate in a lifestyle intervention program encompassing diet and physical activity modifications following the signing of the informed consent and assent forms (Visit 1 [Week -2]) through the end of the extension period (Week 52).

Figure 1 Study Design



Abbreviations: EQW, exenatide once weekly; P, phone call
Note: All visits scheduled during the controlled assessment period and during the open-label extension period should occur within ±2 days of the scheduled date, relative to Visit 2 (Week 0).
Visit 11 must occur at least 10 weeks from final dose but no more than 12 weeks.
The Investigator and/or qualified study-site personnel will contact patients by phone at Week 2, Week 16, and Week 26 to discuss study compliance, address any questions related to study medication, and review adverse events.

- Protocol BCB114 consists of a 24-week controlled assessment period and a 28-week open-label extension period.

- The study includes 11 visits to the clinical study site. The study will begin with Visit 1 (Screening) to obtain written informed consent and assent, and assess patient eligibility. Patients will also be asked to participate in a lifestyle intervention program encompassing diet and physical activity modifications. Patient eligibility must be confirmed prior to randomization. The drug screen will be done locally. Eligible patients will return to the study site within 35 days following screening procedures for

randomization at Visit 2 (Week 0), the start of the controlled assessment period. At Visit 2 (Week 0), following baseline efficacy, safety, pharmacodynamic (PD), and pharmacokinetic (PK) assessments will be done. A medically-qualified staff member will demonstrate the preparation of SC study medication for the patient or a designated caregiver and will administer the first dose of SC study medication. In addition to receiving study medications, all patients will be asked to continue the lifestyle intervention program encompassing diet and physical activity modifications.

- At Week 2 and Week 16 of the controlled assessment period, patients will be contacted by phone by qualified study-site personnel to discuss study compliance, address any questions related to study medication, and review AEs.

- During the controlled assessment period, patients will return to the clinical study site at 4- and 6-week intervals at Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 18), and Visit 7 (Week 24) to complete efficacy, PD, PK, and safety assessments.

- Following the controlled assessment period, all patients enter a 28-week extension period. Group A patients will continue to receive EQW for an additional 28 weeks up to Visit 10 (Week 52). Group B patients will initiate treatment with EQW for 28 weeks up to Visit 10 (Week 52). During the 28-week extension period, patients will be required to return to the clinical study site at 6-, 10-, and 12-week intervals at Visit 8 (Week 28), Visit 9 (Week 40), and Visit 10 (Week 52) for efficacy, safety, PD, and PK assessments.

- At Week 26 of the controlled assessment period, patients will be contacted by phone by qualified study-site personnel to discuss study compliance, address any questions related to study medication, and review AEs

- Patients who withdraw from the investigational product after Visit 2 (Week 0) and prior to Visit 10 (Week 52) will be invited to return to the study site for an Early Termination visit for HbA1c, fasting plasma glucose, body weight, and clinical safety laboratory measures.

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

- All patients will return to the site on Visit 11 (Week 62/Study Termination).

A detailed schedule of study procedures by visit is presented in Table 1 (Study Plan).

Table 1 Study Plan

Evaluation	Visit 1 Screening	Controlled Assessment Period 24 weeks									Extension Period 28 Weeks				
		Visit 2 Week 0	Week 2 Phone Call	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12	Week 16 Phone Call	Visit 6 Week 18	Visit 7 Week 24	Week 26 Phone Call	Visit 8 Week 28	Visit 9 Week 40	Visit 10 Week 52 (End of Study Treatment)	Visit 11 Week 62* (Study Termination)	Early Termination
Fast (≥8 Hours Prior to Visit)	X	X		X	X	X			X				X		X
Informed Consent/Patient Assent/HIPAA	X														
Review of Inclusion and Exclusion Criteria	X	X													
Randomization		X													
Complete Medical History/Urine Drug and Alcohol Screen	X														
Adverse Event Assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medication Review	X	X		X	X	X		X	X		X	X	X		X
Physical Examination		X				X							X	X	X
ECG		X													
Body Weight, Height, and Vital Signs	X	X		X	X	X		X	X		X	X	X	X	X
Blood Sample for Serum βhCG Test (Females)	X													X	X

		Controlled Assessment Period 24 weeks									Extension Period 28 Weeks				
Evaluation	**Visit 1 Screening**	**Visit 2 Week 0**	**Week 2 Phone Call**	**Visit 3 Week 4**	**Visit 4 Week 8**	**Visit 5 Week 12**	**Week 16 Phone Call**	**Visit 6 Week 18**	**Visit 7 Week 24**	**Week 26 Phone Call**	**Visit 8 Week 28**	**Visit 9 Week 40**	**Visit 10 Week 52 (End of Study Treatment)**	**Visit 11 Week 62* (Study Termination)**	**Early Termination**
Urine βhCG Test (Females)		X		X	X	X		X	X		X	X	X		
Tanner Pubertal Stage		X				X			X			X	X		X
Injection site reaction assessment				X	X	X		X	X		X	X	X		
Chemistry, Hematology, Urinalysis	X	X				X			X				X	X	X
HbA1c	X	X		X	X	X		X	X		X	X	X		X
Blood Samples for Fasting Glucose and Insulin	X	X		X	X	X			X				X		X
C-peptide	X														
GAD65 and ICA 512 antibodies	X														
Urinary Albumin Creatinine		X				X							X		X
Calcitonin	X	X				X							X	X	X
Blood samples for pancreatic amylase and lipase		X				X							X		X
Blood Samples for Fasting Lipids (TC, HDL-C, LDL-C, TG)		X				X			X				X		X
TSH, FSH, LH, Estradiol, Free		X				X			X				X		X

Evaluation	Visit 1 Screening	Controlled Assessment Period 24 weeks								Extension Period 28 Weeks				
		Visit 2 Week 0	Week 2 Phone Call	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12	Week 16 Phone Call	Visit 6 Week 18	Visit 7 Week 24	Week 26 Phone Call	Visit 8 Week 28	Visit 9 Week 40	Visit 10 Week 52 (End of Study Treatment)	Visit 11 Week 62* (Study Termination)	Early Termination
T4, DHEAS, Cortisol, Prolactin, IGF-1															
Total testosterone, SHBG		X				X			X			X	X		X
CEA		X				X							X		X
Bone Specific Alkaline Phosphatase and N-telopeptide		X				X			X				X		X
Bone age assessment by X-ray		X											X		X
Plasma Exenatide		X		X	X	X			X				X	X	X
Antibodies to Exenatide		X		X	X	X			X				X	X	X
Diet and Nutritional Counseling		X		X	X	X		X	X		X	X			
Training in Administration of Study Medication		X													
Study Medication Compliance Review			X	X	X	X	X	X	X	X	X	X	X		X
Dispense Study Medication		X		X	X	X		X	X		X	X			
Drug Administration		X		X [1]	X [1]	X [1]		X [1]	X [1]		X [1]	X [1]			

Evaluation	Visit 1 Screening	Controlled Assessment Period 24 weeks								Week 26 Phone Call	Extension Period 28 Weeks			Visit 11 Week 62* (Study Termination)	Early Termination
		Visit 2 Week 0	Week 2 Phone Call	Visit 3 Week 4	Visit 4 Week 8	Visit 5 Week 12	Week 16 Phone Call	Visit 6 Week 18	Visit 7 Week 24		Visit 8 Week 28	Visit 9 Week 40	Visit 10 Week 52 (End of Study Treatment)		
Return Used/Unused Study Medication				X	X	X		X	X		X	X	X		X

Abbreviations: βhCG, human chorionic gonadotropin, beta subunit; CEA, carcinoembryonic antigen; DHEAS, dehydroepiandrosterone; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; HIPAA, Health Insurance Portability and Accountability Act; LH, luteinizing hormone; GAD65, glutamic acid decarboxylase; ICA512, islet cell antigen; IGF-1, insulin-like growth factor-1; LDL-C, low-density lipoprotein cholesterol; free T4, thyroxine; SHBG, sex hormone-binding globulin; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone.

Note: Study plan applies only to the 24-Week Controlled Assessment Period and 28-Week Extension Period of Study BCB114. See Appendix E for details of study procedures for the Extended Safety Follow-up Period.

*Visit 11 should take place 10 weeks after last dose of EQW and no later than 12 weeks

[1] If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patient and/or caregiver will administer the study medication at the study site after completion of all other study procedures.

3.2 Study duration

Total study duration will be approximately 67 weeks (excluding the Extended Safety Follow-up Period), including up to a 5-week screening period, a 24-week controlled assessment period, and a 28-week extension period, and a 10-week post-treatment follow-up period. The beginning of the treatment period should occur within 35 days following screening.

3.3 Rationale for study design, doses and control groups

This Phase 3 study is being conducted with the primary objective to compare the therapeutic efficacy, safety, and tolerability of EQW compared to placebo following 24 weeks of treatment. In addition, the study is designed to evaluate the long-term efficacy and safety of EQW following 28 weeks in an open-label, uncontrolled extension period. The study design and primary/secondary objectives reflect those recommended to evaluate the efficacy, safety, and tolerability of EQW in children and adolescent patients with type 2 diabetes.

3.3.1 Study design and regulatory requirement

A previous randomized, placebo-controlled, single-blind, dose-escalation crossover study (Study 2993-124) examined the PK, PD, safety, and tolerability of exenatide BID (2.5 and 5 μg) in adolescents between the ages of 10 and 16 with type 2 diabetes and an average body mass index (BMI) of 32.5 kg/m^2 (23.2 to 40.8 kg/m^2). Consistent with clinical trials in adults, 5 μg exenatide nearly eliminated postprandial glucose excursions in adolescents. This study, and the results of previous studies with EQW conducted in adults, demonstrated that, in general, exenatide was well tolerated with a safety and efficacy profile that was comparable to that observed in adults (Malloy et al, 2009).

Given the decreased patient burden of once weekly injections, and the favorable efficacy and safety profile of EQW, the next step in the clinical development would be a Phase 3 study to demonstrate that this treatment may prove to be a useful adjunct therapy in adolescents with type 2 diabetes. The current study will enroll either patients treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (metformin and/or SU) and/or insulin for at least 2 months prior to screening.

3.3.1.1 Extended Safety Follow-up Period

Following Visit 11 (Week 62/Study Termination), patients whose height increase is at least 5 mm between Visit 8 (Week 28) and Visit 11 (Week 62/Study Termination) will participate in an Extended Safety Follow-up Period. Patients who discontinue study medication prior to Visit 11 (Week 62/Study Termination) will also participate in the Extended Safety Follow-up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study-site visits prior to discontinuation of study medication. 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 Extended Safety Follow-up Period. The Extended Safety Follow-up Period will continue for up to 3 years or until the difference between two 6-month interval visits is less than a 5 mm increase (whichever comes first). No study medication will be

administered during the Extended Safety Follow-up Period. Blood samples will be collected for calcitonin and carcinoembryonic antigen (CEA) laboratory measurements. Details of the Extended Safety Follow-up Period are provided in Appendix E.

3.3.2 Study doses and control groups

3.3.2.1 Dosage selection

Pharmacokinetic analyses of the data collected with the immediate-release formulation of exenatide from 12 adolescent patients enrolled in Study 2993-124 concluded that adolescents have a faster rate of exenatide elimination than adults (clearance=14.7 L/hr and 9.57 L/hr, respectively; AstraZeneca, data on file). Despite this decrease in exposure, the results of this trial were consistent with clinical trials of exenatide conducted in adults, in that the administration of 5 µg exenatide was efficacious and well tolerated (Study 2993-124) (Malloy et al, 2009). BYETTA 10 µg BID is currently under investigation in adolescents with type 2 diabetes (Study H8O-MC-GWBQ).

Given the information from Study 2993-124, coupled with the results of previous studies with EQW conducted in adults, the 2 mg weekly dose of EQW will be examined in the current study. This dose regimen resulted in steady state exenatide concentrations that were well tolerated, and produced robust improvements in mean HbA1c and body weight in adults.

3.3.2.2 Control group

This is a double-blind, placebo-controlled study.

4 PATIENT SELECTION CRITERIA

Investigators should keep a record, the patient screening log, of patients who entered pre-study screening.

4.1 Population to be studied

A total of 77 male or female children and adolescents of 10 to <18 years of age, diagnosed with type 2 diabetes mellitus and treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agent (eg, metformin and/or SU) and/or insulin for at least 2 months prior to screening, will be randomized into this study to yield 70 evaluable patients.

At least 60% of study patients must be included for analysis of the primary and secondary endpoints (Evaluable Population) at Week 24.

At least 40% and not more than 60% of randomized study patients must be female.

At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states.

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

4.2 Inclusion criteria

For inclusion in the study patients should fulfil the following criteria:

1. Is a child or an adolescent of 10 to <18 years old, at Visit 1 (Screening)

2. Has been diagnosed with type 2 diabetes mellitus per American Diabetes Association diagnostic criteria

3. HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/SU, and of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at Visit 1 (Screening)

4. Has a C-peptide of >0.6 ng/mL at Visit 1 (Screening)

5. Has been treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (eg, metformin and/or SU) and/or insulin for their type 2 diabetes for at least 2 months prior to Visit 1 (Screening)

6. Has a fasting plasma glucose concentration <280 mg/dL (15.5 mmol/L) at Visit 1 (Screening)

7. Either is not treated with or has been on a stable treatment regimen with any of the following medications for a minimum of 1 month prior to Visit 1 (Screening):

(a) Oral contraceptives (female patients)

(b) Antihypertensive agents

(c) Lipid-lowering agents

(d) Thyroid replacement therapy

(e) Antidepressant agents

8. Is male, or is female and meets all the following criteria:

(a) Not breastfeeding

(b) Negative serum pregnancy test result (human chorionic gonadotropin, beta subunit [βhCG]) at Visit 1 (Screening)

(c) If of childbearing potential, must practice and be willing to continue to practice appropriate birth control (defined as at least 1 method which results in a low failure rate, ie, less than 1% per year, when used consistently and correctly, such as implants, injectables, hormonal contraceptives, some intrauterine contraceptive

devices, sexual abstinence, tubal ligation or occlusion, or a vasectomized partner) during the entire duration of the study and must not be planning to conceive

9. Has clinical laboratory test values (clinical chemistry, hematology, and urinalysis) judged as not clinically significant by the Investigator at Visit 1 (Screening)

10. Has physical examination and ECG results deemed not clinically significant by the Investigator at Visit 2 (Week 0)

11. Both patient and parent/caretaker are able to read, understand, and sign the Informed Consent Form (ICF) and Child Assent Form and if applicable, an Authorization to Use and Disclose Protected Health Information form, if applicable (consistent with Health Insurance Portability and Accountability Act of 1996 [HIPAA] legislation), communicate with the Investigator, and understand and comply with protocol requirements

12. Both patient and parent/caretaker are able to read and understand the lifestyle modification program and the parent/caretaker is willing to assist the patient's adherence to the lifestyle modification program.

4.3 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the Investigator, including but not limited to the following conditions:

(a) Hepatic disease (defined by aspartate or alanine transaminase >3.0 times the upper limit of normal (ULN)

(b) Renal disease or serum creatinine >1.5 mg/dL (132.6 µmol/L) (males) or 1.4 mg/dL (123.8 µmol/L) (females)

(c) Gastrointestinal disease deemed significant by the Investigator

(d) Organ transplantation

(e) Chronic infection (eg, tuberculosis, human immunodeficiency virus, hepatitis B virus, or hepatitis C virus)

(f) Clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of Visit 1 (Screening).

2. Has positive antibody titers to glutamic acid decarboxylase (GAD65) or islet cell antigen (ICA512) at Visit 1 (Screening)

3. Has a personal or family history of elevated calcitonin, calcitonin >100 ng/L, medullary thyroid carcinoma, or multiple endocrine neoplasia-2

4. Has donated blood within 2 months of Visit 1 (Screening), is planning to donate blood during the study, or has a hematocrit of <30%

5. Has had a major surgery or a blood transfusion within 2 months of Visit 1 (Screening)

6. Has received any investigational drug within 1 month (or 5 half-lives of the investigational drug, whichever is greater) of Visit 1 (Screening)

7. Has ever used exenatide (exenatide once weekly [exenatide LAR], exenatide BID, BYETTA, or any other formulation) or any glucagon-like peptide-1 (GLP-1) receptor agonist (eg, liraglutide [Victoza®])

8. Currently abuses drugs or alcohol or has a history of abuse that in the Investigator's opinion would cause the individual to be noncompliant with study procedures

9. Has known allergies or hypersensitivity to any component of study treatment (including PLG and Microsphere Diluent)

10. Has been treated, is currently being treated, or is expected to require or undergo treatment with any of the following medications:

(a) Oral glucocorticoids or corticosteroids within the last 30 days or more than 20 days within the past year. However, glucocorticoid treatment for some infections for less than 10 days is allowed

(b) TZD within 90 days prior to Visit 1 (Screening)

(c) Inhaled glucocorticoids at a dose equal to or above 1,000 μg Flovent® (fluticasone propionate) daily

(d) Weight loss medication(s) (including over the counter) within 30 days of Visit 1 (Screening)

(e) Alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide for >1 week in the 1 month prior to Visit 1 (Screening)

(f) DPP-4 inhibitors within 30 days prior to Visit 1 (Screening).

11. Has admitted use of anabolic steroids within the past 60 days or is planning use during the study

12. Is an immediate family member (spouse, parent, child, or sibling; biological or legally adopted) of personnel directly affiliated with the study at the clinical study site, or is directly affiliated with the study at the clinical study site

13. Is pregnant

14. Is employed by AstraZeneca (ie, an employee, temporary contract worker, or designee responsible for the conduct of the study).

5 STUDY CONDUCT

5.1 Restrictions during the study

Once screened and qualified for entry, patients will be instructed as follows:

- Take no new prescription medications or over-the-counter preparations without prior approval of the Investigator (who may contact the Sponsor for consultation). For restrictions on concomitant medications, refer to Section 5.6.
- Avoid strenuous exercise and alcohol 24 hours prior to each scheduled visit.
- Do not donate blood for the duration of the study.

The Sponsor should be contacted if the Investigator is informed of any restriction violations. The Sponsor will decide whether a patient with restriction violations will be allowed to continue study participation.

For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.

5.2 Patient enrollment and randomization

The Principal Investigator will:

1. Obtain signed and dated informed consent from parent or caretaker and patient assent and HIPAA Authorization if applicable before any study specific procedures are performed.

2. Determine patient eligibility. See Sections 4.2 and 4.3.

3. The Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will assign an eligible patient unique randomization code, beginning with '#'.

If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.

5.2.1 Procedures for randomization

Patients who meet all study requirements based on inclusion and exclusion criteria will be randomized and assigned to 1 of 2 treatment groups in 5:2 ratio (Group A:Group B) at Visit 2 (Week 0). The randomization will be stratified by baseline HbA1c (<9.0% or ≥9.0%) and country.

Study medication kits will be labeled with unique package numbers (this is **not** the patient randomization number). At Visit 2 (Week 0), the study-site pharmacist or other medically qualified personnel must contact the IVRS or the IWRS to randomly assign patients and for kit assignment. If medication is allocated to a patient incorrectly, the Sponsor must be notified.

The study-site personnel must call the IVRS/IWRS at all subsequent visits to record the visit and confirm the kit assignment. The calls to the IVRS/IWRS will ensure the resupply of additional kits required for upcoming visits.

5.3 Procedures for handling patients incorrectly enrolled or randomized

Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized to receive study medication. There can be no exceptions to this rule. Patients who are screened, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment. These patients (who have not been randomized) should be withdrawn from the study. Where a patient does not meet all eligibility criteria, but is randomized in error or incorrectly started on treatment, the Investigator should inform the study physician immediately, and a discussion should occur between the study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The study physician and the Investigator must ensure all decisions are appropriately documented.

5.4 Blinding and procedures for unblinding the study

5.4.1 Methods for ensuring blinding

The Sponsor, the study-site personnel, and the patients will be blinded to treatment allocation during the double-blind controlled assessment period. Every effort should be made to ensure that patients remain blinded to their treatment during this period.

The exception to the above is for those personnel analyzing the PK and antibody samples. The randomization information will be provided to ensure that only samples from patients who were on active study treatment are analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a “for cause” basis, for example, if there is suspicion that a patient has been dosed incorrectly.

During the open-label extension period, the Sponsor, study-site personnel, and the patients will be unblinded to the identity of the study medication.

5.4.2 Methods for unblinding the study

Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each center.

The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff.

AstraZeneca and the safety data entry site retain the right to break the code for serious adverse events (SAEs) that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented.

5.4.2.1 24-Week Controlled Assessment Period

The patient, Investigator (and all study-site personnel), and Sponsor will be blinded to treatment during the controlled assessment period. Every effort should be made to ensure that patients remain blinded to their treatment during this period. If a patient's treatment is unblinded only to a Global Safety Case delegate and related personnel required for case processing for the purpose of FDA submission, the patient's status in the study may remain unchanged. Otherwise, the code may be unblinded only after an irrevocable decision has been made to withdraw the patient from the investigational product and immediate knowledge of the study medication is needed to optimize the clinical management of the patient. The Investigator is to notify the AstraZeneca medical monitor if an event occurs that requires a patient's treatment assignment to be unblinded.

5.4.2.2 28-Week Extension Period

The patient, Investigator (and all study-site personnel), and Sponsor will be unblinded to study medication during the 28-week extension period.

5.5 Treatments

5.5.1 Identity of investigational product(s)

5.5.1.1 Prefilled syringes

Table 2 Identity of investigational product delivered via prefilled syringes

Investigational product	Dosage form and strength	Manufacturer
Exenatide once weekly (EQW)	2.0 mg powder for injection	AstraZeneca [a]
Placebo to match exenatide once weekly	Placebo powder for injection	AstraZeneca [a]

[a] Responsible for supply of Investigational Product and placebo.

All study medication sufficient for 4-week treatment will be packed into patient kits. The vials containing the exenatide/placebo powder for injections will be packed into a small box containing 4 vials. Four prefilled syringes with diluent for suspension of EQW and matching placebo will be packed into another box also containing 6 vial adaptors and 6 23-Gauge×5/16 inch needles.

Study materials will be provided to patients by the Investigator or medically qualified subinvestigator named on Form FDA 1572, or other qualified study-site personnel. Under no circumstance will the Investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than patients participating in the study. Medically-qualified staff members will be responsible for instructing patients/caregivers on the preparation and administration of the correct doses of study medication.

5.5.1.2 Dual chamber pen

Table 3 Identity of investigational product delivered via dual chamber pen

Investigational product	Dosage form and strength	Manufacturer
Exenatide once weekly (EQW)	2.0 mg powder and solvent for prolonged release suspension for injection, prefilled pen [b]	AstraZeneca [a]
Placebo to match exenatide once weekly	Placebo powder and solvent for suspension for injection, prefilled pen [c]	AstraZeneca [a]

[a] Responsible for supply of Investigational Product and placebo.
[b] Dosage form and strength for non-US sites. For sites in the US only, dosage form and strength are as follows: Extended release for injectable suspension (2 mg of exenatide per 0.65 mL suspension) in a single dose pen.
[c] Dosage form and strength for non-US sites. For sites in the US only, dosage form and strength are as follows: Placebo powder and solvent for injectable suspension in a single dose pen.

All study medication sufficient for 4-weeks treatment will be packed into patient kits. The prefilled single use injection pens containing the exenatide/placebo will first be individually packed into blister packages and then packed into a box containing 4 prefilled pens.

Study materials will be provided to patients by the Investigator or medically qualified subinvestigator named on Form FDA 1572, or other qualified study-site personnel. Under no circumstance will the Investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than patients participating in the study. Medically-qualified staff members will be responsible for instructing patients/caregivers on the preparation and administration of the correct doses of study medication.

5.5.2 Formulation, Packaging, and Storage

The EQW is an extended release formulation of exenatide and consists of 5% exenatide, sucrose, and 50:50 poly D,L lactide-co-glycolide.

For use in the prefilled syringes, the EQW microspheres and matching placebo will be supplied in vials containing the white to off white dry powder (40 mg of EQW microspheres).

For use in the dual chamber pen, the exenatide microspheres or matching placebo and the diluent for suspension will be supplied in a prefilled single-use injection pen. Diluent for suspension will be supplied in prefilled syringes. Each syringe will contain 0.75 mL. The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided.

For both formulations, the investigational product must be stored in a refrigerator between 2ºC and 8ºC and protected from light. EQW matching placebo is the identical formulation with the active ingredient omitted. Diluent for suspension of the EQW and placebo microspheres contains carboxymethylcellulose low viscosity, polysorbate 20, sodium chloride, and water for injection.

For both formulations, specific instructions for dose preparation of the EQW injection will be provided in the Patients Instructions for Use. The reconstituted dose of study medication (EQW or matching placebo) should not be stored for future use. The injection must be administered immediately after preparation of the dose.

Packaging

All study medication will be packed into kits with enough for 4-weeks of treatment.

The vials containing the exenatide/placebo powder for injections will be packed into a small box containing 4 vials. Four prefilled syringes with diluent for suspension of EQW and matching placebo will be packed into another box also containing 6 vial adaptors and 6 23-Gauge×5/16 inch needles.

The prefilled single use injection pens containing the exenatide or placebo will first be individually packed into blister packages and then packed into a box containing 4 prefilled pens.

Doses and Treatment Regimens

Doses of study medication are to be injected into SC tissue. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly.

At Visit 2 (Week 0), a medically-qualified staff member will demonstrate the preparation of study medication for the patient. At this visit, the study medication will be administered by a medically-qualified staff member following all study-related procedures.

Caregiver will subsequently administer study medication to the patient (or the patient will self-administer if the medically qualified site staff member assesses that this is appropriate, taking into account the patient's capabilities and characteristics) once weekly (±2 days), relative to the date of the first dose of exenatide once weekly (Visit 2 [Week 0]), for the duration of the study. On weeks with no scheduled study-site visits, patients may opt to return to the study site to have the injection procedure monitored or provided by study-site personnel, although such visits will not be required. On weeks of scheduled study visits, patients should bring their study medication treatment kit with them to the clinic (if the study visit is scheduled on the same day as patient's weekly administration) and will self-administer study medication after completion of the study procedures (at the study site or after leaving the study site).

Adjustments to dosing regimens are not permitted. If a patient is unable to tolerate the study medication (eg, patient experiences AEs that are judged by the Investigator to be unacceptable), the Sponsor should be contacted to evaluate the patient's continued participation in the study.

5.5.3 Rescue Treatment

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

Patients meeting rescue criteria will be treated with antihyperglycemic therapy (eg, insulin) by the Investigator or referred to their treating physician to seek conventional antihyperglycemic intervention. Patients meeting these criteria should remain in the study and continue to receive study medication, at the discretion of the Investigator. AstraZeneca will not supply the rescue medication. Acute decompensation due to an intercurrent illness treated briefly with insulin will be allowed for 2 weeks, if longer this should be considered as rescue treatment.

5.5.4 Labeling

Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labeling. Label text will be translated into local language.

5.5.5 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the kit specifies the appropriate storage.

5.6 Concomitant and post-study treatments

Patients must follow the medication restrictions outlined in the inclusion and exclusion criteria (Section 4.2 and 4.3) during the study. Dosages for certain concomitant medications should be maintained constant during the study (Section 4.2), unless instructed otherwise by the Investigator or a treating physician. For patients on insulin, the dose should be kept constant as far as possible, though modifications of the dose of insulin may have to be made to reduce the risk of hypoglycemia. Any change in regimen for any concomitant medication, including restricted concomitant medications, must be reported to the Sponsor.

Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form (CRF).

5.7 Treatment compliance

The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the CRF.

The study drug dispensation as per visits has been summarized in Table 4.

Table 4 Study Drug Dispensation per Visits Schedule

Visit (week)	Exenatide/placebo vial 4-weeks kit. (24-Week Controlled assessment Period).	Exenatide vial 4-weeks kit (28-Week Extension Period).	Diluent 4-weeks kit
Visit 2 (Week 0)	1	N/A	1
Visit 3 (Week 4±2 days)	1	N/A	1
Visit 4 (Week 8±2 days)	1	N/A	1
Visit 5 (Week 12±2 days)	2	N/A	2
Visit 6 (Week 18±2 days)	2	N/A	2
Visit 7 (Week 24±2 days)	N/A	1	1
Visit 8 (Week 28±2 days)	N/A	3	3
Visit 9 (Week 40±2 days)	N/A	3	3
Visit 10 (Week 52±2 days)	N/A	N/A	N/A

Abbreviation: N/A=not applicable

Visit 2 (Week 0): At Visit 2, a 4-week supply of blinded study medication kits will be dispensed to all patients, according to their assigned treatment group.

Visit 3 (Week 4) and Visit 4 (Week 8): At Visit 3 and Visit 4 an additional 4-week supply of study medication will be dispensed to all patients, according to their assigned treatment group.

Visit 5 (Week 12) and Visit 6 (Week 18): At Visit 5 and Visit 6 an additional 8-week supply of study medication will be dispensed to all patients, according to their assigned treatment group.

Visit 7 (Week 24): At Visit 7 a 4-week supply of open label study medication will be dispensed to all patients.

Visit 8 (Week 28) and Visit 9 (Week 40): At Visit 8 and Visit 9 a 12-week supply of open label study medication will be dispensed to all patients.

Visit 10 (Week 52/End of Treatment): Patients to return all used and unused study medication to the study site.

5.7.1 Accountability

The study drug provided for this study will be used only as directed in the study protocol.

The study personnel will account for all study drugs dispensed to and returned from the patient. Upon receipt of diluent prefilled syringes and study medication, study-site personnel should open the shipment, verify that the amount and identity of the contents match that stated on the enclosed shipping form, indicate the condition of the contents on the form, and then sign and date the form. The study-site personnel should make a photocopy of the shipping form for the site's file, and return the original completed form to the Sponsor (or designee). In addition, the study-site personnel will contact IVRS/IWRS to verify receipt of study medication. The Sponsor (or designee) should be notified immediately about any irregularities, discrepancies, or damage.

A drug disposition form will be provided to record all study medication dispensed to or returned from each patient. Upon completion of the study, all used and unused remaining study vials, unused microsphere diluents prefilled syringes, and copies of completed drug disposition forms should be returned to the Sponsor (or designee).

A clinical supplies return authorization form will be prepared by the clinical research associate at the closeout visit. The clinical supplies return form should be enclosed with the return drug shipment. The study-site personnel must maintain documentation of any missing or unreturned study medication.

5.8 Discontinuation of investigational product

Patients may be discontinued from investigational product (IP) in the following situations:

- Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse event (AE)
- Severe non-compliance to study protocol

- Accelerated sexual maturation as assessed by measurement of Tanner stage, bone age, and hormonal levels

Development of any study specific criteria for discontinuation is presented in Section 5.9.

5.8.1 Procedures for discontinuation of a patient from investigational product

A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any AEs (Section 1.3.1). If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the patient.

Patients who discontinue study medication prior to Visit 11 (Week 62/Study Termination) should enter the Extended Safety Follow-up Period, as described in Appendix E, 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 do not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication will enter the Extended Safety Follow-up Period.

If a patient is withdrawn from the investigational product, see Section 5.9.

5.9 Withdrawal from study

Patients are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the patient.

Every effort should be made to conduct all protocol-required procedures to complete the study. Patients may be removed from the study for the following reasons:

1. **Withdrawal by Patient:** Patient wishes to exercise the right to withdraw from the study as stated in the ICF (all patients reserve the right to withdraw from the study without prejudice).

2. **Adverse Event:** Patient experiences an AE that, in the Investigator's opinion, necessitates withdrawal from the investigational product.

3. **Investigator Decision:** Investigator feels it is in the patient's best interest to terminate participation for reasons other than an AE, leading to withdrawal from the investigational product.

4. **Protocol Violation:** Patient is noncompliant with protocol procedures, becomes pregnant, violates study entry criteria, or starts an exclusionary concomitant medication, leading to withdrawal from the investigational product.

5. **Lost to Follow-up:** Patient fails to return for study visits and cannot be reached with reasonable, repeated attempts.

6. **Study Terminated by Sponsor:** AstraZeneca discontinues the study protocol.

7. **Administrative Reason:** The FDA, or other regulatory authority discontinues the study protocol or the clinical study site discontinues participation.

8. **Loss of Glucose Control:** If rescue criteria are met during the controlled assessment period or during the extension period and the Investigator believes it is in the patient's best interest to terminate participation, leading to withdrawal from the investigational product (for specific guidelines see Section 5.5.3 and Section 1.3.1).

Any withdrawal must be fully documented in the patient's source records and recorded on the disposition page of the electronic case report form (eCRF). The documentation must include the reason for the withdrawal and details of any sequelae (followed until symptoms resolve or improve, as appropriate). Withdrawals due to an AE must be documented on both the disposition page and the AE page of the eCRF.

When a patient is lost to follow-up (ie, fails to return for study visits), a reasonable effort (eg, documented by receipts for certified mailings) will be made to contact the patient to determine why the patient failed to return and to attempt to schedule the Early Termination visit.

Withdrawn patients will not be replaced.

6 COLLECTION OF STUDY VARIABLES

6.1 Recording of data

The Inform Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

6.2 Data collection at enrollment and follow-up

6.2.1 Enrollment procedures

The procedures to be performed during the study are listed by visit in Table 1 (Study Plan). Specific procedures to be performed during the study by visit are described in detail in Sections 6.2.2 and 6.2.3.

All patients will be instructed to arrive in the morning of each scheduled study visit. Patients are to have fasted overnight (no food or beverage except water) for ≥8 hours at Visit 1

(Screening), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52/End of Treatment) or Early Termination. If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patients will be instructed to delay administration of study medication, bring their study medication to the study site, and administer study medication at the study site. If patients are taking concomitant antidiabetic medication they should administer their usual concomitant antidiabetic medication therapy at approximately the same time each day throughout the study.

6.2.2 Screening procedures

Prior to Visit 1 (Screening), patients will have fasted overnight for ≥8 hours.

At Visit 1 (Screening), parent or caretaker informed consent, patient assent, and HIPAA Authorization, if applicable, will be signed prior to initiation of screening procedures. The following procedures will be performed during this visit after informed consent is obtained:

- Review of concomitant medication
- The patient's complete medical history will be recorded
- Review of inclusion and exclusion criteria
- Patients will complete a urine drug and alcohol screen
- Body weight, height, and vital signs will be measured
- Urine will be collected for urinalysis
- Blood samples will be collected for:
  - Serum pregnancy test (βhCG) for all female patients
  - Chemistry and hematology
  - HbA1c
  - Fasting plasma glucose
  - Fasting insulin
  - C-peptide
  - GAD65 and ICA512 antibodies
  - Calcitonin.

Individuals will be disqualified if results of any laboratory test are abnormal and clinically significant as judged by the Investigator or medical monitors. Individuals may requalify for study randomization within 35 days of Visit 1 (Screening) following an abnormal test result by having that test repeated once with acceptable results as judged by the Investigator and medical monitors (or designees). If greater than 35 days have elapsed since Visit 1 (Screening), patients who wish to requalify for study randomization following an abnormal test result must be indicated as a screen failure prior to repeating all screening assessments. Prior to initiation of rescreening procedures, patients will complete a new parent or caretaker informed consent, patient assent, and HIPAA Authorization, if applicable. Rescreened patients will be assigned a new IWRS number.

When all of the screening results are available, individuals will be notified by telephone of their eligibility status. Those who qualify will be eligible to return to the clinical study site within 35 days after Visit 1 (Screening) to complete eligibility requirements for enrollment.

6.2.3 Study schedule

A negative pregnancy test must be confirmed prior to administration of study medication at all applicable visits.

6.2.3.1 Visit 2 (Week 0): Randomization – (Controlled assessment period)

Prior to Visit 2 (Week 0), patients will have fasted overnight (≥8 hours).

All patients will undergo the following procedures:

- Review of concomitant medication and AEs
- Verify inclusion and exclusion criteria
- Physical examination and ECG will be performed
- Patients will be randomized
- Urine will be collected for:
  - Pregnancy test (females only)
  - Urinalysis
  - Urinary albumin creatinine ratio
  - N-telopeptide
- Body weight, height, and vital signs will be measured
- Assessment of Tanner pubertal stage

- Blood samples will be collected for:
  - Chemistry and Hematology
  - HbA1c
  - Fasting plasma glucose
  - Fasting insulin
  - Calcitonin
  - Pancreatic amylase and lipase
  - Fasting lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], low-density lipoprotein cholesterol [LDL-C], and triglycerides [TG])
  - Thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, sex hormone-binding globulin (SHBG), estradiol, free T4 (thyroxine), prolactin, cortisol, insulin like growth factor-1 (IGF-1), dehydroepiandrosterone (DHEAS), and bone specific alkaline phosphatase
  - Carcinoembryonic antigen (CEA)
  - Measurement of plasma exenatide
  - Measurement of antibodies to exenatide.
- Bone age assessment by X-ray
- Patients will receive diet and nutritional counseling
- Study medication will be dispensed and patients and/or caregiver will receive training in injection of study medication
- A medically-qualified staff member will administer the first dose of study medication following all other study-related procedures.

6.2.3.2 Week 2 – Telephone contact

The Investigator and/or qualified study-site personnel will contact patients by telephone at Week 2 to discuss study compliance, address any questions related to study medication administration, and review AEs.

6.2.3.3 Visit 3 (Week 4) and Visit 4 (Week 8) – (Controlled assessment period)

Prior to Visit 3 (Week 4) and Visit 4 (Week 8), patients will have fasted overnight (≥8 hours). If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patients should delay administration of study medication on the morning of the study-site visit and bring the study medication to the site.

All patients will undergo the following procedures:

- Review of concomitant medication and AEs
- Body weight, height, and vital signs will be measured
- Urine will be collected for a pregnancy test (females only)
- Injection site reaction assessment will be performed
- Blood samples will be collected for:
  - HbA1c
  - Fasting plasma glucose
  - Fasting insulin
  - Measurement of plasma exenatide
  - Measurement of antibodies to exenatide.
- Patients will receive diet and nutritional counseling
- Patients will have a study medication compliance review
- Study medication will be dispensed
- Patient and/or parent/caregiver will administer study drug at the study site (if applicable)
- Patients will be asked to return used/unused study medication.

6.2.3.4 Visit 5 (Week 12) – (Controlled assessment period)

Prior to Visit 5 (Week 12), patients will have fasted overnight (≥8 hours). If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patients should delay administration of study medication on the morning of the study-site visit and bring the study medication to the site.

All patients will undergo the following procedures:

- Review of concomitant medication and AEs
- Physical examination will be performed
- Body weight, height, and vital signs will be measured
- Assessment of Tanner pubertal stage
- Injection site reaction assessment will be performed
- Urine will be collected for:
  - Pregnancy test (females only)
  - Urinalysis
  - Urinary albumin creatinine ratio
  - N-telopeptide.
- Blood samples will be collected for:
  - Chemistry and hematology
  - HbA1c
  - Fasting plasma glucose
  - Fasting insulin
  - Calcitonin
  - Pancreatic amylase and lipase
  - Fasting lipids (TC, HDL-C, LDL-C, and TG)
  - TSH, FSH, LH, total testosterone, SHBG, estradiol, free T4, prolactin, cortisol, IGF-1, DHEAS, and bone specific alkaline phosphatase
  - CEA
  - Measurement of plasma exenatide
  - Measurement of antibodies to exenatide.

- Patients will receive diet and nutritional counseling
- Patients will have a study medication compliance review
- Study medication will be dispensed
- Patient and/or parent/caregiver will administer study drug at the study site (if applicable)
- Patients will be asked to return used/unused study medication.

6.2.3.5 Week 16 - Telephone contact

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

6.2.3.6 Visit 6 (Week 18) - (Controlled assessment period)

If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patients should delay administration of study medication on the morning of the study-site visit and bring the study medication to the site.

All patients will undergo the following procedures:

- Review of concomitant medication and AEs
- Body weight, height, and vital signs will be measured
- Urine will be collected for a pregnancy test (females only)
- Injection site reaction assessment will be performed
- Blood samples will be collected for:
  - HbA1c
- Patients will receive diet and nutritional counseling
- Patients will have a study medication compliance review
- Study medication will be dispensed
- Patient and/or parent/caregiver will administer study drug at the study site (if applicable)
- Patients will be asked to return used/unused study medication.

6.2.3.7 Visit 7 (Week 24) – (Controlled assessment period)

Prior to Visit 7 (Week 24), patients will have fasted overnight (≥8 hours). If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patients should delay administration of study medication on the morning of the study-site visit and bring the study medication to the site.

All patients will undergo the following procedures:

- Review of concomitant medication and AEs
- Body weight, height, and vital signs will be measured
- Urine will be collected for:
  - Pregnancy test (females only)
  - Urinalysis
  - N-telopeptide.
- Assessment of Tanner pubertal stage
- Injection site reaction assessment will be performed
- Blood samples will be collected for:
  - Chemistry and hematology
  - HbA1c
  - Fasting plasma glucose
  - Fasting insulin
  - Fasting lipids (TC, HDL-C, LDL-C, and TG)
  - TSH, FSH, LH, total testosterone, SHBG, estradiol, free T4, prolactin, cortisol, IGF-1, DHEAS, and bone specific alkaline phosphatase
  - Measurement of antibodies to exenatide
  - Measurement of plasma exenatide.
- Patients will receive diet and nutritional counseling
- Patients will have a study medication compliance review

- Study medication will be dispensed
- Patient and/or parent/caregiver will administer study drug at the study site (if applicable)
- Patients will be asked to return used/unused study medication.

6.2.3.8 Week 26 – Telephone contact

The Investigator and/or qualified study-site personnel will contact patients by telephone at Week 26 to discuss study compliance, address any questions related to study medication administration, and review AEs

6.2.3.9 Visit 8 (Week 28) and Visit 9 (Week 40) – (Extension Period)

If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patients should delay administration of study medication on the morning of the study-site visit and bring the study medication to the site.

All patients will undergo the following procedures:

- Review of concomitant medication and AEs
- Body weight, height, and vital signs will be measured
- Urine will be collected for a pregnancy test (females only)
- Assessment of Tanner pubertal stage (Visit 9 [Week 40] only)
- Injection site reaction assessment will be performed
- Blood samples will be collected for:
  - HbA1c
  - Total testosterone and SHBG (Visit 9 [Week 40] only).
- Patients will receive diet and nutritional counseling
- Patients will have a study medication compliance review
- Study medication will be dispensed
- Patient and/or parent/caregiver will administer study drug at the study site (if applicable)
- Patients will be asked to return used/unused study medication.

6.2.3.10 Visit 10 (Week 52) - End of Treatment or Early Termination

Prior to Visit 10 (Week 52) or Early Termination, patients will have fasted overnight (≥8 hours).

All patients will undergo the following procedures:

- Review of concomitant medication and AEs
- Physical examination will be performed
- Body weight, height, and vital signs will be measured
- Assessment of Tanner pubertal stage
- Injection site reaction assessment will be performed
- Urine will be collected for:
  - Pregnancy test (females only) (only for Visit 10 [Week 52])
  - Urinalysis
  - Urinary albumin creatinine ratio
  - N-telopeptide.
- Blood samples will be collected for:
  - Serum pregnancy test (βhCG) for all female patients (only for early termination visit)
  - Chemistry and hematology
  - HbA1c
  - Fasting plasma glucose
  - Fasting insulin
  - Calcitonin
  - Pancreatic amylase and lipase
  - Fasting lipids (TC, HDL-C, LDL-C, and TG)
  - TSH, FSH, LH, total testosterone, SHBG, estradiol, free T4, prolactin, cortisol, IGF-1, DHEAS, and bone specific alkaline phosphatase

  - CEA
  - Measurement of antibodies to exenatide
  - Measurement of plasma exenatide.

- Bone age assessment by X-ray
- Patients will have a study medication compliance review
- Patients will be asked to return used/unused study medication.

6.2.3.11 Visit 11 (Week 62) - Study Termination

All patients will undergo the following procedures:

- Review of AEs and hypoglycemic episodes
- Physical examination will be performed
- Body weight, height, and vital signs will be measured
- Urine will be collected for urinalysis
- Blood samples will be collected for:
  - Serum pregnancy test (βhCG) for all female patients
  - Chemistry and hematology
  - Calcitonin
  - Measurement of antibodies to exenatide
  - Measurement of plasma exenatide.

6.3 Efficacy

Samples and measurements will be collected as discussed in this section and according to the schedules presented in Study Plan (Table 1) and Section 6.2.

6.3.1 HbA1c

Blood samples for the measurement of HbA1c will be collected at every visit as specified in the schedules presented in Study Plan (Table 1) and Section 6.2. The centralized laboratory will provide specific instructions for collection, processing, packaging, and shipping of all HbA1c samples.

6.4 Safety

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section. Safety will be assessed throughout the study by examination of AEs, concomitant medications, clinical laboratory evaluations, antibody measurements, vital signs, physical examinations, and other safety observations. Safety assessments by visit are listed in Sections 6.4.5 - 6.4.9.

6.4.1 Definition of adverse events

An AE is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (eg, nausea, chest pain), signs (eg, tachycardia, enlarged liver) or the abnormal results of an investigation (eg, laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout periods, even if no study treatment has been administered.

The term AE is used to include both serious and non-serious AEs.

6.4.2 Definitions of serious adverse event

A serious adverse event (SAE) is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfils 1 or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent 1 of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.

6.4.3 Recording of adverse events

All AEs that occur after the patient has signed the informed consent will be recorded on source documents. Adverse events for patients who enroll in the study will be entered on source documents and the eCRFs. Adverse events include those reported spontaneously by the patient and those noted incidentally or as the result of nondirected questioning by the

Investigator or study personnel. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded on the eCRFs using standard medical terminology that is as specific as possible, rather than the patient's own words. Whenever the Investigator is confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results should be grouped together as a single AE on the eCRF (eg, cough and rhinitis should be reported as an "upper respiratory tract infection"). Adverse events will be evaluated for intensity and causal relationship with the use of the study medication by the Investigator.

Time period for collection of adverse events

Adverse Events will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period.

All clinically significant abnormalities noted upon physical examination, ECG, and clinical laboratory and vital sign measurements that occur during the study and were not present prior to the signing of the ICF, should be reported as an AE, except for abnormalities present at Screening that may be considered part of the medical history.

Follow-up of unresolved adverse events

All clinically significant AEs that are unresolved at Study Termination are followed up by the Investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolution occurs. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary. Follow-up information should be recorded on the source documents and reported to the Sponsor.

Adverse events that occur following completion of study termination/early termination procedures should be recorded on the AE page of the eCRF only if the Investigator considers the event as clinically significant and as related to study medication or study procedures. All SAEs that occur within 90 days of administration of the last dose of study medication (regardless of causality) must be reported immediately (Section 6.4.4). Concomitant medications used following study termination procedures should be recorded only if relevant to treatment of patients for events described above.

Variables

The following variables will be collect for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- If AE is of maximum intensity
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product (yes or no)

- Action taken with regard to investigational product
- AE caused patient's withdrawal from study *(*yes or no*)*
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Other medication
- Description of AE.

6.4.3.1 Intensity

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For eg, nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

The intensity of each AE will be characterized as MILD, MODERATE, or SEVERE, as follows:

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

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

SEVERE: Interrupts a patient's usual daily activities and generally requires systemic drug therapy or other treatment.

6.4.3.2 Causality collection

The Investigator will assess causal relationship between Investigational Product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.

The Investigator will grade the association of the AE as NOT RELATED or RELATED to study medication. The following criteria should be considered for determining relatedness:

NOT RELATED: The AE is judged to be produced by the patient's clinical state or by other therapies administered to the patient.

RELATED: The AE is judged to be related to the administration of study medication.

A guide to the interpretation of the causality question is found in Appendix B to the Clinical Study Protocol.

6.4.3.3 Hypoglycemia

All patients will be asked to record a blood glucose measurement if they experience symptoms of hypoglycemia. Patients will be instructed to report any symptoms of hypoglycemia and blood glucose values associated with these symptoms.

If the clinician determines that a patient experienced symptoms consistent with hypoglycemia, the event should be documented in the patient's source documentation and the hypoglycemia AE eCRF page must be completed. If a blood glucose value of <54 mg/dL (3.0 mmol/L) is noted within the data, which is asymptomatic, the clinician should assess whether the circumstances around the value are consistent with hypoglycemia. If the assessment is that the value is consistent with hypoglycemia, the hypoglycemia AE eCRF page should be completed. Study-site personnel must obtain accurate information for the patient's file and for the hypoglycemia AE page of the eCRF. If the hypoglycemic episode intensity is classified as severe, the Investigator is required to contact the Sponsor.

The criteria for evaluating the intensity of a hypoglycemic episode are the following:

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

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

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

Adverse Events based on signs and symptoms

All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: Have you had any health problems since the previous visit/you were last asked?, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

Adverse Events based on examinations and tests

The results from protocol mandated laboratory tests and vital signs will be summarized in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (eg, anaemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AEs.

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

NB. Cases where a patient shows an aspartate aminotransferase (AST) **or** alanine aminotransferase (ALT) ≥3× ULN **and** total bilirubin ≥2× ULN must be reported as SAEs, please refer to Appendix D ‘Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy’s Law’, for further instructions.

6.4.4 Reporting of serious adverse events

All SAEs that occur after the signing of the ICF through 90 days after administration of the last dose of study medication must be reported immediately (within 24 hours of knowledge), whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. Fax the SAE report form to the number listed on the form.

If any SAE occurs in the course of the study, the study-site personnel should make every effort (within 24 hours) to obtain the Investigator’s clinical opinion about the information

available for the event. The Investigator should first initiate appropriate procedures to treat the patient.

The Investigators or other site personnel should inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it. However, if the information cannot be obtained, the Sponsor should still be contacted with all available information. The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

Once the Investigators or other site personnel indicate an AE is serious in the WBDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the WBDC system is not available, then the Investigator or other study-site personnel reports an SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study-site personnel how to proceed.

The reference document for definition of expectedness/listedness is the Investigator's Brochure (IB) for the AstraZeneca drug.

An AE eCRF must be completed within 24 hours of the initial report for patients enrolled in the study. For these enrolled patients, the concomitant medications eCRF, medical history eCRF, and demographics eCRF must be completed and faxed within 72 hours of the initial report. Pertinent laboratory reports or diagnostic results should be faxed within 72 hours of the initial report to AstraZeneca Global Safety at the fax number on the SAE form.

The Institutional Review Board (IRB) must be notified in writing of any experiences that fall into the categories defined for SAEs. The Sponsor will be responsible for meeting all US FDA and other applicable regulatory authorities reporting requirements.

6.4.5 Laboratory safety assessment

Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan (Table 1).

NB. In case a patient shows an AST **or** ALT ≥3× ULN **and** total bilirubin ≥2× ULN please refer to Appendix D 'Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law', for further instructions.

The Investigator will evaluate all screening and safety laboratory reports, and will sign and date the review. Any out of range laboratory results should be assessed for clinical significance. The Investigator should follow all clinically significant laboratory abnormalities occurring during the study that were not present at baseline. These abnormalities should be evaluated with additional tests, if necessary, until the underlying cause is diagnosed or resolution occurs. The diagnosis and resolution date must be reported to the Sponsor.

Samples will be collected according to the schedules presented in Study Plan (Table 1) and Section 6.2. The centralized laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

The following laboratory variables will be measured:

6.4.5.1 Chemistry

Chemistry assessments will be performed from blood samples collected according to the schedules presented in Study Plan (Table 1) and Section 6.2. Chemistry assessments will include the following: urea nitrogen, creatinine, total protein, albumin, uric acid, total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyltranspeptidase, creatine phosphokinase (CPK), creatine kinase-MB (CK-MB, if CPK is elevated), sodium, potassium, chloride, bicarbonate, phosphorus, and calcium (or other routine chemistry panels as approved by the Sponsor).

6.4.5.2 Hematology

Hematology assessments will be performed from blood samples to be collected according to the schedules presented in Study Plan (Table 1) and Section 6.2. Hematology assessments will include the following: red cell count, hemoglobin, hematocrit, white cell count, platelets, differential count, mean cell volume, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration (or other routine hematology assessments as approved by the Sponsor).

6.4.5.3 Urinalysis

Urinalysis assessments will be performed according to the schedules presented in Study Plan (Table 1) and Section 6.2. Urinalysis assessments will include the following: pH, specific gravity, glucose, blood, ketones, protein, and microscopic analysis (or other routine urinalysis as approved by the Sponsor).

6.4.5.4 Urinary Albumin-Creatinine Ratio

Urinary albumin creatinine ratio will be performed from spot urine samples according to the schedules presented in Study Plan (Table 1) and Section 6.2.

6.4.5.5 Other Clinical Laboratory Evaluations

Pregnancy Testing

A negative pregnancy test must be confirmed prior to administration of study medication according to the schedules presented in the Study Plan (Table 1) and Section 6.2. For all female patients, pregnancy tests will be performed from blood or urine samples collected according to the schedules presented in Study Plan (Table 1) and Section 6.2.

Urine Drug and Alcohol Screen

A urine screen for drugs of abuse and alcohol will be performed from a urine sample collected at Visit 1 (Screening) according to the schedules presented in Study Plan (Table 1) and Section 6.2. Positive results due to prescription medications (eg, opioid-containing pain medications) are not necessarily exclusionary.

C-Peptide

Blood will be drawn for the measurement of C-peptide at Visit 1 (Screening) according to the schedules presented in Study Plan (Table 1) and Section 6.2.

GAD65 and ICA512

Blood will be drawn for the measurement of antibody titers to GAD65 and ICA512 Visit 1 (Screening) according to the schedules presented in Study Plan (Table 1) and Section 6.2.

Calcitonin

An assessment of calcitonin will be performed from blood samples collected according to the schedules presented in Study Plan (Table 1) and Section 6.2.

Pancreatic Amylase and Lipase

Blood samples will be collected for the measurement of pancreatic amylase and lipase according to the schedules presented in Study Plan (Table 1) and Section 6.2.

Growth and Development Hormones

An assessment of growth and development hormones including TSH, FSH, LH, total testosterone, SHBG, estradiol, free T4, prolactin, cortisol, DHEAS, and IGF-1 will be performed from blood samples collected at according to the schedules presented in Study Plan (Table 1) and Section 6.2.

Carcinoembryonic Antigen

Blood will be drawn for the assessment of tumor marker CEA according to the schedules presented in Study Plan (Table 1) and Section 6.2. The utility of monitoring CEA in the adolescent population is unknown.

Bone Turnover Markers

Blood will be drawn for the assessment of bone specific alkaline phosphatase and urine will be collected for assessment of N-telopeptide according to the schedules presented in Study Plan (Table 1) and Section 6.2. The utility of monitoring bone specific alkaline phosphatase and N-telopeptide in the adolescent population is unknown.

Bone age assessment by X-ray

Radiography of hand and wrist will be used to calculate bone age.

Antibodies to exenatide

Blood samples will be collected for the measurement of antibodies to exenatide according to the schedule presented in the Study Plan (Table 1, Section 6.2). Samples for determination of anti-exenatide antibodies will be analyzed by a selected laboratory on behalf of AstraZeneca, using an appropriate method.

Only samples from patients who were on active study treatment will be analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a "for cause" basis, for eg, if there is suspicion that a patient has been dosed incorrectly.

The method details and results will be reported in a separate report appended to the CSR. Anti-exenatide antibody samples received by the analytical group will be disposed of after the anti-exenatide antibody report finalization or 6 months after issuance of the draft antibody report (whichever is earlier), unless requested for future analyses or in support of the development or conduct of the assay.

6.4.6 Physical examination

A complete physical examination will be performed according to the schedules presented in Study Plan (Table 1) and Section 6.2. Complete physical examinations will include measurements of weight and evaluation of all body systems listed in the eCRFs.

Height measurements will be standardized across all study sites by using stadiometer or other similar device. The height will be measured by patient standing with bare feet close together, with legs straight, and arms at side and shoulders relaxed.

6.4.7 ECG

Standard 12-lead ECGs will be performed after approximately 5 minutes of quiet rest with the patient in a supine position. If the ECG must be performed with the patient in another position (sitting, standing, etc.), the Investigator should record the alternate position on the ECG eCRF page. The Investigator should date and sign the ECG tracing and record the clinical significance of any abnormal result on the tracing. ECGs will be interpreted by a qualified physician (the Investigator or qualified designee) at the clinical study site.

Standard 12-lead ECGs will be performed according to the schedules in Study Plan (Table 1) and Section 6.2.

6.4.8 Vital signs

Vital sign measurements will be conducted at every visit during the conduct of the study according to the schedules presented in Study Plan (Table 1) and Section 6.2. Vital sign measurements in this study will include sitting systolic and diastolic blood pressure, heart rate, and respiratory rate. Vital signs should be measured after the patient rests for approximately 5 minutes and with the patient in a sitting position.

6.4.8.1 Pulse and blood pressure

The blood pressure measurement should be repeated after at least 30 seconds and the average of the 2 readings recorded. For timings of assessments refer to the Study Plan (Table 1) and Section 6.2.

6.4.8.2 Body temperature

Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan (Table 1) and Section 6.2.

6.4.9 Tanner Pubertal Scale

The assessment of Tanner pubertal stages based on measurements of primary and secondary sex characteristics will be conducted for all patients regardless of sex by a trained staff using accepted guidelines such as Washington Manual of Pediatrics, according to the schedules presented in Study Plan (Table 1) and Section 6.2.

Tanner staging in males should include assessment of testicular volume using an orchidometer for testicular assessments. The correlation of testicular volume to Tanner stage is as given below:

Testicular volume	Tanner stage
4 mL	Onset of pubertal development
4 - 6 mL	Tanner 2
8 - 10 mL	Tanner 3
12 - 15 mL	Tanner 4
20 - 25 mL	Tanner 5

Details of the pubertal assessment will be specified in the statistical analysis plan (SAP).

Pediatric patients normally progress from 1 Tanner stage to another over a period of 12 to 15 months. Any accelerated sexual maturation will be evaluated as a possible drug effect. Per the Investigator discretion, hormonal assessments could be conducted in patient with rapid progression of Tanner stage.

6.4.10 Injection site reaction assessment

Small, asymptomatic, SC nodule formation at the injection site is an expected event associated with sustained release delivery systems.

The assessment of injection site reactions will be performed by the Investigator or subinvestigator according to the schedules presented in the Study Plan (Table 1) and Section 6.2.

Assessments should be done by interviewing the patient and/or the patient's parent(s) or caregiver(s), and be performing physical assesement of the injection site. All relevant information regarding injection site reactions, including reaction type, location, severity, and action taken, should be reported by the Investigator in the Injection Site Reaction Module of the eCRF, including all injection site reactions that meet the criteria for an AE.

Classification of whether an injection site reaction is an AE or not an AE should be made based on the definition of an AE as described in Section 6.4.1. Determination of whether an injection site reaction AE should be classified as serious should be done based on the standard SAE definition as described in Section 6.4.2, as with all other AEs.

6.5 Pharmacokinetics

6.5.1 Collection of samples

Blood samples for determination of exenatide concentrations in plasma will be taken at the times presented in the Study Plan (Table 1, Section 6.2). Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual.

6.5.2 Determination of drug concentration

Samples for determination of drug concentration in plasma will be analyzed by an appointed laboratory on behalf of AstraZeneca using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report.

Only samples from patients who were on active study treatment will be analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a "for cause" basis, for eg, if there is suspicion that a patient has been dosed incorrectly.

6.5.3 Storage and destruction of pharmacokinetic samples

The PK samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed.

The PK samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately in the clinical study report (CSR).

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report.

Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterization of metabolites, if consent for this exploratory research has been obtained.

6.6 Pharmacodynamics

6.6.1 Body Weight

For the measurement of body weight, patients must:

- Wear standard hospital-type gown or equivalent light clothing, with no shoes
- Have fasted for a minimum of 8 hours (if applicable)
- Have consumed no more than one 8-ounce glass of water within 2 hours prior to measurement of body weight
- Void, if possible, before measurement of body weight

Body weight will be measured in all patients at all study-site visits. The study-site personnel should use a digital precision scale, if possible, and record the weight (in kg or lbs) to the first decimal point (eg, 95.3 kg). The same scale should be used at each visit.

6.6.2 Fasting Plasma Glucose and Fasting Serum Insulin

Blood will be drawn for the measurement of fasting plasma glucose and fasting serum insulin concentrations according to the schedules presented in Study Plan (Table 1) and Section 6.2.

6.6.3 C-Peptide

Blood will be drawn for the measurement of C-peptide according to the schedules presented in Study Plan (Table 1) and Section 6.2

6.6.4 Serum Lipids

Blood will be drawn for the measurement of fasting serum lipids according to the schedules presented in Study Plan (Table 1) and Section 6.2. Fasting lipid measurements will include determination of circulating concentrations of TC, LDL-C, HDL-C, and TG.

6.6.5 Collection of pharmacodynamic markers

Samples and measurements will be collected as discussed in this section and according to the schedules presented in Study Plan (Table 1) and Section 6.2. The centralized laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual.

7 BIOLOGICAL SAMPLING PROCEDURES

7.1 Volume of blood

During this study, blood will be drawn for various analytes and panels, including chemistry, hematology and other safety assessments, PK and PD assessments.

7.2 Handling, storage and destruction of biological samples

The samples will be used up or disposed of upon study completion

7.3 Labeling and shipment of biohazard samples

The Principal Investigator ensures that samples are labelled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix C 'International Airline Transport Association (IATA) 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

7.4 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator keeps full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the AstraZeneca biobank system during the entire life cycle.

7.5 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analyzed, AstraZeneca is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed, the action documented and the signed document returned to the study site
- Ensures that the patient and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the central laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

8 ETHICAL AND REGULATORY REQUIREMENTS

8.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Council for Harmonisation (ICH)/Good Clinical Practice (GCP), applicable regulatory requirements and the AstraZeneca policy on Bioethics and Human Biological Samples.

The protocol and ICF will be reviewed and approved by a duly constituted Ethics Committee or IRB before individuals are screened for study entry. The Investigator will ensure that all aspects of the Ethics Committee or IRB review are conducted in accordance with current institutional, local, and national regulations. A letter documenting the Ethics Committee or IRB approval will be provided to the Sponsor prior to initiation of the study. Amendments to the protocol will be subject to the same requirements as the original protocol. The Investigator will submit all periodic reports and updates that the Ethics Committee or IRB may require, including any final closeout reports. The Investigator will inform the Ethics Committee or IRB of any reportable AEs.

8.2 Patient data protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

8.3 Ethics and regulatory review

An Ethics Committee or IRB should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the

patients. The Investigator will ensure the distribution of these documents to the applicable Ethics Committee, and to the study-site staff.

The opinion of the Ethics Committee or IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrollment of any patient into the study.

The Ethics Committee or IRB should approve all advertising used to recruit patients for the study.

AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the Ethics Committee or IRB annually.

Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

AstraZeneca will handle the distribution of any of these documents to the national regulatory authorities.

AstraZeneca will provide Regulatory Authorities, Ethics Committees or IRBs, and Principal Investigators with safety updates/reports according to local requirements, including Suspected Unexpected Serious Adverse Reactions (SUSARs), where relevant.

Each Principal Investigator is responsible for providing the Ethics Committees/IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. AstraZeneca will provide this information to the Principal Investigator so that he/she can meet these reporting requirements.

8.4 Informed consent

The Principal Investigators at each center will:

- Ensure each patient and parent/caretaker are given full and adequate oral and written information about the nature, purpose and duration of the study, participation/termination conditions, possible risk and benefit of the study.

- Ensure each patient is notified that they are free to discontinue from the study at any time.

- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.

- Ensure each patient and their parent/caretaker for patients under 18 years of age provides signed and dated informed consent before conducting any procedure specifically for the study. Patients under 18 years of age will review the ICF and sign a Child Assent Form. Patients and their parent/caretaker for patients under 18 years of age participating in the US will also sign and date an authorization form required under HIPAA, if applicable, that authorizes the use and disclosure of the patient's protected health information.

- Ensure the original, signed ICF, Child Assent Form, and HIPAA authorization forms are in the Investigator's Study File and retained with the study center's records.

- Ensure a copy of each form they have signed is given to the patient.

- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an Ethics Committee.

8.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the International Co-ordinating Investigator and AstraZeneca.

The Investigator is not to deviate from the protocol. In medical emergencies, the Investigator will use medical judgment and will remove the patient from immediate hazard. The Investigator will immediately notify the Sponsor and IRB regarding the nature of the emergency and the course of action taken. The Investigator is to notify the Sponsor of any inadvertent protocol deviations upon discovery, and is to document the deviations appropriately in the study files or on the eCRFs. The Sponsor assumes no responsibility or liability for any unapproved deviations.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol (Revised Clinical Study Protocol).

The amendment is to be approved by the IRB and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

AstraZeneca will distribute any subsequent amendments and new versions of the protocol to each Principal Investigators. For distribution to Ethics Committee see Section 8.3.

If a protocol amendment requires a change to a center's ICF, AstraZeneca and the center's Ethics Committee are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each Ethics Committee.

8.6 Audits and inspections

Authorized representatives of AstraZeneca, a regulatory authority, or an Ethics Committee may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. If such an audit occurs, the Investigator agrees to allow the auditor direct access to all relevant documents and to allocate his or her time and that of the study-site personnel to the auditor to discuss findings and any relevant issues. In addition, regulatory agencies may conduct a regulatory inspection of this study. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center. The Investigator agrees to allow the inspector direct access to all relevant documents and to allocate his or her time and that of the study-site personnel to the inspector to discuss findings and any relevant issues. The Investigator will allow AstraZeneca personnel to be present as an observer during a regulatory inspection, if requested.

9 STUDY MANAGEMENT BY ASTRAZENECA

9.1 Pre-study activities

Before the first patient is entered into the study, it is necessary for a representative of AstraZeneca to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the Investigators (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of AstraZeneca or its representatives. This will be documented in a Clinical Study Agreement between AstraZeneca and the Investigator.

9.1.1 Study Initiation and Discontinuation

Prior to initiation of the study, the Investigator must provide the Sponsor with the following documents (copies of which must be retained by the Investigator):

- Signed original copy of the protocol acceptance statement that commits the Investigator to follow the protocol exactly and to conduct the study according to GCP.
- Original copy of the Investigator's Brochure acceptance page signed by the Investigator.
- Completed and signed original Form FDA 1572.

- Current curriculum vitae, as indicated by version date in the footer or the Investigator's signature and date. Also required is a state license for the Investigator and for other medically qualified subinvestigators.

- Signed financial disclosure forms for the Investigator and all subinvestigators listed on Form FDA 1572.

- Signed copy of the IRB approval letter that lists the approved items.

- List of the IRB members who voted on the approval, including their specialty and affiliation, or the IRB assurance numbers if the roster cannot be obtained.

- Copy of the IRB approved ICF.

- Copy of the IRB approved Authorization to Use and Disclose Protected Health Information form, consistent with HIPAA legislation, if applicable.

- Copy of the local laboratory license, certification, and reference range values for any determinations required by the protocol, if applicable.

Upon receipt of all necessary paperwork, the Sponsor will arrange for all study materials to be delivered to the clinical study site. The Sponsor has the right to terminate the study at any time for any of the following reasons:

- Nonadherence of study-site personnel to the protocol or GCP

- Unavailability of the Investigator or study-site personnel to the Sponsor's monitoring personnel or designee(s)

- Other administrative reasons

Additionally, individual patients may be excluded from the study if a medical records review indicates protocol violations or if other factors appear to jeopardize the validity of the study. Throughout the course of the study, the Investigator is to make a reasonable effort to maintain the enrollment rate that was agreed upon with the Sponsor. The Investigator will also make a reasonable effort to enroll appropriate patients. The Sponsor may elect to terminate the study at a given site if the enrollment rate lags or if significant numbers of nonevaluable patients are enrolled.

9.2 Medical supervision

Medical supervision is the responsibility of the Investigator named on Form FDA 1572. The Investigator may delegate day to day activities to a subinvestigator listed on Form FDA 1572, but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the study protocol. A list will be maintained that includes all qualified persons to whom the Investigator may delegate significant study-related duties. The Investigator is responsible for ensuring that drugs and devices are available for treating

possible medical emergencies, or that emergency medical facilities are available and accessible. The Investigator is responsible for ensuring that the study is conducted according to GCP, other applicable regulatory guidelines, and sound medical practices.

9.3 Training of study-site personnel

Before the first patient is entered into the study, an AstraZeneca representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study specific procedures and the WBDC system(s) utilized.

The Sponsor or designee will ensure that appropriate training relevant to the study is given to all of the staff expected to be involved in the study, and that any new information relevant to the performance of this study is forwarded to the staff involved. This training may include a review of the study protocol, instructions for eCRF completion, and a review of overall responsibilities, including drug accountability and study file maintenance.

The Principal Investigator will maintain a record of all individuals involved in the study (medical, nursing, and other staff).

9.4 Laboratory accreditation

The laboratory facility used for analysis of clinical laboratory samples must provide evidence of adequate licensure or accreditation. Copies of laboratory certification, licensure, and reference ranges (as appropriate) will be supplied to the Sponsor prior to study initiation. The Sponsor or designee should be notified of any changes in reference range values or certification/license renewal during the course of the study. If a central laboratory is used, AstraZeneca will provide a copy of accreditation for the central laboratory and related reference range values.

9.5 Data Reporting

Data for each patient will be recorded on the eCRF. An eCRF must be completed for every patient enrolled in the study. When data are complete, the Investigator or medically qualified subinvestigator listed on Form FDA 1572 will apply his/her electronic signature on the eCRF indicating he/she has reviewed and approves of the data collected on eCRF.

9.6 Monitoring of the study

During the study, an AstraZeneca representative or designee(s) will have regular contacts with the study site, including visits to:

- Provide information and support to the Investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in

accordance with the Laboratory Manual and that study drug accountability checks are being performed.

- Conduct periodic audits of all eCRFs and to review all eCRFs and corresponding portions of office, clinical, and laboratory records for each patient at each clinical study site.

- Perform source data verification (a comparison of the data in the eCRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients.- This will require direct access to all original records for each patient (eg, clinic charts). Study data reviews will be performed during routine monitoring visits, both during the study and following study completion. These visits are to provide the Sponsor with the opportunity to evaluate study progress; verify the accuracy and completeness of eCRFs; and ensure that all protocol requirements, applicable US FDA or country-specific regulations, and Investigator obligations are being fulfilled. Finally, any inconsistencies in the study records should be resolved during these visits.

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the patient.

The AstraZeneca representative will be available between visits if the Investigator(s) or other staff at the center needs information and advice about the study conduct.

The Sponsor may terminate study participation by a clinical study site if study-site personnel do not follow the protocol or GCP. Additionally, individual patients may be excluded if a medical records review indicates protocol violations or if other factors appear to jeopardize the validity of the study.

9.6.1 Source data

Refer to the Clinical Study Agreement for location of source data.

9.7 Study agreements

The Principal Investigator at each center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of patients and in all other respects, not relating to study conduct or treatment of patients, the terms of the Clinical Study Agreement shall prevail.

Agreements between AstraZeneca and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.7.1 Archiving of study documents

The Investigator follows the principles outlined in the Clinical Study Agreement.

Investigators will maintain adequate records for the study, including patients' eCRFs, medical records, laboratory reports, signed consent forms, drug accountability records, safety reports, information regarding patients who discontinued the study, and any other pertinent data. All records and reports will be retained by the Investigator for at least 2 years after the last approval of a marketing application in an ICH region. If the marketing application is rejected or if the marketing application is not filed, the records must be retained for 2 years following notification by the Sponsor that investigations have been discontinued and that the US FDA and other government regulatory agencies have been notified. Records should be available for copying and inspection if requested by a properly authorized employee of the US FDA or other government regulatory agency, in accordance with federal regulations. The Investigator must notify the Sponsor immediately in the event of accidental loss or destruction of any study records.

Sponsor specific essential documents will be retained at least 2 years after the last approval of a marketing application in an ICH region or at least 2 years following the formal discontinuation of clinical development of the study medication. These documents should be retained for a longer period, however, if required by applicable country regulatory requirements. For eg, patient identification codes must be retained for at least 15 years following the completion or discontinuation of the study, according to Directive 91/507/EEC.

9.8 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study is expected to start in Q2 2015 and to end by Q2 2021.

The study may be terminated at individual centers if the study procedures are not being performed according to GCP, or if recruitment is slow. AstraZeneca may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with EQW.

9.9 Final report

All data, including patient characteristics, methodology, and clinical findings, will be presented in a final clinical/statistical report to be prepared by the Sponsor or designee.

10 DATA MANAGEMENT

Data management will be performed by the designated contract research organization (CRO). A data management plan outlining the data management systems, procedures, and agreements between the CRO and Sponsor will be written. The plan will be reviewed and signed off by a representative of the Sponsor's data management department.

The data collected through third-party sources will be obtained and reconciled against study data.

Clinical study data will be reported (captured) on by study site personnel on eCRFs. The eCRF data will be entered by study-site personnel and then reviewed and electronically signed by the Investigator listed on Form FDA 1572. All study-site personnel must use an electronic signature access method to enter, review, or correct study data. Electronic signature procedures shall comply with the Code of Federal Regulations (CFR) Title 21 Part II and the ICH Guidelines for GCP (Topic E6, April 2000) Section 5.5.3. Passwords and electronic signatures will be strictly confidential.

All eCRF data will be downloaded from the electronic data capture (EDC) system and reformatted into SAS data sets. The Sponsor's data management department will receive electronic transfers of laboratory data from a central laboratory as well as other data from third-party vendors as appropriate. The electronic data format of all transfers will be agreed upon with the Sponsor.

Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the CRO.

Data queries will be raised for inconsistent, impossible, or missing data. All entries to the study database will be available in an audit trail.

The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked.

Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca.

11 EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR ITS DELEGATE

Refer to the SAP for further details.

11.1 Calculation or derivation of efficacy variables

Refer to the SAP for further details.

11.2 Calculation or derivation of safety variables

11.2.1 Other significant adverse events (OAE)

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs and AEs leading to discontinuation (DAEs). Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Patient Safety Physician, be considered other significant AEs (OAEs) and reported as such in the Clinical Study Report. A similar review of laboratory/vital signs/ECG data will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.3 Calculation or derivation of pharmacokinetic variables

If deemed necessary, appropriate PK parameters will be calculated for each patient and summarized by treatment.

11.4 Calculation or derivation of pharmacodynamic variables

Refer to the SAP for further details.

11.4.1 Calculation or derivation of the relationship between pharmacokinetic and pharmacodynamic variables

Refer to the SAP for further details.

11.4.2 Population analysis of pharmacokinetic/pharmacodynamic variables

Refer to the SAP for further details.

12 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION BY ASTRAZENECA OR DELEGATE

12.1 Description of analysis populations

Efficacy analyses will be performed in the Intent-to-Treat (ITT) Population or in a set of evaluable patients coming from the ITT Population, ie, the Evaluable Population and/or the Per-Protocol (PP) population. The Evaluable Population will be used for the primary analysis. Safety analyses will be performed for the ITT Population unless stated otherwise.

The following populations will be used for the summaries and analyses of the study data. The populations are defined as follows:

- Intent-to-Treat (ITT): The ITT Population will consist of all randomized patients who receive at least 1 dose of randomized study medication.

- Evaluable Population: The Evaluable Population will consist of all ITT patients who receive at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment.

- Per-Protocol (PP): The per-protocol analysis set will be a subset of the ITT population through the exclusion of those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis. Detailed exclusion criteria for the PP population will be specified in the SAP. Patients excluded from the PP analysis will be identified before database lock.

12.2 Study endpoints

12.2.1 Primary endpoint

- Change in HbA1c from baseline Visit 2 (Week 0) to Visit 7 (Week 24)

12.2.2 Secondary endpoints

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

- Change in fasting plasma glucose concentration from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

- Proportions of patients achieving HbA1c goals of ≤6.5% and <7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit

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

- Change in fasting insulin and C-peptide from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

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

- Change in lipids from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

- Change in blood pressure from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

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

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

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

12.2.3 Exploratory endpoints

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

- Change in body weight percentile and height percentile from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit. The height and weight percentile will be determined based on the standardized growth chart for boys and girls (developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (Center for Disease Control and Prevention, 2010).

12.2.4 Safety endpoints

- Safety and tolerability endpoints including the incidence of treatment emergent AEs, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable

- Change in calcitonin, pancreatic amylase, and lipase from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52)

- Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)

- Tanner pubertal stage at baseline Visit 2 (Week 0), Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52)

12.2.5 Exploratory safety endpoints

- Change in CEA from baseline Visit 2 (Week 0) to Visit 5 (Week 12) and Visit 10 (Week 52)

- Change in bone specific alkaline phosphatase and N-telopeptide from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24) and Visit 10 (Week 52)

- Change in FSH, LH, FSH/LH, total testosterone*, SHBG*, and estradiol from baseline Visit 2 (Week 0) to Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)

*Change in total testosterone and SHBG also at Visit 9 (Week 40). Free testosterone will be calculated from total testosterone and SHBG values at Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52).

12.3 Demographic and baseline characteristics

Demographic and relevant baseline characteristics will be presented and summarized descriptively by treatment for the ITT and Evaluable Population. The baseline measurement is defined as the last value collected prior to the first dose of study medication.

12.4 Treatment compliance

Treatment compliance (number of doses received relative to doses planned) will be summarized by treatment for the ITT Population.

12.5 Prior and concomitant medication

Prior and concomitant medications will be summarized for the ITT Population. The number and percentage of patients receiving such medications will be summarized by treatment and Anatomic Therapeutic Chemical (ATC) classification.

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

12.6 Methods of statistical analyses

12.6.1 General considerations

Efficacy analyses will be performed for the ITT and/or Evaluable Populations and/or the PP population. Safety analyses will be performed for the ITT Populations unless stated otherwise.

The analysis of the primary endpoint will be performed using the Evaluable Population. The analyses of all other efficacy endpoints will be performed in ITT population.

For patients who discontinue from the study prior to completing all study procedures through Visit 7 (Week 24), the analyses of the change in HbA1c, change in body weight, change in body weight percentile, height percentile, change in BMI, change in fasting plasma glucose concentration, fasting insulin and lipids, change in blood pressure, change in beta-cell function and insulin sensitivity will be based on the observed data and the Mixed Models Repeated Measures (MMRM) method will be implemented (see Section 12.6.2).

For summary statistics and Cochran-Mantel-Haenszel (CMH) analyses related to proportions, such as proportions of patients achieving HbA1c goals of ≤6.5% and <7.0%, for those patients who discontinue from the study prior to completing all study procedures through Visit 7 (Week 24), but have data collected for at least 1 visit subsequent to Visit 2 (Week 0), missing values for efficacy, PD, and anthropometric measures up to Visit 7 (Week 24) will be imputed

using the values at the last visit (including Early Termination visit) in accordance to the last observation carried forward approach. Values at Visit 2 (Week 0) will not be carried forward.

For patients who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the efficacy analysis to draw statistical inference.

Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the SAP.

All tests of treatment effects will be conducted at a 2-sided significance level of 0.05. More information on the interim analysis and the statistical significance has been described in Section 12.6.8.

12.6.2 Analysis of the primary endpoint

The MMRM approach will be used to analyze the change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 7 (Week 24). The model will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and region as the fixed effects, baseline HbA1c as the covariate, and patients as the random effects. The variance – covariance structure to be used for this modeling 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 maximum likelihood (ML) method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between the EQW and PBO groups at Visit 7 (Week 24) will be provided.

All observed HbA1c data from post-baseline visits (including Early Termination) will be included in the MMRM analysis. In addition, if a patient's last available measurement during the 24-week assessment period is from an unscheduled visit or Early Termination visit, the value will be programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. For patients who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM analysis.

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

The consistency of the primary analysis will be checked by the same MMRM of the primary endpoint as described above performed in the PP population.

Summaries and descriptive analysis of the primary endpoint will be performed in the ITT population.

Summaries and analyses may also be conducted for subgroups defined by baseline HbA1c 12 strata (<9.0% or ≥9.0%) and country in the ITT population.

12.6.3 Analysis of the secondary endpoints

Analysis of all secondary endpoints will be performed in the ITT population. Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment.

Proportions of patients having HbA1c target values of ≤6.5% and <7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit will be compared between treatments using the CMH procedure, in which baseline HbA1c strata will serve as the stratification factors. Any ITT patient who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint.

As a supportive analysis, the probabilities of patients reaching HbA1c targets of ≤6.5% and <7.0% will also be analyzed using a logistic regression model. The independent variables will include treatment group, HbA1c baseline strata (<9.0% or ≥9.0%), and country as factors, and baseline HbA1c as a continuous covariate.

The same CMH procedure and logistic regression as described above will be used to analyze data on proportion of patients discontinuing the study, needing rescue due to failure to maintain glycemic control. However, the number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit will be analyzed in a exploratory fashion, using descriptive statistics only.

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

The MMRM approach will be used to analyze the change in HbA1c, body weight, blood pressure, fasting plasma glucose, fasting insulin, lipids, HOMA-B, and HOMA-S from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and each intermediate visit. The MMRM method for change in HbA1c will be the same as stated in Section 12.6.2. The models for changes in body weight, blood pressure, fasting plasma glucose, fasting insulin, lipids, HOMA-B, and HOMA S will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline of the dependent variable as the covariate, and patients as the random effects. The ML method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be provided.

Similar to the primary endpoint analysis, all observed data will be included in the MMRM and logistic regression analysis. Data collected from an Early Termination visit will be mapped to

the next closest scheduled visit. For patients who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM and logistic regression analysis.

Because the introduction of the dual chamber pen injection device does not affect the randomization scheme or blinding of patients, no sensitivity analysis will be performed to assess the treatment effect due to change in the device.

The proportions of patients (N [%]) reporting different injection site reactions will be summarized at Visit 3 (Week 4) through Visit 10 (Week 52) using descriptive statistics.

12.6.4 Analysis of exploratory endpoints

Analysis of all exploratory endpoints will be performed in the ITT population. Baseline values, the values at each visit, and changes from baseline values will be summarized for percentiles of body weight, percentile of height, and BMI by treatment. A similar MMRM modeling approach (see Section 12.6.3) will be implemented to compare changes in body weight percentile, height percentile, and BMI between treatment groups.

12.6.5 Pharmacokinetic analyses

Analysis of all PK endpoints will be performed in the ITT population. Descriptive statistics for plasma exenatide concentrations will be presented by treatment and visit. If deemed necessary, appropriate PK parameters will be calculated for each patient and summarized by treatment.

12.6.6 Pharmacodynamic analyses

Analysis of all PD endpoints will be performed in the ITT population. Descriptive statistics for PD endpoints including absolute values and change in fasting plasma glucose concentration, and fasting serum insulin concentration will be presented by treatment and visit. Also see Section 12.6.3 for inferential statistical analysis.

12.6.7 Safety analyses

Analysis of safety data will be performed in the ITT population. Safety will be assessed by examination of AEs, clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide.

12.6.7.1 Adverse events

On treatment AEs will be defined as those occurring after the first administration of study medication on Visit 2 (Week 0) through Study Termination or Early Termination or after Study Termination but considered by the Investigator as clinically significant and as related to study medication or study procedure; or an SAE reported within 90 days of the last administration of EQW; or existing prior to the time of and worsening after the time of the first administration of study medication. Adverse events prior to the first administration of study medication on Visit 2 (Week 0) will be classified as pretreatment

(non-treatment-emergent). Detailed rules for classification of on treatment AEs in the extension period will be specified in the SAP.

On treatment AEs will be summarized by treatment, system organ class, and preferred term defined by MedDRA. The number of events, the number of patients, and the percent of patients who experienced at least 1 on treatment AE will be presented for each system organ class and for each preferred term by treatment group. On treatment AEs that are related to study medication, on treatment AEs that lead to early withdrawals, and serious on treatment AEs will be summarized in the same manner.

12.6.7.2 Clinical laboratory evaluations

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

Baseline values, the values at each visit, and changes from baseline values will be summarized for each of the quantitative laboratory assessments by treatment.

Shift tables of hematology, clinical chemistry, and urinalysis results will be used to summarize changes from Baseline Visit 2 (Week 0) to Study Termination (Visit 11 [Week 62] or Early Termination), and to each intermediate visit.

Antibody to exenatide data will be listed and summarized. A shift table of antibodies to exenatide will be used to summarize the change from baseline Visit 2 (Week 0) to each scheduled measurement. 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. The incidence of treatment-emergent antibodies to exenatide will be summarized by study visit, as appropriate.

12.6.7.3 Vital signs and physical examinations

For vital signs, baseline values, the values at each scheduled visit, and changes from baseline values will be summarized by treatment. Physical examination findings will be listed.

12.6.7.4 Other safety endpoints evaluations

The proportion of patients discontinuing the study, and the proportion of patients needing rescue due to failure to maintain glycemic control, and the number of rescue episodes will be evaluated.

Absolute and change in calcitonin, pancreatic amylase, and lipase, TSH, free T4, prolactin, cortisol, IGF-1, DHEAS, Tanner pubertal stages, FSH, LH, FSH/LH, total testosterone, SHBG, estradiol, CEA, and bone specific alkaline phosphatase and N-telopeptide will be summarized by visit.

12.6.8 Interim analyses

One interim analysis is planned when 40 patients will have completed 24 weeks of treatment, including early withdrawal. This interim analysis will be performed by the independent Data Monitoring Committee (DMC) that does not directly involve with the study design, conduct and data analysis. No study personnel will have access to the unblinded clinical data to maintain the integrity of the double-blind study design.

Purpose of the interim analysis is to ensure safety of the patient population. Hence, the DMC will only look at the safety data collected in this study. The DMC will review the safety data first in a blinded fashion and then, if needed, will look at the unblinded data to assess the risk of the pediatric patients' being exposed to the active drug compared to placebo, using the AE and/or safety laboratory data of the study population.

12.6.9 Stratification during randomization

Randomization will be stratified by screening HbA1c (%) <9.0% and ≥9.0%. The restriction on gender in the study population (female patients between 40% and 60%) and also on the ethnicity and lifestyle (40%-60% patients with European ethnicity and lifestyle) will be enforced through putting caps on enrollment of patients with different genders and from the different regions (Europe, US, and others).

12.7 Determination of sample size

Approximately 77 patients who have met all study requirements will be randomized in a ratio of 5:2 to the exenatide or placebo treatment group on Visit 2 (Week 0) and will be carried out with stratification to achieve a balanced distribution of patients across treatment groups with regard to the screening HbA1c strata (<9.0% or ≥9.0%).

The analysis will be performed in the set of evaluable patients coming from the ITT population. Assuming a 10% drop-out rate, approximately 70 patients will complete the 24-week controlled treatment period of study. Based on calculation done using the software NQuery Advisor Version 7, an overall power of 74% will be provided to reject the null hypothesis of no difference between the 2 treatment arms assuming a true treatment difference of -0.7% between exenatide and placebo in changes from baseline for HbA1c (%). This power computation also assumes a common standard deviation of 1.0% and a 2-sided significance level of 0.05.

12.8 Data Monitoring Committee

The purpose of the DMC is to advise the Sponsor regarding the continuing safety of study participants and the continuing validity and scientific merit of the trial. Further details can be found in the DMC Charter.

13 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

13.1 Medical emergencies and AstraZeneca contacts

The Principal Investigator is responsible for ensuring that procedures and expertise are available to handle medical emergencies during the study. **A medical emergency usually constitutes an SAE and is to be reported as such, see Section 6.4.4.**

13.2 Overdose

An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the eCRF and on the Overdose eCRF module.

An overdose without associated symptoms is only reported on the Overdose eCRF module.

If an overdose on an AstraZeneca study drug occurs in the course of the study, then Investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with SAE, standard reporting timelines apply, see Section 6.4.4. For other overdoses, reporting should be done within 30 days.

13.3 Pregnancy

All outcomes of pregnancy should be reported to AstraZeneca.

13.3.1 Maternal exposure

For female patients, a pregnancy test will be performed according to the schedules presented in Table 1 and Section 6.4.5.5. A negative pregnancy test must be confirmed prior to the administration of study medication according to the schedule in the Study Plan (Table 1) and Section 6.2.

If a patient becomes pregnant during the course of the study they will not receive any additional injections of study medication and should be discontinued immediately upon confirmation of pregnancy. The reason for withdrawal will be documented on the disposition eCRF page as a "protocol violation." These patients will be required to return to the clinical study site for early termination or study termination procedures depending on last visit completed.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then Investigators or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 days for SAEs, see Section 6.4.4 and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

In addition, the Sponsor will monitor all documented pregnancies through outcome. While pregnancy itself is not considered an AE or SAE, any pregnancy complications will be recorded as an AE or SAE.

The PREGREP module in the eCRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

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Clinical Study Protocol Appendix B

Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	01
Date	09 April 2015

Appendix B
Additional Safety Information

FURTHER GUIDANCE ON THE DEFINITION OF A SERIOUS ADVERSE EVENT (SAE)

Life threatening

'Life-threatening' means that the subject was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the subject's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

A GUIDE TO INTERPRETING THE CAUSALITY QUESTION

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

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Clinical Study Protocol Appendix C

Drug Substance	Exenatide
Study Code	D5551C00002
Edition Number	01
Date	09 April 2015

Appendix C
International Airline Transportation Association (IATA) 6.2 Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

International Airline Transportation Association (IATA) classifies biohazardous agents into 3 categories **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm).** For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations (DGR) in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus (HIV) types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging **(http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)**
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable

- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Clinical Study Protocol Appendix D	
Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	01
Date	09 April 2015

Appendix D
Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

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1. INTRODUCTION

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Adverse Events (AE) and Serious Adverse Events (SAE) according to the outcome of the review and assessment in line with standard safety reporting processes.

2. DEFINITIONS

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) **together with** Total Bilirubin (TBL) ≥ 2xULN at any point during the study following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN **together with** TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

3. IDENTIFICATION OF POTENTIAL HY'S LAW CASES

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3xULN
- AST ≥ 3xULN
- TBL ≥ 2xULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to AstraZeneca representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the AstraZeneca representative
- Request a repeat of the test (new blood draw) by the central laboratory
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results)

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the patient meets PHL criteria (see Section 2 of this Appendix for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

4. FOLLOW-UP

4.1 Potential Hy's Law Criteria not met

If the patient does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the patient has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

4.2 Potential Hy's Law Criteria met

If the patient does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated
- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which of the tests available in the Hy's law lab kit should be used.
- Complete the three Liver CRF Modules as information becomes available
- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures

5. REVIEW AND ASSESSMENT OF POTENTIAL HY'S LAW CASES

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP. The AstraZeneca Medical Science Director and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF

- If the alternative explanation is an AE/SAE, record the AE /SAE in the CRF accordingly and follow the AZ standard processes

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Report an SAE (report term 'Hy's Law') according to AstraZeneca standard processes.

  – The 'Medically Important' serious criterion should be used if no other serious criteria apply

  – As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review

6. REFERENCES

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

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Clinical Study Protocol Appendix E	
Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	2.0
Date	09 April 2015

Appendix E
Extended Safety Follow-Up Period

1. Overview and Rationale

In response to a request from the European Medicines Agency Committee, patients participating in Study BCB114 will be observed in an Extended Safety Follow-Up Period following discontinuation of study medication administration. Long-term follow-up of pediatric patients participating in Study BCB114 will allow observation of ongoing development and growth on an individual patient basis and a description of the occurrence of selected adverse events in pediatric patients in the absence of EQW treatment following up to 52 weeks of EQW administration.

2. Objective

The objectives of this Extended Safety Follow-Up Period are:

- To describe safety parameters over time following discontinuation of study medication administration, including the following:
  - Adverse events (AEs) of special interest
  - Ongoing prescription medications
  - Height and weight
  - Tanner pubertal stage
  - Carcinoembryonic antigen (CEA) concentration
  - Calcitonin concentration

3. Study Design

Following discontinuation of study medication administration, patients with a height increase of at least 5 mm between Visit 8 (Week 28) and Visit 11 (Week 62/Study Termination) will enter the Extended Safety Follow-Up Period. Patients who discontinue study medication administration prior to Visit 10 (Week 52/Study Termination) will also enter the Extended Safety Follow-Up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study-site visits prior to discontinuation of study medication. 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 Extended Safety Follow-Up Period.

During the Extended Safety Follow-Up Period, 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 a 5 mm increase (whichever comes first). During the Extended Safety Follow-Up period, adverse events of special interest (AESIs) (see Table 1), and ongoing prescription medication will be reviewed, height, weight, and Tanner pubertal stage will be assessed, and CEA and calcitonin concentrations will be measured.

4. Visit Structure

The Extended Safety Follow-Up Period will include up to 6 study-site visits (6-month intervals for a period of up to 36 months). The first visit during the Extended Safety Follow-Up Period is to occur 6 months after discontinuation of study medication administration or 6 months after Visit 10 (Week 52), whichever comes first. Patients will subsequently return to the study site at 6-month intervals (±2 weeks). Patients will discontinue participation in the Extended Safety Follow-Up period after 3 years or once they have a height increase of less than 5 mm between two 6-month interval visits.

5. Study Duration

The duration of the Extended Safety Follow-Up Period will be a maximum of 3 years.

6. Study Population

Patients who have participated in Study BCB114 who have a height increase of at least 5 mm between Visit 8 (Week 28) and Visit 11 (Week 62/Study Termination) will participate in the Extended Safety Follow-Up Period. Patients who discontinue study medication prior to Visit 10 (Week 52) will also participate in the Extended Safety Follow-Up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study-site visits prior to discontinuation of study medication. 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 Extended Safety Follow-Up Period.

Patients participating in the standardized meal test (Appendix F) will also participate in the Extended Safety Follow-Up Period, with no changes to the procedures and study site visits associated with Appendix F

7. Patient Restrictions

There are no patient restrictions for the Extended Safety Follow-Up Period. No fasting or withholding of medications is required prior to Extended Safety Follow-Up Period visits.

8. Restricted Medications

During the Extended Safety Follow-Up Period, patients will be treated at the discretion of their healthcare provider, with no medication restrictions.

9. Study Medications

No study medications will be administered during the Extended Safety Follow-Up Period.

10. Study Methods

During the Extended Safety Follow-Up Period, patients will return to the study site at 6-month intervals.

All patients will undergo the following procedures during each Extended Safety Follow-Up Period visit:

- Review of ongoing prescription medication
- Review of AESIs (see Table 1)
- Assessment of body weight and height
- Assessment of Tanner pubertal stage
- Blood samples will be collected for assessment of:
  - Calcitonin
  - CEA

Patients with an increase in height of 5 mm or greater, compared to a height measurement obtained 6 months previously, will be asked to return for additional safety follow-up visits at 6-month intervals, for a maximum observation period of 3 years or 36 months.

11. Safety Assessments

Assessment of body weight, height, Tanner pubertal stage, calcitonin concentration, and CEA concentration in the Extended Safety Follow-Up Period will be performed as described in the main protocol.

Review of medications during the Extended Safety Follow-Up period will focus on ongoing prescription medications.

Adverse events of special interest (Table 1) will be assessed at all visits during the Extended Safety Follow-Up Period and the eCRF will be completed if it is determined that the patient has experienced one or more of the listed AESIs. Other serious and nonserious AEs will be collected through routine postmarketing spontaneous reporting and according to the relevant medication(s) the patient is receiving (which may or may not include exenatide).

Table 1. List of Adverse Events of Special Interest to be Recorded in CRF

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

Note: Table to be updated in the case that additional adverse events of special interest are identified.

12. Statistical Considerations

a. Analysis Populations

Safety data will be listed for the **Extended Safety Follow-Up Population**, which will consist of all patients who participate in at least one Extended Safety Follow-Up Period visit.

13. General Considerations

Data collected in the Extended Safety Follow-Up Period is for descriptive purposes and is not associated with a predefined hypothesis or test. Data will be listed by individual patient. Missing data will not be imputed. No descriptive summaries will be prepared. In addition, data collected throughout the treatment period and the Extended Safety Follow-Up Period will be listed for each individual patient in the Extended Safety Follow-Up Population in individual patient profiles.

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Clinical Study Protocol Appendix F

Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	2
Date	14 December 2017

Appendix F
Mixed Meal Substudy

Appendix F: Mixed Meal Substudy

Study Title: Mixed Meal Substudy

Protocol Number: BCB114 D5551C00002

Amendment Number: 04

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LIST OF TABLES

1. PURPOSE

The purpose of this exploratory substudy is to evaluate the change in postprandial beta-cell function after approximately 28 weeks of exenatide once weekly therapy and at approximately 10 to 12 weeks following cessation of drug therapy.

2. SCOPE

A standardized mixed-meal test will be implemented prior to treatment at baseline Visit 2 (Week 0), Visit 10 (Week 52), and at Visit 11 (Week 62) (approximately 10 to 12 weeks following Visit 10 (Week 52) in a subset of subjects enrolled in Protocol BCB114.

The standardized mixed-meal test will be conducted in approximately 20 subjects at a number of sites participating in Protocol BCB114. As all subjects who remain in the trial will receive at least 28 weeks of treatment with exenatide once weekly, subjects from either treatment arm (exenatide once weekly or placebo) are eligible to participate in the addendum. At the time of the first post-baseline assessment (Visit 10 (Week 52), subjects participating in the addendum will have been exposed to exenatide once weekly for at least 28 weeks.

3. BACKGROUND AND RATIONALE

Exenatide improves glycemic control in subjects with type 2 diabetes mellitus, enhances glucose-dependent insulin secretion by the pancreatic beta cell, suppresses inappropriately elevated glucagon secretion during periods of hyperglycemia, and slows gastric emptying.

Several clinical studies have shown that exenatide reduces fasting and postprandial glucose concentrations through mechanisms of actions including glucose-dependent suppression of glucagon secretion[1-2], slowed gastric emptying and enhanced splanchnic glucose uptake, resulting in slowed appearance of meal-derived glucose in the circulation[1-2], and effects on the beta-cell including the enhancement of glucose-dependent insulin secretion[1, 3] and the restoration of first-phase insulin secretion.[4]

Diminished first-phase insulin secretion is an early pathophysiologic feature of type 2 diabetes, and plays a key role in sustained postmeal hyperglycemia. A number of different beta-cell markers suggest that exenatide treatment is associated with improvements in both first--and second-phase insulin secretion in subjects with type 2 diabetes.[4]

This substudy is designed to assess postprandial beta-cell function specifically evaluating potential restoration of the beta-cell response following approximately 28 weeks of exenatide once weekly treatment and at approximately 10 to 12 weeks following cessation of drug therapy.

4. OBJECTIVES

The primary objective of this exploratory substudy is:

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

The secondary objective of this exploratory substudy is:

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

5. STUDY DESIGN

5.1 Design Description

At baseline Visit 2 (Week 0), the study procedures to be assessed are outlined in the main protocol and in Section 9.1.1 of this substudy. Study medication will be administered after all study procedures outlined in the main protocol and substudy are completed.

At Visit 10 (Week 52), the study procedures to be assessed are outlined in the main protocol and in Section 9.1.2 of this addendum.

10 to 12 weeks following the discontinuation of study medication administration, subjects will return to the study site for Visit 11 (Week 62/Study Termination). At this visit, the study procedures to be assessed are outlined in the main protocol and in addition, subjects will receive the standardized mixed-meal test and have blood drawn for additional postprandial pharmacodynamic assessments for the purpose of the substudy. Substudy procedures to be performed at this visit are outlined in Section 9.1.3.

6. STUDY DURATION

The total duration of the substudy will be approximately 62 weeks; the substudy will be initiated at baseline Visit 2 (Week 0) and concluded at Visit 11 (Week 62/Study Termination), approximately 10 to 12 weeks following the discontinuation of study medication at Visit 10 (Week 52).

7. STUDY POPULATION

Approximately 20 subjects participating in Protocol BCB114 who have volunteered to participate will be included in the substudy.

7.1 Inclusion Criteria

All subjects participating in the substudy should adhere to the inclusion criteria listed in Protocol BCB114.

7.2 Exclusion Criteria

All subjects participating in the substudy should adhere to the exclusion criteria listed in Protocol BCB114.

7.3 Restricted Medications

During the approximately 10 to 12 week off-drug period, substudy subjects should not be treated with:

- Insulin secretagogues (e.g., meglitinide, nateglinide, and sulfonylureas), DPP-4 inhibitors, or GLP-1 receptor agonists (e.g., exenatide and liraglutide)

8. STUDY MEDICATION

Following the completion of study procedures at Visit 2 (Week 0) outlined in the main protocol and this substudy, subjects participating in the substudy will administer study medication (exenatide once weekly 2 mg or placebo) as described in Protocol BCB114, according to their assigned treatment group.

9. STUDY METHODS

9.1 Study Schedule

In addition to the procedures outlined in Protocol BCB114, additional procedures for the substudy will be performed at baseline Visit 2 (Week 0), Visit 10 (Week 52), at Visit 11 (Week 62/Study Termination) as outlined below:

9.1.1 Baseline Visit 2 (Week 0)

Prior to Visit 2 (Week 0), subjects will have fasted overnight (≥8 hours).

The study procedures outlined in the main protocol and collection of fasting and all other blood samples for assessments listed here and in the main protocol are to be collected prior to the start of the standardized meal.

In addition to the procedures outlined in the main protocol, the following procedures will be performed:

- Ingestion of a standardized meal (Section 18), containing approximately 55% carbohydrates, 15% protein, and 30% fat. The meal is to be completed within 15 minutes with one fasting blood sample taken anytime within the 30 min prior to the start of the meal, and subsequent samples taken at 15 min, 30 min, 60 min, 120 min, 180 min, and 240 min relative to the start of the meal for the assessment of:
  - Glucose
  - C-peptide
  - Glucagon
- Subjects should wait to inject study medication until all blood draws are collected and all procedures described in the main protocol have been completed.

9.1.2 Visit 10 (Week 52)

Prior to Visit 10 (Week 52), subjects will have fasted overnight (≥8 hours).

The study procedures outlined in the main protocol and all other blood samples for assessments listed here and in the main protocol are to be collected prior to the start of the standardized meal.

In addition to the procedures outlined in the protocol, the following procedures will be performed:

- Ingestion of a standardized meal (Section 18), containing approximately 55% carbohydrates, 15% protein, and 30% fat. The meal is to be completed within 15 minutes with one fasting blood sample taken anytime within the 30 min prior to the start of the meal, and subsequent samples taken at 15 min, 30 min, 60 min, 120 min, 180 min, and 240 min relative to the start of the meal for the assessment of:
  - Glucose
  - C-peptide
  - Glucagon

9.1.3 Visit 11 (Week 62/Study Termination)

Subjects who complete Visit 10 (Week 52) will return for Visit 11 (Week 62/Study Termination) 10-12 weeks after the cessation of study drug medication. Subjects who terminate early from the study will not receive the Substudy procedures. Prior to Visit 11 (Week 62/Study Termination), subjects will have fasted overnight (≥8 hours).

In addition to the procedures outlined in the protocol, the following procedures will be performed:

At this visit, subjects will undergo the following procedures:

- Ingestion of standardized meal (Section 18), containing approximately 55% carbohydrates, 15% protein, and 30% fat. The meal is to be completed within 15 minutes with one fasting blood sample taken anytime within the 30 min prior to the start of the meal, and subsequent samples taken at 15 min, 30 min, 60 min, 120 min, 180 min, and 240 min relative to the start of the meal for the assessment of:
  - Insulin (-30 min only)
  - Glucose
  - C-peptide
  - Glucagon
- A blood sample will be collected within the 30 min prior to the start of the meal for:
  - Pharmacokinetic and antibody assessments of exenatide once weekly

10. PHARMACODYNAMIC ASSESSMENTS

Samples and measurements will be collected as discussed in this section. The centralized laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples.

10.1 Plasma Glucose, Serum Insulin, C-Peptide, and Glucagon

Blood will be drawn for the measurement of glucose, insulin, C-peptide, and glucagon concentrations according to the schedules presented in Sections 9.1.1, 9.1.2, and 9.1.3. For each assessment specified in Sections 9.1.1, 9.1.2, and 9.1.3, one fasting blood sample will be taken anytime within the 30 min prior to the start of the standardized meal at baseline Visit 2 (Week 0), Visit 10 (Week 52), and Visit 11 (Week 62/Study Termination). Subsequent blood samples will be taken at 15 min, 30 min, 60 min, 120 min, 180 min, and 240 min, relative to the start of the standardized meal.

11. PHARMACOKINETIC ASSESSMENTS

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

Refer to the main protocol for additional details on the storage of blood samples for pharmacokinetic assessments.

12. STATISTICAL CONSIDERATIONS

12.1 Analysis Population

The Standardized Mixed-Meal Test Evaluable Population will consist of all intent-to-treat subjects who participate in the Standardized Mixed-Meal Test, complete study procedures in compliance with the main protocol and the substudy, and have valid and adequate pharmacodynamic measurements for data analysis.

Adjustments may be made to refine the definition of the Standardized Mixed-Meal Test Evaluable Population prior to database lock. The final definition of the Standardized Mixed-Meal Test Evaluable Population will be documented in the statistical analysis plan.

12.2 Study Endpoints

12.2.1 Primary Endpoint

- The primary endpoint for this substudy is the change in incremental $AUC_{(0\text{-}240)}$ for C-peptide from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and Visit 11 (Week 62/Study Termination)

12.2.2 Secondary Endpoints

- Change in C_{max}, C_{ave}, T_{max}, and incremental $AUC_{(0\text{-}30)}$ for C-peptide from baseline Visit 2 (Week 0) to Visit 10 (Week 52) and Visit 11 (Week 62/Study Termination)
- Change in incremental $AUC_{(0\text{-}240)}$ and incremental $AUC_{(0\text{-}30)}$, C_{max}, C_{ave}, and T_{max}, for glucose and glucagon, from baseline Visit 2 (Week 0) to Visit 10 (Week 52) and Visit 11 (Week 62/Study Termination)
- Change in HOMA-B, HOMA-S and insulinogenic index from baseline Visit 2 (Week 0) to Visit 10 (Week 52) and Visit 11 (Week 62/Study Termination) in patients not taking insulin

12.2.3 Safety Endpoints

- Adverse events will be evaluated as the safety endpoint

12.3 Analysis of Study Endpoints

12.3.1 General Considerations

All pharmacodynamic parameters (i.e., AUC , C_{max}, C_{ave} and T_{max}) will be calculated using noncompartmental methods. Details on analysis methods will be provided in the statistical analysis plan.

12.3.2 Analysis of the Primary Endpoint

Summary statistics will be provided for incremental $AUC_{(0-240)}$ of C-peptide at baseline Visit 2 (Week 0), Visit 10 (Week 52), and Visit 11 (Week 62/Study Termination).

The paired t-test will be utilized to analyze the change in incremental $AUC_{(0-240)}$ of C-peptide from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to Visit 11 (Week 62/Study Termination). The 95% confidence intervals will be provided.

12.3.3 Analyses of Secondary Endpoints

Summary statistics will be provided for all pharmacodynamic parameters for C-peptide, glucose, and glucagon, as well as HOMA-B, HOMA-S and insulinogenic index. Changes from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and to Visit 11 (Week 62/Study Termination) will be analyzed using a paired t-test. The 95% confidence intervals will be provided.

Further analyses may be conducted if deemed appropriate.

12.4 Justification of Sample Size

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

Table 1. Summary of the Power Calculation Based on Paired T-test and Different Sample Sizes

Sample Size (N)	Alpha	Change in Incremental $AUC_{(0-240)}$ in the EQW group [1]	Standard Deviation	Power
20	0.05	60	110	0.63867
20	0.05	70	110	0.77027
20	0.05	80	110	0.86956
20	0.05	90	110	0.93430
20	0.05	100	110	0.97080
20	0.05	110	110	0.98859
15	0.05	60	110	0.50282
15	0.05	70	110	0.63064
15	0.05	80	110	0.74528
15	0.05	90	110	0.83781
15	0.05	100	110	0.90506
15	0.05	110	110	0.94909

Abbreviations: AUC, area under the curve; EQW, exenatide once weekly.
[1] AUC values are presented in nmol*min/L.

13. INVESTIGATOR AND SPONSOR OBLIGATION

13.1 Record Retention

The record retention policies outlined in Protocol BCB114 also apply to the substudy data.

14. DISCLOSURE OF DATA AND PUBLICATIONS

The data disclosure and publication policies outlined in the main protocol also apply to the substudy data.

15. INFORMED CONSENT

Each individual will be provided with oral and written information describing the nature, purpose and duration of the study, participation/termination conditions, and risks and benefits. Prior to initiation of any study-related procedures, subjects and their parent/caretaker for subjects under 18 years of age will sign and date the ICF to participate in the study. Subjects under 18 years of age will review the ICF and sign a Child Assent Form. Subjects and their parent/caretaker for subjects under 18 years of age participating in the US will also sign and date an authorization form required under HIPAA, if applicable, that

authorizes the use and disclosure of the subject's protected health information. The signed original ICF (or Child Assent Form as applicable) and HIPAA authorization forms will be retained with the study center's records and each subject will receive a copy of each form they have signed.

16. INVESTIGATOR'S ACCEPTANCE

I have read the protocol Appendix F described above. I agree to comply with all applicable regulations and to conduct the substudy as described in the main protocol and this appendix. I agree to its terms and will conduct the study according to Good Clinical Practices.

_____

Investigator Name (Printed)

_____ _____

Investigator Signature Date

17. REFERENCES

1. Kolterman OG, Buse JB, Fineman MS, et al. Synthetic exendin-4 (exenatide) significantly reduces postprandial and fasting plasma glucose in subjects with type 2 diabetes. Journal of Clinical Endocrinology and Metabolism. 2003;88(7):3082-3089.

2. Cervera A, Wajcberg E, Sriwijitkamol A, et al. Mechanism of action of exenatide to reduce postprandial hyperglycemia in type 2 diabetes. American Journal of Physiology - Endocrinology and Metabolism. 2008;294(5):E846-E852.

3. Egan JM, Clocquet AR, Elahi D. The insulinotropic effect of acute exendin-4 administered to humans: comparison of nondiabetic state to type 2 diabetes. Journal of Clinical Endocrinology and Metabolism. 2002;87(3):1282-1290.

4. Fehse F, Trautmann M, Holst JJ, et al. Exenatide augments first- and second-phase insulin secretion in response to intravenous glucose in subjects with type 2 diabetes. Journal of Clinical Endocrinology and Metabolism. 2005;90(11):5991-5997.

18. COMPOSITION OF THE STANDARDIZED MEAL

The approximately 560-kilocalorie (Calorie) standardized meal will have a composition of approximately 55% carbohydrate, 15% protein, and 30% fat and will consist of the items listed in Table 2. Subjects who are lactose intolerant or who do not like cheese will consume a similar standardized meal consisting of the items listed in Table 3.

Standard menus, quantities and suggested brands for the meals are detailed in Table 2 and Table 3. If the above items are not available, alternatives can be considered but must be approved by the Sponsor or Designee and must approximate the carbohydrate, protein, and fat distribution noted above. Each subject must receive the same meal in the same quantity at Visit 2 (Week 0), Visit 10 (Week 52), and at Visit 11 (Week 62/Study Termination).

Table 2. Regular Standardized Breakfast Menu (Protocol BCB114)

Menu Item	Quantity	Calories (Total = 562)
2% Milk	240 mL [1]	137
Plain Bagel [2]	1 bagel	290
Cream Cheese [3]	3 tablespoons	135

Note: Calories = kilocalories.
[1] 240 mL = 1 cup (8 ounces).
[2] Thomas New York Style Plain Bagel, or substitute a plain bagel with 290 Calories.
[3] Kraft Philadelphia Soft Cream Cheese, or substitute other soft cream cheese with ~135 Calories and 13.5 g fat.

Table 3. Lactose-Free Standardized Breakfast Menu (Protocol BCB114)

Menu Item	Quantity	Calories (Total = 563)
Soy Milk	240 mL [1]	130
Plain Bagel [2]	1 bagel	290
Smooth Peanut Butter [3]	1.5 tablespoons	143

Note: Calories = kilocalories.
[1] 240 mL = 1 cup (8 ounces).
[2] Thomas New York Style Plain Bagel, or substitute a plain bagel with 290 Calories.
[3] Jif Creamy Peanut Butter, or substitute other brand of peanut butter with ~143 Calories and 12 g fat.

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Clinical Study Protocol Appendix G	
Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	2.0
Date	09 April 2015

Appendix G
Protocol Amendment 01: Summary of Changes

1. SUMMARY OF CHANGES

The primary purpose of Amendment 01 was to 1) clarify inclusion criterion # 1 that subjects ages 10 to 17, inclusive, at Visit 1 (Screening) are eligible to participate in the study 2) update the study plan and study procedures to include a compliance procedure, and 3) provide additional guidance surrounding rescue treatment following the loss of glycemic control. Additional changes made to the protocol were editorial in nature.

List of changes

SECTION	ORIGINAL TEXT	AMENDMENT 01 TEXT
Section 4.2 Inclusion Criteria	1. Is 10 to less than 17 years old, inclusive, at Visit 1 (Screening)	1. Is 10 to 17 years old, inclusive, at Visit 1 (Screening)
Section 5.6 Rescue Treatment	A loss of glycemic control observed by either 1) increase from baseline in HbA1c values by 0.5% or more at 2 consecutive clinic visits that are at least 1 month apart, or 2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home self-monitored blood glucose (SMBG), and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, will result in rescue treatment.	A loss of glycemic control observed by either 1) increase from baseline in HbA1c values by 0.5% or more at 2 consecutive clinic visits that are at least 1 month apart, or 2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home self-monitored blood glucose (SMBG), and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, will result in rescue treatment. .A clinic visit to confirm the values obtained by home SMBG or fasting/random glucose tests must take place within 2 weeks following the aforementioned self-measurements.
Section 6.3.3 Visit 3 (Week 4) and Visit 4 (Week 9) – (Controlled Assessment Period)	*None*	• Subjects will have a study medication compliance review
Section 6.3.4 Visit 5 (Week 14) – (Controlled Assessment Period)	*None*	• Subjects will have a study medication compliance review
Section 6.3.6 Visit 6 (Week 22) – (Extension Period)	*None*	• Subjects will have a study medication compliance review
Section 6.3.7 Visit 7 (Week 30) – (Extension Period)	*None*	• Subjects will have a study medication compliance review
Section 6.3.8 Visit 8 (Week 42) and Visit 9 (Week 54) – (Extension Period)	*None*	• Subjects will have a study medication compliance review
Section 6.3.9 Visit 10 (Week 66) - Study Termination or Early Termination	*None*	• Subjects will have a study medication compliance review
Section 6.4 Ethical Considerations	*None*	A clinic visit to confirm the values obtained by home SMBG or fasting/random glucose tests must take place within 2 weeks following the aforementioned self-measurements.
Section 12 DISCONTINUING AND UNBLINDING OF SUBJECTS	Loss of Glucose Control: If rescue criteria are met during the controlled assessment period or during the extension period and the Investigator believes it is in the	**Loss of Glucose Control:** If rescue criteria are met during the controlled assessment period or during the extension period and the Investigator believes it is in the

SECTION	ORIGINAL TEXT	AMENDMENT 01 TEXT
	subject's best interest to terminate participation (for specific guidelines see Section 6.4).	subject's best interest to terminate participation (for specific guidelines see Section 5.6 and Section 6.4).
Appendix 1	*None*	Addition of study compliance medication review at every visit starting at Week 2 (phone call)
Appendix 1	*None*	Visually displayed the 2 phone calls to subjects by the addition of columns at the respective scheduled timing of the phone calls

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Clinical Study Protocol Appendix H	
Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	1.0
Date	09 April 2015

Appendix H
Protocol Amendment 02: Summary of Changes

1. SUMMARY OF CHANGES

The primary purpose of Amendment 02 was to add a long-term safety follow-up period in response to the European Medicines Agency Pediatric Committee agreement. Following discontinuation of study medication administration, subjects will be monitored at 6-month intervals for up to 3 years or until the difference between 2 height measurements obtained over a 6-month interval is less than a 5 mm increase (whichever comes first). Subjects who have an increase of less than 5 mm in height over a 6-month interval during the treatment period do not need to participate in the long-term safety follow-up period. Additional changes include allowing subjects who meet prespecified rescue criteria to remain in the study following implementation of rescue therapy. Clarifications and updates have been made to the objectives, inclusion/exclusion criteria, statistical analysis, and serious adverse event reporting sections and additional safety assessments were added. Remaining changes made to the protocol were editorial in nature.

List of changes

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Title Page	PPD	PPD
Title Page	PPD	PPD
Signature Page	PPD	PPD
Signature Page	PPD	PPD
Signature Page	PPD	PPD
Protocol Summary PRIMARY OBJECTIVES	To evaluate the safety and tolerability of exenatide once weekly in adolescents with type 2 diabetes mellitus	To evaluate the safety and tolerability of exenatide once weekly compared to placebo following 14 weeks of treatment in adolescents with type 2 diabetes mellitus
Protocol Summary SECONDARY OBJECTIVES	• To compare the effects of exenatide once weekly to those achieved by placebo in adolescents with type 2 diabetes mellitus on the following:	• To compare the effects of exenatide once weekly following 14 weeks of treatment to those achieved by placebo in adolescents with type 2 diabetes mellitus on the following:
Protocol Summary SECONDARY OBJECTIVES	– Parameters related to glycemic control including proportion of subjects achieving HbA1c goals and fasting plasma glucose concentration	– Parameters related to glycemic control, including HbA1c, fasting plasma glucose concentration, and proportion of subjects achieving HbA1c goals

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Protocol Summary STUDY DESIGN	*None*	• Following Visit 10 (Week 66/Study Termination), subjects whose height increase is at least 5 mm between Visit 8 (Week 42) and Visit 10 (Week 66/Study Termination) will participate in a long-term safety follow-up period. Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) will also participate in the Safety Follow-Up Period unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. Subjects 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. • The Safety Follow-Up Period will continue for up to 3 years or until the increase in height between two 6-month interval visits is less than 5 mm (whichever comes first). No study medication will be administered during the Safety Follow-Up Period. • Details of the Safety Follow-Up Period are provided in Appendix 2.
Protocol Summary VISIT STRUCTURE	• This study will be composed of 10 visits to the clinical study site, occurring at approximately 4-, 5-, 8-, or 12-week intervals through Visit 10 (Week 66/Study Termination).	• This study will be composed of at least 10 visits to the clinical study site, occurring at approximately 4-, 5-, 8-, or 12-week intervals through Visit 10 (Week 66/Study Termination), with the potential for 6 additional study-site visits during the Safety Follow-Up Period.
Protocol Summary VISIT STRUCTURE	*None*	• Following discontinuation of study medication at an Early Termination Visit or Visit 10 (Week 66/Study Termination), subjects with a height increase of at least 5 mm over a 6-month interval will participate in the Safety Follow-Up Period. Subjects who do not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication will also enter the Safety Follow-Up Period. • A detailed schedule of study procedures during the Safety Follow-Up Period by visit is presented in Appendix 2.
Protocol Summary STUDY DURATION	*None*	• The duration of the Safety Follow-Up Period (Appendix 2) is up to 3 years or until the difference between height measurements between two 6-month interval visits is less than a 5 mm increase (whichever comes first).

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Protocol Summary STUDY METHODS	*None*	• Following Visit 10 (Week 66/Study Termination), subjects whose height increase is at least 5 mm between Visit 8 (Week 42) and Visit 10 (Week 66/Study Termination) will participate in a long-term safety follow-up period. Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) will also participate in the Safety Follow-Up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. Subjects 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. • The Safety Follow-Up Period will continue for up to 3 years or until the difference between two 6-month interval visits is less than a 5 mm increase (whichever comes first). No study medication will be administered during the Safety Follow-Up Period. • Details of the Safety Follow-Up Period are provided in Appendix 2.
Protocol Summary Pharmacodynamic Assessments	*None*	• Lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides)
Protocol Summary SAFETY ASSESSMENTS	• Lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides) • Thyroid stimulating hormone (TSH), free T4 (thyroxine), prolactin, cortisol, dehydroepiandrosterone (DHEAS), insulin-like growth factor 1(IGF-1), bone specific alkaline phosphatase, and deoxypridinoline	• Thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, estradiol, free T4 (thyroxine), prolactin, cortisol, dehydroepiandrosterone (DHEAS), insulin-like growth factor 1(IGF-1), bone specific alkaline phosphatase, and deoxypridinoline
Protocol Summary SAFETY ASSESSMENTS	• Amylase and lipase	• Pancreatic amylase and lipase
Protocol Summary STATISTICAL CONSIDERATIONS	Efficacy analyses will be performed for the Intent-to-Treat (ITT) Population and the Evaluable Population, with the ITT Population used for the primary efficacy analyses. Safety analyses will be performed for the ITT Population unless stated otherwise.	Efficacy analyses will be performed for the Intent-to-Treat (ITT) Population and the Evaluable Population, with the ITT Population as the primary population. Safety analyses will be performed for the ITT Population and the Evaluable Population unless stated otherwise.
Protocol Summary STATISTICAL CONSIDERATIONS	Adjustments may be made to refine the definition of the Evaluable Population prior to the conduct of any analytical procedures.	Adjustments may be made to refine the definition of the Evaluable Population prior to study unblinding and database lock.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Protocol Summary STATISTICAL CONSIDERATIONS	**Secondary Endpoints**	**Secondary Endpoints** • Change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable
Protocol Summary STATISTICAL CONSIDERATIONS	*None*	*Order of secondary endpoints altered to emphasize fasting plasma glucose, HbA1c goals, and body weight over other endpoints*
Protocol Summary STATISTICAL CONSIDERATIONS	• Proportions of subjects achieving HbA1c goals of <6.5%, ≤6.5%, and <7% from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination)	• Proportions of subjects achieving HbA1c goals of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit.
Protocol Summary STATISTICAL CONSIDERATIONS	*None*	• Plasma exenatide concentrations at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 10 (Week 66/Study Termination) and each intermediate visit, as applicable
Protocol Summary STATISTICAL CONSIDERATIONS	• Change in calcitonin, amylase and lipase, TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Tanner pubertal stage at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), and Visit 10 (Week 66/Study Termination)	• Change in calcitonin, pancreatic amylase, and lipase from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination) • Tanner pubertal stage at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination)
Protocol Summary STATISTICAL CONSIDERATIONS	*None*	• Change in FSH, LH, FSH/LH, total testosterone, and estradiol from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination)
Protocol Summary STATISTICAL CONSIDERATIONS	• Proportions of subjects needing rescue due to failure to maintain glycemic control or for safety and/or tolerability issues at Visit 5 (Week 14) and to Visit 10 (Week 66/Study Termination), and each intermediate visit	• Proportions of subjects discontinuing the study, needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit
Protocol Summary STATISTICAL CONSIDERATIONS	The variance-covariance structure will be selected based on the Akaike's Information Criterion among the unstructured, heterogeneous order 1, autoregressive order 1, and compound symmetry structure.	The variance-covariance structure will be selected based on the Akaike's Information Criterion among the unstructured (UN), autoregressive order 1 (AR [1]), heterogeneous autoregressive order 1(ARH [1]), and compound symmetry (CS) structures

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Protocol Summary STATISTICAL CONSIDERATIONS	The least squares mean and 2-sided 95% confidence interval of the difference in the change of HbA1c between EQW and PBO groups at Visit 5 (Week 14) will be obtained.	The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between EQW and PBO groups at Visit 5 (Week 14) will be provided. All observed HbA1c data from post-baseline visits (including Early Termination) will be included in the MMRM analysis. In addition, if a subject's last available measurement during the 14-week assessment period is from an unscheduled visit or Early Termination visit, the value will be programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. For subjects who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM analysis. Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the Statistical Analysis Plan.
Protocol Summary STATISTICAL CONSIDERATIONS	Proportions of subjects having HbA1c target values of <6.5%, ≤6.5%, and <7% at Visit 5 (Week 14) will be compared between treatments using the Cochran-Mantel-Haenszel (CMH) procedure, in which baseline HbA1c strata will serve as the stratification factors	Proportions of subjects having HbA1c target values of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit will be compared between treatments using the Cochran-Mantel-Haenszel (CMH) procedure, in which baseline HbA1c strata will serve as the stratification factors
Protocol Summary STATISTICAL CONSIDERATIONS	*None*	Any ITT subject who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint.
Protocol Summary STATISTICAL CONSIDERATIONS	The GEE model for binary data with logit link function based on the observed data will be used as a supportive analysis for patients achieving target. The MMRM method for change in HbA1c and other continuous secondary endpoints will be conducted similarly to the analysis conducted for the primary endpoint. The least squares mean and 2-sided 95% confidence interval of the difference in the endpoints of interests between the EQW and PBO groups will be obtained.	The generalized linear mixed model (GLMM) based on the observed data will be used as a supportive analysis for probabilities of patients achieving target. The MMRM method, similar to the analysis conducted for the primary endpoint, will be applied to all continuous secondary endpoints, if multiple post-baseline measurements are planned per protocol. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be provided.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Protocol Summary STATISTICAL CONSIDERATIONS	The proportion of subjects discontinuing the study, and the proportion of subjects needing rescue treatment due to failure to maintain glycemic control will be analyzed using the CMH procedure. Tanner pubertal stages will be summarized for baseline (Visit 2 [Week 0]), Visit 5 (Week 14), and Visit 10 (Week 66).	The proportion of subjects discontinuing the study, the proportion of subjects needing rescue treatment due to failure to maintain glycemic control, and the number of rescue episodes will be evaluated. Absolute and change in calcitonin, pancreatic amylase, and lipase, TSH, free T4, prolactin, cortisol, IGF-1, DHEAS, Tanner pubertal stages, FSH, LH, FSH/LH, total testosterone, estradiol, CEA, and bone specific alkaline phosphatase and deoxypyridinoline will be summarized by visit.
Protocol Summary STATISTICAL CONSIDERATIONS	*None*	**Analysis of Safety Follow-Up Period** Details are provided in Appendix 2.
Protocol Summary SAMPLE SIZE	Assuming a 20% drop-out rate, approximately 80 subjects will complete the study.	Assuming a 20% drop-out rate, approximately 80 subjects will complete the 14-week controlled treatment period of the study
LIST OF ABBREVIATIONS	*None*	ARH (1) heterogeneous autoregressive order 1 CS compound symmetry FSH follicle-stimulating hormone GLMM generalized linear mixed model LH luteinizing hormone UN unstructured
Section 1.1 Description of Exenatide Once Weekly	BYETTA has also been approved by the European Commission as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), or a combination of metformin and an SU or metformin and a TZD but have not achieved glycemic control.	BYETTA has also been approved by the European Commission as adjunctive therapy to improve glycemic control in patients with type 2 diabetes mellitus who are taking metformin, a sulfonylurea (SU), a thiazolidinedione (TZD), a combination of metformin and an SU or metformin and a TZD, or insulin glargine but have not achieved glycemic control.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 1.1 Description of Exenatide Once Weekly	Exenatide once weekly (EQW) is an extended release formulation of BYETTA under development as a line extension to provide patients the option of a weekly dosing regimen. The EQW formulation prolongs systemic exposure within the known therapeutic range of BYETTA by slow release from the site of injection to the systemic circulation.	Exenatide once weekly (EQW; BYDUREON™ [exenatide for extended-release injectable suspension]) is an extended release formulation of BYETTA that is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (NDA 022-200) and by the European Commission for treatment of type 2 diabetes in combination with oral therapy. The EQW formulation prolongs systemic exposure within the known therapeutic range of BYETTA by slow release from the site of injection to the systemic circulation and provides patients with the option of a weekly dosing regimen.
Section 1.4 Safety Follow-Up Period	*None*	**1.4 Safety Follow-Up Period** Following Visit 10 (Week 66/Study Termination), subjects whose height increase is at least 5 mm between Visit 8 (Week 42) and Visit 10 (Week 66/Study Termination) will participate in a long-term safety follow-up period. Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) will also participate in the Safety Follow-Up Period unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. Subjects 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. The Safety Follow-Up Period will continue for up to 3 years or until the difference between two 6-month interval visits is less than a 5 mm increase (whichever comes first). No study medication will be administered during the Safety Follow-Up Period. Details of the Safety Follow-Up Period are provided in Appendix 2.
Section 2.1 Primary Objectives	To evaluate the safety and tolerability of exenatide once weekly in adolescents with type 2 diabetes mellitus	To evaluate the safety and tolerability of exenatide once weekly compared to placebo following 14 weeks of treatment in adolescents with type 2 diabetes mellitus
Section 2.2 Secondary Objectives	• To compare the effects of exenatide once weekly to those achieved by placebo in adolescents with type 2 diabetes mellitus on the following:	• To compare the effects of exenatide once weekly following 14 weeks of treatment to those achieved by placebo in adolescents with type 2 diabetes mellitus on the following:

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 2.2 Secondary Objectives	– Parameters related to glycemic control including proportion of subjects achieving HbA1c goals and fasting plasma glucose concentration	– Parameters related to glycemic control, including HbA1c, fasting plasma glucose concentration, and proportion of subjects achieving HbA1c goals
Section 4.2 Inclusion Criteria	4. Has a fasting C-peptide of >0.6 ng/L	4. Has a fasting C-peptide of >0.6 ng/L at Visit 1 (Screening)
Section 4.3 Exclusion Criteria	b. Renal disease or serum creatinine >1.5 mg/dL (141.4 µmol/L) (males) or 1.4 mg/dL (123.8 µmol/L) (females)	b. Renal disease or serum creatinine >1.5 mg/dL (132.6 µmol/L) (males) or 1.4 mg/dL (123.8 µmol/L) (females)
Section 4.3 Exclusion Criteria	6. Urinary albumin creatinine ratio (>15 mg/dL)	*Deleted; remaining exclusion criteria renumbered*
Section 5.2 Dispensing of Study Medication	Subjects will use that supply of study medication through Visit 3 (Week 4) and will bring the study medication to the study site at Visit 3 (Week 4). At Visit 3 (Week 4) an 8-week supply of study medication will be dispensed to subjects as specified by their assigned treatment group. At Visit 4 (Week 9), a 4-week supply of study medication will be dispensed to all subjects, according to their assigned treatment group.	Subjects will use that supply of study medication through Visit 3 (Week 4) and will bring the study medication to the study site at Visit 3 (Week 4). At Visit 3 (Week 4) an 8-week supply of study medication will be dispensed to subjects as specified by their assigned treatment group. Subjects will use that supply of study medication through Visit 4 (Week 9) and will bring used and unused study medication to the study site at Visit 4 (Week 9). At Visit 4 (Week 9), the partially used kit will be redispensed to subjects after study medication is reviewed for compliance and an additional 4-week supply of study medication will be dispensed to all subjects, according to their assigned treatment group. All vials of study medication must remain in their original kit.
Section 5.4 Randomization Schedule and Blinding Procedures	The randomization will be stratified by baseline HbA1c (<9.0% or ≥9.0%).	The randomization will be stratified by baseline HbA1c (<9.0% or ≥9.0%) and country.
Section 5.6 Rescue Treatment	Subjects meeting rescue criteria will be referred to their treating physicians to seek conventional anti-hyperglycemic intervention (e.g. insulin). Subjects meeting these criteria during the controlled assessment period will be discontinued from the study and will complete early termination procedures. Subjects meeting these criteria during the extension who do not initiate insulin therapy may remain in the study and continue to receive study medication, at the discretion of the investigator.	Subjects meeting rescue criteria will be treated with antihyperglycemic therapy (e.g., insulin) by the investigator or referred to their treating physician to seek conventional antihyperglycemic intervention. Subjects meeting these criteria may remain in the study and continue to receive study medication, at the discretion of the investigator.
Section 6.2 Screening Procedures	– Urinary albumin creatinine ratio	*Deleted*

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 6.2 Screening Procedures	*None*	If greater than 35 days have elapsed since Visit 1 (Screening), subjects who wish to requalify for study enrollment following an abnormal test result must have all screening assessments repeated.
Section 6.2 Screening Procedures	• Subjects will receive diet and nutritional counseling	*Deleted*
Section 6.3.1 Visit 2 (Week 0): Enrollment and Randomization – (Controlled Assessment Period)	• Urine will be collected for a pregnancy test (females only) and for urinalysis	• Urine will be collected for: – Pregnancy test (females only) – Urinalysis – Urinary albumin creatinine ratio – Deoxypyridinoline
Section 6.3.1 Visit 2 (Week 0): Enrollment and Randomization – (Controlled Assessment Period)	– Amylase and lipase	– Pancreatic amylase and lipase
Section 6.3.1 Visit 2 (Week 0): Enrollment and Randomization – (Controlled Assessment Period)	– Thyroid stimulating hormone (TSH), free T4 (thyroxine), prolactin, cortisol, insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone (DHEAS), bone specific alkaline phosphatase, and deoxypyridinoline	– Thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, estradiol, free T4 (thyroxine), prolactin, cortisol, insulin-like growth factor-1 (IGF-1), dehydroepiandrosterone (DHEAS), and bone specific alkaline phosphatase
Section 6.3.3 Visit 3 (Week 4) and Visit 4 (Week 9) – (Controlled Assessment Period)	• Subjects will be asked to return used/unused study medication	• Subjects will be asked to return used/unused study medication (unused study medication from that dispensed at Visit 3 [Week 4] will be returned to the subject at Visit 4 [Week 9] after review for compliance)
Section 6.3.4 Visit 5 (Week 14 – (Controlled Assessment Period)	• Urine will be collected for a pregnancy test (females only) and for urinalysis	• Urine will be collected for: – Pregnancy test (females only) – Urinalysis – Urinary albumin creatinine ratio – Deoxypyridinoline
Section 6.3.4 Visit 5 (Week 14 – (Controlled Assessment Period)	– Amylase and lipase	– Pancreatic amylase and lipase
Section 6.3.4 Visit 5 (Week 14 – (Controlled Assessment Period)	– Urinary albumin creatinine ratio	*Deleted*

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 6.3.4 Visit 5 (Week 14 – (Controlled Assessment Period)	– TSH, free T4, prolactin, cortisol, IGF-1, DHEAS, bone specific alkaline phosphatase, and deoxypyridinoline	– TSH, FSH, LH, total testosterone, estradiol, free T4, prolactin, cortisol, IGF-1, DHEAS, and bone specific alkaline phosphatase
Section 6.3.8 Visit 8 (Week 42) and Visit 9 (Week 54) – (Extension Period)	• Urine will be collected for a pregnancy test (females only) • Blood samples will be collected for: – HbA1c	• Urine will be collected for a pregnancy test (females only) and for deoxypyridinoline • Assessment of Tanner pubertal stage (Visit 8 [Week 42] only) • Blood samples will be collected for: – HbA1c – TSH, FSH, LH, total testosterone, estradiol, free T4, prolactin, cortisol, IGF-1, DHEAS, and bone specific alkaline phosphatase (Visit 8 [Week 42] only)
Section 6.3.9 Visit 10 (Week 66) – Study Termination or Early Termination	Prior to Visit 10 (Week 66), subjects will have fasted overnight (≥8 hours).	Prior to Visit 10 (Week 66/Study Termination) or Early Termination, subjects will have fasted overnight (≥8 hours).
Section 6.3.9 Visit 10 (Week 66) – Study Termination or Early Termination	• Urine will be collected for urinalysis	• Urine will be collected for: – Urinalysis – Urinary albumin creatinine ratio – Deoxypyridinoline
Section 6.3.9 Visit 10 (Week 66) – Study Termination or Early Termination	– Amylase and lipase	– Pancreatic amylase and lipase
Section 6.3.9 Visit 10 (Week 66) – Study Termination or Early Termination	– Urinary albumin creatinine ratio	*Deleted*
Section 6.3.9 Visit 10 (Week 66) – Study Termination or Early Termination	– TSH, free T4, prolactin, cortisol, IGF-1, DHEAS, bone specific alkaline phosphatase, and deoxypyridinoline	– TSH, FSH, LH, total testosterone, estradiol, free T4, prolactin, cortisol, IGF-1, DHEAS, and bone specific alkaline phosphatase

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 6.4 Ethical Safety Considerations	Based on safety data from previous clinical studies of EQW (where the majority of subjects had type 2 diabetes), development of small, asymptomatic, subcutaneous injection-site nodules is expected. Nodule formation should not be categorized as an adverse event (AE) unless accompanied by symptoms such as pain, induration, redness, bleeding, or inflammation.	Based on safety data from previous clinical studies of EQW (where the majority of subjects had type 2 diabetes), development of small, asymptomatic, subcutaneous injection-site nodules is the most likely risk of exenatide once weekly suspension injections.
Section 6.4 Ethical Safety Considerations	Subjects meeting rescue criteria will be referred to their treating physicians to seek conventional anti-hyperglycemic intervention (e.g. insulin). Subjects meeting these criteria during the controlled assessment period will be discontinued from the study and will complete early termination procedures. Subjects meeting these criteria during the extension who do not initiate insulin therapy may remain in the study and continue to receive study medication, at the discretion of the investigator.	Subjects meeting rescue criteria will be treated with antihyperglycemic therapy (e.g., insulin) by the investigator or referred to their treating physician to seek conventional antihyperglycemic intervention. Subjects meeting these criteria may remain in the study and continue to receive study medication, at the discretion of the investigator.
Section 9.3 Serum Lipids	*None*	**9.3 Serum Lipids** Blood will be drawn for the measurement of fasting serum lipids according to the schedules presented in Appendix 1 and Section 6. Fasting lipid measurements will include determination of circulating concentrations of TC, LDL-C, HDL-C, and TG.
Section 10.1.1.2 Causality	The investigator will grade the association of the AE as UNRELATED or RELATED to study medication. The following criteria should be considered for determining relatedness: UNRELATED: The AE is judged to be produced by the subject's clinical state or by other therapies administered to the subject.	The investigator will grade the association of the AE as NOT RELATED or RELATED to study medication. The following criteria should be considered for determining relatedness: NOT RELATED: The AE is judged to be produced by the subject's clinical state or by other therapies administered to the subject.
Section 10.1.1.3 Pregnancy	All pregnancies should be reported immediately to Lilly Global Patient Safety.	All pregnancies should be reported immediately to Amylin Global Safety.
Section 10.1.1.4 Hypoglycemia	If a blood glucose value of <45 mg/dL (2.5 mmol/L) is noted within the data, which is asymptomatic, the clinician should assess whether the circumstances around the value are consistent with hypoglycemia.	If a blood glucose value of <54 mg/dL (3.0 mmol/L) is noted within the data, which is asymptomatic, the clinician should assess whether the circumstances around the value are consistent with hypoglycemia.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 10.1.1.5 Urinary Albumin Creatinine Ratio	All subjects are required to undergo urinary albumin creatinine testing according to the schedules presented in Appendix 1 and Section 6. Subjects who exhibit a urine albumin creatinine ratio >15 mg/g will be notified by study-site personnel within 72 hours after collection of the result. Subjects should discontinue study medication and be withdrawn from the study, with the reason for withdrawal documented on the disposition as an adverse event.	*Deleted*
Section 10.1.2 Serious Adverse Events	**ANY SERIOUS ADVERSE EVENT (SAE) THAT OCCURS AFTER THE SIGNING OF THE ICF THROUGH 90 DAYS AFTER ADMINISTRATION OF THE LAST DOSE OF STUDY MEDICATION MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS OF KNOWLEDGE) TO LILLY GLOBAL PATIENT SAFETY. FAX THE SAE REPORT FORM TO THE NUMBER LISTED ON THE FORM.**	**ANY SERIOUS ADVERSE EVENT (SAE) THAT OCCURS AFTER THE SIGNING OF THE ICF THROUGH 90 DAYS AFTER ADMINISTRATION OF THE LAST DOSE OF STUDY MEDICATION MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS OF KNOWLEDGE) TO AMYLIN GLOBAL SAFETY. FAX THE SAE REPORT FORM TO THE NUMBER LISTED ON THE FORM.**
Section 10.1.2 Serious Adverse Events	Pertinent laboratory reports or diagnostic results should be faxed within 72 hours of the initial report to Lilly Global Patient Safety at the fax number on the SAE form.	Pertinent laboratory reports or diagnostic results should be faxed within 72 hours of the initial report to Amylin Global Safety at the fax number on the SAE form.
Section 10.2.5.6 Pancreatic Amylase and Lipase	**10.2.5.6 Amylase and Lipase** Blood samples will be collected for the measurement of amylase and lipase according to the schedules presented in Appendix 1 and Section 6.	**10.2.5.6 Pancreatic Amylase and Lipase** Blood samples will be collected for the measurement of pancreatic amylase and lipase according to the schedules presented in Appendix 1 and Section 6.
Section 10.2.5.7 Serum Lipids	**10.2.5.7 Serum Lipids** Blood will be drawn for the measurement of fasting serum lipids according to the schedules presented in Appendix 1 and Section 6. Fasting lipid measurements will include determination of circulating concentrations of TC, LDL-C, HDL-C, and TG.	*Section deleted and moved to Section 9.3* *Remaining sections under 10.2.5 renumbered*
Section 10.2.5.7 Growth and Development Hormones	An assessment of growth and development hormones including TSH, free T4, prolactin, cortisol, DHEAS, and IGF-1 will be performed from blood samples collected at according to the schedules presented in Appendix 1 and Section 6.	An assessment of growth and development hormones including TSH, FSH, LH, total testosterone, estradiol, free T4, prolactin, cortisol, DHEAS, and IGF-1 will be performed from blood samples collected at according to the schedules presented in Appendix 1 and Section 6.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 10.2.5.9 Bone Turnover Markers	Blood will be drawn for the assessment of bone specific alkaline phosphatase and deoxypridinoline according to the schedules presented in Appendix 1 and Section 6.	Blood will be drawn for the assessment of bone specific alkaline phosphatase and urine will be collected for assessment of deoxypridinoline according to the schedules presented in Appendix 1 and Section 6.
Section 11 Blood Volume	The total amount of blood to be drawn during the entire study is expected to be approximately 156.5 mL for each subject.	The total amount of blood to be drawn during the entire study, including the Safety Follow-Up Period described in Appendix 2, is expected to be approximately 192 mL for each subject.
Section 12 Discontinuing and Unblinding of Subjects	*None*	Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) should enter the Safety Follow-Up Period, as described in Appendix 2, 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. Subjects 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.
Section 14.1 Analysis Populations	Efficacy analyses will be performed for the Intent-to-Treat (ITT) Population and the Evaluable Population, with the ITT Population used for the primary efficacy analyses. Safety analyses will be performed for the ITT Population unless stated otherwise.	Efficacy analyses will be performed for the Intent-to-Treat (ITT) Population and the Evaluable Population, with the ITT Population as the primary population. Safety analyses will be performed for the ITT Population and the Evaluable Population unless stated otherwise.
Section 14.1 Analysis Populations	Adjustments may be made to refine the definition of the Evaluable Population prior to the conduct of any analytical procedures.	Adjustments may be made to refine the definition of the Evaluable Population prior to study unblinding and database lock.
Section 14.2.2 Secondary Endpoints	*None*	• Change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable
Section 14.2.2 Secondary Endpoints	*None*	*Order of secondary endpoints altered to emphasize fasting plasma glucose, HbA1c goals, and body weight over other endpoints*
Section 14.2.2 Secondary Endpoints	• Proportions of subjects achieving HbA1c goals of <6.5%, ≤6.5%, and <7% from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination)	• Proportions of subjects achieving HbA1c goals of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit.
Section 14.2.2 Secondary Endpoints	*None*	• Plasma exenatide concentrations at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and each intermediate visit, as applicable

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 14.2.4 Safety Endpoints	• Change in calcitonin, amylase and lipase, TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Tanner pubertal stage at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), and Visit 10 (Week 66/Study Termination) • Proportions of subjects needing rescue due to failure to maintain glycemic control or for safety and/or tolerability issues at Visit 5 (Week 14) and to Visit 10 (Week 66/Study Termination), and each intermediate visit	• Change in calcitonin, pancreatic amylase, and lipase from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination) • Tanner pubertal stage at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination) • Proportions of subjects discontinuing the study, needing rescue due to failure to maintain glycemic control and number of rescue episodes at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit
Section 14.2.4.1 Exploratory Safety Endpoints	*None*	• Change in FSH, LH, FSH/LH, total testosterone, and estradiol from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination)
Section 14.6.1 General Considerations	Efficacy analyses will be performed for the ITT and Evaluable Populations. Safety analyses will be performed for the ITT Population unless stated otherwise.	Efficacy analyses will be performed for the ITT and Evaluable Populations. Safety analyses will be performed for the ITT and Evaluable Populations unless stated otherwise.
Section 14.6.1 General Considerations	For summary statistics and Cochran-Mantel-Haenszel (CMH) analyses related to proportions, such as proportions of subjects achieving HbA1c goals of <6.5%, ≤6.5%, and <7% for those subjects who discontinue from the study prior to completing all study procedures through Visit 5 (Week 14), but have data collected for at least one visit subsequent to Visit 2 (Week 0), missing values for efficacy, pharmacodynamic, and anthropometric measures up to Visit 5 (Week 14) will be imputed using the values at the last scheduled visit (including Early Termination visit) in accordance to the last observation carried forward approach.	For summary statistics and Cochran-Mantel-Haenszel (CMH) analyses related to proportions, such as proportions of subjects achieving HbA1c goals of ≤6.5% and <7% for those subjects who discontinue from the study prior to completing all study procedures through Visit 5 (Week 14), but have data collected for at least one visit subsequent to Visit 2 (Week 0), missing values for efficacy, pharmacodynamic, and anthropometric measures up to Visit 5 (Week 14) will be imputed using the values at the last visit (including Early Termination visit) in accordance to the last observation carried forward approach.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 14.6.1 General Considerations	*None*	For subjects who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the efficacy analysis to draw statistical inference. Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the Statistical Analysis Plan.
Section 14.6.2 Analysis of the Primary Endpoint	The covariance structures to be tested in this model include unstructured covariance, heterogeneous order 1, autoregressive order 1 (AR [1]) and Compound Symmetry (CS). The best covariance structure will be selected based on the Akaike's Information Criterion.	The variance - covariance structures to be tested in this model include the unstructured (UN), autoregressive order 1 (AR [1]), heterogeneous autoregressive order 1 (ARH [1]), and compound symmetry (CS) structures. The best variance - covariance structure will be selected based on the Akaike's Information Criterion.
Section 14.6.2 Analysis of the Primary Endpoint	The least squares mean and 2-sided 95% confidence interval of the difference in the change of HbA1c between the EQW and PBO groups at Visit 5 (Week 14) will be obtained.	The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between the EQW and PBO groups at Visit 5 (Week 14) will be provided.
Section 14.6.2 Analysis of the Primary Endpoint	The observed data will be used in the MMRM modeling procedure.	All observed HbA1c data from post-baseline visits (including Early Termination) will be included in the MMRM analysis. In addition, if a subject's last available measurement during the 14-week assessment period is from an unscheduled visit or Early Termination visit, the value will be programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. For subjects who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM analysis.
Section 14.6.2 Analysis of the Primary Endpoint	Summaries and analyses will also be conducted for subgroups defined by baseline HbA1c strata (<9.0% or ≥9.0%).	Summaries and analyses may also be conducted for subgroups defined by baseline HbA1c strata (<9.0% or ≥9.0%) and country.
Section 14.6.3 Analysis of the Secondary Endpoints	Proportions of subjects having HbA1c target values of <6.5%, ≤6.5%, and <7% at Visit 5 (Week 14) will be compared between treatments using the CMH procedure, in which baseline HbA1c strata will serve as the stratification factors.	Proportions of subjects having HbA1c target values of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit will be compared between treatments using the CMH procedure, in which baseline HbA1c strata will serve as the stratification factors. Any ITT subject who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 14.6.3 Analysis of the Secondary Endpoints	As a supportive analysis, the percent of patients who reach HbA1c targets of <6.5%, ≤6.5%, and <7% will also be analyzed using the Generalized Estimating Equation (GEE) for binary data with logit link function. The independent variables will include treatment group, visit, and treatment-by-visit interaction as factors, and baseline HbA1c as a continuous covariate. The "unstructured" variance-covariance structure will be used. If this model does not converge, then the AR (1) or CS structure will be further explored. The CMH will be the main analysis of patients achieving target, with the GEE model being a supportive analysis.	As a supportive analysis, the probabilities of patients reaching HbA1c targets of ≤6.5% and <7% will also be analyzed using a generalized linear mixed model (GLMM). The independent variables will include treatment group, visit, treatment-by-visit interaction, HbA1c baseline strata (<9.0% or ≥9.0%), and country as factors, and baseline HbA1c as a continuous covariate. The UN, AR (1), ARH (1), and CS variance-covariance structures will be explored. The CMH will be the main analysis of patients achieving target, with the GLMM model being a supportive analysis.
Section 14.6.3 Analysis of the Secondary Endpoints	The models for changes in body weight, blood pressure, fasting plasma glucose, fasting insulin, lipids, HOMA-B, and HOMA-S will include treatment group, visit, interaction between visit and treatment as the fixed effects, baseline of the dependent variable as the covariate, and subjects as the random effects.	The models for changes in body weight, blood pressure, fasting plasma glucose, fasting insulin, lipids, HOMA-B, and HOMA-S will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline of the dependent variable as the covariate, and subjects as the random effects.
Section 14.6.3 Analysis of the Secondary Endpoints	The least squares mean and 2-sided 95% confidence interval of the difference in the endpoints of interests between the EQW and PBO groups will be obtained.	The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be provided. Similar to the primary endpoint analysis, all observed data will be included in the MMRM and the GLMM analysis. Data collected from an Early Termination visit will be mapped to the next closest scheduled visit. For subjects who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM and GLMM analysis.
Section 14.6.6 Pharmacodynamic Analysis	*None*	Also refer to Section 14.6.3 for inferential statistical analysis.
Section 14.6.7 Safety Analyses	The analysis of safety data will be performed for the ITT Population.	The analysis of safety data will be performed for the ITT and Evaluable Populations.
Section 14.6.7.3 Vital Signs and Physical Examinations	Physical examination findings will be summarized descriptively.	Physical examination findings will be listed.

SECTION	AMENDMENT 01 TEXT	AMENDMENT 02 TEXT
Section 14.6.7.4 Other Safety Endpoints Evaluations	The proportion of subjects discontinuing the study, and the proportion of subjects needing rescue due to failure to maintain glycemic control will be analyzed using the CMH procedure. Tanner pubertal stages will be summarized for the baseline (Visit 2 [Week 0]), Visit 5 (Week 14), and Visit 10 (Week 66/Study Termination).	The proportion of subjects discontinuing the study, the proportion of subjects needing rescue due to failure to maintain glycemic control, and the number of rescue episodes will be evaluated. Absolute and change in calcitonin, pancreatic amylase, and lipase, TSH, free T4, prolactin, cortisol, IGF-1, DHEAS, Tanner pubertal stages, FSH, LH, FSH/LH, total testosterone, estradiol, CEA, and bone specific alkaline phosphatase and deoxypyridinoline will be summarized by visit.
Section 14.8 Justification of Sample Size and Randomization Schedule	Assuming a 20% drop-out rate, approximately 80 subjects will complete the study.	Assuming a 20% drop-out rate, approximately 80 subjects will complete the 14-week controlled treatment period of the study.
Appendix 1	Visit 1 Screening Diet and Nutritional Counseling X	*Deleted*
Appendix 1	*None*	Visit 8 Week 42 Tanner Pubertal Stage X
Appendix 1	Visit 1 Screening Urinary Albumin Creatinine X	Visit 2 Week 0 Urinary Albumin Creatinine X
Appendix 1	Blood samples for amylase and lipase	Blood samples for pancreatic amylase and lipase
Appendix 1	Visit 8 Week 42 **TSH, Free T4, DHEAS, Cortisol, Prolactin, IGF-1**	Visit 8 Week 42 **TSH, FSH, LH, Total testosterone, Estradiol, Free T4, DHEAS, Cortisol, Prolactin, IGF-1 X**
Appendix 1	Visit 8 Week 42 **Bone Specific Alkaline Phosphatase and Deoxypyridinoline**	Visit 8 Week 42 **Bone Specific Alkaline Phosphatase and Deoxypyridinoline X**
Appendix 1	*None*	FSH, follicle-stimulating hormone; LH, luteinizing hormone
Appendix 1	*None*	Note: Study plan applies only to the Controlled Assessment Period and 52-Week Extension Period of Study BCB114. See Appendix 2 for details of study procedures for the Safety Follow-Up Period.
Appendix 2	*None*	*Includes the study design for the long-term safety follow-up period*
Appendix 3	*None*	*Includes the Protocol Amendment 01 Summary of Changes.*

AstraZeneca

Clinical Study Protocol Appendix I	
Drug Substance	EXENATIDE
Study Code	D5551C00002
Edition Number	1
Date	14 December 2017

Appendix I
Protocol Amendment 03: Summary of Changes

1. SUMMARY OF CHANGES

Amendment 03 was done to incorporate the European Medicines Agency Paediatric Committee's Decision (P/0197/2014) on an EU PIP modifications procedure of the BYETTA & BYDUREON Paediatric Investigational Plan. One part of this procedure was the modification of the Bydureon pediatric study as reflected in this Amendment.

Minor typographical errors and format changes that did not affect the substance of the protocol were made as applicable throughout the document. In addition, the information was transferred into AstraZeneca format.

List of changes

Sections	AMENDMENT 02 TEXT	AMENDMENT 03 TEXT
TITLE PAGE	Sponsor: Amylin Pharmaceuticals, Inc. 9360 Towne Centre Drive San Diego, CA 92121 USA	Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden
TITLE PAGE	**Medical Monitor:** Steve Chen, MD PPD **Safety Physician:** PPD	**International Co-ordinating Investigator** PPD USA
TITLE PAGE: Confidentiality Statement	This protocol is a confidential communication and is the property of Amylin Pharmaceuticals, Inc (Amylin). Acceptance implies an agreement not to disclose the information contained herein that is not otherwise publicly available, except for use by an Institutional Review Board (IRB) for the purpose of obtaining approval to conduct the study. The IRB is requested and expected to maintain confidentiality. This document may not be used or published in whole or in part without the consent of Amylin.	This submission/document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.
SIGNATURE PAGE	PPD	*Signature page deleted from the Synopsis and has been included in the Protocol as Appendix A.*
Throughout the Protocol	Subject	Patient
Protocol Synopsis	*None.*	**Study centres and number of patients planned** A planned total of 77 patients will be randomized at approximately 20 centers in the United States (US) and in other countries **Study period** / **Phase of development** Estimated date of first patient enrolled: Q3 2015 / 3

		Estimated date of last patient completed: Q2 2021 — 3
Protocol Synopsis PRIMARY OBJECTIVES	• To assess the effect on glycemic control, as measured by HbA1c, of exenatide once weekly following 14 weeks of treatment compared to placebo in adolescents with type 2 diabetes mellitus • To evaluate the safety and tolerability of exenatide once weekly compared to placebo following 14 weeks of treatment in adolescents with type 2 diabetes mellitus	• To assess the effect on glycemic control, as measured by glycosylated hemoglobin (HbA1c), of exenatide once weekly (EQW) following **24 weeks** of treatment compared to placebo in **children and** adolescents with type 2 diabetes mellitus • To evaluate the safety and tolerability of EQW compared to placebo following **24 weeks** of treatment in **children and** adolescents with type 2 diabetes mellitus
Protocol Synopsis SECONDARY OBJECTIVES	• To compare the effects of exenatide once weekly following 14 weeks of treatment to those achieved by placebo in adolescents with type 2 diabetes mellitus on the following: • To examine the effect of EQW on beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostatic model assessment (HOMA) in children and adolescents with type 2 diabetes	• To compare the effects of EQW following **24 weeks** of treatment to those achieved by placebo in **children and** adolescents with type 2 diabetes mellitus on the following: • To examine the effect of EQW on beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostatic model assessment (HOMA) in children and adolescents with type 2 diabetes **who are not taking insulin**
Protocol Synopsis STUDY DESIGN	Study BCB114 is a Phase 3, double-blind (controlled assessment period), placebo-controlled, randomized, study conducted at multiple clinical study sites	Study BCB114 is a Phase 3, double-blind (controlled assessment period), placebo-controlled, randomized, **parallel** study conducted at multiple clinical study sites.
Protocol Synopsis STUDY DESIGN	*None.*	• This study will assess safety and efficacy of EQW (as monotherapy and adjunctive therapy to oral antidiabetic agents and/or insulin). • At least 40% and not more than 60% of the randomized patients must be females. At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states
Protocol Synopsis STUDY DESIGN	• Approximately 100 subjects will be randomly assigned across 2 treatment groups in a 2:1 ratio to receive either subcutaneous (SC) administration of exenatide once weekly (EQW) 2 mg or placebo (PBO), respectively. – Group A: EQW 2 mg (66 weeks) – Group B: PBO (14 weeks), EQW 2 mg (52 weeks)	• Approximately **77 patients** will be randomly assigned across 2 treatment groups in a **5:2** ratio to receive either subcutaneous (SC) administration of EQW 2 mg or placebo (PBO), respectively, **with at least 50 patients in the exenatide and at least 20 patients in the PBO group.** – Group A: EQW 2 mg (**52 weeks**) – Group B: PBO (24 weeks), EQW 2 mg (**28 weeks**)

Protocol Synopsis STUDY DESIGN	Study BCB114 includes a 14-week, controlled assessment period, during which subjects will receive study medication according to their randomized treatment group, followed by a 52-week, open-label, uncontrolled extension period in which all subjects will receive EQW.	The study includes a **24-week**, controlled assessment period, during which patients will receive study medication according to their randomized treatment group, followed by a **28-week**, open-label, uncontrolled extension period in which all **patients** will receive EQW.
Protocol Synopsis STUDY DESIGN	In addition to receiving study medications, all subjects will participate in a lifestyle intervention program encompassing diet and physical activity modifications.	In addition to receiving study medications, all patients will participate in a lifestyle intervention program encompassing diet and physical activity modifications. **If patients are taking concomitant antidiabetic medication they should administer their usual concomitant antidiabetic medication therapy at approximately the same time each day throughout the study.**
Protocol Synopsis STUDY DESIGN	*None*	• At Visit 1 (Screening), patients will complete eligibility evaluations and screening procedures. Patients who meet eligibility requirements will be randomly assigned to a treatment group (Group A: EQW 2 mg, Group B: PBO) at Visit 2 (Week 0). At Visit 2 (Week 0), patients will complete baseline safety, efficacy, pharmacodynamic (PD), and pharmacokinetic (PK) assessments. Following baseline assessments, patients and parents/caretaker will be trained on study medication administration and the first dose of study medication will be administered. During the controlled assessment period, patients or parent/caretaker will administer study medication. Patients will return to the study site at 4- or 6-week intervals for safety, efficacy, PD, and PK assessments. On weeks with no scheduled study-site visits, patients may opt to return to the study site to have the injection procedure monitored or provided by study-site personnel. • Following the 24-week controlled assessment period, all patients will enter the 28-week extension period. During the 28-week extension period, all patients will receive EQW 2 mg for 28 weeks up to Visit 10 (Week 52/End of Treatment). The patients will return to the study site at 6- or 12-week intervals for safety, efficacy, PD, and PK assessments and will complete study termination procedures at Visit 11 (Week 62/Study Termination).

		• All patients will have Visit 11 (Week 62/Study Termination) which is a follow-up visit occurring 10 weeks after the last dose administration at Visit 10 (Week 52)
Protocol Synopsis STUDY DESIGN	Following Visit 10 (Week 66/Study Termination), subjects whose height increase is at least 5 mm between Visit 8 (Week 42) and Visit 10 (Week 66/Study Termination) will participate in a long-term safety follow-up period. Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) will also participate in the Safety Follow-Up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. Subjects 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.	Following **Visit 11 (Week 62**/Study Termination), **patients** whose height increase is at least 5 mm between Visit 8 (**Week 28**) and **Visit 11 (Week 62**/Study Termination) will participate in an **Extended** Safety Follow-Up Period. **Patients** who discontinue study medication prior to Visit 10 (**Week 52**) will also participate in the **Extended** Safety Follow-Up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. **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 **Extended** Safety Follow-Up Period.
Protocol Synopsis STUDY DESIGN	The Safety Follow-Up Period will continue for up to 3 years or until the increase in height between two 6-month interval visits is less than 5 mm (whichever comes first). No study medication will be administered during the Safety Follow-Up Period.	The **Extended** Safety Follow-Up Period will continue for up to 3 years or until the increase in height between two 6 month interval visits is less than 5 mm (whichever comes first). No study medication will be administered during the **Extended** Safety Follow-Up Period.
Protocol Synopsis STUDY POPULATION	**STUDY POPULATION** • Approximately 100 male or female adolescents 10 to 17 years of age, inclusive, diagnosed with type 2 diabetes mellitus and treated with diet and exercise alone or in combination with a stable dose of metformin for at least 2 months prior to screening, will be randomized into this study. • At least 60% of study subjects must be included for analysis of the primary and secondary endpoints (Evaluable Population) at Week 14. • Approximately 50% of randomized study subjects must be female. • At least 40% of subjects are to be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states.	**TARGET PATIENT POPULATION** • A total of **77** male or female children and adolescents of 10 to **<18** years of age, diagnosed with type 2 diabetes mellitus and treated with diet and exercise alone or in combination with a stable dose of **an oral antidiabetic agent (metformin and/or sulfonylurea [SU]) and/or insulin** for at least 2 months prior to screening, will be randomized into this study to yield 70 evaluable patients.
Protocol Synopsis STUDY POPULATION	*None*	**Key Inclusion Criteria** 1. Each patient must meet the following criteria to be enrolled in this study. 2. Is a child or an adolescent of 10 to

		<18 years old, at Visit 1 (Screening) 3. Has been diagnosed with type 2 diabetes mellitus per American Diabetes Association diagnostic criteria 4. HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/SU, and of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at Visit 1 (Screening) 5. Has a C-peptide of >0.6 ng/L at Visit 1 (Screening) 6. Has been treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (e.g., metformin and/or SU) and/or insulin for their type 2 diabetes for at least 2 months prior to Visit 1 (Screening) 7. Has a fasting plasma glucose concentration <280 mg/dL (15.5 mmol/L) at Visit 1 (Screening) **Key Exclusion Criteria** Patients who meet any of the following criteria will be excluded from the study. 1) Has a clinically significant medical condition that could potentially affect study participation and/or personal well-being, as judged by the Investigator, including but not limited to the following conditions: a) Hepatic disease (defined by aspartate or alanine transaminase >3.0 times the upper limit of normal b) Renal disease or serum creatinine >1.5 mg/dL (132.6 µmol/L) (males) or 1.4 mg/dL (123.8 µmol/L) (females) c) Gastrointestinal disease deemed significant by the Investigator d) Organ transplantation e) Chronic infection (e.g., tuberculosis, human immunodeficiency virus, hepatitis B virus, or hepatitis C virus) f) Clinically significant malignant disease (with the exception of basal and squamous cell carcinoma of the skin) within 5 years of Visit 1 (Screening) 2) Has positive antibody titers to glutamic acid decarboxylase (GAD65) or islet cell antigen (ICA512) at Visit 1 (Screening) 3) Has a personal or family history of elevated calcitonin, calcitonin >100 ng/L, medullary thyroid carcinoma, or multiple endocrine

		neoplasia-2 4) Has ever used exenatide (exenatide once weekly [exenatide LAR], exenatide BID, BYETTA, or any other formulation) or any glucagon-like peptide-1 (GLP-1) receptor agonist (e.g., liraglutide [Victoza®]) 5) Is pregnant
Protocol Synopsis STUDY DURATION	**STUDY DURATION** • Total study duration will be approximately 71 weeks, including up to a 5-week screening period, a 14-week controlled assessment period, and a 52-week extension period. • The duration of the Safety Follow-Up Period (Appendix 2) is up to 3 years or until the difference between height measurements between two 6-month interval visits is less than a 5 mm increase (whichever comes first).	**Duration of treatment** • The total study duration will be approximately **67 weeks**, including up to a 5-week screening period, a **24-week** controlled assessment period, a **28-week** extension period, and **a 10-week post-treatment follow-up period**. • The duration of the **Extended** Safety Follow-Up Period for selected patients is up to 3 years or until the difference between height measurements between two 6-month interval visits is less than a 5 mm increase (whichever comes first).
Protocol Synopsis STUDY MEDICATION	**STUDY MEDICATIONS** • EQW (2 mg) is an extended-release, injectable formulation of exenatide containing 5% exenatide sucrose, and 50:50 poly D, L lactic-co-glycolic acid. • Placebo injection will be the same formulation without the active ingredient.	**Investigational product, dosage and mode of administration** • Exenatide once weekly (EQW) (2 mg) is an extended-release, **self-administered,** injectable formulation of exenatide containing 5% exenatide sucrose, and 50:50 poly D, L lactic-co-glycolic acid. **Weekly doses of EQW will be injected into SC tissue.** **Comparator, dosage and mode of administration** • Placebo injection will be the same formulation as EQW without the active ingredient **injected into SC tissue**.
Protocol Synopsis STUDY METHOD	**STUDY METHODS** • The schedule and timing of study procedures by visit are presented in Appendix 1 (Study Plan). • If subjects are taking metformin they should administer their usual metformin therapy at approximately the same time each day throughout the study. • At Visit 1 (Screening), subjects will complete eligibility evaluations and screening procedures. • Subjects who meet eligibility requirements will be randomly assigned to a treatment group (Group A: EQW 2 mg, Group B: PBO) at Visit 2 (Week 0). • At Visit 2 (Week 0), subjects will complete baseline safety, efficacy,	*None*

	pharmacodynamic, and pharmacokinetic assessments. Following baseline assessments, subjects and parents/caretaker will be trained on study medication administration and the first dose of study medication will be administered. • During the controlled assessment period, subjects or parent/caretaker will administer study medication. Subjects will return to the study site at 4- or 5-week intervals for safety, efficacy, pharmacodynamic, and pharmacokinetic assessments. On weeks with no scheduled study-site visits, subjects may opt to return to the study site to have the injection procedure monitored or provided by study-site personnel. • Following the 14-week controlled assessment period, all subjects will enter the 52-week extension period. • During the 52-week extension period, all subjects will receive EQW 2 mg for 52 weeks up to Visit 10 (Week 66/Study Termination). • During the 52-week extension period, subjects will return to the study site at 8- or 12-week intervals for safety, efficacy, pharmacodynamic, and pharmacokinetic assessments. • Subjects will complete study termination procedures at Visit 10 (Week 66/Study Termination). • Following Visit 10 (Week 66/Study Termination), subjects whose height increase is at least 5 mm between Visit 8 (Week 42) and Visit 10 (Week 66/Study Termination) will participate in a long-term safety follow-up period. Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) will also participate in the Safety Follow-Up Period unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. Subjects 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. • The Safety Follow-Up Period will continue for up to 3 years or until the difference between two 6-month interval visits is less than a 5 mm increase	

	(whichever comes first). No study medication will be administered during the Safety Follow-Up Period.	
Protocol Synopsis Pharmacodynamic ASSESSMENTS	• Body Weight • Fasting plasma glucose • Fasting serum insulin concentration • Lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides)	• Body Weight • Fasting plasma glucose • Fasting serum insulin concentration • **C-peptide** • Lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and triglycerides)
Protocol Synopsis SAFETY ASSESSMENTS	**SAFETY ASSESSMENTS** • Adverse event review • Concomitant medication review • Physical examinations • Vital signs • Tanner pubertal stage • Clinical chemistry, hematology, and urinalysis • Thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, estradiol, free T4 (thyroxine), prolactin, cortisol, dehydroepiandrosterone (DHEAS), insulin-like growth factor 1(IGF-1), bone specific alkaline phosphatase, and deoxypridinoline • Carcinoembryonic antigen (CEA) • Calcitonin • Pancreatic amylase and lipase • Antibodies to exenatide	**SAFETY ASSESSMENTS** • Adverse event **(AE)** review • Concomitant medication review • Physical examinations • Vital signs • **Pregnancy testing** • Tanner pubertal stage • Clinical chemistry, hematology, and urinalysis • Thyroid stimulating hormone (TSH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), total testosterone, **sex hormone-binding globulin (SHBG)**, estradiol, free T4 (thyroxine), prolactin, cortisol, dehydroepiandrosterone (DHEAS), insulin-like growth factor 1(IGF-1), bone specific alkaline phosphatase, and deoxypridinoline • Carcinoembryonic antigen (CEA) • Calcitonin • Pancreatic amylase and lipase • Antibodies to exenatide
Protocol Synopsis STATISTICAL CONSIDERATIONS	**Analysis Populations:** Efficacy analyses will be performed for the Intent-to-Treat (ITT) Population and the Evaluable Population, with the ITT Population as the primary population. Safety analyses will be performed for the ITT Population and the Evaluable Population unless stated otherwise. **Intent-to-Treat**: The ITT Population will consist of all randomized subjects who receive at least one dose of randomized study medication. **Evaluable Population**: The Evaluable Population will consist of all ITT subjects who complete study procedures through Visit 5 (Week 14) in compliance with the protocol and have adequate medication exposure and valid pharmacokinetic, pharmacodynamic measurements for data analysis. Adjustments may be made to	**Analysis Populations** • Efficacy analyses will be performed in the Intent-to-Treat (ITT) Population or in a set of evaluable patients coming from the ITT Population, i.e., the Evaluable Population and/or the **Per-Protocol (PP) population**. The Evaluable Population will be used for the primary analysis. Safety analyses will be performed for the ITT Population unless stated otherwise. • The following populations will be used for the summaries and analyses of the study data. The populations are defined as follows: • Intent-to-Treat (ITT): The ITT Population will consist of all randomized patients who receive at least one dose of randomized study medication.

	refine the definition of the Evaluable Population prior to study unblinding and database lock.	• Evaluable Population: The Evaluable Population will consist of all ITT patients who receive at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment. • **Per-Protocol (PP): The per protocol analysis set will be a subset of the ITT population through the exclusion of those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis. Detailed exclusion criteria for the PP population will be specified in the SAP. Patients excluded from the PP analysis will be identified before database lock.**
Protocol Synopsis PRIMARY ENDPOINT	• Change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14)	• Change in HbA1c from baseline Visit 2 (Week 0) to **Visit 7 (Week 24)**
Protocol Synopsis SECONDARY ENDPOINT	• Change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in fasting plasma glucose concentration from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Proportions of subjects achieving HbA1c goals of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit • Change in body weight from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in fasting insulin from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments in EQW patients from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in lipids from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10	• Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (**Week 52**), and to each intermediate visit as applicable • Change in fasting plasma glucose concentration from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to intermediate visit as applicable • Proportions of patients achieving HbA1c goals of ≤6.5% and <7.0% at **Visit 7 (Week 24), Visit 10 (Week 52)**, and at each intermediate visit • Change in body weight from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit as applicable • Change in fasting insulin **and C-peptide** from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to intermediate visit as applicable • Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments in EQW patients **not taking insulin** from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52),** and to each intermediate visit as applicable • Change in lipids from baseline Visit 2 (Week 0) to **Visit 5 (Week 12), Visit 7 (Week 24), Visit 10 (Week 52)** as applicable

	(Week 66/Study Termination), and to each intermediate visit as applicable • Change in blood pressure from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Plasma exenatide concentrations at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 10 (Week 66/Study Termination) and each intermediate visit, as applicable	• Change in blood pressure from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit as applicable • Plasma exenatide concentrations at baseline Visit 2 (Week 0), **Visit 7 (Week 24), Visit 10 (Week 52)** and intermediate visit, as applicable • **Proportions of patients discontinuing the study, needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit**
Protocol Synopsis EXPLORATORY ENDPOINT	• Change in BMI from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit • Change in body weight percentile and height percentile from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit.	• Change in **body mass index** (BMI) from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52),** and to each intermediate visit • Change in body weight percentile and height percentile from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit.
Protocol Synopsis SAFETY ENDPOINT	• Safety and tolerability endpoints including incidence of treatment-emergent adverse events, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in calcitonin, pancreatic amylase, and lipase from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination) • Tanner pubertal stage at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination) • **Proportions of subjects discontinuing the study, needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate**	• Safety and tolerability endpoints including incidence of treatment emergent AEs, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline Visit 2 (Week 0) to Visit 7 (Week 24), Visit 10 (Week 52), and to each intermediate visit as applicable • Change in calcitonin, pancreatic amylase, and lipase from baseline Visit 2 (Week 0) to Visit 5 (**Week 12**) and Visit 10 (**Week 52**) • Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline Visit 2 (Week 0) to **Visit 5 (Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)** • Tanner pubertal stage at baseline Visit 2 (Week 0), **Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52)**

	visit	
Protocol Synopsis SAFETY EXPLORATORY ENDPOINT	• Change in CEA from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in bone specific alkaline phosphatase and deoxypyridinoline from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in FSH, LH, FSH/LH total testosterone, and estradiol from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination)	• Change in CEA from baseline Visit 2 (Week 0) to Visit 5 (**Week 12**) and Visit 10 (**Week 52**) • Change in bone specific alkaline phosphatase and deoxypyridinoline from baseline Visit 2 (Week 0) to Visit 5 (**Week 12**), **Visit 7 (Week 24),** and Visit 10 (**Week 52**) • Change in FSH, LH, FSH/LH total testosterone*****, **SHBG***, and estradiol from baseline Visit 2 (Week 0) to Visit 5 (**Week 12**), **Visit 7 (Week 24),** and Visit 10 (**Week 52**) • ***Change in total testosterone and SHBG will be measured also at Visit 9 (Week 40). Free testosterone will be calculated from total testosterone and SHBG values at Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52).**
Protocol Synopsis STATISTICAL ANALYSIS OF PRIMARY ENDPOINTS	The mixed models repeated measures (MMRM) approach using observed data will be utilized to analyze the change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14). The model will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline HbA1c as the covariate, and subjects as the random effects. The variance-covariance structure will be selected based on the Akaike's Information Criterion among the unstructured (UN), autoregressive order 1 (AR [1]), heterogeneous autoregressive order 1(ARH [1]), and compound symmetry (CS) structures. The maximum likelihood method will be used for estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between EQW and PBO groups at Visit 5 (Week 14) will be provided. All observed HbA1c data from post-baseline visits (including Early Termination) will be included in the MMRM analysis. In addition, if a subject's last available measurement during the 14-week assessment period is from an unscheduled visit or Early Termination visit, the value will be programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. For subjects who initiate rescue therapy and	The mixed models repeated measures (MMRM) approach will be used to analyze the change in HbA1c from baseline Visit 2 (Week 0) to **Visit 7 (Week 24)**. The model will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline HbA1c as the covariate, and patients as the random 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.** Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the Statistical Analysis Plan (SAP).

	continue study participation, only data through the initiation of rescue therapy will be included in the MMRM analysis. • Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the Statistical Analysis Plan	
Protocol Synopsis STATISTICAL ANALYSIS OF SECONDARY ENDPOINTS	Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment. Proportions of subjects having HbA1c target values of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit will be compared between treatments using the Cochran-Mantel-Haenszel (CMH) procedure, in which baseline HbA1c strata will serve as the stratification factors. For the CMH analyses and summaries related to proportions, missing values will be imputed using the values at the last visit (including the Early Termination visit) in accordance with the last observation carried forward approach. Values at Visit 2 (Week 0) will not be carried forward. Any ITT subject who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint. The generalized linear mixed model (GLMM) based on the observed data will be used as a supportive analysis for probabilities of patients achieving target. • The MMRM method, similar to the analysis conducted for the primary endpoint, will be applied to all continuous secondary endpoints, if multiple post-baseline measurements are planned per protocol. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be provided	**Analysis of all secondary endpoints will be performed in the ITT population**. Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment. Proportions of patients having HbA1c target values of ≤6.5% and <7.0% at **Visit 7 (Week 24), Visit 11 (Week 62/Study Termination),** and at each intermediate visit will be compared between treatments using the Cochran-Mantel-Haenszel (CMH) procedure, in which baseline HbA1c strata will serve as the stratification factors. Any ITT patient who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint. • **As a supportive analysis, the probabilities of patients reaching HbA1c targets of ≤6.5% and <7.0% will also be analyzed using a logistic regression model. The independent variables will include treatment group, visit, treatment-by-visit interaction, HbA1c baseline strata (<9.0% or ≥9.0%), and country as factors, and baseline HbA1c as a continuous covariate. The variance - covariance structure to be used for this modelling will be UN; if the model does not converge with unstructured variance – covariance matrix, then 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 same CMH procedure and logistic regression as described above will be used to analyze data on proportion of patients discontinuing the study, needing rescue due to failure to maintain glycemic control. However, the number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit will be analyzed using descriptive**

		statistics only.
Protocol Synopsis STATISTICAL ANALYSIS OF EXPLORATORY ENDPOINTS	• Baseline values, the values at each visit, and changes from baseline values will be summarized for percentiles of body weight, percentile of height, and BMI by treatment	**Analysis of all exploratory endpoints will be performed in the ITT population.** Baseline values, the values at each visit, and changes from baseline values will be summarized for percentiles of body weight, percentile of height, and BMI by treatment.
Protocol Synopsis STATISTICAL ANALYSIS OF SAFETY ENDPOINTS	The proportion of subjects discontinuing the study, the proportion of subjects needing rescue treatment due to failure to maintain glycemic control, and the number of rescue episodes will be evaluated. Treatment-emergent adverse events will be summarized by treatment, system organ class, and preferred term defined by MedDRA.	The proportion of **patients** discontinuing the study, the proportion of patients needing rescue treatment due to failure to maintain glycemic control, and the number of rescue episodes will be evaluated. **On treatment** adverse events will be summarized by treatment, system organ class, and preferred term defined by Medical Dictionary for Regulatory Activities (MedDRA).
Protocol Synopsis STRATIFICATION DURING RANDOMIZATION	• *None*	Randomization will be stratified by screening HbA1c (%) < 9.0% and ≥ 9.0%. The restriction on gender in the study population (female patients between 40% and 60%) and also on the ethnicity and lifestyle (40%-60% patients with European ethnicity and lifestyle) will be enforced through putting caps on enrollment of patients with different genders and from different regions (Europe and US and others)
Protocol Synopsis INTERIM ANALYSIS	One interim analysis is planned when 60 subjects have completed 14 weeks of treatment, including early withdrawal. This interim analysis will be performed by the independent Data Safety Monitoring Board that is not directly involved with the study design, conduct and data analysis. The study will be stopped for futility if the observed mean difference of change in HbA1c from baseline at Week 14 or early withdrawal between EQW and PBO (exenatide-placebo) is greater than 0.45%. Stopping on the basis of futility does not impact the overall Type I error since the conclusions from the interim analysis will not be used to declare treatment superiority. Therefore, the final analyses will be conducted at the 0.05 significance level with no adjustment for type I error rate for the interim analysis.	One interim analysis is planned when **40** patients will have completed 24 weeks of treatment, including early withdrawal. This interim analysis will be performed by the independent **Data Monitoring Committee (DMC)** that does not directly involve with the study design, conduct and data analysis. No study personnel will have access to the unblinded clinical data to maintain the integrity of the double-blind study design. **Purpose of the interim analysis is to ensure safety of the patient population. Hence, the DMC will only look at the safety data collected in this study. The DMC will review the safety data first in a blinded fashion and then, if needed, will look at the unblinded data to assess the risk of the paediatric patients' being exposed to the active drug compared to placebo, using the AE and/or safety laboratory data of the study population.**

Protocol Synopsis SAMPLE SIZE	Approximately 100 subjects who have met all study requirements will be randomized in a ratio of 2:1 to the exenatide or placebo treatment group on Visit 2 (Week 0) and will be carried out with stratification to achieve a balanced distribution of subjects across treatment groups according to country and screening HbA1c strata (<9.0% or ≥9.0%). • Assuming a 20% drop-out rate, approximately 80 subjects will complete the 14-week controlled treatment period of study. Based on 100,000 rounds of simulation, an overall power of 96% will be provided to reject the null hypothesis of no difference between the two treatment arms assuming the true mean changes in HbA1c of -0.9% for subjects receiving exenatide and 0 for the placebo arm. This power computation assumes a common standard deviation of 1.0% and a two-sided significance level of 0.05. A total power of over 94% will be achieved for a 28% drop-out rate based on simulation if the same true mean changes in HbA1c are assumed.	Approximately **77 patients** who have met all study requirements will be randomized in a ratio of **5:2** to the exenatide or placebo treatment group on Visit 2 (Week 0) and will be carried out with stratification to achieve a balanced distribution of patients across treatment groups with regard to the screening HbA1c strata (<9.0% or ≥9.0%). **The analysis will be performed in the set of evaluable patients coming from the ITT population.** Assuming a **10%** drop-out rate, approximately **70 patients** will complete the **24-week** controlled treatment period of study. **Based on calculation done using the software NQuery Advisor Version 7, an overall power of 74% will be provided to reject the null hypothesis of no difference between the 2 treatment arms assuming a true treatment difference of -0.7% between exenatide and placebo in changes from baseline for HbA1c (%). This power computation also assumes a common standard deviation of 1.0% and a two-sided significance level of 0.05.**
Section 1.1 BACKGROUND	Exenatide once weekly (EQW; BYDUREON™ [exenatide for extended-release injectable suspension]) is an extended release formulation of BYETTA that is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (NDA 022-200) and by the European Commission for treatment of type 2 diabetes in combination with oral therapy.	Exenatide once weekly (EQW; BYDUREON™ [**powder and solvent for prolonged release suspension for injection**]) is an extended release formulation of BYETTA that is approved by the FDA as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (NDA 022-200) and by the European Commission (**EU Marketing Authorization EU/1/11/696/001**) for treatment of type 2 diabetes in combination with oral therapy.
Section 1.1 BACKGROUND	The 19 completed and ongoing studies of the exenatide once weekly development program have evaluated the efficacy, pharmacokinetics, and safety of the once weekly formulation of exenatide in healthy volunteers and in subjects with type 2 diabetes. EQW has demonstrated robust glucose-lowering effects in the fasting, preprandial, and postprandial states, resulting in improvement in 24-hour glucose control in subjects with type 2 diabetes.	The 19 completed and ongoing studies of the **EQW** development program have evaluated the efficacy, pharmacokinetics, and safety of the once weekly formulation of exenatide in healthy volunteers and in **patients** with type 2 diabetes. The EQW has demonstrated robust glucose-lowering effects in the fasting, preprandial, and postprandial states, resulting in improvement in 24-hour glucose control in **patients** with type 2 diabetes
Section 1.2 RATIONALE FOR CONDUCTING THE STUDY	Study 2993-124 was a randomized, placebo-controlled, single-blind, dose-escalation crossover study that examined the pharmacokinetics, pharmacodynamics,	**The purpose of this study is to examine the effects of 2 mg EQW in children and adolescent patients with type 2 diabetes with respect to glycemic**

	safety, and tolerability of exenatide BID (2.5 and 5 mcg) in adolescents between the ages of 10 and 16 with type 2 diabetes and an average body mass index (BMI) of 32.5 kg/m^2 (range 23.2 to 40.8 kg/m^2). Consistent with clinical trials in adults, 5 mcg exenatide nearly eliminated postprandial glucose excursions in adolescents. This study demonstrated that, in general, exenatide was well tolerated with a safety and efficacy profile that was comparable to that observed in adults.[17] Given the decreased patient burden of once weekly injections, and the favorable efficacy and safety profile of EQW, this treatment may prove to be a useful adjunct therapy in adolescents with type 2 diabetes. The proposed study will be conducted to evaluate the efficacy, safety, and tolerability of EQW in adolescent subjects with type 2 diabetes. The current study will enroll either subjects treated with diet and exercise alone or in combination with a stable dose of metformin for at least 2 months prior to screening	**control, safety, and tolerability.**
Section 1.3 BENEFIT/RISK AND ETHICAL ASSESSMENT	*None.*	Details regarding potential risks associated with administration of EQW are provided in the Investigator's Brochure. The study will provide efficacy and safety information for EQW, with or without metformin, SU, and/or insulin, in children and adolescent patients with Type 2 Diabetes mellitus (T2DM). Patients in the placebo group will receive EQW-matching placebo, with or without metformin, SU, and/or insulin. All patients will be monitored throughout the study to ensure adequate glycemic control
Section 1.3.1 ETHICAL SAFETY CONSIDERATIONS	Section 6.4 If patients experience a loss of glucose control, defined as 1) an increase from baseline in HbA1c values by 0.5% or more at 2 consecutive clinic visits that are at least 1 month apart, or 2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home self-monitored blood glucose (SMBG), and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, rescue treatment will be initiated (See Section 0).	Section 1.3.1 *(numbering of the section is different).* If patients experience a loss of glucose control, defined as 1) an increase from baseline in HbA1c values by **1.0**% or more at 2 consecutive clinic visits that are at least 1 month apart, or 2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home self-monitored blood glucose (SMBG), and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, rescue treatment will be

		initiated (See Section 0). **Patients meeting rescue criteria will be treated with antihyperglycemic therapy (e.g., insulin) by the Investigator or referred to their treating physician to seek conventional antihyperglycemic intervention. Patients meeting these criteria may remain in the study and continue to receive study medication, at the discretion of the Investigator. Acute decompensation due to an intercurrent illness treated briefly with insulin will be allowed for 2 weeks, if longer this should be considered as rescue treatment.**
Section 2.1 PRIMARY OBJECTIVE	**Primary Objectives** The primary objectives of the study are: • To assess the effect on glycemic control, as measured by HbA1c, of exenatide once weekly following 14 weeks of treatment compared to placebo in adolescents with type 2 diabetes mellitus • To evaluate the safety and tolerability of exenatide once weekly compared to placebo following 14 weeks of treatment in adolescents with type 2 diabetes mellitus	**Primary objectives** The primary objectives of the study are: • To assess the effect on glycemic control, as measured by HbA1c, of exenatide once weekly following **24 weeks** of treatment compared to placebo in **children and** adolescents with type 2 diabetes mellitus • To evaluate the safety and tolerability of exenatide once weekly compared to placebo following **24 weeks** of treatment in **children and** adolescents with type 2 diabetes mellitus
Section 2.2 SECONDARY OBJECTIVE	**Secondary Objectives** The secondary objectives of this study are: • To compare the effects of exenatide once weekly following 14 weeks of treatment to those achieved by placebo in adolescents with type 2 diabetes mellitus on the following: – Fasting plasma glucose concentration – Proportion of subjects achieving HbA1c goals – Body weight and Tanner pubertal stage – Blood pressure and lipids • To assess the effects of long-term exenatide once weekly therapy (~1 year) in adolescents with type 2 diabetes mellitus on the following: – Long-term safety and tolerability – Parameters related to glycemic control, including HbA1c, fasting plasma glucose concentration, and proportion of subjects achieving HbA1c goals – Body weight and Tanner pubertal stage	**Secondary Objectives** The secondary objectives of this study are: • To compare the effects of exenatide once weekly following **24 weeks** of treatment to those achieved by placebo in **children and** adolescents with type 2 diabetes mellitus on the following: – Fasting plasma glucose concentration – Proportion of patients achieving HbA1c goals – Body weight and Tanner pubertal stage – Blood pressure and lipids • To assess the effects of long-term exenatide once weekly therapy (~1 year) in **children and** adolescents with type 2 diabetes mellitus on the following: – Long-term safety and tolerability – Parameters related to glycemic control, including HbA1c, fasting plasma glucose concentration, and proportion of patients achieving HbA1c

	– Blood pressure and lipids • To examine the effect of exenatide once weekly on beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostasis model assessment (HOMA) in adolescents with type 2 diabetes • To assess the pharmacokinetics of exenatide once weekly in adolescents with type 2 diabetes	goals – Body weight and Tanner pubertal stage – Blood pressure and lipids • To examine the effect of exenatide once weekly on beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by the homeostasis model assessment (HOMA) in **children and** adolescents with type 2 diabetes **who are not taking insulin** • To assess the pharmacokinetics of exenatide once weekly in **children and** adolescents with type 2 diabetes
Section 3.1 OVERALL STUDY DEIGN AND FLOW CHART	**Section 3.1 Design Description** This Phase 3, double-blind (controlled assessment period), randomized, multicenter, placebo-controlled study is designed to examine the efficacy and safety of EQW compared to placebo (PBO) in adolescents with type 2 diabetes for 14 weeks. Long-term safety and efficacy of EQW will subsequently be monitored for 52 weeks in the open-label, uncontrolled extension period (through Week 66). This study will be conducted in approximately 100 subjects with type 2 diabetes treated with diet and exercise alone or in combination with a stable dose of metformin for at least 2 months prior to screening. A schematic overview of the study design is presented in Figure 1. During the controlled assessment period, subjects will be randomly assigned in a 2:1 ratio to either EQW 2 mg (Group A) or PBO (Group B). Following the 14-week controlled assessment period, subjects assigned to the EQW 2 mg treatment (Group A) will continue to be treated with EQW 2 mg during the extension period (through Week 66). Subjects randomized to PBO (Group B) will receive EQW 2 mg beginning at the start of the extension period through Week 66. In addition to receiving study medications, all subjects will participate in a lifestyle intervention program encompassing diet and physical activity modifications following the signing of the informed consent and assent forms (Week -2) through the end of the extension period (Week 66). **Section 3.2 Visit Structure** Protocol BCB114 consists of a 14-week	**Overall Study Deign and Flow Chart** • This Phase 3, double-blind (controlled assessment period), randomized, multicenter, placebo-controlled **parallel study** is designed to examine the efficacy and safety of EQW compared to placebo (PBO) in adolescents with type 2 diabetes for **24 weeks**. • This study will assess safety and efficacy of exenatide once weekly (as monotherapy and adjunctive therapy to oral antidiabetic agents and/or insulin). • At least 40% and not more than 60% of the randomized patients must be females. At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states. • Long-term safety and efficacy of EQW will subsequently be monitored for 28 weeks in the open-label, uncontrolled extension period (through Week 52). • The study will be terminated at Visit 11 (Week 62/Study Termination) which will be a follow-up visit occurring 10 weeks after the last dose administration at Visit 10 (Week 52). • This study will be conducted in 77 patients with type 2 diabetes treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agents and/or insulin for at least 2 months prior to screening. A schematic overview of the study design is presented in Figure 1. During the controlled assessment period, approximately 77 patients will be randomly assigned in a 5:2 ratio to either EQW 2 mg (Group A) or PBO

	controlled assessment period and a 52-week open-label extension period. The study includes 10 visits to the clinical study site. The study will begin with Visit 1 (Screening) to obtain written informed consent and assess subject eligibility. Subjects will also be asked to participate in a lifestyle intervention program encompassing diet and physical activity modifications. Subject eligibility must be confirmed prior to randomization. Eligible subjects will return to the study site between 14 and up to 35 days following screening procedures for enrollment and randomization at Visit 2 (Week 0), the start of the controlled assessment period. At Visit 2 (Week 0), following baseline efficacy, safety, pharmacodynamic, and pharmacokinetic assessments, a medically-qualified staff member will demonstrate the preparation of SC study medication for the subject or a designated caregiver and will administer the first dose of SC study medication. In addition to receiving study medications, all subjects will be asked to continue the lifestyle intervention program encompassing diet and physical activity modifications. At Week 2 of the controlled assessment period, subjects will be contacted by phone by qualified study-site personnel to discuss study compliance, address any questions related to study medication, and review adverse events. During the controlled assessment period, subjects will return to the clinical study site at 4- and 5-week intervals at Visit 3 (Week 4), Visit 4 (Week 9), and Visit 5 (Week 14) to complete efficacy, pharmacodynamic, pharmacokinetic, and safety assessments. Following the controlled assessment period, all subjects enter a 52-week extension period. Group A subjects will continue to receive EQW for an additional 52 weeks up to Visit 10 (Week 66/Study Termination). Group B subjects will initiate treatment with EQW for 52 weeks up to Visit 10 (Week 66/Study Termination). During the 52-week extension period, subjects will be required to return to the clinical study site at 8- and 12-week intervals at Visit 6 (Week 22), Visit 7 (Week 30), Visit 8 (Week 42), Visit 9 (Week 54), and Visit 10 (Week 66/Study Termination) for efficacy, safety, pharmacodynamic, and	(Group B), to yield at least 70 evaluable patients: at least 50 patients in the exenatide and at least 20 patients in the PBO group. • Following the 24-week controlled assessment period, patients assigned to the EQW 2 mg treatment (Group A) will continue to be treated with EQW 2 mg during the extension period (through Week 52). Patients randomized to PBO (Group B) will receive EQW 2 mg beginning at the start of the extension period, Week 25 through Week 52. • In addition to receiving study medications, all patients will participate in a lifestyle intervention program encompassing diet and physical activity modifications following the signing of the informed consent and assent forms (Visit 1 [Week -2]) through the end of the extension period (Week 52). • Protocol BCB114 consists of a 24-week controlled assessment period and a 28-week open-label extension period. • The study includes 11 visits to the clinical study site. The study will begin with Visit 1 (Screening) to obtain written informed consent and assent, and assess patient eligibility. Patients will also be asked to participate in a lifestyle intervention program encompassing diet and physical activity modifications. Patient eligibility must be confirmed prior to randomization. The drug screen will be done locally. Eligible patients will return to the study site between 14 and up to 35 days following screening procedures for randomization at Visit 2 (Week 0), the start of the controlled assessment period. At Visit 2 (Week 0), following baseline efficacy, safety, pharmacodynamic (PD), and pharmacokinetic (PK) assessments, a medically-qualified staff member will demonstrate the preparation of SC study medication for the patient or a designated caregiver and will administer the first dose of SC study medication. In addition to receiving study medications, all patients will be asked to continue the lifestyle intervention program encompassing diet and physical activity modifications. • At Week 2 and Week 16 of the

	pharmacokinetic assessments. Subjects will also be contacted by phone at Week 18 to discuss study compliance, any issues related to study conduct or study medication, and to review adverse events. Subjects who withdraw from the study after Visit 2 (Week 0) and prior to Visit 10 (Week 66/Study Termination) will be invited to return to the study site for an Early Termination visit for HbA1c, fasting plasma glucose, body weight, and clinical safety laboratory measures. All visits scheduled during the controlled assessment and 52-week extension period should occur within ± 2 days of the scheduled date relative to Visit 2 (Week 0).	controlled assessment period, patients will be contacted by phone by qualified study-site personnel to discuss study compliance, address any questions related to study medication, and review adverse events. • During the controlled assessment period, patients will return to the clinical study site at 4- and 6-week intervals at Visit 3 (Week 4), Visit 4 (Week 8), Visit 5 (Week 12), Visit 6 (Week 18), and Visit 7 (Week 24) to complete efficacy, PD, PK, and safety assessments. • Following the controlled assessment period, all patients enter a 28-week extension period. Group A patients will continue to receive EQW for an additional 28 weeks up to Visit 10 (Week 52). Group B patients will initiate treatment with EQW for 28 weeks up to Visit 10 (Week 52). During the 28-week extension period, patients will be required to return to the clinical study site at 6-, 10-, and 12-week intervals at Visit 8 (Week 28), Visit 9 (Week 40), and Visit 10 (Week 52) for efficacy, safety, PD, and PK assessments. • **At Week 26 of the controlled assessment period, patients will be contacted by phone by qualified study-site personnel to discuss compliance, address any questions related to study medication, and review AEs** • Patients who withdraw from the investigational product after Visit 2 (Week 0) and prior to Visit 10 (Week 52) will be invited to return to the study site for an Early Termination visit for HbA1c, fasting plasma glucose, body weight, and clinical safety laboratory measures. • All visits scheduled during the 24-week controlled assessment and 28-week extension period should occur within ± 2 days of the scheduled date relative to Visit 2 (Week 0). • All patients will return to the site on Visit 11 (Week 62/Study Termination)
Table 1 STUDY PLAN	*Controlled assessment period* Extension period - 52 weeks Visit 4 Week 9	1.1.1.1 Controlled assessment period - **24** Weeks Extension period - **28**-weeks Visit 4 Week **8**

	Visit 5 Week 14 Week 18 Phone call Visit 6 Week 22 Visit 7 Week 30 Visit 8 Week 42 Visit 9 Week 54 Visit 10 Week 66 (Study Termination) Subject Assent Blood Sample for Serum βhCG Test (females)- Screening, Visit 10, and early termination Urine βhCG Test (Females) – Visits 2-9 Tanner pubertal stage test – Visits 2, 5, 8, 10, and early termination TSH, FSH, LH, Total testosterone, Estradiol, Free T4, DHEAS, Cortisol, Prolactin, IGF-1 - Visits 2, 5, 8, 10, and early termination *None*. Bone Specific Alkaline Phosphatase and Deoxypyridinoline - Visits 2, 5, 8, 10, and early termination *None*. Drug dispensing *None.*	Visit 5 Week **12** Week **16** Phone call Visit 6 Week **18** Visit 7 Week **24** **Week 26 Phone Call** Visit 8 Week **28** Visit 9 Week **40** Visit 10 Week **52 (End of Study Treatment**) **Visit 11 Week 62 (Study Termination)** **Patient** Assent *Blood Sample for Serum βhCG Test (females)- Screening, Visit **11**, and early termination* Urine βhCG Test (Females) – Visits 2-**10** Tanner pubertal stage test – Visits 2, 5, 7, 9, 10, and early termination TSH, FSH, LH, Estradiol, Free T4, DHEAS, Cortisol, Prolactin, IGF-1 - Visits 2, 5, 7, 10, and early termination Total testosterone, SHBG - Visits 2, 5, 7, 9, 10, and early termination Bone Specific Alkaline Phosphatase and Deoxypyridinoline - Visits 2, 5, 7, 10, and early termination Bone age assessment by X-ray - Visits 2, 10, and early termination Dispense Study Medication All the assessments at Visit 11 (Adverse event assessment; physical examination; body weight, height, and vital signs; Blood Sample for Serum βhCG Test (females); chemistry, hematology, urinalysis; calcitonin; plasma exenatide; and antibodies to exenatide) have been added new. Week 26 Phone call – added Adverse Event Assessment and Study Medication Compliance Review
Table 1 STUDY PLAN footnote	Abbreviations: βhCG, human chorionic gonadotropin, beta subunit; CEA, carcinoembryonic antigen; DHEAS, dehydroepiandrosterone; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; LH, luteinizing hormone; GAD65, glutamic acid decarboxylase; ICA512, islet cell antigen; IGF-1, insulin-like growth factor-1; LDL-C, low-density lipoprotein cholesterol; free T4, thyroxine; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone.	Abbreviations: βhCG, human chorionic gonadotropin, beta subunit; CEA, carcinoembryonic antigen; DHEAS, dehydroepiandrosterone; ECG, electrocardiogram; FSH, follicle-stimulating hormone; HDL-C, high-density lipoprotein cholesterol; HIPAA, Health Insurance Portability and Accountability Act; LH, luteinizing hormone; GAD65, glutamic acid decarboxylase; ICA512, islet cell antigen; IGF-1, insulin-like growth factor-1; LDL-C, low-density lipoprotein cholesterol; free T4,

	Note: Study plan applies only to the Controlled Assessment Period and 52-Week Extension Period of Study BCB114. See Appendix 2 for details of study procedures for the Safety Follow-Up Period. *[1] If the study visit is scheduled on the same day as the subject's weekly administration of study medication, subject and/or caregiver will administer the study medication at the study site after completion of all other study procedures*	thyroxine; **SHBG, sex hormone-binding globulin**; TC, total cholesterol; TG, triglycerides; TSH, thyroid stimulating hormone. Note: Study plan applies only to the 24-Week Controlled Assessment Period and 28-Week Extension Period of Study BCB114. See Appendix E for details of study procedures for the Extended Safety Follow-Up Period. *Visit 11 should take place 10 weeks after last dose of EQW and no later than 12 weeks [1] If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patient and/or caregiver will administer the study medication at the study site after completion of all other study procedures
Section 3.2 STUDY DURATION	**Section 3.3** Total study duration will be approximately 71 weeks, including up to a 5-week screening period, a 14-week controlled assessment period, and a 52-week extension period. *The interval between screening and the beginning of the treatment period should occur between14 days to up to 35 days following screening*	**Section 3.2** Total study duration will be approximately 67 weeks, including up to a 5-week screening period, a 24-week controlled assessment period, and a 28-week extension period, and a 10-week post-treatment follow-up period. The interval between screening and the beginning of the treatment period should occur between 14 days to up to 35 days following screening
Section 3.3.1 STUDY DESIGN AND REGULATORY REQUIREMENT	***Section 1.3.1***	***Section 3.3.1*** (Text is same, only the numbering of the section is different).
Section 3.3.1.1 SAFETY FOLLOW-UP PERIOD	***1.4 Safety Follow-Up Period*** Following Visit 10 (Week 66/Study Termination), subjects whose height increase is at least 5 mm between Visit 8 (Week 42) and Visit 10 (Week 66/Study Termination) will participate in a long-term safety follow-up period. Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) will also participate in the Safety Follow-Up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. Subjects 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. The Safety Follow-Up Period will continue for up to 3 years or until the difference between	**3.3.1.1 Extended Safety follow-up period** Following Visit 11 (Week 62/Study Termination), patients whose height increase is at least 5 mm between Visit 8 (Week 28) and Visit 11 (Week 62/Study Termination) will participate in a long-term safety follow-up period. Patients who discontinue study medication prior to Visit 11 (Week 62/Study Termination) will also participate in the Extended Safety Follow-Up Period, unless they have a height increase of less than 5 mm over a 6-month interval at study site visits prior to discontinuation of study medication. 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 Extended Safety Follow-Up

	two 6-month interval visits is less than a 5 mm increase (whichever comes first). No study medication will be administered during the Safety Follow-Up Period. Details of the Safety Follow-Up Period are provided in Appendix 2.	Period. The Extended Safety Follow-Up Period will continue for up to 3 years or until the difference between two 6-month interval visits is less than a 5 mm increase (whichever comes first). No study medication will be administered during the Extended Safety Follow-Up Period. Blood samples will be collected for calcitonin and CEA laboratory measurements. Details of the Extended Safety Follow-Up Period are provided in Appendix E.
Section 3.3.2.1 DOSAGE SELECTION	Section 1.3.2	**Section 3.3.2.1** *(Text is same, only the numbering of the section is different).* **Section 3.3.2.2 Control group** This is a double-blind, placebo-controlled study.
Section 4.1 POPULATIONS TO BE STUDIED	**Section 4.1: Populations to be studied** • Approximately 100 male or female adolescents 10 to 17 years of age, inclusive, diagnosed with type 2 diabetes mellitus and treated with diet and exercise alone or in combination with a stable dose of metformin for at least 2 months prior to screening, will be randomized into this study. • At least 60% of study subjects must be included for analysis of the primary and secondary endpoints (Evaluable Population) at Week 14. • Approximately 50% of randomized study subjects must be female. At least 40% of subjects are to be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states	Investigators should keep a record, the patient screening log, of patients who entered pre-study screening. **Section 4.1: Populations to be studied** • A total of 77 male or female children and adolescents of 10 to <18 years of age, diagnosed with type 2 diabetes mellitus and treated with diet and exercise alone or in combination with a stable dose of oral antidiabetic agent (e.g., metformin and/or SU) and/or insulin for at least 2 months prior to screening, will be randomized into this study to yield 70 evaluable patients. • At least 60% of study patients must be included for analysis of the primary and secondary endpoints (Evaluable Population) at Week 24. • At least 40% and not more than 60% of randomized study patients must be female. • At least 40% of patients should be recruited from areas with similar ethnicity and lifestyle to those of the European Union member states. Each patient should meet all of the inclusion criteria and *None* of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule
Section 4.2 INCLUSION CRITERIA 1	Is 10 to 17 years old, inclusive, at Visit 1 (Screening)	Is a child or an adolescent of 10 to <18 years old, at Visit 1 (Screening)
Section 4.2 INCLUSION CRITERIA 3	Has HbA1c of 6.5% to 11%, inclusive, at Visit 1 (Screening)	HbA1c of 6.5% to 11.0%, inclusive, in patients not taking insulin/SU, and of 6.5% to 12.0%, inclusive, in patients taking insulin/SU, at Visit 1 (Screening).

Section 4.2 INCLUSION CRITERIA 4	Has a **fasting** C-peptide of >0.6 ng/L at Visit 1 (Screening)	Has a C-peptide of >0.6 ng/L at Visit 1 (Screening**)**
Section 4.2 INCLUSION CRITERIA 5	Has been treated with diet and exercise alone or in combination with a stable dose of metformin for their type 2 diabetes for at least 2 months prior to Visit 1 (Screening)	Has been treated with diet and exercise alone or in combination with a stable dose of an oral antidiabetic agent (e.g., metformin and/or SU) and/or insulin for their type 2 diabetes for at least 2 months prior to Visit 1 (Screening)
Section 4.2 INCLUSION CRITERIA 7	Either is not treated with or has been on a stable treatment regimen with any of the following medications for a minimum of 3 months prior to Visit 1 (Screening):	Either is not treated with or has been on a stable treatment regimen with any of the following medications for a minimum of 1 month prior to Visit 1 (Screening):
Section 4.2 INCLUSION CRITERIA 10	Has physical examination and ECG results deemed not clinically significant by the Investigator at Visit 2	Has physical examination and ECG results deemed not clinically significant by the Investigator at Visit 2 (Week 0)
Section 4.3 EXCLUSION CRITERIA	Subjects who meet any of the following criteria will be excluded from the study.	Patients should not enter the study if any of the following exclusion criteria are fulfilled.
Section 4.3 EXCLUSION CRITERIA	Criterion 4. Has used insulin for >10 weeks in the last 3 months prior to Visit 1 (Screening).	*None.*
Section 4.3 EXCLUSION CRITERIA 7	Has ever used exenatide (exenatide once weekly [exenatide LAR], exenatide BID, BYETTA, or any other formulation) or any GLP-1 receptor agonist (e.g. liraglutide [Victoza®])	Has ever used exenatide (exenatide once weekly [exenatide LAR], exenatide BID, BYETTA, or any other formulation) or any glucagon-like peptide-1 (GLP-1) receptor agonist (e.g. liraglutide [Victoza®])
Section 4.3 EXCLUSION CRITERIA 10 a	Oral glucocorticoids or corticosteroids within the last 60 days or more than 20 days within the past year.	Oral glucocorticoids or corticosteroids within the last 30 days or more than 20 days within the past year. However, glucocorticoid treatment for some infections for less than 10 days is allowed.
Section 4.3 EXCLUSION CRITERIA	Criterion 10 c. SU within 90 days prior to Visit 1 (Screening)	*None.*
Section 4.3 EXCLUSION CRITERIA 10 c	Inhaled glucocorticoids within at a dose equal to or above 1,000 mcg Flovent® (fluticasone propionate) daily	Inhaled glucocorticoids at a dose equal to or above 1,000 µg Flovent® (fluticasone propionate) daily
Section 4.3 EXCLUSION CRITERIA 10 e	Alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide for >1 week in the 3 months prior to Visit 1 (Screening)	Alpha-glucosidase inhibitors, meglitinide, nateglinide, or pramlintide for >1 week in the 1 month prior to Visit 1 (Screening)
Section 4.3 EXCLUSION CRITERIA 10 f	DPP-4 inhibitors within 90 days prior to Visit 1 (Screening)	DPP-4 inhibitors within 30 days prior to Visit 1 (Screening)
Section 4.3 EXCLUSION CRITERIA 13	*None.*	Is pregnant
Section 4.3 EXCLUSION CRITERIA 14	Is employed by Amylin Pharmaceuticals, Inc (Amylin) or Eli Lilly and Company (Lilly); (that is an employee, temporary contract worker, or designee responsible for	Is employed by AstraZeneca (i.e., an employee, temporary contract worker, or designee responsible for the conduct of the study)

	the conduct of the study)	
Section 5.1	Section 4.4 Restrictions	Section 5.1 Restrictions during the study
Section 5.1 RESTRICTIONS DURING THE STUDY	Refer to Section 4.5 *None.*	Refer to Section 5.6 For procedures for withdrawal of incorrectly enrolled patients see Section 5.3.
Section 5.2 PATIENT ENROLLMENT AND RANDOMIZATION	*None.*	The Principal Investigator will: 1. Obtain signed and dated informed consent from parent or caretaker and patient assent and HIPAA Authorization before any study specific procedures are performed. 2. Determine patient eligibility. See Sections 4.2 and 4.3. 3. The Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) will assign an eligible patient unique randomization code, beginning with '#'. 4. If a patient withdraws from participation in the study, then his/her enrollment/randomization code cannot be reused.
Section 5.2.1 PROCEDURES FOR RANDOMIZATION	Section 5.4	Section 5.2 *(A part of Section 5.4 [Patients who meet….. upcoming visits] has been shifted as Section 5.2)*
Section 5.3 PROCEDURES FOR HANDLING PATIENTS INCORRECTLY ENROLLED OR RANDOMIZED	*None.*	Patients who fail to meet the inclusion/exclusion criteria should not, under any circumstances, be randomized to receive study medication. There can be no exceptions to this rule. Patients who are screened, but subsequently found not to meet all the eligibility criteria must not be randomized or initiated on treatment. These patients (who have not been randomized) should be withdrawn from the study. Where a patient does not meet all eligibility criteria, but is randomized in error or incorrectly started on treatment, the Investigator should inform the study physician immediately, and a discussion should occur between the study physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The study physician and the Investigator must ensure all decisions are appropriately documented.
Section 5.4 BLINDING AND PROCEDURES FOR UNBLINDING	**Section 12.1** Section 12.1.1 Controlled Assessment Period The subject, investigator (and all study-site personnel), and sponsor will be blinded to	**Section 5.4.1** The exception to the above is for those personnel analyzing the PK and antibody samples. The randomization information will be provided to ensure that only

	treatment during the controlled assessment period. Every effort should be made to ensure that subjects remain blinded to their treatment during this period. If a subject's treatment is unblinded only to a Global Safety Case delegate and related personnel required for case processing for the purpose of FDA submission, the subject's status in the study may remain unchanged. Otherwise, the code may be unblinded only after an irrevocable decision has been made to withdraw the subject from the study and if immediate knowledge of the study medication is needed to optimize the clinical management of the subject. The investigator is to notify the Amylin medical monitor if an event occurs that requires a subject's treatment assignment to be unblinded. Section 12.1.2 52-Week Extension Period The subject, investigator (and all study-site personnel), and sponsor will be unblinded to study medication during the 52-week extension period.	samples from patients who were on active study treatment are analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a "for cause" basis, for example, if there is suspicion that a patient has been dosed incorrectly. Section 5.4.2 Methods for unblinding the study Individual treatment codes, indicating the treatment randomization for each randomized patient, will be available from the IVRS/IWRS. Routines for this will be described in the IVRS/IWRS user manual that will be provided to each centre. The treatment code should not be broken except in medical emergencies when the appropriate management of the patient requires knowledge of the treatment randomization. The Investigator documents and reports the action to AstraZeneca, without revealing the treatment given to patient to the AstraZeneca staff. AstraZeneca and the safety data entry site retain the right to break the code for SAEs that are unexpected and are suspected to be causally related to an investigational product and that potentially require expedited reporting to regulatory authorities. Treatment codes will not be broken for the planned analyses of data until all decisions on the evaluability of the data from each individual patient have been made and documented. Section 5.4.2.1 24-Week Controlled Assessment Period The patient, Investigator (and all study-site personnel), and Sponsor will be blinded to treatment during the controlled assessment period. Every effort should be made to ensure that patients remain blinded to their treatment during this period. If a patient's treatment is unblinded only to a Global Safety Case delegate and related personnel required for case processing for the purpose of FDA submission, the patient's status in the study may remain unchanged. Otherwise, the code may be unblinded only after an irrevocable decision has been made to withdraw the patient from the investigational product and immediate knowledge of the study medication is

<table>
<tr><td></td><td></td><td>needed to optimize the clinical management of the patient. The Investigator is to notify the AstraZeneca medical monitor if an event occurs that requires a patient's treatment assignment to be unblinded.
Section 5.4.2.2 28-Week Extension Period
The patient, Investigator (and all study-site personnel), and Sponsor will be unblinded to study medication during the 28-week extension period</td></tr>
<tr><td>Section 5.5.1 IDENTITY OF INVESTIGATIONAL PRODUCT(S)</td><td>None.</td><td>
<table>
<tr><th>Investigational product</th><th>Dosage form and strength</th><th>Manufacturer</th></tr>
<tr><td>Exenatide once weekly (EQW)</td><td>2.0 mg powder for injection</td><td>AstraZeneca [a]</td></tr>
<tr><td>Placebo to match exenatide once weekly</td><td>Placebo powder for injection</td><td>AstraZeneca [a]</td></tr>
</table>
[a] Responsible for supply of Investigational Product
All study medication sufficient for 4-week treatment will be packed into kits. The vials containing the exenatide/placebo powder for injections will be packed into a small box containing 4 vials. Four pre-filled syringes with diluent for suspension of EQW and matching placebo will be packed into another box also containing 6 vial adaptors and 6 23-Gauge x 5/16 inch needles.
Study materials will be provided to patients by the Investigator or medically qualified subinvestigator named on Form FDA 1572, or other qualified study-site personnel. Under no circumstance will the Investigator or subinvestigators allow the study medication to be used other than as directed by the protocol or to be administered to any persons other than patients participating in the study. Medically-qualified staff members will be responsible for instructing patients/caregivers on the preparation and administration of the correct doses of study medication</td></tr>
<tr><td>Section 5.5.2 FORMULATION,</td><td>EQW (formulation AC2993 F17) is an extended release formulation of exenatide</td><td>The EQW is an extended release formulation of exenatide and consists of</td></tr>
</table>

PACKAGING AND STORAGE	and consists of 5% exenatide, sucrose, and 50:50 poly D,L lactide-co-glycolide. The vial containing the white to off white dry powder (2.8 mg of EQW microspheres) must be stored in a refrigerator between 2ºC and 8ºC and protected from light. EQW matching placebo is the identical formulation with the active ingredient omitted. The Microsphere Diluent for suspension of the EQW and placebo microspheres contains carboxymethylcellulose low viscosity, polysorbate 20, sodium chloride, and water for injection. The Microsphere Diluent must be stored between 2°C and 27°C (36°F and 81°F). The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the EQW injection will be provided in the Patients Instructions for Use. The reconstituted dose of study medication (EQW or matching placebo) should not be stored for future use. The injection must be administered immediately after preparation of the dose.	5% exenatide, sucrose, and 50:50 poly D,L lactide-co-glycolide. The EQW microspheres and matching placebo will be supplied in vials containing the white to off white dry powder (40 mg of EQW microspheres). The vials must be stored in a refrigerator between 2ºC and 8ºC and protected from light. EQW matching placebo is the identical formulation with the active ingredient omitted. The Diluent for suspension of the EQW and placebo microspheres contains carboxymethylcellulose low viscosity, polysorbate 20, sodium chloride, and water for injection. Diluent for suspension will be supplied in pre-filled syringes. Each syringe will contain 0.75 mL. The EQW or matching placebo dose is prepared by reconstitution of the microspheres in the diluent provided. Specific instructions for dose preparation of the EQW injection will be provided in the Patients Instructions for Use. The reconstituted dose of study medication (EQW or matching placebo) should not be stored for future use. The injection must be administered immediately after preparation of the dose. Packaging. All study medication will be packed into kits enough for 4-week treatment. The vials containing the exenatide/placebo powder for injections will be packed into a small box containing 4 vials. Four pre-filled syringes with diluent for suspension of EQW and matching placebo will be packed into another box also containing 6 vial adaptors and 6 23-Gauge x 5/16 inch needles.
Section 5.5.2 Dose and Treatment Regimens	Section 5.3 Doses of study medication are to be injected into SC tissue **of the abdomen**. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly	Section 5.5.2 *(Section numbering has changed.)* Doses of study medication are to be injected into SC tissue. The site of injection should be rotated on a regular basis so that the same site is not used repeatedly.
Section 5.5.3 RESCUE TREATMENT	Section 5.6 A loss of glycemic control observed by either 1) increase from baseline in HbA1c values by 0.5% or more at 2 consecutive	Section 5.5.3 *(Section numbering has changed.)* A loss of glycemic control observed by either 1) increase from baseline in HbA1c

	clinic visits that are at least 1 month apart, or 2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home SMBG, and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, will result in rescue treatment Patients meeting rescue criteria will be treated with antihyperglycemic therapy (e.g., insulin) by the Investigator or referred to their treating physician to seek conventional antihyperglycemic intervention. Patients meeting these criteria should remain in the study and continue to receive study medication, at the discretion of the Investigator. AstraZeneca will not supply the rescue medication.	values by **1.0**% or more at 2 consecutive clinic visits that are at least 1 month apart, or 2) fasting glucose value ≥250 mg/dL or random blood glucose >300 mg/dL for 4 days during a 7-day period measured by home SMBG, and confirmed by fasting or random glucose test within the same range of values (measured by local laboratory) at a clinic visit, will result in rescue treatment. Patients meeting rescue criteria will be treated with antihyperglycemic therapy (e.g., insulin) by the Investigator or referred to their treating physician to seek conventional antihyperglycemic intervention. Patients meeting these criteria should remain in the study and continue to receive study medication, at the discretion of the Investigator. AstraZeneca will not supply the rescue medication. **Acute decompensation due to an intercurrent illness treated briefly with insulin will be allowed for 2 weeks, if longer this should be considered as rescue treatment.**
Section 5.5.4 LABELLING	*None.*	Labels will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The labels will fulfil GMP Annex 13 requirements for labelling. Label text will be translated into local language
Section 5.5.5 STORAGE	*None.*	All study drugs should be kept in a secure place under appropriate storage conditions. The investigational product label on the kit specifies the appropriate storage
Section 5.6 CONCOMITANT AND POST-STUDY TREATMENTS	Any change in regimen for any concomitant medication, including restricted concomitant medications, must be reported to the sponsor	For patients on insulin, the dose should be kept constant as far as possible, though modifications of the dose of insulin may have to be made to reduce the risk of hypoglycemia. Any change in regimen for any concomitant medication, including restricted concomitant medications, must be reported to the Sponsor. Other medication, which is considered necessary for the patient's safety and well being, may be given at the discretion of the Investigator and recorded in the

<table>
<tr><td></td><td></td><td>appropriate sections of the Case Report Form</td></tr>
<tr><td>Section 5.7 TREATMENT COMPLIANCE</td><td>None.</td><td>The administration of all study drugs (including investigational products) should be recorded in the appropriate sections of the Case Report Form.
The study drug dispensation as per visits has been summarized in Table 1.

Table 1: Study Drug Dispensation per Visits Schedule
<table>
<tr><th>Visit (week)</th><th>Exenatide/placebo vial 4-weeks kit. (24-Week Controlled assessment Period).</th><th>Exenatide vial 4-weeks kit (28-Week Extension Period).</th><th>Diluent 4-weeks kit</th></tr>
<tr><td>Visit 2 (Week 0)</td><td>1</td><td>N/A</td><td>1</td></tr>
<tr><td>Visit 3 (Week 4±2 days)</td><td>1</td><td>N/A</td><td>1</td></tr>
<tr><td>Visit 4 (Week 8±2 days)</td><td>1</td><td>N/A</td><td>1</td></tr>
<tr><td>Visit 5 (Week 12±2 days)</td><td>2</td><td>N/A</td><td>2</td></tr>
<tr><td>Visit 6 (Week 18±2 days)</td><td>2</td><td>N/A</td><td>2</td></tr>
<tr><td>Visit 7 (Week 24±2 days)</td><td>N/A</td><td>1</td><td>1</td></tr>
<tr><td>Visit 8 (Week 28±2 days)</td><td>N/A</td><td>3</td><td>3</td></tr>
<tr><td>Visit 9 (Week 40±2 days)</td><td>N/A</td><td>3</td><td>3</td></tr>
<tr><td>Visit 10 (Week 52±2 days)</td><td>N/A</td><td>N/A</td><td>N/A</td></tr>
</table>
Abbreviation: N/A=not applicable
Visit 2 (Week 0): At Visit 2, a 4-week supply of blinded study medication kits will be dispensed to all patients, according to their assigned treatment</td></tr>
</table>

		group. Visit 3 (Week 4) and Visit 4 (Week 8): At Visit 3 and Visit 4 an additional 4-week supply of study medication will be dispensed to all patients, according to their assigned treatment group. Visit 5 (Week 12) and Visit 6 (Week 18): At Visit 5 and Visit 6 an additional 8-week supply of study medication will be dispensed to all patients, according to their assigned treatment group. Visit 7 (Week 24): At Visit 7 a 4-week supply of open label study medication will be dispensed to all patients. Visit 8 (Week 28) and Visit 9 (Week 40): At Visit 8 and Visit 9 a 12-week supply of open label study medication will be dispensed to all patients. Visit 10 (Week 52/End of Treatment): Patients to return all used and unused study medication to the study site.
Section 5.7.7 ACCOUNTABILITY	Section 5.5	Section 5.7.1 *(The text is same, only the Section numbering has changed.)*
Section 5.8 DISCONTINUATION OF INVESTIGATIONAL PRODUCT	*None.*	Patients may be discontinued from investigational product (IP) in the following situations: • Patient decision. The patient is at any time free to discontinue treatment, without prejudice to further treatment • Adverse event • Severe non-compliance to study protocol • Accelerated sexual maturation as assessed by measurement of Tanner stage, bone age, and hormonal levels Development of any study specific criteria for discontinuation is presented in Section 5.9. Procedures for discontinuation of a patient from investigational product A patient that decides to discontinue investigational product will always be asked about the reason(s) and the presence of any AEs (Section 1.3.1). If possible, they will be seen and assessed by an Investigator(s). Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the patient. Patients who discontinue study medication prior to Visit 11 (Week 62/Study Termination) should enter the Extended Safety Follow-Up Period, as

		described in Appendix E, 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 do not have height assessments at study site visits over a 6-month interval prior to discontinuation of study medication will enter the Extended Safety Follow-Up Period. If a patient is withdrawn from the investigational product, see Section 5.9
Section 5.9 WITHDRAWAL FROM THE STUDY	Subjects who discontinue study medication prior to Visit 10 (Week 66/Study Termination) should enter the Safety Follow-Up Period, as described in Appendix 2, 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. Subjects 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 are at any time free to withdraw from study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such patients will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an Investigator. Adverse events will be followed up (See Sections 6.4.3 and 6.4.4); and all study drugs should be returned by the patient.
Section 6.1 RECORDING OF DATA	*None.*	The Express Web Based Data Capture (EWBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the electronic Case Report Forms as specified in the study protocol and in accordance with the instructions provided. The Investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement
Section 6.2.1 ENROLLMENT PROCEDURES	All subjects will be instructed to arrive in the morning of each scheduled study visit. Subjects are to have fasted overnight (no food or beverage except water) for ≥8 hours at Visit 1 (Screening), Visit 2 (Week 0), Visit 3 (Week 4), Visit 4 (Week 9), Visit 5 (Week 14), Visit 7 (Week 30), and Visit 10 (Week 66/Study Termination) or Early Termination. If the study visit is scheduled on the same day as the subject's weekly administration of study medication, subjects will be instructed to delay administration of study medication, bring their study medication to the study site, and administer study medication at the study site. If subjects are taking metformin they should administer their usual metformin therapy at	All patients will be instructed to arrive in the morning of each scheduled study visit. Patients are to have fasted overnight (no food or beverage except water) for ≥8 hours at Visit 1 (Screening), Visit 2 (Week 0), Visit 3 (Week 4**),** Visit 4 (Week **8),** Visit 5 (Week **12),** Visit 7 (Week **24),** and Visit 10 (Week **52/End of Treatment**) or Early Termination. If the study visit is scheduled on the same day as the patient's weekly administration of study medication, patients will be instructed to delay administration of study medication, bring their study medication to the study site, and administer study medication at the study site. If patients are taking **concomitant antidiabetic**

	approximately the same time each day throughout the study.	**medication** they should administer their usual **concomitant antidiabetic medication** therapy at approximately the same time each day throughout the study.
Section 6.2.2 SCREENING PROCEDURES	Individuals will be disqualified if results of any laboratory test are abnormal and clinically significant as judged by the investigator or medical monitors. Individuals may requalify for study enrollment within 35 days of Visit 1 (Screening) following an abnormal test result by having that test repeated once with acceptable results as judged by the investigator and medical monitors (or designees). If greater than 35 days have elapsed since Visit 1 (Screening), subjects who wish to requalify for study enrollment following an abnormal test result must have all screening assessments repeated. • Blood samples will be collected for: – Serum pregnancy test (βhCG) for all female patients – Chemistry and hematology – HbA1c – Fasting plasma glucose – Fasting insulin – **Fasting** C-peptide – GAD65 and ICA512 antibodies – Calcitonin	Individuals will be disqualified if results of any laboratory test are abnormal and clinically significant as judged by the **Investigator** or medical monitors. Individuals may requalify for study **randomization** within 35 days of Visit 1 (Screening) following an abnormal test result by having that test repeated once with acceptable results as judged by the **Investigator** and medical monitors (or designees). If greater than 35 days have elapsed since Visit 1 (Screening), **patients** who wish to requalify for study **randomization** following an abnormal test result must have all screening assessments repeated. • Blood samples will be collected for: – Serum pregnancy test (βhCG) for all female patients – Chemistry and hematology – HbA1c – Fasting plasma glucose – Fasting insulin – C-peptide – GAD65 and ICA512 antibodies – Calcitonin
Section 6.2.3.1 VISIT 2 (WEEK 0)	*None.*	• Sex hormone-binding globulin (SHBG) • Bone age assessment by X-ray
Section 6.2.3.3	Visit 4 Week 9	Visit 4 Week **8**
Section 6.2.3.4	Visit 5 Week 14 *None.*	Visit 5 Week **12** SHBG
Section 6.2.3.5	Week 18 Phone call	Week **16 Telephone contact**
Section 6.2.3.6	Visit 6 Week 22	Visit 6 Week **18**
Section 6.2.3.7	Visit 7 Week 30	Visit 7 Week **24**
Section 6.2.3.7	*None.*	• Tanner pubertal stage test • TSH, FSH, LH, Estradiol, Free T4, DHEAS, Cortisol, Prolactin, IGF-1 • Total testosterone, SHBG • Bone Specific Alkaline Phosphatase and Deoxypyridinoline
Section 6.2.3.8	*None*	**Week 26 – Telephone contact** **The Investigator and/or qualified**

		study-site personnel will contact patients by telephone at Week 26 to discuss study compliance, address any questions related to study medication administration, and review AEs
Section 6.2.3.9	Visit 8 Week 42	Visit 8 Week **28**
Section 6.2.3.9	• Tanner pubertal stage test • TSH, FSH, LH, Estradiol, Free T4, DHEAS, Cortisol, Prolactin, IGF-1 • Bone Specific Alkaline Phosphatase and Deoxypyridinoline	*None*.
Section 6.2.3.9	Visit 9 Week 54	Visit 9 Week **40**
Section 6.2.3.9	*None*.	• Tanner pubertal stage test • Total testosterone, SHBG
Section 6.2.3.10	Visit 10 Week 66 (Study Termination)	Visit 10 Week **52 (End of Study Treatment**)
Section 6.2.3.10	Blood Sample for Serum βhCG Test (females)	*None*.
Section 6.2.3.10	*None*.	• Urine Pregnanacy Test (Females only) • Total testosterone, SHBG • Bone age assessment by X-ray
Section 6.2.3.11	*None.*	**Visit 11 Week 62 (Study Termination)** • Adverse event assessment • Physical examination • Body weight, height, and vital signs • Blood Sample for Serum βhCG Test (females) • Chemistry, hematology, urinalysis • Calcitonin • Plasma exenatide • Antibodies to exenatide
Section 6.3 EFFICACY	Section 7	Section 6.3 *(Text is same, only the numbering of the section is different).*
Section 6.3.1 HbA1c	Section 7.1	Section 6.3.1 *(Text is same, only the numbering of the section is different).*
Section 6.4 SAFETY	*None*.	The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.
Section 6.4.1 DEFINITION OF ADVERSE EVENT	An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.18 ALL ADVERSE EVENTS THAT OCCUR AFTER THE SUBJECT HAS SIGNED	An adverse event is the development of an undesirable medical condition or the deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product, whether or not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g., tachycardia, enlarged liver) or the abnormal results of an investigation (e.g., laboratory findings, electrocardiogram). In clinical studies, an AE can include an undesirable medical condition occurring at any time, including run-in or washout

	THE INFORMED CONSENT WILL BE RECORDED ON SOURCE DOCUMENTS. ADVERSE EVENTS FOR SUBJECTS WHO ENROLL IN THE STUDY WILL BE ENTERED ON SOURCE DOCUMENTS AND THE ELECTRONIC CASE REPORT FORMS (eCRFs).	periods, even if no study treatment has been administered. The term AE is used to include both serious and non-serious AEs.
Section 6.4.2 DEFINITION OF SERIOUS ADVERSE EVENT	ANY SERIOUS ADVERSE EVENT (SAE) THAT OCCURS AFTER THE SIGNING OF THE ICF THROUGH 90 DAYS AFTER ADMINISTRATION OF THE LAST DOSE OF STUDY MEDICATION MUST BE REPORTED IMMEDIATELY (WITHIN 24 HOURS OF KNOWLEDGE) TO AMYLIN GLOBAL SAFETY. FAX THE SAE REPORT FORM TO THE NUMBER LISTED ON THE FORM. Any AE that results in any of the following outcomes will be considered an SAE. The following outcomes are defined according to Code of Federal Regulations (CFR) Title 21 Part 312.32. • Death • Life threatening situation (subject was at risk of death at the time of the event. This does not refer to an event that might have caused death if it was of greater intensity.) • Inpatient hospitalization or prolongation of inpatient hospitalization • Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions • Congenital anomaly or birth defect • Important medical events that may not result in death, be life threatening, or require hospitalization but may jeopardize the subject and may require medical or surgical intervention to prevent one of the above outcomes (based upon appropriate medical judgment), e.g., allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse	A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up), that fulfils one or more of the following criteria: • Results in death • Is immediately life-threatening • Requires in-patient hospitalization or prolongation of existing hospitalization • Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions • Is a congenital abnormality or birth defect • Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above. For further guidance on the definition of a SAE, see Appendix B to the Clinical Study Protocol.
Section 6.4.3 RECORDING OF ADVERSE EVENT	Adverse events include those reported spontaneously by the subject and those noted incidentally or as the result of nondirected questioning by the investigator or study personnel. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded on the eCRFs using	All AEs that occur after the patient has signed the informed consent will be recorded on source documents. Adverse events for patients who enroll in the study will be entered on source documents and the eCRFs. Adverse events include those reported spontaneously by the patient and

	standard medical terminology that is as specific as possible, rather than the subject's own words. Whenever the investigator is confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results should be grouped together as a single AE on the eCRF (e.g., cough and rhinitis should be reported as an "upper respiratory tract infection"). All clinically significant abnormalities noted upon physical examination, ECG, and clinical laboratory and vital sign measurements that occur during the study and were not present prior to the signing of the ICF, should be reported as an AE, except for abnormalities present at Screening that may be considered part of the medical history. In addition, all clinically significant AEs that continue at Study Termination should be followed up by the investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolution occurs. Follow-up information should be recorded on the source documents and reported to the sponsor. Adverse events will be evaluated for intensity and causal relationship with the use of the study medication by the investigator. Adverse events that occur following completion of study termination/early termination procedures should be recorded on the AE page of the eCRF only if the investigator considers the event as clinically significant and as related to study medication or study procedures. All serious adverse events (SAEs) that occur within 90 days of administration of the last dose of study medication (regardless of causality) must be reported immediately (Section 10.1.2). Concomitant medications used following study termination procedures should be recorded only if relevant to treatment of subjects for events described above	those noted incidentally or as the result of nondirected questioning by the Investigator or study personnel. To avoid vague, ambiguous, or colloquial expressions, the AE should be recorded on the eCRFs using standard medical terminology that is as specific as possible, rather than the patient's own words. Whenever the Investigator is confident in making a unifying diagnosis, all related signs, symptoms, and abnormal test results should be grouped together as a single AE on the eCRF (e.g., cough and rhinitis should be reported as an "upper respiratory tract infection"). Adverse events will be evaluated for intensity and causal relationship with the use of the study medication by the Investigator. **Time period for collection of adverse events** Adverse Events will be collected from time of signature of informed consent, throughout the treatment period and including the follow-up period. All clinically significant abnormalities noted upon physical examination, ECG, and clinical laboratory and vital sign measurements that occur during the study and were not present prior to the signing of the ICF, should be reported as an AE, except for abnormalities present at Screening that may be considered part of the medical history. **Follow-up of unresolved adverse events** All clinically significant AEs that are unresolved at Study Termination are followed up by the Investigator and evaluated with additional tests if necessary, until the underlying cause is diagnosed or resolution occurs. AstraZeneca retains the right to request additional information for any patient with ongoing AEs/SAEs at the end of the study, if judged necessary. Follow-up information should be recorded on the source documents and reported to the Sponsor. Adverse events that occur following completion of study termination/early termination procedures should be recorded on the AE page of the eCRF only if the Investigator considers the event as clinically significant and as related to study medication or study procedures. All serious adverse events

		(SAEs) that occur within 90 days of administration of the last dose of study medication (regardless of causality) must be reported immediately (Section 6.4.4). Concomitant medications used following study termination procedures should be recorded only if relevant to treatment of patients for events described above. **Variables** The following variables will be collect for each AE; • AE (verbatim) • The date when the AE started and stopped • If AE is of maximum intensity • Whether the AE is serious or not • Investigator causality rating against the Investigational Product (yes or no) • Action taken with regard to investigational product • AE caused patient's withdrawal from study (yes or no) • Outcome In addition, the following variables will be collected for SAEs: • Date AE met criteria for serious AE • Date Investigator became aware of serious AE • AE is serious due to • Date of hospitalization • Date of discharge • Probable cause of death • Date of death • Autopsy performed • Causality assessment in relation to Study procedure(s) • Causality assessment in relation to Other medication • Description of AE
Section 6.4.3.1 INTENSITY	*None.*	It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.4.2. An AE of severe intensity need not necessarily be considered serious. For e.g., nausea that persists for several hours may be considered severe nausea, but not an SAE. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE
Section 6.4.3.2 CAUSALITY	*None.*	The Investigator will assess causal relationship between Investigational

		Product and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?' For SAEs, causal relationship will also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure, the causal relationship is implied as 'yes'.
Section 6.4.3.3 HYPOGLYCEMIA	Section 10.1.1.4	Section 6.4.3.3 *(Text is same, only the numbering of the section is different).*
Section 6.4.3.3	*None.*	**Adverse Events based on signs and symptoms** All AEs spontaneously reported by the patient or care provider or reported in response to the open question from the study personnel: Have you had any health problems since the previous visit/you were last asked?, or revealed by observation will be collected and recorded in the eCRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately. **Adverse Events based on examinations and tests** The results from protocol mandated laboratory tests and vital signs will be summarised in the clinical study report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product. If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated

		parameters should be reported as AEs. Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE. Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE. **NB.** Cases where a patient shows an aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 x ULN and total bilirubin ≥ 2 x ULN must be reported as SAEs, please refer to Appendix D 'Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions
Section 6.4.4 REPORTING OF SERIOUS ADVERSE EVENTS	If an SAE occurs, the investigator should first initiate appropriate procedures to treat the subject. Study-site personnel should make every effort (within 24 hours) to obtain the investigator's clinical opinion about the information available for the event. However, if the information cannot be obtained, the sponsor should still be contacted with all available information. Specifically, the investigator must assess the following: • That the term chosen to describe the event is as specific and accurate as possible and represents the investigator's unifying diagnosis (when applicable) for the event. • The relationship of the event to study medication (related or unrelated [Section 10.1.1.2]). • The relationship of the event to study conduct (related or unrelated). Examples of SAEs related to study conduct may include an event caused by a study procedure (e.g., blood draw, imaging) or an event that occurred as a result of discontinuing medications in a washout period. • The treatment phase during which the event occurred (e.g., placebo lead-in, washout, dose titration, randomized treatment period, open-label). • Whether the event is life threatening or is persistently or significantly disabling. • Whether hospitalization or prolongation of hospitalization was required due to the	All SAEs that occur after the signing of the ICF through 90 days after administration of the last dose of study medication must be reported immediately (within 24 hours of knowledge), whether or not considered causally related to the investigational product or to the study procedure(s). All SAEs will be recorded in the eCRF. Fax the SAE report form to the number listed on the form. If any SAE occurs in the course of the study, the study-site personnel should make every effort (within 24 hours) to obtain the Investigator's clinical opinion about the information available for the event. The Investigator should first initiate appropriate procedures to treat the patient. The Investigators or other site personnel should inform appropriate AstraZeneca representatives immediately, or no later than 24 hours of when he or she becomes aware of it. However, if the information cannot be obtained, the Sponsor should still be contacted with all available information. The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site within 1 calendar day of initial receipt for fatal and life threatening events and within 5 calendar days of initial receipt for all other SAEs. For fatal or life-threatening adverse events where important or relevant

	event. • Description of the event. • Intensity of the event (Section 10.1.1.1). • That the onset date and time of the first symptoms and/or signs, as well as the investigations performed, are consistent with and reflect the clinical start of the event and the unifying diagnosis for the event. • Treatment received. • The end date (if applicable) of the resolution of all symptoms, signs, abnormal test results; determination of a final diagnosis; or the date of return to a new stable baseline. • Outcome and planned follow-up. • Subject's status in clinical study participation (e.g., continuing study, early terminator.) The following information is also required: • Investigator's name and site number • Protocol number and title • Subject's initials and screening number • Subject's date of birth, gender, and race • Dates of administration of study medication(s) and dosage (if applicable) • Subject's medical history relevant to the SAE • Concomitant medications, including dosage, route of administration, duration of therapy, and indication In cases where the investigator learns of the event after its occurrence and resolution, the time and circumstances of the event should be recorded. The reporting requirements must still be followed.	information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or no later than 24 hours of when he or she becomes aware of it. Once the Investigators or other site personnel indicate an AE is serious in the EWBDC system, an automated email alert is sent to the designated AstraZeneca representative. If the EWBDC system is not available, then the Investigator or other study site personnel reports a SAE to the appropriate AstraZeneca representative by telephone. The AstraZeneca representative will advise the Investigator/study site personnel how to proceed. The reference document for definition of expectedness/listedness is the Investigator's Brochure (IB) for the AstraZeneca drug.
Section 6.4.5 LABORATORY SAFETY ASSESSMENTS	*None.*	Blood and urine samples for determination of clinical chemistry, hematology, and urinalysis will be taken at the times indicated in the Study Plan (Table 1). NB. In case a patient shows an AST or ALT ≥3 x ULN and total bilirubin ≥ 2 x ULN please refer to Appendix D Actions required in cases of combined increase of Aminotransferase and Total Bilirubin – Hy's Law', for further instructions
Section 6.4.5.1 CHEMISTRY	Section 10.2.1	Section 6.4.5.1 *(Text is same, only the numbering of the section is different).*
Section 6.4.5.2 HEMATOLOGY	Section 10.2.2	Section 6.4.5.2 *(Text is same, only the numbering of the section is different).*
Section 6.4.5.3 URINALYSIS	Section 10.2.3	Section 6.4.5.3 *(Text is same, only the numbering of the section is different).*
Section 6.4.5.4	Section 10.2.4	Section 6.4.5.4 *(Text is same, only the*

URINARY ALBUMIN-CREATININE RATIO		*numbering of the section is different).*
Section 6.4.5.5 OTHER CLINICAL LABORATORY EVALUATIONS	Section 10.2.5 **C-Peptide** Blood will be drawn for the measurement of **fasting** C-peptide at Visit 1 (Screening) according to the schedules presented in Study Plan (**Error! Reference source not found.**) and Section **Error! Reference source not found.**	Section 6.4.5.5 *(Text is same until 'C-Peptide' and then again through 'Bone Turnover Markers', only the numbering of the section is different).* **C-Peptide** Blood will be drawn for the measurement of C-peptide at Visit 1 (Screening) according to the schedules presented in Study Plan (**Error! Reference source not found.**) and Section **Error! Reference source not found.** **Bone age assessment by X-ray** Radiography of hand and wrist will be used to calculate bone age. **Antibodies to exenatide** Blood samples will be collected for the measurement of antibodies to exenatide according to the schedule presented in the Study Plan (Table 1, Section 6.2). Samples for determination of anti-exenatide antibodies will be analyzed by a selected laboratory on behalf of AstraZeneca, using an appropriate method. Only samples from patients who were on active study treatment will be analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a "for cause" basis, for e.g., if there is suspicion that a patient has been dosed incorrectly. The method details and results will be reported in a separate report appended to the CSR. Anti-exenatide antibody samples received by the analytical group will be disposed of after the anti-exenatide antibody report finalization or 6 months after issuance of the draft antibody report (whichever is earlier), unless requested for future analyses or in support of the development or conduct of the assay.
Section 6.4.6 PHYSICAL EXAMINATION	Section 10.3.2	Section 6.4.6 *(Text is same until '..... in the eCRFs', only the numbering of the section is different).* Height measurements will be standardized across all study sites by

		using stadiometer or other similar device. The height will be measured by patient standing with bare feet close together, with legs straight, and arms at side and shoulders relaxed
Section 6.4.7 ECG	Section 10.3.3	Section 6.4.7 *(Text is same, only the numbering of the section is different).*
Section 6.4.8 VITAL SIGNS	Section 10.3.1 The blood pressure measurement should be repeated after at least 30 seconds and the average of the two readings recorded.	Section 6.4.8 *(Text is same until '….. in a sitting position', only the numbering of the section is different).* **Pulse and blood pressure** The blood pressure measurement should be repeated after at least 30 seconds and the average of the two readings recorded. For timings of assessments refer to the Study Plan (Table 1) and Section 6.2. **Body temperature** Body temperature will be measured in degrees Celsius using an automated thermometer at the times indicated in the Study Plan (Table 1) and Section 6.2.
Section 6.4.9 TANNER PUBERTAL SCALE	The assessment of Tanner pubertal stages based on measurements of primary and secondary sex characteristics will be conducted according to the schedules presented in Appendix 1 and Section 6. Details of the pubertal assessment will be specified in the statistical analysis plan	The assessment of Tanner pubertal stages based on measurements of primary and secondary sex characteristics will be conducted **by a trained staff using accepted guidelines such as Washington Manual of Pediatrics,** according to the schedules presented in Study Plan (Table 1) and Section 6.2.
Section 6.5 PHARMACOKINETICS	Samples and measurements will be collected as discussed in this section and according to the schedules presented in Appendix 1 and Section 6. The centralized laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples. Plasma Exenatide Concentrations Blood samples for pharmacokinetic measurement of plasma exenatide concentrations will be collected prior to the administration of study medication as indicated by the schedules presented in Appendix 1 and Section 6. Plasma exenatide samples should be stored at -20°C to -70°C until packaged for shipping. Plasma concentrations of exenatide will be measured using an immunoassay from the blood samples collected from subjects randomized to receive EQW only. For subjects who withdrew from the study during the controlled assessment period, blood samples for the pharmacokinetic measurement of plasma exenatide	**Collection of samples** Blood samples for determination of exenatide concentrations in plasma will be taken at the times presented in the Study Plan (Table 1, Section 6.2). Samples will be collected, labelled, stored, and shipped as detailed in the laboratory manual. **Determination of drug concentration** Samples for determination of drug concentration in plasma will be analyzed by an appointed laboratory on behalf of AstraZeneca using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate bioanalytical report. Only samples from patients who were on active study treatment will be analyzed. Samples from patients not dosed with the relevant active study treatment will only be analyzed on a "for cause" basis, for e.g., if there is suspicion that a patient has been dosed incorrectly. **Storage and destruction of pharmacokinetic samples**

	concentrations will be collected at the early termination visit. Specific instructions will be provided for collection, processing, packaging, and shipping of all samples	The PK samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses. All samples still within the known stability of the analytes of interest at the time of receipt by the bioanalytical laboratory will be analyzed. The PK samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled PK samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately in the clinical study report (CSR). Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report. Any residual sample remaining after PK analysis has been performed may be used for exploratory biomarker research and characterization of metabolites, if consent for this exploratory research has been obtained
Section 6.6 PHARMACODYNAMICS	Sections 9.1-3	Sections 6.6.1. 6.6.2, 6.6.4 *(Text is same, only the numbering of the section is different).* **6.6.3 C-Peptide** **Blood will be drawn for the measurement of C-Peptide according to the schedules presented in Study Plan (Table 1) and Section 6.2** **Collection of pharmacodynamic markers** Samples and measurements will be collected as discussed in this section and according to the schedules presented in Study Plan (Table 1) and Section 6.2. The centralized laboratory will provide specific instructions for collection, processing, packaging, and shipping of all samples. Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual
Section 7.1 VOLUME OF	During this study, blood will be drawn for various analytes and panels, including	During this study, blood will be drawn for various analytes and panels, including

BLOOD	chemistry, hematology and other safety assessments, pharmacokinetic and pharmacodynamic assessments. The total amount of blood to be drawn during the entire study, including the Safety Follow-Up Period described in Appendix 2, is expected to be approximately 192 mL for each subject.	chemistry, hematology and other safety assessments, PK and PD assessments.
Section 8 ETHICAL AND REGULATORY REQUIREMENTS	*Sections 17 and 18 are replaced with new Sections 8.1-6.*	*New Sections 8.1-6 are added.*
Section 9 STUDY MANAGEMENT BY ASTRAZENECA	*Section 15 is replaced with new Sections 9.*	*New Section 9 is added,*
Section 10 DATA MANAGEMENT	General considerations The sponsor's data management department or designated contract research organization (CRO) will perform all data management activities. A data management plan outlining the data management systems, procedures, and agreements between the CRO and sponsor will be written. The plan will be reviewed and signed off by a representative of the sponsor's data management department. Clinical study data will be reported (captured) on by study site personnel on eCRFs. The eCRF data will be entered by study-site personnel and then reviewed and electronically signed by the investigator listed on Form FDA 1572. All study-site personnel must use an electronic signature access method to enter, review, or correct study data. Electronic signature procedures shall comply with the CFR Title 21 Part II and the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP) (Topic E6, April 2000) Section 5.5.3. Passwords and electronic signatures will be strictly confidential. All eCRF data will be downloaded from the electronic data capture (EDC) system and reformatted into SAS data sets. The sponsor's data management department will receive electronic transfers of laboratory data from a central laboratory as well as other data from third-party vendors as appropriate. The electronic data format of all transfers will be agreed upon with the sponsor. The clinical monitoring staff will verify data	Data management will be performed by the designated contract research organization (CRO). A data management plan outlining the data management systems, procedures, and agreements between the CRO and Sponsor will be written. The plan will be reviewed and signed off by a representative of the Sponsor's data management department. The data collected through third party sources will be obtained and reconciled against study data. Clinical study data will be reported (captured) on by study site personnel on eCRFs. The eCRF data will be entered by study-site personnel and then reviewed and electronically signed by the Investigator listed on Form FDA 1572. All study-site personnel must use an electronic signature access method to enter, review, or correct study data. Electronic signature procedures shall comply with the Code of Federal Regulations (CFR) Title 21 Part II and the ICH Guidelines for GCP (Topic E6, April 2000) Section 5.5.3. Passwords and electronic signatures will be strictly confidential. All eCRF data will be downloaded from the electronic data capture (EDC) system and reformatted into SAS data sets. The Sponsor's data management department will receive electronic transfers of laboratory data from a central laboratory as well as other data from third-party vendors as appropriate. The electronic data format of all transfers will be agreed upon with the Sponsor.

	recorded in the EDC system with source documents at the clinical study sites according to the clinical monitoring plan. The data will be subjected to consistency and validation checks within the EDC system with supplemental validation following download to a SAS data set. Adverse events will be coded using a current version of Medical Dictionary for Regulatory Activities (MedDRA), and concomitant medications using a current version of the WHO Drug Dictionary. The sponsor will perform a medical safety review of the coding. Completed eCRF images with a date- and time-stamped electronic audit trail indicating the user, the data entered, and any reason for change (if applicable) will be archived at the investigator's site and archived with backup at the sponsor's site.	Adverse events and medical/surgical history will be classified according to the terminology of the latest version the Medical Dictionary for Regulatory Activities (MedDRA). Medications will be classified according to the AstraZeneca Drug Dictionary. All coding will be performed by the CRO. Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. The data will be validated as defined in the Data Management Plan. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. When all data have been coded, validated, signed and locked, clean file will be declared. Any treatment revealing data may thereafter be added and the final database will be locked. Data associated with biological samples will be transferred to laboratories internal or external to AstraZeneca
Section 11 EVALUATION AND CALCULATION OF VARIABLES BY ASTRAZENECA OR ITS DELEGATE	*None.*	*New Section 11 is added.*
Section 12.1 DESCRIPTION OF ANALYSIS POPULATIONS	Efficacy analyses will be performed for the Intent-to-Treat (ITT) Population and the Evaluable Population, with the ITT Population as the primary population. Safety analyses will be performed for the ITT Population and the Evaluable Population unless stated otherwise. The following populations will be used for the summaries and analyses of the study data. These populations are defined as follows: • Intent-to-Treat (ITT): The ITT Population will consist of all randomized subjects who receive at least one dose of randomized study medication. • Evaluable: The Evaluable Population will consist of all ITT subjects who complete study procedures through Visit 5 (Week 14) in compliance with the	Efficacy analyses will be performed in the Intent-to-Treat (ITT) Population or in a set of evaluable patients coming from the ITT Population, i.e., the Evaluable Population and/or the **Per-Protocol (PP) population**. The Evaluable Population will be used for the primary analysis. Safety analyses will be performed for the ITT Population unless stated otherwise. The following populations will be used for the summaries and analyses of the study data. The populations are defined as follows: • Intent-to-Treat (ITT): The ITT Population will consist of all randomized patients who receive at least one dose of randomized study medication. • Evaluable Population: The Evaluable

	protocol and have adequate medication exposure and valid pharmacokinetic, pharmacodynamic measurements for data analysis. Adjustments may be made to refine the definition of the Evaluable Population prior to study unblinding and database lock. The final definition of the Evaluable Population will be documented in the statistical analysis plan	Population will consist of all ITT patients who receive at least 1 dose of study medication and have at least 1 post-baseline HbA1c assessment. • **Per-Protocol (PP): The per protocol analysis set will be a subset of the ITT population through the exclusion of those with important protocol violation(s). Important protocol violations are those that have the potential to affect the result of the primary analysis. Detailed exclusion criteria for the PP population will be specified in the SAP. Patients excluded from the PP analysis will be identified before database lock.**
Section 12.2.1 PRIMARY ENDPOINT	• Change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14)	• Change in HbA1c from baseline Visit 2 (Week 0) to **Visit 7 (Week 24)**
Section 12.2.2 SECONDARY ENDPOINT	• Change in HbA1c from baseline (Visit 2 [Week 0]) to Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in fasting plasma glucose concentration from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Proportions of subjects achieving HbA1c goals of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit • Change in body weight from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit • Change in fasting insulin from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66), and to each intermediate visit • Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments in EQW patients from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in lipids from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in blood pressure from baseline	• Change in HbA1c from baseline Visit 2 (Week 0) to Visit 10 (**Week 52**), and to each intermediate visit as applicable • Change in fasting plasma glucose concentration from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit as applicable • Proportions of patients achieving HbA1c goals of ≤6.5% and <7.0% at **Visit 7 (Week 24), Visit 10 (Week 52)**, and at each intermediate visit • Change in body weight from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit as applicable • Change in fasting insulin **and C-Peptide** from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit. as applicable • Change in beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) as measured by homeostasis model assessments in EQW patients **not taking insulin** from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52),** and to each intermediate visit as applicable • Change in lipids from baseline Visit 2 (Week 0) to **Visit 5 (Week 12), Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit as applicable • Change in blood pressure from baseline Visit 2 (Week 0) to **Visit 7 (Week 24),**

	(Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Plasma exenatide concentrations at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and each intermediate visit, as applicable	**Visit 10 (Week 52)**, and to each intermediate visit as applicable • Plasma exenatide concentrations at baseline Visit 2 (Week 0), **Visit 7 (Week 24), Visit 10 (Week 52)**, and each intermediate visit, as applicable • **Proportions of patients discontinuing the study, needing rescue due to failure to maintain glycemic control, and number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit**
Section 12.2.3 EXPLORATORY ENDPOINT	• Change in BMI from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit • Change in body weight percentile and height percentile from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit. The height and weight percentile will be determined based on the standardized growth chart for boys and girls (developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion.1	• Change in BMI from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit • Change in body weight percentile and height percentile from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit. The height and weight percentile will be determined based on the standardized growth chart for boys and girls (developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (**Center for Disease Control and Prevention, 2010**).
Section 12.2.4 SAFETY ENDPOINT	• Safety and tolerability endpoints including the incidence of treatment-emergent adverse events, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and to each intermediate visit as applicable • Change in calcitonin, pancreatic amylase, and lipase from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination) • Tanner pubertal stage at baseline (Visit 2 [Week 0]), Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination)	• Safety and tolerability endpoints including the incidence of treatment emergent adverse events, antibodies to exenatide, physical examinations, laboratory measurements (clinical, chemistry/hematology), and vital sign measurements from baseline Visit 2 (Week 0) to **Visit 7 (Week 24), Visit 10 (Week 52)**, and to each intermediate visit as applicable • Change in calcitonin, pancreatic amylase, and lipase from baseline Visit 2 (Week 0) to Visit 5 (**Week 12) and Visit 10 (Week 52)** • Change in TSH, free T4, prolactin, cortisol, IGF-1, and DHEAS from baseline Visit 2 (Week 0) to Visit 5 **(Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)** • Tanner pubertal stage at baseline Visit 2 (Week 0), Visit 5 (**Week 12), Visit 7 (Week 24), Visit 9 (Week 40), and Visit 10 (Week 52)**

	• Proportions of subjects discontinuing the study, needing rescue due to failure to maintain glycemic control, and number of rescue epidoses at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit	
Section 12.2.5 SAFETY EXPLORATORY ENDPOINT	• Change in CEA from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in bone specific alkaline phosphatase and deoxypyridinoline from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14) and Visit 10 (Week 66/Study Termination) • Change in FSH, LH, FSH/LH, total testosterone, and estradiol from baseline (Visit 2 [Week 0]) to Visit 5 (Week 14), Visit 8 (Week 42), and Visit 10 (Week 66/Study Termination)	• Change in CEA from baseline Visit 2 (Week 0) to Visit 5 **(Week 12) and Visit 10 (Week 52)** • Change in bone specific alkaline phosphatase and deoxypyridinoline from baseline Visit 2 (Week 0) to Visit 5 **(Week 12), Visit 7 (Week 24) and Visit 10 (Week 52)** • Change in FSH, LH, FSH/LH, total testosterone*****, **SHBG***, and estradiol from baseline Visit 2 (Week 0) to Visit 5 **(Week 12), Visit 7 (Week 24), and Visit 10 (Week 52)** • ***Change in total testosterone and SHBG also at Visit 9 (Week 40). Free testosterone will be calculated from total testosterone and SHBG values at Visit 5 (Week 12), Visit 7 (Week 24), Visit 9 (Week 40)**, and Visit 10 (Week 52).
Section 12.3 Demographic and baseline characteristics	Section 14.3	Section 12.3 *(Text is same, only the numbering of the section is different).*
Section 12.4 TREATMENT COMPLIANCE	Section 14.4	Section 12.4 *(Text is same, only the numbering of the section is different).*
Section 12.5 PRIOR AND CONCOMITANT MEDICATIONS	Section 14.5	Section 12.5 *(Text is same, only the numbering of the section is different).*
Section 12.6.1 GENERAL CONSIDERATIONS	Efficacy analyses will be performed for the ITT and Evaluable Populations. Safety analyses will be performed for the ITT and Evaluable Populations unless stated otherwise. The efficacy analysis using the ITT Population will be considered the primary analysis, with the analysis using the Evaluable Population considered the supportive analysis. For subjects who discontinue from the study prior to completing all study procedures through Visit 5 (Week 14), the analyses of the change in HbA1c, change in body weight, change in body weight percentile, height percentile, change in BMI, change in fasting plasma glucose concentration,	Efficacy analyses will be performed for the ITT and/or Evaluable Populations and/or **the PP population**. Safety analyses will be performed for the ITT Populations unless stated otherwise. The analysis of the primary endpoint will be performed using the Evaluable Population. The analyses of all other efficacy endpoints will be performed in ITT population. For patients who discontinue from the study prior to completing all study procedures through Visit 7 (Week 24), the analyses of the change in HbA1c, change in body weight, change in body weight percentile, height percentile, change in BMI, change in fasting plasma glucose

	fasting insulin and lipids, change in blood pressure, change in beta-cell function and insulin sensitivity will be based on the observed data and the mixed model repeated measures (MMRM) method will be implemented (see Section 14.6.2). For summary statistics and Cochran-Mantel-Haenszel (CMH) analyses related to proportions, such as proportions of subjects achieving HbA1c goals of ≤6.5% and <7%, for those subjects who discontinue from the study prior to completing all study procedures through Visit 5 (Week 14), but have data collected for at least one visit subsequent to Visit 2 (Week 0), missing values for efficacy, pharmacodynamic, and anthropometric measures up to Visit 5 (Week 14) will be imputed using the values at the last visit (including Early Termination visit) in accordance to the last observation carried forward approach. Values at Visit 2 (Week 0) will not be carried forward. For subjects who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the efficacy analysis to draw statistical inference. Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the Statistical Analysis Plan. All tests of treatment effects will be conducted at a 2-sided significance level of 0.05. More information on the interim analysis and the statistical significance has been described in Section 14.7.	concentration, fasting insulin and lipids, change in blood pressure, change in beta-cell function and insulin sensitivity will be based on the observed data and the MMRM method will be implemented (see Section 14.6.2). For summary statistics and CMH analyses related to proportions, such as proportions of patients achieving HbA1c goals of ≤6.5% and <7.0%, for those patients who discontinue from the study prior to completing all study procedures through Visit 7 (Week 24), but have data collected for at least one visit subsequent to Visit 2 (Week 0), missing values for efficacy, PD, and anthropometric measures up to Visit 7 (Week 24) will be imputed using the values at the last visit (including Early Termination visit) in accordance to the last observation carried forward approach. Values at Visit 2 (Week 0) will not be carried forward. For patients who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the efficacy analysis to draw statistical inference. Missing data patterns will be assessed and more details on sensitivity analysis will be provided in the SAP. All tests of treatment effects will be conducted at a 2-sided significance level of 0.05. More information on the interim analysis and the statistical significance has been described in Section 12.6.8.
Section 12.6.2 ANALYSIS OF THE PRIMARY ENDPOINT	The MMRM approach will be used to analyze the change in HbA1c from baseline (Visit 2[Week 0]) to Visit 5 (Week 14). The model will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline HbA1c as the covariate, and subjects as the random effects. The variance - covariance structures to be tested in this model include the unstructured (UN), autoregressive order 1 (AR [1]), heterogeneous autoregressive order 1 (ARH [1]), and compound symmetry (CS) structures. The best variance - covariance structure will be selected based on the Akaike's Information Criterion. The maximum likelihood (ML) method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence	The MMRM approach will be used to analyze the change in HbA1c from baseline (Visit 2 [Week 0]) to **Visit 7 (Week 24)**. The model will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline HbA1c as the covariate, and patients as the random 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

	interval, and p-value of the difference in the change of HbA1c between the EQW and PBO groups at Visit 5 (Week 14) will be provided. All observed HbA1c data from post-baseline visits (including Early Termination) will be included in the MMRM analysis. In addition, if a subject's last available measurement during the 14-week assessment period is from an unscheduled visit or Early Termination visit, the value will be programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. For subjects who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM analysis. The analysis using the ITT Population will be considered the primary analysis, with the analysis from the Evaluable Population considered as supportive analysis. Summaries and analyses may also be conducted for subgroups defined by baseline HbA1c strata (<9.0% or ≥9.0%) and country.	criterion. The maximum likelihood (ML) method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the change of HbA1c between the EQW and PBO groups at Visit 7 (Week 24) will be provided. All observed HbA1c data from post-baseline visits (including Early Termination) will be included in the MMRM analysis. In addition, if a patient's last available measurement during the 24-week assessment period is from an unscheduled visit or Early Termination visit, the value will be programmatically mapped to the next closest scheduled visit and included in the MMRM analysis. For patients who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM analysis. The MMRM analysis of the primary endpoint in evaluable population will be considered the primary analysis. The consistency of the primary analysis will be checked by the same MMRM of the primary endpoint as described above performed in the PP population. Summaries and descriptive analysis of the primary endpoint will be performed in the ITT population. Summaries and analyses may also be conducted for subgroups defined by baseline HbA1c 12 strata (<9.0% or ≥9.0%) and country in the ITT population.
Section 12.6.3 ANALYSIS OF THE SECONDARY ENDPOINT	Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment. Proportions of subjects having HbA1c target values of ≤6.5% and <7% at Visit 5 (Week 14), Visit 10 (Week 66/Study Termination), and at each intermediate visit will be compared between treatments using the CMH procedure, in which baseline HbA1c strata will serve as the stratification factors. Any ITT subject who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint. As a supportive analysis, the probabilities of patients reaching HbA1c targets of ≤6.5%	**Analysis of all secondary endpoints will be performed in the ITT population**. Summary statistics and frequency tables will be provided for all secondary endpoints by visit and treatment. Proportions of patients having HbA1c target values of ≤6.5% and <7.0% at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit will be compared between treatments using the CMH procedure, in which baseline HbA1c strata will serve as the stratification factors. Any ITT patient who only has baseline HbA1c value but no post-baseline HbA1c value will be considered as not achieving HbA1c goal at endpoint. As a supportive analysis, the probabilities

	and <7% will also be analyzed using a generalized linear mixed model (GLMM). The independent variables will include treatment group, visit, treatment-by-visit interaction, HbA1c baseline strata (<9.0% or ≥9.0%), and country as factors, and baseline HbA1c as a continuous covariate. The UN, AR (1), ARH (1), and CS variance-covariance structures will be explored. The CMH will be the main analysis of patients achieving target, with the GLMM model being a supportive analysis. The effects of the study medications on the homeostatic model assessment (HOMA) will be examined. The pancreatic beta-cell function (% HOMA-B) and peripheral and hepatic insulin sensitivity (% HOMA-S) will be computed from a computerized HOMA model, which can predict the plasma glucose, insulin, c-peptide, and proinsulin concentrations for any possible combination of these two parameters in the fasting state. The MMRM approach will be used to analyze the change in HbA1c, body weight, blood pressure, fasting plasma glucose, fasting insulin, lipids, HOMA-B, and HOMA-S from baseline (Visit 2 [Week 0]) to Visit 10 (Week 66/Study Termination), and each intermediate visit. The MMRM method for change in HbA1c will be the same as stated in Section 14.6.2. The models for changes in body weight, blood pressure, fasting plasma glucose, fasting insulin, lipids, HOMA-B, and HOMA-S will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline of the dependent variable as the covariate, and subjects as the random effects. The ML method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be provided. Similar to the primary endpoint analysis, all observed data will be included in the MMRM and the GLMM analysis. Data collected from an Early Termination visit will be mapped to the next closest scheduled visit. For subjects who initiate rescue therapy and continue study participation,	of patients reaching HbA1c targets of ≤6.5% and <7.0% will also be analyzed using a logistic regression model. The independent variables will include treatment group, visit, treatment-by-visit interaction, HbA1c baseline strata (<9.0% or ≥9.0%), and country as factors, and baseline HbA1c as a continuous covariate. The variance - covariance structure to be used for this modelling will be UN; if the model does not converge with unstructured variance – covariance matrix, then AR (1) and ARH (1) structures will be tried and the covariance structure will be decided based on model convergence status and the Akaike information criterion. **The same CMH procedure and logistic regression as described above will be used to analyze data on proportion of patients discontinuing the study, needing rescue due to failure to maintain glycemic control. However, the number of rescue episodes at Visit 7 (Week 24), Visit 10 (Week 52), and at each intermediate visit will be analyzed in an exploratory fashion, using descriptive statistics only.** The effects of the study medications on the homeostatic model assessment (HOMA) will be examined. The pancreatic beta-cell function (% HOMA-B) and peripheral and hepatic insulin sensitivity (% HOMA-S) will be computed from a computerized HOMA model, which can predict the plasma glucose, insulin, c-peptide, and proinsulin concentrations for any possible combination of these two parameters in the fasting state **in patients not taking insulin.** The MMRM approach will be used to analyze the change in HbA1c, body weight, blood pressure, fasting plasma glucose, fasting insulin, lipids, HOMA-B, and HOMA-S from baseline Visit 2 (Week 0) to Visit 10 (Week 52), and each intermediate visit. The MMRM method for change in HbA1c will be the same as stated in Section 0. The models for changes in body weight, blood pressure, fasting plasma glucose, fasting insulin,

	only data through the initiation of rescue therapy will be included in the MMRM and GLMM analysis.	lipids, HOMA-B, and HOMA S will include treatment group, visit, interaction between visit and treatment, HbA1c baseline strata (<9.0% or ≥9.0%), and country as the fixed effects, baseline of the dependent variable as the covariate, and patients as the random effects. The ML method will be used for parameter estimation. The least squares mean, 2-sided 95% confidence interval, and p-value of the difference in the endpoints of interests between the EQW and PBO groups will be provided. Similar to the primary endpoint analysis, all observed data will be included in the MMRM and logistic regression analysis. Data collected from an Early Termination visit will be mapped to the next closest scheduled visit. For patients who initiate rescue therapy and continue study participation, only data through the initiation of rescue therapy will be included in the MMRM and logistic regression analysis.
Section 12.6.4 ANALYSIS OF THE EXPLORATORY ENDPOINT	Baseline values, the values at each visit, and changes from baseline values will be summarized for percentiles of body weight, percentile of height, and BMI by treatment. A similar MMRM modeling approach (See Section 14.6.2) will be implemented to compare changes in body weight percentile, height percentile, and BMI between treatment groups.	**Analysis of all exploratory endpoints will be performed in the ITT population**. Baseline values, the values at each visit, and changes from baseline values will be summarized for percentiles of body weight, percentile of height, and BMI by treatment. A similar MMRM modeling approach (See Section 12.6.3) will be implemented to compare changes in body weight percentile, height percentile, and BMI between treatment groups.
Section 12.6.5 PHARMACOKINETIC ANALYSES	Descriptive statistics for plasma exenatide concentrations will be presented by treatment and visit. If deemed necessary, appropriate pharmacokinetic parameters will be calculated for each subject and summarized by treatment	**Analysis of all PK endpoints will be performed in the ITT population.** Descriptive statistics for plasma exenatide concentrations will be presented by treatment and visit. If deemed necessary, appropriate PK parameters will be calculated for each patient and summarized by treatment.
Section 12.6.6 PHARMACODYNAMIC ANALYSES	Descriptive statistics for pharmacodynamic endpoints including absolute values and change in fasting plasma glucose concentration, and fasting serum insulin concentration will be presented by treatment and visit. Also refer to Section 14.6.3 for inferential statistical analysis.	**Analysis of all PD endpoints will be performed in the ITT population.** Descriptive statistics for PD endpoints including absolute values and change in fasting plasma glucose concentration, and fasting serum insulin concentration will be presented by treatment and visit. Also refer to Section 12.6.3 for inferential statistical analysis.
Section 12.6.7	The analysis of safety data will be	Analysis of safety data will be performed

SAFETY ANALYSES	performed for the ITT and Evaluable Populations. Safety will be assessed by examination of AEs, clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide.	in the ITT population. Safety will be assessed by examination of AEs, clinical laboratory measurements, physical examination findings, vital signs, and antibodies to exenatide.
Section 12.6.7.1 ADVERSE EVENTS	Treatment-emergent AEs	On treatment AEs
Section 12.6.8 INTERIM ANALYSIS	One interim analysis is planned when 60 subjects have completed 14 weeks of treatment, including early withdrawal. This interim analysis will be performed by the independent Data Safety Monitoring Board that does not directly involve with the study design, conduct and data analysis. No study personnel will have access to the unblinded clinical data to maintain the integrity of the double-blind study design. Upon the data unblinding, if the observed mean difference of change in HbA1c from baseline at Week 14 or early withdrawal between exenatide once weekly and placebo (exenatide-placebo) is greater than 0.45%, the study will be stopped for futility. Stopping on the basis of futility does not impact the overall Type I error since the conclusions from the interim analysis will not be used to declare treatment superiority. Therefore, there is no adjustment of the Type I error for the interim analysis, i.e., the final analyses will be conducted at the 0.05 significance level.	One interim analysis is planned when **40 patients** will have completed **24 weeks** of treatment, including early withdrawal. This interim analysis will be performed by the independent **Data Monitoring Committee** (DMC) that does not directly involve with the study design, conduct and data analysis. No study personnel will have access to the unblinded clinical data to maintain the integrity of the double-blind study design. Purpose of the interim analysis is to ensure safety of the patient population. Hence, the DMC will only look at the safety data collected in this study. The DMC will review the safety data first in a blinded fashion and then, if needed, will look at the unblinded data to assess the risk of the paediatric patients' being exposed to the active drug compared to placebo, using the AE and/or safety laboratory data of the study population.
Section 12.6.9 STRATIFICATION DURING RANDOMIZATIO N	*None.*	Randomization will be stratified by screening HbA1c (%) < 9.0% and > 9.0%. The restriction on gender in the study population (female patients between 40% and 60%) and also on the ethnicity and lifestyle (40%-60% patients with European ethnicity and lifestyle) will be enforced through putting caps on enrollment of patients with different genders and from the different regions (Europe and US and others).
Section 12.7 DETERMINATION OF SAMPLE SIZE	Approximately 100 subjects who have met all study requirements will be randomized in a ratio of 2:1 to the exenatide or placebo treatment group on Visit 2 (Week 0) and will be carried out with stratification to achieve a balanced distribution of subjects across treatment groups according to country and screening HbA1c strata (<9.0% or ≥9.0%). Assuming a 20% drop-out rate,	Approximately **77 patients** who have met all study requirements will be randomized in a ratio of **5:2** to the exenatide or placebo treatment group on Visit 2 (Week 0) and will be carried out with stratification to achieve a balanced distribution of patients across treatment groups with regard to the screening HbA1c strata (<9.0% or ≥9.0%). The analysis will be performed in the set

	approximately 80 subjects will complete the 14-week controlled treatment period of the study. Based on 100,000 rounds of simulation, an overall power of 96% will be provided to reject the null hypothesis of no difference between the two treatment arms assuming the true mean changes in HbA1c of -0.9% for subjects receiving exenatide and 0 for the placebo arm. This power computation assumes a common standard deviation of 1.0% and a two-sided significance level of 0.05. A total power of over 94% will be achieved for a 28% drop-out rate based on simulation if the same true mean changes in HbA1c are assumed	of evaluable patients coming from the ITT population. Assuming a **10% drop-out** rate, approximately 70 patients will complete the 24-week controlled treatment period of study. Based on calculation done using the software NQuery Advisor Version 7, an overall power of 74% will be provided to reject the null hypothesis of no difference between the 2 treatment arms assuming a true treatment difference of -0.7% between exenatide and placebo in changes from baseline for HbA1c (%). This power computation also assumes a common standard deviation of 1.0% and a two-sided significance level of 0.05
Section 12.8 DATA MONITORING COMMITTEE	*None.*	The purpose of the DMC is to advise the Sponsor regarding the continuing safety of study participants and the continuing validity and scientific merit of the trial. Further details can be found in the Data Monitoring Committee Charter.
Section 13 IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR	*Section 15 is replaced with new Sections 13.*	*New Section 13 is added.*
DISCLOSURE OF DATA AND PUBLICATIONS	*Section 16 Disclosure of data and publications is deleted.*	*None.*