1. Protocol H8O-MC-GWBQ(e)
Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

Confidential Information

Exenatide (LY2148568)

This Phase 3, multicenter, double-blind, placebo-controlled, randomized, three-arm trial is designed to compare the effects of exenatide (5 µg and 10 µg, both administered twice daily [BID]) versus placebo (BID) with respect to glycemic control as measured by hemoglobin A1c in approximately 195 adolescent patients with type 2 diabetes. Patients will have inadequate glycemic control and will be either antidiabetic drug-naïve, defined as treatment with diet and exercise alone, or receiving treatment with oral antidiabetic agent(s) (with or without diet and exercise). Patients are to be treated with study drug for 28 weeks.

Amylin Pharmaceuticals, LLC
San Diego, California USA 92121
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3. Abbreviations and Definitions

ADA	American Diabetes Association
ANCOVA	Analysis of covariance
Audit	A systematic and independent examination of the trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, applicable standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).
BMI	Body mass index
Blinding/Masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the patient(s) being unaware, and double-blinding usually refers to the patient(s), investigator(s), monitor(s), and in some cases, select Sponsor personnel being unaware of the treatment assignment(s).
CDE	Certified Diabetes Educator
CEA	Carcinoembryonic antigen
CMH	Cochran-Mantel-Haenszel
CRF/eCRF	Case Report Form (sometimes referred to as Clinical Report Form). A printed or electronic form for recording study participants' data during a clinical study, as required by the protocol.
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
Compliance	Adherence to all the trial-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
Confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Amylin is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be retested at some defined time point, depending on the steps required to obtain confirmed results.
DMC	Data Monitoring Committee
Drug Naïve	No previous exposure to oral antidiabetic drugs and treatment with diet and exercise alone.
ECG	Electrocardiogram
End of Study (Trial)	End of study (trial) is the date of the last visit or last scheduled procedure shown in the Study Schedule for the last active patient in the study.
EU	European Union
FSG	Fasting serum glucose

GCP	Good clinical practices
GLMM	Generalized linear mixed model
GLP-1	Glucagon-like peptide 1
HbA1c	Glycated hemoglobin
HOMA-B	Homeostasis model assessment of beta cell function
HOMA-S	Homeostasis model assessment of insulin sensitivity
IB	Investigator's Brochure
ICD	Informed Consent Document
IRB/ERB	Institutional review board/ethical review board: a board or committee (institutional, regional, or national) composed of medical professional and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the subjects participating in a clinical trial are protected.
IV	Intravenous
IVRS	Interactive voice response system
IND	Investigational New Drug application
Intention to Treat (ITT)	The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a subject (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that subjects allocated to a treatment arm should be followed up, assessed and analyzed as members of that arm irrespective of their compliance to the planned course of treatment. (continued)
Interim Analysis	Any analysis intended to compare treatment arms at any time prior to the formal completion of a trial.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
LMP	Lifestyle modification program
LOCF	Last observation carried forward
LS	Least squares
Legal Representative	An individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective subject, to the patient's participation in the clinical trial.
MAR	Missing at random
MedDRA	Medical dictionary for regulatory activities
MMRM	Mixed-model repeated measures
Patient	A subject with a defined disease

Per-protocol	The set of data generated by the subset of patients who sufficiently complied with the protocol to ensure that these data would be likely to exhibit the effects of treatment, according to the underlying scientific model.
OGTT	Oral glucose tolerance test
QD	Once daily
QT	Interval on electrocardiogram between the beginning of the Q wave and end of the T wave
QTc	QT corrected for heart rate
RD	Registered dietitian
RQA	Research Quality Assurance
SAP	Statistical Analysis Plan
SC	Subcutaneous
SMBG	Self-monitored blood glucose
Sponsor	Throughout this protocol, unless otherwise specified, the term "Amylin" is used to refer to Amylin Pharmaceuticals, LLC. Amylin is a wholly owned subsidiary of AstraZeneca PLC ("AZ"). AZ will take responsibility for the conduct of Clinical Study GWBQ.
Study Entry Terms	**Screen** The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical trial. In this study, screening involves invasive or diagnostic procedures and/or tests (for example, blood draws). For this type of screening, informed consent for these screening procedures and/or tests shall be obtained; this consent may be separate from obtaining consent for the study. **Enter/Consent** The act of obtaining informed consent for participation in a clinical trial from patients deemed eligible or potentially eligible to participate in the clinical trial. Patients entered into a trial are those who sign the informed consent document directly or through their legally acceptable representatives. **Enroll/Randomize** The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
SU	Sulfonylurea
TZD	Thiazolidinedione
US	United States

Protocol H8O-MC-GWBQ(d)
Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

4. Introduction

4.1. Exenatide

Exenatide (BYETTA®) is the first in a class of medicines called incretin mimetics. Exenatide enhances glucose-dependent insulin secretion by the pancreatic beta cell, suppresses inappropriately elevated glucagon secretion, and slows gastric emptying. Exenatide has been approved for use in the United States (US) as an adjunctive therapy to diet and exercise for adults with type 2 diabetes with inadequate glycemic control and in the European Union (EU) for adults with type 2 diabetes with inadequate glycemic control despite treatment with metformin, a sulfonylurea (SU), or combination of metformin, thiazolidinedione (TZD), and an SU. BYETTA is administered twice daily, subcutaneously (SC), at least 6 hours apart, before the 2 main meals of the day.

Incretins, such as glucagon-like peptide 1 (GLP-1), enhance glucose-dependent insulin secretion and exhibit other antihyperglycemic actions following their release into the circulation from the gut (Drucker 2001). When administered in vivo, exenatide, a 39 amino acid peptide, mimics certain antihyperglycemic actions of GLP-1. Exenatide has been shown to bind to and activate the known human GLP-1 receptor in vitro, which leads to an increase in both glucose-dependent synthesis of insulin, and in vivo secretion of insulin from pancreatic beta cells, by mechanisms involving cyclic adenosine monophosphate and/or other intracellular signaling pathways. Exenatide promotes insulin release from beta cells in the presence of elevated glucose concentrations.

Exenatide improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through the following multiple mechanisms of action:

- Insulin secretion: Exenatide has acute effects on pancreatic beta cell responsiveness to glucose and leads to insulin release only in the presence of elevated glucose concentrations (Parkes et al. 2001; Kolterman et al. 2003). This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. In healthy individuals, robust insulin secretion occurs during the first 10 minutes following intravenous (IV) glucose administration. This secretion, known as the "first-phase insulin response," is characteristically absent in most patients with type 2 diabetes. The loss of the first-phase insulin response is an early beta cell defect in type 2 diabetes. Administration of exenatide at therapeutic plasma concentrations restored first-phase insulin response to an IV

bolus of glucose in patients with type 2 diabetes. Both first-phase insulin secretion and second-phase insulin secretion were significantly increased in patients with type 2 diabetes treated with exenatide compared with saline ($p<.001$ for both).

- Glucagon secretion: In patients with type 2 diabetes, exenatide suppresses glucagon secretion and lowers serum glucagon concentrations during periods of hyperglycemia (Gedulin et al. 1999). Lower glucagon concentrations lead to decreased hepatic glucose output and decreased insulin demand. However, exenatide does not impair the normal glucagon response to hypoglycemia (Degn et al. 2004).
- Gastric emptying: Exenatide slows gastric emptying, thereby reducing the rate at which meal-derived glucose appears in the circulation (Jodka et al. 1998; Kolterman et al. 2003).
- Food intake: In both animals and humans, administration of exenatide has been shown to reduce food intake (Edwards et al. 2001).

The effect of exenatide is immediate with respect to its effect on hyperglycemia in the fasting state. In addition, a single dose of exenatide in patients with type 2 diabetes significantly reduces the abnormal rise in postprandial glucose concentrations.

The main risks associated with exenatide treatment include mild or moderate nausea (for approximately half of treated patients) that is more frequent at the initiation of therapy and an increased risk of mild or moderate hypoglycemia if the patient is also using an SU. Approximately 43% of adult patients taking exenatide exhibit a temporal rise in antibodies to exenatide, which are mostly of low titer (<1/125). In about 3% of all patients in the three 30-week registration trials, the formation of antibodies to exenatide at high titers was associated with failure to achieve adequate improvement in glycemic control. Postmarketing reports have linked exenatide use to acute pancreatitis and to altered renal function. As it is eliminated by the kidneys, exenatide should not be used by patients with severe renal impairment or end-stage renal disease.

Type 2 diabetes accounts for approximately 45% of all new cases of diabetes in adolescents (Dietz and Robinson 2005). Evidence has shown that a diagnosis of type 2 diabetes in childhood, coupled with inadequate glycemic control, increases the risk of early mortality as well as early end organ damage (Cavallo 2006). The current study will investigate the safety and efficacy of exenatide in the treatment of type 2 diabetes in adolescents, and will provide important information on the potential clinical use of exenatide in that population.

More detailed information about the known benefits and risks of exenatide may be found in the Investigator's Brochure (IB).

4.2. Study Rationale

Insulin and metformin are currently the only approved drugs for the treatment of type 2 diabetes in adolescents. It is important to identify additional safe and effective diabetes therapies for this age group. The current study will include patients who are naïve to antidiabetes drug therapy, defined as treatment with diet and exercise alone, and patients previously treated with metformin, an SU, or both (with or without diet and exercise). Although SU use is not an approved therapy for adolescents, published reports have described its clinical use in this age group (Bloomgarden 2004; Von and Hewett 2007). Since a monotherapy indication for exenatide exists in the US for treatment of adults with type 2 diabetes, such use might also be of benefit in adolescents with type 2 diabetes.

A recent study (Study 2993-124) in 13 adolescent patients with type 2 diabetes investigated the pharmacokinetics, pharmacodynamics, safety, and tolerability of exenatide in patients between the ages of 10 and 16 with type 2 diabetes and an average body mass index (BMI) of 32.5 (range: 23.2 to 40.8). Consistent with clinical trials in adults, exenatide 5 µg nearly eliminated postprandial glucose excursions in adolescents. Exenatide was well-tolerated, with 1 patient who experienced moderate gastrointestinal events. No hypoglycemic events were reported. Thus, it appears that the pharmacokinetics, pharmacodynamics, and tolerability of exenatide 5 µg in adolescents are comparable to those observed in adults. Therefore, the 5- and 10-µg doses of exenatide will be included in this study, both compared with placebo.

5. Objectives

5.1. Primary Objective

The primary objective of this study is to test the hypothesis that glycemic control, as measured by change in hemoglobin A1c (HbA1c) from baseline to endpoint, with exenatide is superior (in at least 1 of the exenatide treatment arms), to that of placebo after 28 weeks of treatment in adolescent patients with type 2 diabetes who are naïve to antidiabetes agents, or patients who are being treated with metformin, an SU, or a combination of metformin and an SU.

5.2. Secondary Objectives

The secondary objectives of the study are to compare exenatide 5 µg twice daily and exenatide 10 µg twice daily versus each other and versus placebo with regards to:

- the proportion of patients achieving an HbA1c at endpoint of <7%, ≤6.5%, and <6.5%
- body weight
- fasting serum glucose (FSG)
- self-monitored blood glucose (SMBG) measurements before and 2 hours after the two main meals of the day
- fasting serum insulin concentrations
- the incidence and rate of hypoglycemia
- beta-cell function and insulin sensitivity as measured by homeostasis model assessments (HOMA-B, HOMA-S) (Matthews et al. 1985)
- the proportion of patients discontinuing the study due to failure to maintain glycemic control
- safety and tolerability including reporting of adverse events, antibodies to exenatide, calcitonin, carcinoembryonic antigen (CEA), vital signs, electrocardiograms (ECGs), laboratory measurements, urinalysis, and pubertal assessment

6. Investigational Plan

6.1. Summary of Study Design

Study H8O-MC-GWBQ is a multicenter, double-blind, placebo-controlled, randomized, parallel, 3-arm trial. Approximately 195 adolescents, ages 10 to 17 years inclusive, with type 2 diabetes will be enrolled. However, the number of patients ≥17 years of age will be limited to no more than 10% of patients in each treatment arm. The patients will be naïve to antidiabetes agents, or they will be receiving oral treatment with metformin, an SU, or a combination of metformin and an SU at the time of enrollment. Randomization will be stratified by the patient's background diabetes therapy and screening HbA1c. The study will commence with a 1-week, single-blind, injectable placebo lead-in period before patients are randomly assigned to add injectable exenatide or injectable placebo to their existing diabetes treatment. Patients will be randomly assigned to 1 of 3 treatment arms: exenatide 5 µg twice daily, exenatide 10 µg twice daily, or placebo twice daily (volume of injection equivalent to exenatide 5 µg or exenatide 10 µg). During the first 4 weeks after randomization, all patients assigned to treatment will receive exenatide 5 µg twice daily or equivalent placebo volume twice daily. A starting dose of exenatide 5 µg twice daily and titration to exenatide 10 µg twice daily has been shown to mitigate the incidence of nausea. At the end of 4 weeks post-randomization, patients assigned to the exenatide 10 µg twice daily treatment arm, or equivalent placebo volume, are then to increase their dose from 5 µg twice daily to 10 µg twice daily, or equivalent placebo volume. Study drug will be administered within 60 minutes before morning and evening meals (or the 2 main meals of the day, approximately 6 hours or more apart) for 28 weeks.

All patients will be expected to participate in a simplified lifestyle modification program (LMP) throughout this study (Attachment 4). The simplified lifestyle modification program will include both dietary education and physical activity components. At the clinic visits, the patients will meet with a study registered dietitian (RD) or certified diabetes educator (CDE) who will review the patient's dietary history and physical activity record. The LMP will be reinforced at each visit.

Patients who are discontinued due to loss of glycemic control will be offered alternative antidiabetes therapy at the discretion of the investigator.

Figure GWBQ.1 illustrates the study design.

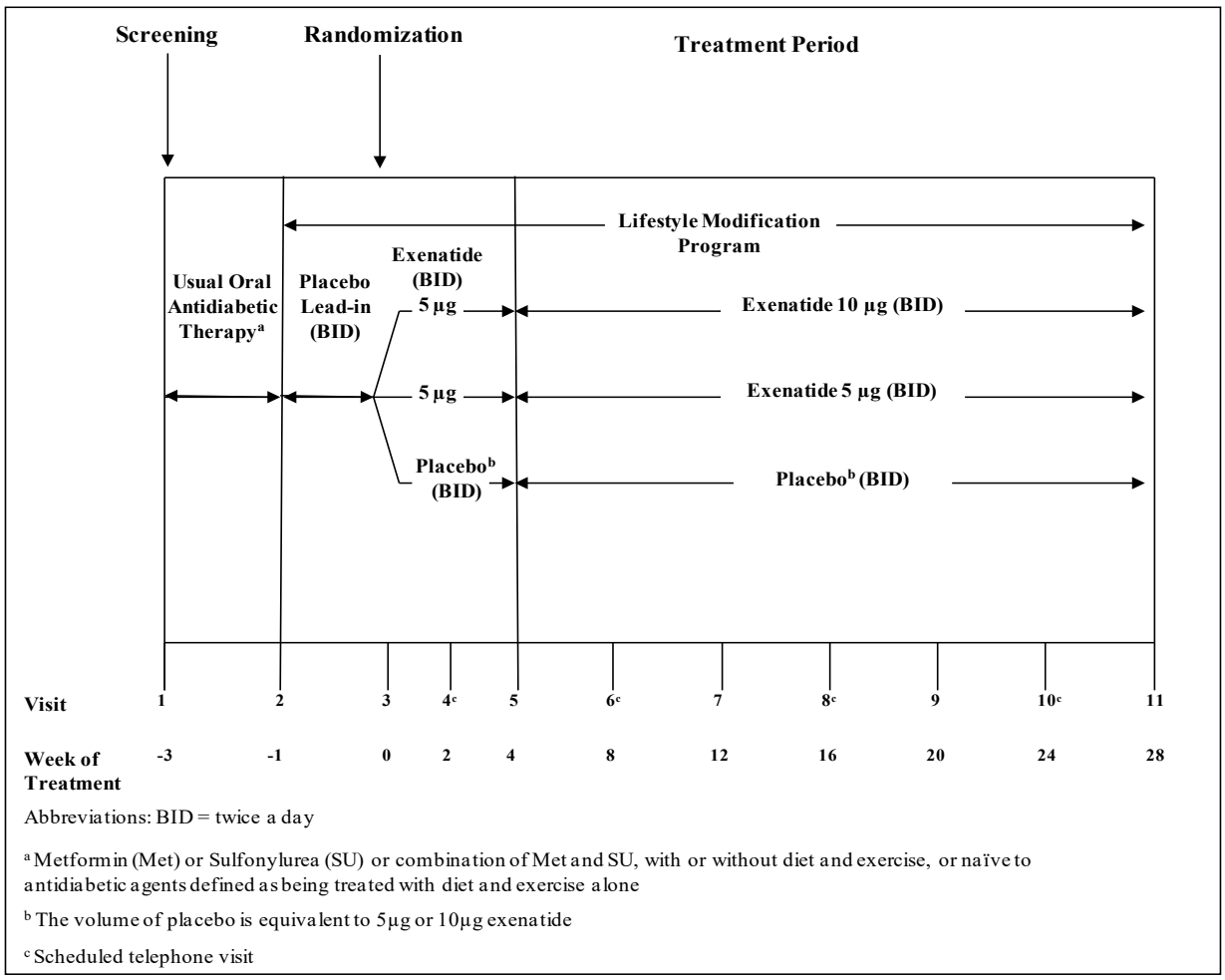

Figure GWBQ.1. Illustration of study design for Protocol H8O-MC-GWBQ.

A brief discussion of the major procedures during the study follows. The Study Schedule (Attachment 1) contains a detailed list of the study events. Clinic visits occur at Visits 1, 2, 3, 5, 7, 9, and 11. Telephone visits occur at Visits 4, 6, 8, and 10. There is a potential for up to 6 additional study-site visits during the safety follow-up period (see Protocol Addendum 4 for details).

6.1.1. Screening (Visit 1)

At Visit 1, parent or legal guardian informed consent and patient assent will be obtained and patients will be screened. The screening includes medical history (including preexisting conditions and concomitant medications), laboratory measures, and physical examination (including measurement of height, weight, waist/hip circumference, vital signs, pubertal assessment, and ECG) for eligibility to participate in the study. Patients will be assigned an identification number that will remain in effect throughout the study, with the exception of patients who are rescreened due to being above the upper bound of HbA1c (see Section 7.3 Rescreening). Patients will continue their oral agent(s), if any, throughout the study (refer to

Section 8.5 for more information). Visit 1 may take place on 2 different dates to accommodate the fasting procedure. If a patient has not fasted prior to arrival for this visit, the site will request that they return in a fasting state within one week for the collection of a glucose and C-peptide specimen. A urine pregnancy test will be performed locally on all female patients of child-bearing potential. If the urine pregnancy test at Visit 1 is positive, a serum pregnancy test will be performed centrally to confirm the result.

6.1.1.1. Height

Height will be measured at each clinic visit throughout the study, preferably at the same time of day. Measurements will be made with the patient standing and without shoes using a standard wall-mounted stadiometer. The instrument should be calibrated using a standard calibration rod. Preferably, the same observer should measure the patients throughout the study, using the same instrument. Any change of instrument during the study should be documented, and cross-calibration between the 2 instruments should be performed by measurement of the standardized calibration rod.

6.1.1.2. Pubertal Assessment

Pubertal development should be assessed at the required visits using the Tanner scale.

6.1.2. Placebo Lead-In Period (Visit 2)

At Visit 2, all patients who have met enrollment criteria will begin a 1-week, single-blind, injectable placebo lead-in period to familiarize the patients to injections. At this visit, patients will receive an injection pen of placebo. Patients and/or their responsible adult party (parent or legal guardian) will be instructed on how to use the injection pen. As part of the pen instruction, at this clinic visit the patient or responsible adult will inject a dose of placebo and they will be instructed that this demonstration injection has no active drug. During the 1-week lead-in period, the patients will inject study drug, placebo, SC into the abdomen within 60 minutes before the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart) beginning on the evening of Visit 2. Patients will receive a glucose meter and glucose monitoring supplies for the measurement of their glucose levels during the study. Patients will be instructed on how to use the glucose meter, how to monitor their glucose, and how to recognize and treat hypoglycemia. Patients will be counseled at each visit, whether by telephone or at an actual clinic visit, by a qualified person (i.e., RD or CDE) to follow an LMP that consists of suggested standard dietary recommendations and recommended level of exercise throughout the study (Attachment 4). Patients will be asked to measure their glucose at home before and 2 hours after the beginning of the 2 main meals of the day on 3 days during the week before clinic Visits 3 and 11.

Additionally, patients' vital signs, height, pubertal status, and body weight will be measured at Visit 2 and each clinic visit through the remainder of the study. A urine pregnancy test will be performed locally on all females of child-bearing potential at Visit 2 and each clinic visit throughout the remainder of the study. If the urine pregnancy test at Visit 2 or any clinic visit throughout the remainder of the study is positive, a serum pregnancy test will be performed centrally to confirm the result.

At Visit 2 and continuing at clinic visits 3, 5, 7, and 9, patients will be given diaries to record episodes of hypoglycemia, illnesses, and concomitant medications. The patient will also be given at least 3 food worksheets and 3 exercise worksheets on which to record dietary and activity information at these visits. Patients will return the completed diaries and food and exercise worksheets beginning at Visit 3 and at each subsequent clinic visit. At each subsequent clinic visit, the patients will be given new diaries and worksheets. Investigative staff will review the diaries at the clinic visit and transfer appropriate data to electronic case report forms (eCRFs), while the RD or CDE reviews the completed worksheets per the LMP (Attachment 4).

Patients will be instructed to return used and unused study drug containers at each subsequent clinic visit.

6.1.3. Randomization and Treatment Initiation (Visit 3)

At Visit 3 (study baseline), patients should arrive at the study site after an overnight fast of at least 8 hours and should omit their morning study drug injection, oral antidiabetes medications, and concomitant medications prior to arriving so that fasting laboratory assessments can be performed. In addition, laboratory assessments for carcinoembryonic antigen (CEA) and calcitonin will be performed at baseline.

Patients will be randomly assigned to 1 of 3 treatment arms: exenatide 5 µg twice daily, exenatide 10 µg twice daily, or placebo twice daily in a double-blind manner. Patients randomized to placebo will be assigned to take the volume equivalent to exenatide 5 µg or to take the volume equivalent to exenatide10 µg. However, the data for all placebo patients will be later combined into 1 group (regardless of injection volume) for analysis purposes. Patients will be randomized to treatment in the proportion of 2:2:1:1 (exenatide 5 µg twice daily; exenatide 10 µg twice daily; placebo volume equivalent of exenatide 5 µg twice daily; placebo volume equivalent exenatide of 10 µg twice daily, respectively) and stratified by screening HbA1c values (≤8% and >8%) as well as background diabetes therapy (drug naïve, metformin only, SU only and metformin+SU) to ensure a balanced distribution of patients within these strata across the treatments. Patients will receive injection pens of exenatide or placebo. Patients will be reinstructed on how to use their injection pen; however, they will not administer their first dose of the assigned therapy until the evening of Visit 3 (within 60 minutes before their evening meal). Dosing of patients participating in the pharmacokinetic addendum at Visit 3 will be altered from that in the main protocol. Patients will administer their first dose of the assigned therapy at Visit 3 (approximately 15 minutes before receipt of first meal at the clinic). Patients taking part in the pharmacokinetic addendum are not required to take an evening dose as per protocol. All injections of study drug (placebo and exenatide) will be SC into the abdomen.

For approximately the first 4 weeks of therapy (until visit 5), patients assigned to both exenatide 5 µg, 10 µg and both placebo groups will inject, either exenatide 5 µg or equivalent volume of placebo, within 60 minutes before the morning and evening meals (or the two main meals of the day, approximately 6 hours or more apart). After visit 5, patients assigned to exenatide 10 µg and its matching placebo will begin injecting 10 µg twice daily.

In the week prior to Visits 3 and 11, patients will be asked to perform pre- and 2-hour postprandial blood glucose measurements at the 2 main meals of the day on 3 separate days. These glucose measurements should be recorded along with study drug dose in the patient diaries. In addition to these requested glucose measurements, patients will be encouraged to measure daily fasting glucose values at home. The diaries are considered source documents and are to be returned to the investigator at the clinic visit. If a patient fails to perform any of the aforementioned measurements, this will not constitute a protocol violation.

Also occurring at Visits 3 and 11, will be the collection of CEA and calcitonin.

6.1.4. Telephone Contact (Visits 4, 6, 8, and 10)

Study site staff will contact patients by phone to review study medication administration, reinforce lifestyle interventions, and answer study questions, as needed. All adverse events and concomitant medications will be collected via telephone and documented. The date of last menses will be collected from all female patients of child-bearing potential. If the patient has missed a menstrual period, she will come into the clinic immediately to have a urine pregnancy test performed.

6.1.5. Interim and Final Treatment Visits (Visit 5, 7, 9, and 11)

Following randomization, patients should attend regular study visits at the intervals described in the Study Schedule (Attachment 1). Efficacy and safety data will be collected at these study visits.

Beginning with Visit 5, patients randomized to exenatide 5 µg will continue administering exenatide 5 µg twice daily while patients assigned to exenatide 10 µg will increase their exenatide dose to 10 µg twice daily. Patients randomized to placebo will remain on placebo volume equivalent to exenatide 5 µg twice daily or increase their placebo dose to the equivalent of exenatide 10 µg twice daily according to treatment assignment. Continuing for the duration of the study, patients should inject the assigned dose of exenatide or the equivalent volume of placebo within 60 minutes before the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).

At Visit 11, (or the early discontinuation visit), patients will participate in end-of-study treatment measures (see Study Schedule) (Attachment 1). At this visit, patients should return all diaries, study drug, and used and unused study drug devices. The patients will not receive exenatide or placebo; however, a treatment regimen, as deemed clinically appropriate, should be initiated. Investigative staff should complete a study summary page for each patient who will not participate in the safety follow up addendum (see Protocol Addendum 4 for details).

At Visit 11 (or the early discontinuation visit), patients should arrive at the study site after an overnight fast of at least 8 hours and should omit their morning study drug injection, oral antidiabetes medications, and concomitant medications prior to arriving at the study site so that fasting laboratory assessments can be performed.

Additional contacts between the patient and the investigator may occur at any time.

6.1.6. Early Discontinuation Visit

If a patient discontinues after randomization but prior to completion of the study treatment period, the patient will be asked to return as soon as possible to the study site for an early discontinuation visit. The early discontinuation visit procedures are described in detail in the Study Schedule (Attachment 1). The patients will not receive exenatide or placebo; however, a treatment regimen, as deemed clinically appropriate, should be initiated. Investigative staff should complete a study summary page for each patient. Patients who discontinue after randomization but prior to completion of the study treatment period should continue with the safety follow-up addendum unless the patient is lost to follow-up or withdraws consent. Patients who do not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication will enter the safety follow-up period (Protocol Addendum 4).

6.1.7. Unscheduled Visit Due to Loss of Glycemic Control

If a patient experiences loss of glycemic control during the treatment period as indicated by fasting blood glucose >250 mg/dL (13.9 mmol/L) or non-fasting glucose >300 mg/dL (16.7 mmol/L) for 4 days during a 7-day period, as measured by home SMBG, the patient will be instructed to return to the clinic for a confirmatory fasting or non-fasting glucose (measured by a local laboratory). If that fasting glucose is >250 mg/dL (13.9 mmol/L), or non-fasting glucose is >300 mg/dL (16.7 mmol/L), the patient will immediately start early discontinuation procedures and this unscheduled visit will be considered an early discontinuation visit (Section 6.1.6, Early Discontinuation Visit). However, if the confirmatory fasting glucose is ≤250 mg/dL (13.9 mmol/L), or non-fasting glucose is ≤300 mg/dL (16.7 mmol/L), the patient will remain in the study and continue to follow the study schedule and confirmatory blood glucose value will be documented in the patient's chart.

In addition, if increase in absolute HbA1c is ≥0.5% from baseline at 2 consecutive scheduled visits which are at least one month apart prior to study completion, the patient will discontinue.

6.1.8. Discussion of Design and Control

This study is designed to support the efficacy and safety of exenatide as a treatment for type 2 diabetes in adolescent patients who are naïve to antidiabetes agents, or who are being treated with metformin, an SU, or combination metformin and an SU.

Approximately 195 patients will be enrolled. Patients will be eligible to participate if they are not achieving adequate glycemic control (HbA1c 6.5% to 10.5%, inclusive) with metformin, an SU, or metformin and an SU, or diet and exercise only. Patients will be stratified to treatment assignment based on diabetes therapy at enrollment and screening HbA1c. The three-arm design is intended to allow comparison of exenatide at doses of 5 µg twice daily and 10 µg twice daily with placebo twice daily.

The primary endpoint for treatment will be assessed at 28 weeks. This timing is intended to allow patients to achieve a stable, representative HbA1c on study treatment. It is expected that exenatide will be more efficacious than placebo when added to the patient's current diabetes

therapy. Consequently, the study is designed to show superiority of exenatide compared with placebo. Fasting serum glucose, fasting serum insulin concentrations, and body weight assessments will also be used to support the assessment of overall metabolic efficacy.

Site visits and telephone contacts are included in the study to provide opportunities for patients to discuss any questions that they have regarding study drug, injections, or study procedures.

Investigators will be instructed to maintain patients on stable doses of metformin and an SU so that treatment arm differences can be attributed to study treatment rather than other agents. For patients using an SU, the SU dose may be reduced if hypoglycemic episodes occur, and eventually stopped, if hypoglycemia continues.

For some patients, glycemic control may decline. Therefore, it is important that the adolescent patients in this study whose HbA1c significantly deteriorates receive active therapy. As a result, any patient whose absolute HbA1c value increases by ≥0.5% from baseline at 2 consecutive scheduled visits which are at least one month apart, despite standard counseling and education available to all study participants at each visit, will be discontinued from the study. Another criterion for discontinuation due to loss of glycemic control will be based on home glucose monitoring. A patient whose fasting blood glucose is >250 mg/dL (13.9 mmol/L) or non-fasting glucose is >300 mg/dL (16.7 mmol/L) for 4 days during a 7-day period, as measured by home SMBG, will return to the clinic for a confirmatory fasting or non-fasting glucose (measured by a local laboratory). If the confirmatory fasting glucose is >250 mg/dL (13.9 mmol/L), or non-fasting glucose is >300 mg/dL (16.7 mmol/L), the patient will be discontinued. If the confirmatory fasting glucose is ≤250 mg/dL (13.9 mmol/L) or non-fasting glucose is ≤300 mg/dL (16.7 mmol/L) the patient will remain in the study and continue to follow the study schedule.

7. Study Population

A sufficient number of individuals will be screened to enroll at least 195 patients (65 per treatment arm). This number is deemed sufficient to allow for approximately 50 subjects per treatment arm to complete treatment.

7.1. Inclusion Criteria

Patients are eligible to be included in the study only if they meet **all** of the following criteria:

[1] are a male or a female between ages 10 to 17 years, inclusive. The number of patients ≥17 years of age will be limited to no more than 10% of patients in each treatment arm

[2] have a history of type 2 diabetes with the original diagnosis based on at least one American Diabetes Association (ADA) diagnostic criteria (Section 7.1.1)

[3] have been treated with metformin, an SU, or both metformin and an SU (with or without diet and exercise), for at least 3 months or are naïve to anti-diabetes agents and being treated with diet and exercise alone. The dose of oral agent(s) should be stable for the 30 days prior to the screening visit

[4] have fasting C-peptide >0.6 ng/mL

[5] have no antibodies to glutamic acid decarboxylase (GAD65) or islet cell antigen (ICA512)

[6] have HbA1c between 6.5% and 10.5%, inclusive

[7] present an appropriately signed assent form

[8] a parent or adult guardian agrees in writing to participate in the patient's treatment by signing a consent form

[9] both the patient and parent or responsible adult guardian are able to understand and comply with a lifestyle modification program

[10] the investigator determines that patient and parent or responsible adult guardian are able to fully participate in and likely to complete the trial.

7.1.1. Disease Diagnostic Criteria

For the purposes of this study, patients with type 2 diabetes are defined by:

- diagnosis of type 2 diabetes, as determined by ADA diagnostic criteria and antibody testing, documented and confirmed in the patient's medical record, which includes laboratory determinations consistent with one or more of the following in the patient's medical history:
    - fasting blood glucose ≥126 mg/dL (7.0 mmol/L)
    - random blood glucose ≥200 mg/dL (11.1 mmol/L)

- two-hour OGTT (Oral Glucose Tolerance Test) ≥200 mg/dL (11.1 mmol/L)

AND one or more of the following:

- no antibodies to GAD65

OR

- no antibodies to islet cell antigen (ICA512)

7.2. Exclusion Criteria

Patients will be excluded from the study if they meet **any** of the following criteria:

[11] are the children or immediate family members of either Amylin, Bristol-Myers Squibb, or AstraZeneca employees or investigator site personnel directly affiliated with this study. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted

[12] have received treatment within the last 60 days with a drug that has not received regulatory approval for any indication at the time of study entry

[13] have previously been exposed to exenatide or, completed or withdrawn from this study or any other study investigating exenatide

[14] are unwilling or unable to inject the study medication

[15] have a genetic syndrome or disorder other than diabetes known to affect glucose tolerance

[16] have a known allergy or hypersensitivity to exenatide or excipients contained in the agent

[17] have used an alpha-glucosidase inhibitor, a meglitinide, or pramlintide for more than 1 week during the 3 months prior to screening

[18] currently use inhaled steroids at a dose equal to or above 1000 μg Flovent® (fluticasone propionate) daily

[19] have used oral steroids within the last 60 days or more than 20 days use within the past year

[20] have used a TZD within 120 days prior to screening

[21] have used any weight loss medication(s) within 30 days of screening

[22] are sexually active female of childbearing potential who is unwilling to appropriately use TWO methods of birth control (for example, use of oral contraceptives; condoms with contraceptive foam; or abstinence) for the duration of the study

[23] are female who is pregnant or planning to become pregnant within 6 months of study screening

[24] are female who is lactating.

[25] have history of renal disease, or serum creatinine >1.6 mg/dL (141.4 µmol/L) (males) or >1.4 mg/dL (123.8 µmol/L) (females)

[26] have hepatic dysfunction, defined by aspartate (AST) or alanine (ALT) transaminase >3.0 times the upper limit of normal (ULN)

[27] have had at least 1 episode of diabetic ketoacidosis after receiving antidiabetes medication. A history of diabetic ketoacidosis at the time of diagnosis will not be an exclusion criterion

[28] have physical limitations that prevent participation in lifestyle intervention

[29] have admitted use of anabolic steroids within the past 60 days

[30] have an active or untreated malignancy, or have been in remission from clinically significant malignancy (other than in situ carcinomas of the cervix) for less than 5 years

[31] have investigator-determined significant organ system illness or condition, including but not limited to psychiatric or developmental disorder that prevent participation in lifestyle intervention

[32] fail to satisfy the investigator of suitability to participate for any other reason

[33] have used insulin for more than 10 weeks during the 3 months prior to screening

7.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criterion [11] reduces the potential bias that may be introduced at the study site. Exclusion Criterion [12] eliminates drugs that cannot be mapped to a standard drug dictionary, or for which little data are known to analyze the potential relationship of adverse events or drug interactions. Exclusion Criterion [13] eliminates the possibility of having two sets of data for one patient.

Exclusion Criteria [14] through [33] include clinical situations that may prevent patients from completing the protocol, or may influence the effect of the study regimens, or are serious conditions that pose a risk for morbidity or mortality.

7.3. Rescreening

Patients who have an HbA1c value less than 0.2% of the lower bound of the criteria for inclusion may be rescreened one more time within 2 weeks of the initial screening visit. For example, a patient who has an HbA1c value of 6.3% or 6.4% at the initial screening visit is eligible for rescreening.

Alternatively, patients who have an HbA1c greater than the upper bound of 10.5% may be rescreened one more time at a later date if, in the investigator's opinion, the patient may meet this criterion following application of an acceptable diabetes regimen (for example, increased diet and exercise). Patients who are rescreened due to being above the upper bound of HbA1c

for study inclusion more than 2 weeks after their initial study screening will be required to be rescreened for all eligibility criteria.

Rescreened patients who meet the HbA1c criteria for inclusion at the rescreen visit will not be documented as screen failures for HbA1c criteria. For these patients, the HbA1c value that is within the inclusion criteria obtained at the rescreening visit will be used as the screening HbA1c value. Rescreened patients who fail to meet HbA1c criteria at the rescreen visit will be documented as screen failures.

Rescreening of patients for reasons other than HbA1c criterion will not be allowed; however, laboratory samples deemed by the lab as not acceptable for testing (for example, clotted hematology specimen) may be re-drawn within 2 weeks of the initial screening visit.

7.4. Discontinuations

The criteria for enrollment must be followed explicitly. If a patient who does not meet enrollment criteria is inadvertently enrolled, that patient will continue in the study unless, in the opinion of the Sponsor's physician responsible for the study, the patient should be discontinued for safety reasons. The Sponsor or its designees must be contacted.

In addition, patients will be discontinued from the treatment period of the study in any of the following circumstances:

- if the patient experiences a loss of glycemic control, as evidenced by:
    - increase in absolute HbA1c ≥0.5% from baseline at 2 consecutive scheduled visits which are at least 1 month apart, prior to study completion
    - fasting blood glucose >250 mg/dL (13.9 mmol/L) or non-fasting glucose >300 mg/dL (16.7 mmol/L) for 4 days in a 7-day period as measured by SMBG. The patient will return to the clinic for a confirmatory fasting glucose, if possible, or a non-fasting glucose. If by local laboratory measurement a fasting glucose is >250 mg/dL (13.9 mmol/L) or a non-fasting glucose is >300 mg/dL (16.7 mmol/L), the patient will be discontinued from the study
- if a female patient becomes pregnant
- if the patient misses more than 10 consecutive days of study therapy
- if the patient misses more than 10 consecutive days of oral antidiabetes therapy
- if metformin or an SU is added or altered for more than 10 consecutive days or 10 days in a 30-day period after study entry
- if a patient uses excluded concomitant medications (Section 7.2, Exclusion Criteria)

- if the investigator decides that the patient should be withdrawn. If this decision is made because of a serious adverse event or a clinically significant laboratory value, the study drug is to be discontinued and appropriate measures are to be taken. The Sponsor or its designee is to be notified immediately
- if the patient or attending physician requests that the patient is withdrawn from the study
- if the investigator or the Sponsor, for any reason, stops the study or stops the patient's participation in the study.

Patients who discontinue the study drug and/or study early will have early discontinuation procedures performed as shown in the Study Schedule (Attachment 1) and be placed on appropriate active antidiabetes therapy. Patients who discontinue study drug administration prior to Visit 11 will enter the safety follow-up period. Refer to the safety follow-up addendum for guidance.

7.4.1. Discontinuation of Study Sites

Study site participation may be discontinued if the Sponsor, the investigator, or the institutional review board (IRB) of the site judges it necessary for any reason.

7.4.2. Discontinuation of the Study

The study will be discontinued if the Sponsor judges it necessary for any reason.

8. Treatment

8.1. Treatments Administered

This study involves a comparison of exenatide 5 µg twice daily and exenatide 10 µg twice daily compared with placebo twice daily.

The investigator or his/her designee is responsible for explaining the correct use of the investigational agent(s) to the patient and parent or responsible adult guardian, verifying that instructions are followed properly, maintaining accurate records of study drug dispensing and collection, and returning all unused medication to the Sponsor or its designee at the end of the study.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the study drug injection pen so that the situation can be assessed.

8.2. Materials and Supplies

The primary study material is exenatide (0.25 mg/mL), a clear, colorless, sterile, preserved solution for SC injection. It consists of exenatide in sodium acetate buffer, pH 4.5, containing 4.3% mannitol as an iso-osmolality modifier and 0.22% metacresol as a preservative.

Placebo is the same sterile, preserved solution; however, the active ingredient, exenatide, is omitted.

Exenatide solution for injection in prefilled pens for twice daily injections has been approved in the US since 2005 under NDA 021773 and in the European Union since 2006, as Byetta® Marketing Authorisation Numbers EU/1/06/362/001-004. In addition to the commercial product Byetta, a clinical trials presentation, hereafter referred to as "exenatide solution for injection 1.2 mL and 2.4 mL", is available to facilitate blinding in clinical trials.

As the manufacturer (Ypsomed AG) of the reusable injection pen (Ypsopen U100) has ceased production of the device, a switch to the Byetta Commercial Like Clinical (CLC) prefilled injection pen is needed.

Exenatide solution for injection 1.2 mL and 2.4 mL is provided by AstraZeneca for the STARZ study, also known as D5550C00002, and H80-MC-GWBQ. Due to the expiry of the previous Ypsopen presentation, the Byetta CLC prefilled injection pen will be made available to this clinical trial.

The currently used Ypsopen U100 reusable injection pen expires in Oct 2018. As patients enroll in a 28 week treatment period, no patient will be randomized to this drug presentation after 31 March 2018. After the switch have been initiated all new patients entering the study will be recruited/randomized to the Byetta CLC prefilled injection pen.

Study medication will be provided in an injection pen. Study medication will be self-administered. Proper measures have been taken to ensure that exenatide and placebo are indistinguishable.

Patients will be provided with commercially available blood glucose meters and test strips for use during the study. Other necessary study supplies will be provided, as needed.

Labels for study agents will comply with the regulatory requirements of the countries participating in the study.

8.3. Method of Assignment to Treatment

At Visit 1, each patient will receive the next consecutive patient number from a block of patient numbers assigned to the investigator. At Visit 3, patients will be randomly assigned to 1 of 3 treatment arms: exenatide 5 µg twice daily, exenatide 10 µg twice daily, or placebo twice daily. Patients will be assigned to the 3 treatment arms by a computer-generated randomized sequence using interactive voice response system (IVRS) with equal probability to 1 of 3 treatment arms. Patients will be randomized to treatment in the proportion of 2:2:1:1 (exenatide 5 µg twice daily; exenatide 10 µg twice daily; placebo volume equivalent of 5 µg exenatide twice daily; and placebo volume equivalent 10 µg exenatide twice daily, respectively) and stratified by screening HbA1c values (≤8% and >8%) as well as background diabetes therapy to ensure a balanced distribution of patients within these strata across the treatments.

8.4. Rationale for Selection of Doses in the Study

A pharmacodynamics and pharmacokinetics study (2993-124) demonstrated that single doses of exenatide 2.5 µg and 5 µg were safe and well tolerated in the adolescent population tested, producing reductions in post-prandial plasma glucose, serum insulin and plasma glucagon concentrations. The pharmacokinetics of exenatide is well characterized in adolescents receiving a single 5 µg dose. Also, in those subjects with quantifiable exenatide levels in response to the 2.5 µg and 5 µg doses, exposure was generally dose proportional.

Given the similarity in exposure, tolerability and pharmacodynamic effects between that study and previous studies in adults, the exenatide doses of 5 µg and 10 µg twice daily were selected for the current study.

8.5. Selection and Timing of Doses

Following randomization, all patients will begin administering either exenatide or placebo. Patients should inject exenatide 5 µg or the equivalent volume of placebo SC into the abdomen within 60 minutes before the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart) for 4 weeks and continue administering exenatide 5 µg or placebo equivalent volume or increase their exenatide dose to 10 µg or placebo equivalent volume, according to assigned treatment. Study drug should not be administered after a meal. If a dose is missed, the treatment should be resumed with the next scheduled dose.

8.5.1. Metformin

Metformin will be continued throughout the study at the same dose and schedule as before study entry.

Although a patient should not change his or her metformin dosage after entering the study, changes will be allowed due to illness for up to 10 consecutive days or 10 days in a 30-day period.

In addition, if a patient requires a procedure involving the injection of a contrast dye, the patient should stop metformin therapy prior to, or at the time of the procedure. Patients should not take metformin within 48 hours after the procedure, but may resume therapy after renal function has been evaluated and found to be normal.

8.5.2. Sulfonylurea

The concomitant SU will be continued throughout the study at the same dose and schedule as before study entry. The SU dosage may be decreased in response to hypoglycemia.

If the patient is receiving a fixed-dose combination of metformin and an SU, the SU dosage may be decreased in response to hypoglycemia; however, the metformin dosage should remain unchanged. If a fixed-dose combination is available that would permit reduction of an SU dosage (as described above) without a change in metformin dosage, a fixed-dose combination pill can be used. If a fixed-dose combination does not meet these criteria, the metformin and SU should be administered as separate pills.

8.5.3. Special Treatment Considerations: Hypoglycemia

Patients will record hypoglycemic episodes in study diaries provided by the Sponsor via the investigative sites. Patients will be encouraged to check their glucose level when signs or symptoms arise, prior to treating the event. Hypoglycemic events will be analyzed according to standard definitions of hypoglycemia.

Confirmed hypoglycemic episodes will be defined as follows in this study:

Minor hypoglycemia:

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

and

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

Major hypoglycemia:

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

or

- documented hypoglycemia (blood glucose <3.0 mmol/L [54 mg/dL]) requiring the assistance of another person because of severe impairment in consciousness or behavior (whether or not symptoms of hypoglycemia are detected by the patient).

Signs and symptoms of hypoglycemia not confirmed with blood glucose values will be reported separately from confirmed episodes described above.

The patient should record the glucose meter reading, associated symptoms, and treatment in the study diary.

Events of hypoglycemia will be closely monitored. If the patient is on an SU and 1 hypoglycemic event or 2 suspected hypoglycemic events occur, the investigator should consider reducing the patient's SU dosage by approximately 50%. If additional confirmed or suspected hypoglycemic events occur, the investigator may consider additional 50% reductions of the patient's SU dosage, with discontinuation of the SU therapy as appropriate.

8.5.4. Special Treatment Considerations: Laboratory Measures

8.5.4.1. Carcinoembryonic Antigen and Calcitonin

Patients will be assessed for the tumor marker CEA and calcitonin levels at visits 3 and 11 or early discontinuation. Calcitonin levels will be measured to determine the possible effect of exenatide on thyroid c-cell function.

8.6. Blinding

This is a double-blinded study; that is, the patient, the investigator and sponsor of all 3 parties are blinded to the assigned treatment. The study also includes a single-blind placebo lead-in period where only the patients are blinded to the treatment. In addition, the Sponsor will be blinded to post-baseline measurements of the primary efficacy variable, HbA1c and antibodies to exenatide data.

Emergency unblinding for adverse events may be performed through an IVRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the patient's well being requires knowledge of the patient's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IVRS.

The investigator should make every effort to contact the Sponsor's clinical research physician prior to unblinding a patient's treatment assignment. If a patient's treatment assignment is unblinded, the Sponsor must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from the Sponsor's clinical research physician for the patient to continue in the study.

8.7. Concomitant Therapy

Patients will not be allowed to take any of the listed excluded medications during the treatment period (Section 7.2, Exclusion Criteria).

For oral medications that are dependent on threshold concentrations for efficacy, such as antibiotics, patients should be advised to take those drugs at least 1 hour before study drug injection. If such drugs are to be administered with food, patients should be advised to take them with a meal or snack when study drug is not administered. Concomitant medications should not be taken or administered on the morning of prescheduled clinic visits.

It may be possible that due to an emergency, some patients will require treatment with insulin. If the period exceeds 10 days during a 3-month period, then the decision to keep the patient in the study should be made after consultation between the investigator and the Sponsor's clinical research physician. Each situation will be considered separately, in order to differentiate between real clinical needs and non-compliance. The decision will be documented by a note to the investigator's file.

8.8. Treatment Compliance

The investigator will assess the compliance of the patient at each visit based on a review of the patient's glycemic control, adherence to the visit schedule, completion of patient diaries, and any other parameters the investigator deems necessary. For patients deemed noncompliant, initial actions will include education, training, and reinforcement of the importance of compliance with the protocol. No specific study data will be collected for analysis of treatment compliance. Any deviation from the prescribed dosage regimen will be recorded in the eCRF.

A patient will be discontinued if he or she misses more than 10 consecutive days of study medication (exenatide or placebo) during the study, misses more than 10 consecutive days of oral antidiabetes therapy during the study, or if the patient's dose of metformin or SU (for reasons other than hypoglycemia) is altered for more than 10 consecutive days or 10 days in a 30-day period after study entry.

9. Efficacy and Safety Evaluations, Sample Collection and Testing, and Appropriateness of Measurements

Study procedures and their timing (including tolerance limits for timing) are summarized in the Study Schedule (Attachment 1).

9.1. Efficacy Measures

9.1.1. Primary Efficacy Measure

The primary efficacy measure is the change in HbA1c from baseline to 28 weeks of treatment in adolescent patients with type 2 diabetes who are naïve to antidiabetes agents or patients who are being treated with metformin, an SU, or combination of metformin and an SU after treatment with exenatide or placebo.

9.1.2. Secondary Efficacy Measures

The following secondary efficacy measures will be collected at the times shown in the Study Schedule (Attachment 1).

- proportion of patient achieving an HbA1c <7%, ≤6.5%, and <6.5%
- body weight
- FSG
- SMBG measurements before and 2 hours after the 2 main meals of the day
- fasting serum insulin concentrations
- beta-cell function and insulin sensitivity as measured by homeostasis model assessment (HOMA-B, HOMA-S) (Matthews et al. 1985)
- proportion of patients who discontinue the study due to failure to maintain glycemic control.

9.2. Safety Evaluations

The following safety measures will be collected at times shown in the schedule of events (Attachment 1):

- adverse events (serious and nonserious)
- incidence and frequency of hypoglycemic events
- laboratory measurements (including clinical chemistry, calcitonin, CEA and hematology and urinalysis)
- antibodies to exenatide
- ECGs
- vital signs

- pubertal assessment
- height.

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting the Sponsor or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

For adverse events that are serious, or that cause the patient to discontinue before completing the study, the investigator remains responsible for following these events using an appropriate health care option. The patient should be followed until the event is resolved or explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

9.2.1. Adverse Events

The Sponsor has standards for reporting adverse events that are to be followed regardless of applicable regulatory requirements that may be less stringent. A clinical trial adverse event is any untoward medical event associated with the use of a drug or drug delivery system in humans, whether or not it is considered related to a drug or drug delivery system.

Lack of drug effect is not an adverse event in clinical trials because the purpose of the clinical trial is to establish drug effect.

Cases of pregnancy that occur during maternal or paternal exposures to study drug or drug delivery system should be reported. Data on fetal outcome and breast-feeding are collected for regulatory reporting and drug safety evaluation.

Study site personnel will record the occurrence and nature of each patient's pre-existing conditions, including clinically significant signs and symptoms of the disease under treatment in the study.

During the study, site personnel will record any change in the condition(s) and the occurrence and nature of any adverse events.

After the informed consent and assent documents are signed, all adverse events related to protocol procedures are reported to the Sponsor or its designee via eCRF.

All adverse events occurring after the patient receives the first dose of study drug must be reported to the Sponsor or its designee via eCRF.

Study site personnel will record any daily dosage that exceeds the maximum dosage in the protocol or in the relevant reference safety document (for example, clinical dosage section for humans in the Investigator Brochure); whichever is greater, via eCRF.

Investigators will be instructed to report to the Sponsor or its designee their assessment of the potential relatedness of each adverse event to protocol procedure, study drug, and/or injection pen via eCRF.

Study site personnel must alert the Sponsor or its designee within 24 hours of the investigator **unblinding** a patient's treatment arm assignment for any reason.

If a patient's dosage is reduced or treatment is discontinued as a result of an adverse event, study site personnel must clearly report to the Sponsor or its designee via eCRF the circumstances and data leading to any such dosage reduction or discontinuation of treatment.

Any clinically significant labs or vital sign measurements that result in a diagnosis should be reported to the Sponsor or its designee using the "Adverse Events/Pre-existing Condition" page of the eCRF. In cases where the investigator notices an unanticipated benefit to the patient, study site personnel should report "unexpected benefit" with the actual event term to the Sponsor or its designee via eCRF (for example, the complete actual term would be "unexpected benefit—sleeping longer").

9.2.1.1. Serious Adverse Events

Serious adverse event collection begins after the patient has signed informed consent and has received study drug. If a patient experiences a serious adverse event after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure.

Study site personnel must alert the Sponsor or its designee of any serious adverse event within 24 hours of investigator awareness of the event via a Sponsor-approved method. Alerts issued via telephone are to be immediately followed with official notification on study-specific serious adverse event forms. A serious adverse event is any adverse event from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious adverse drug events when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

The Sponsor or its designee will be alerted to a study-specific outcome as a serious adverse event only if the investigator deems it to be related to use of the study drug or injection pen or by a protocol procedure.

When a condition related to the injection pen necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Serious adverse events occurring within 30 days after the last dose of study drug will be collected, regardless of the investigator's opinion of causation. Thereafter, serious adverse events are not required to be reported unless the investigator feels the events were related to either study drug, drug delivery system, or a protocol procedure. For information on the collection of serious adverse events during the safety follow-up period, please see Protocol Addendum 4.

9.2.2. Other Safety Measures

Twelve-lead ECGs will be obtained according to the Study Schedule (Attachment 1). ECGs are to be performed locally.

The ECGs will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon as possible after the time of ECG collection, and ideally while the patient is still present, for immediate patient management and to determine whether the patient meets entry criteria. If a clinically significant increase in the QTc interval from baseline is present, then the investigator should assess the patient for symptoms (such as palpitations, near syncope, syncope). The physician must document his/her review of each ECG.

Patients will record hypoglycemic episodes in study diaries provided by the Sponsor via investigative sites. Patients will be encouraged to check their glucose level when signs or symptoms arise (as described in Section 8.5.3) before treating the event and record the glucose meter reading, associated symptoms, and treatment in the study diary.

Pubertal assessment will be summarized based on Tanner Scale.

9.2.3. Safety Monitoring

The Sponsor’s clinical research physician or scientist will monitor safety data throughout the course of the study.

The Sponsor’s clinical research physician or scientist will review serious adverse events within time frames mandated by company procedures and will review trends, laboratory analytes, and adverse events at periodic intervals.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring committee (DMC); (a group created to advise the Sponsor regarding the continuing safety of study participants and the continuing validity and scientific merit of the trial) can conduct additional analyses of the safety data.

9.2.4. Complaint Handling

The Sponsor collects product complaints on study drugs and drug delivery systems used in clinical trials in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Complaints related to unblinded comparator drugs or concomitant drugs/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies, all product complaints associated with material packaged, labeled, and released by the Sponsor will be reported via product complaint forms.

The investigator or his/her designee is responsible for handling the following aspects of the product complaint process in accordance with the instructions provided for this study:

- recording a complete description of the product complaint reported and any associated adverse events using the study-specific complaint forms provided for this purpose
- faxing the completed product complaint form within 24 hours to the Sponsor or its designee
- determining when a drug/drug delivery system is to be returned for investigation.

If the investigator believes that an adverse event is related to the drug delivery system, but the patient has not communicated a complaint, the investigator should assume a complaint and report the product complaint to the Sponsor or its designee within 24 hours.

9.3. Sample Collection and Testing

Attachment 2 lists the specific tests performed for this study.

9.3.1. Samples for Standard Laboratory Testing

Blood samples will be collected at the times specified in the Study Schedule (Attachment 1). Standard clinical laboratory tests, including chemistry, hematology, and urinalysis panels will be performed and analyzed by a central laboratory. A urine pregnancy test will be performed locally at all clinic visits for females of childbearing potential. If the urine pregnancy test at any clinic visit is positive, a serum pregnancy test will be performed centrally to confirm the result.

Laboratory analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Investigators must document their review of each laboratory report.

Samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.3.2. Stored Samples

At Visits 3 and 11, or if the patient exits the study early (after Visit 3 but prior to Visit 11), blood samples will be drawn and the serum and plasma will be stored and may be used for future testing to support investigation of the primary and secondary endpoints of the study or for other markers of metabolic or cardiovascular interest. A sponsor-designated referral laboratory will perform any testing of the stored samples. Results of stored sample testing will not be reported to investigative sites.

Stored samples will retain the patient identifier (for example, trial patient numbers) and, therefore, will not be stored indefinitely. Samples will be stored at a Sponsor designated site for

a maximum of 3 years after last patient visit for the study; any sample remaining at that time will be destroyed.

9.3.3. Collection Procedures

Blood (sampled by venipuncture) and urine will be collected from patients during the course of the study. All lab specimens will be collected at the times specified in Study Schedule (Attachment 1).

9.4. Appropriateness of Measurements

All efficacy assessments included in this study are generally regarded as reliable and accurate assessments of diabetes control. Safety assessments will be consistent with good clinical practice (GCP) guidelines.

10. Data Quality Assurance

To ensure accurate, complete, and reliable data, the Sponsor or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- conduct a start-up training session to instruct the investigators and study coordinators. This session will give instruction on the protocol, the completion of the eCRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and evaluate eCRF data and use standard computer edits to detect errors in data collection
- conduct a quality review of the database.

In addition, the Sponsor or its representatives may periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Amylin or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

To ensure the safety of participants in the study, and to ensure accurate, complete, and reliable data, the investigator will keep records of laboratory tests, clinical notes, and patient medical records in the patient files as original source documents for the study. If requested, the investigator will provide the Sponsor, applicable regulatory agencies, and applicable ethical review boards (ERBs) with direct access to original source documents.

10.1. Direct Data Entry and Computerized Systems

An electronic data capture system will be used in this trial. Some or all of a patient's data (for example, a rating scale, daily dosing schedule, patient diary, event diary) may be directly entered into the system on an eCRF (for example, personal desk assistant or by means of IVRS) at the time that the information is obtained. In these instances where there is no prior written or electronic record of the data, the eCRF (for example, personal desk assistant, or by means of IVRS) will serve as the source document.

Electronic case report form data will be encoded and stored in a clinical trial database.

Any data for which the eCRF will serve as the source document will be identified and documented by each site in that site's study file.

Data from complaint forms submitted to the Sponsor will be encoded and stored in the global product complaint management system.

11. Sample Size and Statistical Methods

11.1. Determination of Sample Size

Approximately 195 patients diagnosed with type 2 diabetes will participate in this study. Approximately 65 patients will be randomized to receive placebo and 130 patients will be randomized to receive exenatide (65 per exenatide treatment arm). A sample of 65 patients per treatment arm would provide >95% power to reject the null hypothesis of no difference among treatments assuming true mean changes in HbA1c of -0.7, -0.5, and 0 for patients receiving exenatide 10 µg twice daily, exenatide 5 µg twice daily, and placebo twice daily, respectively (based on results of previous Studies 2993-112, CCI , H8O-MC-GWAA, H8O-MC-GWAD). This power computation also assumes a common standard deviation of 1.0% and a two-sided significance level of 0.05. Assuming the same true mean changes in HbA1c, common standard deviation, and two-sided significance level, 65 patients per treatment arm would also provide >95% power to detect a difference between 10 µg exenatide twice daily and placebo treatments, and 80% power to detect a difference between 5 µg exenatide twice daily and placebo with a Fisher Protected Testing procedure (Hayter 1986).

Due to an approximate 23% discontinuation rate in the exenatide arms (based on results from 2993-112), 65 patients randomized per treatment arm will be sufficient to observe 50 completers per treatment arm.

11.2. Statistical and Analytical Plans

11.2.1. General Considerations

All of the data will be entered, verified, and archived at Amylin Pharmaceuticals, LLC or its delegate. All data listings, summaries, and analyses will be performed under the guidance and approval of the assigned statisticians. A detailed statistical analysis plan (SAP) will be developed before database lock. The full analysis set will use the intent-to-treat (ITT) principle and include the data from all randomized patients who received at least 1 dose of study drug.

Although, patients randomly assigned to placebo will be assigned to take the volume equivalent to 5 µg exenatide twice daily, or to take the volume equivalent to 10 µg exenatide twice daily, those patients will be combined into 1 group for analysis purposes.

Multiplicity adjustments for the primary analysis will be performed using Fisher Protected Testing procedure. No imputation of missing data will be performed with the exception of the last observation carried forward (LOCF) of post-baseline values in change from baseline to endpoint analyses. All tests of treatment effects will be conducted at a two-sided significance level of 0.05 unless otherwise stated.

Supportive analyses will be performed on the per-protocol analysis set. Per-protocol patients will be randomized to study drug, adhere to the inclusion/exclusion criteria, and have a Week 28 HbA1c measurement.

Any change to the data analysis methods described in the protocol will require an amendment ONLY if it affects the primary analysis. Any other change to the data analysis methods described in the protocol and the justification for making the change will be described in the SAP as well as the clinical study report.

11.2.2. Patient Disposition

The primary reasons for discontinuation will be listed and summarized as frequencies and percentages for all patients by the treatment arm and by visit.

11.2.3. Patient Characteristics

Categorical variables (for example, gender and ethnic origin) will be summarized by frequencies and percentages. Continuous variables (for example, age, body weight, and baseline HbA1c) will be summarized by means, standard deviations, and extremes (minimum and maximum).

11.2.4. Concomitant Therapy

Summaries as well as patient listings of concomitant drug therapy will be provided.

11.2.5. Treatment Compliance

No specific study data will be collected for analysis of treatment compliance.

11.2.6. Primary Outcome and Methodology

The primary outcome is the change in HbA1c from baseline to treatment endpoint at 28 weeks. The ITT analysis set will be used to demonstrate superiority of exenatide to placebo.

The method for the primary efficacy analysis will be a mixed model repeated measures (MMRM) ANCOVA under the assumption that data are missing at random (MAR). The model will include change in HbA1c as the dependent variable and treatment, screening HbA1c strata (≤8% and >8%), baseline HbA1c, background diabetes therapy strata (drug naïve, metformin, an SU, and a combination of metformin and an SU), week of visit, and treatment-by-week interaction as fixed effects and patient as the random effects. The plan for determining a covariance structure to be used for this model will be described in the SAP. All post-baseline measurements of the change in HbA1c will be included in the analysis with no imputation of missing data other than that inherent in the MMRM model. If the last efficacy measurement is collected at a visit for which the efficacy measurement is not planned to be collected, the measurement collected at the early termination visit will be mapped to the following planned visit. Using SAS® PROC MIXED, least squares (LS) means and 95% confidence interval will be produced from the model to estimate the magnitudes of treatment effects. The p-value for the overall test for differences among treatments will be obtained directly from the MMRM analysis. Pairwise comparisons between each exenatide treatment and placebo will be obtained from the MMRM model. Inferences will be based on the estimate of the treatment difference at Week 28. Superiority of exenatide treatment to placebo with regard to change in HbA1c will be concluded if the p-value adjusted using the Fisher Protected Testing procedure for at least one of the exenatide treatment arms is less than 0.05.

An analysis of covariance (ANCOVA) with change in HbA1c as the dependent variable and treatment, screening HbA1c strata (≤8% and >8%), baseline HbA1c, and background diabetes therapy strata (drug naïve, metformin, an SU, and a combination of metformin and an SU) as the independent variables will be done to provide further supportive evidence of superiority of exenatide to placebo. Least squares (LS) means and 95% confidence interval will be produced from the model to estimate the magnitudes of treatment effects. The p-value for the overall test for differences among treatments will be obtained directly from the ANCOVA. Pairwise comparisons between each exenatide treatment and placebo will be obtained from the ANCOVA model. For the purpose of supporting the primary analysis, inferences will be based on the estimate of the treatment difference at Week 28 (LOCF). Superiority of exenatide treatment to placebo with regard to change in HbA1c will be concluded if the p-value adjusted using the Fisher Protected Testing procedure for at least one of the exenatide treatment arms is less than 0.05.

11.2.7. Efficacy Analyses - Secondary Endpoints

In addition to the primary efficacy analysis for superiority in HbA1c, the efficacy measures (both actual and change values) will be summarized at baseline, endpoint, and, if measured, at each visit.

Other secondary efficacy measures include:

- proportion of patient achieving an HbA1c at endpoint of <7%, ≤6.5%, and <6.5 %
- body weight
- FSG
- SMBG measurements before and 2 hours after the 2 main meals of the day
- fasting serum insulin concentrations
- beta-cell function and insulin sensitivity as measured by homeostasis model assessment (HOMA-B, HOMA-S) (Matthews et al. 1985)
- proportion of patients who discontinue the study due to failure to maintain glycemic control.

Similar to the analysis for HbA1c, the continuous secondary efficacy measures will be summarized by treatment and by visit, and treatments will be compared using an MMRM analysis where multiple post-baseline measurements are collected. If only an endpoint measurement is collected, an ANCOVA model will be used. As in the analyses of HbA1c, inferences will be based on the estimate of the treatment difference at Week 28 for the MMRM analysis, and at Week 28 (LOCF) for the ANCOVA analysis. Treatment comparisons and LS estimates will be reported only for scheduled visits. Furthermore, the proportion of patients reaching HbA1c <7%, ≤6.5%, and <6.5%, as well as the proportion of patients who discontinue due to failure to maintain glycemic control (termination reason = “loss of glycemic control”), will be summarized and compared by treatment using the Cochran-Mantel-Haenszel (CMH) test, where screening HbA1c strata (≤8% and >8%) and background diabetes therapy strata will serve

as the stratification factors. In addition a Generalized Linear Mixed Model (GLMM) analysis will be done using the binary HbA1c outcome (achieved vs. not achieved HbA1c goal) as the dependent variable. Details of analyses will be specified in the SAP.

11.2.8. Safety Analyses

Descriptive statistics of changes from baseline, measured from Visit 3 (Week 0) for clinical chemistry, hematology, urinalysis, CEA, calcitonin, and vital signs will be generated. Physical examinations (including height and pubertal assessments) and ECGs will be summarized and listed.

Antibodies to exenatide data will be listed and summarized.

11.2.8.1. Study Drug Exposure

Exposure to each therapy during the treatment period of the study will be calculated for each patient and summarized by treatment arm.

11.2.8.2. Adverse Events

Adverse events will be summarized by presenting patient incidence and event frequency in each system organ class and in each preferred term defined by the Medical Dictionary for Regulatory Activities (MedDRA®), by treatment. Adverse events will be collected if they occur during or after the administration of randomized study medication at Visit 3 (Week 0) through study completion (Week 28) or early termination, if applicable.

Adverse events will be summarized as treatment-emergent adverse events. Treatment-emergent adverse events will be defined as those occurring on or after randomization or worsened through study completion, and will be analyzed by treatment and summarized. Adverse events that occur on or after Visit 2 (Week -1) through Visit 3 (Week 0) will be classified as pretreatment (non-treatment-emergent) and will be listed only. All adverse events will be listed by patient, visit, preferred term, treatment arm, severity, and relationship to the treatment. The frequency and percentage of treatment-emergent adverse events will be presented for each treatment arm.

11.2.8.3. Laboratory and Vital Signs Analyses

Categorical changes in laboratory analyses (clinical chemistry and hematology, calcitonin, CEA and urinalysis) will be evaluated by examining the proportion of patients whose test values are outside the reference ranges at their final visit. The treatment effect on change from baseline in laboratory analytes and vital signs will be assessed using descriptive statistics.

11.2.8.4. Episodes of Hypoglycemia

The distribution of hypoglycemic episodes and hypoglycemia incidence will be summarized by treatment. Hypoglycemia rate (adjusted for duration of exposure to study drug therapy) will be summarized by treatment. Similar reports will be created for daytime and nocturnal hypoglycemia episodes. A method of analysis to compare treatments will be described in the SAP.

11.2.8.5. Pubertal Assessments

Pubertal assessments (based on Tanner scale) will be performed at Visits 1, 2, 3, 5, 7, 9, and 11 (or at early discontinuation visit prior to Visit 11). Details of analyses of pubertal assessment data will be specified in the SAP.

11.2.9. Subgroup Analyses

Analyses of population subgroups of interest (gender, or BMI) will be performed. Other subgroup analyses may be performed if deemed appropriate. Subgroup analyses will be described in detail in the SAP.

11.2.10. Interim Analyses

Three safety analyses are planned for this trial beginning when at least 25% of the patients have been randomized. In order to minimize the operational and statistical bias that result from performing a safety assessment, the assessment for this study will be conducted under the auspices of a DMC. 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.

Details regarding the safety updates will be given in the Data Monitoring Committee Charter.

12. Informed Consent, Ethical Review, and Regulatory Considerations

12.1. Informed Consent

The investigator is responsible for ensuring that the patient understands the risks and benefits of participating in the study, including answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the trial.

The informed consent document (ICD) will be used to explain the risks and benefits of study participation to the patient in simple terms before the patient is entered into the study, and to document that the patient is satisfied with his or her understanding of the risks and benefits of participating in the study and desires to participate in the study.

The investigator is responsible for ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the ICD prior to the performance of any protocol procedures and prior to the administration of study drug.

A legal representative must give informed consent for a child to participate in this study. In addition to informed consent given by the legal representative, the child may be required to give documented assent, if applicable.

As used in this protocol, the term "informed consent" includes all consent and assent given by patients or their legal representatives.

12.2. Ethical Review

The Sponsor must agree with all ICDs before they are submitted to the ERB and are used at investigative sites(s). All ICDs must be compliant with the International Conference on Harmonisation guideline on GCP. Informed consent obtained under special circumstances may occur only if allowed by local laws and regulations and performed in accordance with a written process approved by the Sponsor.

Documentation of ERB approval of the protocol and the ICD must be provided to the Sponsor *before* the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

Any member of the ERB who is directly affiliated with this study as an investigator or as site personnel must abstain from the ERB’s vote on the approval of the protocol.

The study site’s ERB(s) should be provided with the following:

- the current IB or package labeling and updates during the course of the study
- ICD
- relevant curricula vitae.

12.3. Regulatory Considerations

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with GCP and the applicable laws and regulations. The investigator, head of the medical institution, or designee will promptly submit the protocol to applicable ERB(s).

Exenatide is being studied in the US under a US Investigational New Drug (IND) application. The US IND number is 57,725.

An identification code assigned by the investigator to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting adverse events and/or other trial-related data.

12.3.1. Investigator Information

Physicians who treat diabetes mellitus in adolescents will participate as investigators in this clinical trial.

12.3.2. Protocol Signatures

After reading the protocol, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Sponsor's representative.

12.3.3. Final Report Signature

The clinical study report coordinating investigator will sign the final clinical study report for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

The investigator with the most enrolled patients will serve as the clinical study report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by the Sponsor to serve as the clinical study report coordinating investigator.

The Sponsor's responsible medical officer will sign the final clinical study report for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

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Attachment 1. Protocol GWBQ Study Schedule

Study Schedule, Protocol H8O-MC-GWBQ — Treatment Period

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

(continued)

Study Schedule, Protocol H8O-MC-GWBQ — Treatment Period (Continued)

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

(continued)

Study Schedule, Protocol H8O-MC-GWBQ — Treatment Period (Continued)

Visit	1[¥]	2	3	4‡	5	6‡	7	8‡	9	10‡	11	UV†	ED***
Laboratory Assessments[k] (continued):													
Time relative to Visit 3 (weeks)	**-3**	**-1**	**0**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**		
Visit Interval (± weeks)*	**1**	**1**	**0**	**1**	**1**	**1**	**1**	**1**	**1**	**1**	**1**		
CEA			**X**								**X**		**X**
Glutamic acid decarboxylase (GAD65) antibodies[m]	**X**												
Islet cell antigen (ICA512) antibodies[m]	**X**												
Antibodies to exenatide[n]			**X**		**X**		**X**		**X**		**X**		**X**
Date of last menses[o]				**X**		**X**		**X**		**X**			
Patient Summary											**X[p]**		**X**

Perform procedure as indicated unless time interval is shaded.

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

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

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

c ECGs will be performed locally.

d Patient's height will be measured without shoes, with a wall mounted stadiometer.

e The patient should be standing with their feet 25-30 cm apart, with their arms hanging naturally at the sides. The measurer should stand to the side of the patient, and fit the tape snugly around the waist on bare skin. Take the measurement at end-expiration with the measuring tape positioned in a horizontal plane (horizontal to the floor) at the level of the top of the bony iliac crest (minimum waist). The hip circumference should be measured at the widest area of the buttocks.

f At visit 1, only pre-existing conditions will be collected. Pre-existing conditions will not be collected at any other visit.

g Patient should complete and record self monitored blood glucose testing on 3 days in the week prior to clinic Visits 3 and 11.

h Hypoglycemic episodes will be collected at all clinic visits (beginning at Visit 3). They will be discussed during the telephone visits

i Patients should not administer injectable therapy (exenatide or placebo) prior to visiting the study site on the day of visit.

j Only applies if the early discontinuation occurs at or after Visit 4 or any subsequent visit.

k Patients should fast about 8 hours prior to visiting the study site on the day of visit 3 and visit 11.

Study Schedule, Protocol H8O-MC-GWBQ — Treatment Period (Concluded)

l Pregnancy test to be administered to females of childbearing potential. All pregnancy tests performed at clinic visits will be urine pregnancy tests performed locally. If the urine pregnancy test at any clinic visit is positive, a serum pregnancy test will be performed centrally to confirm the result.

m A positive result will be reconfirmed by a second test at screening, as false positives have occurred.

n Blood samples will be collected for antibodies to exenatide analysis. Samples that test positive for antibodies to exenatide may be subjected to further immunologic characterization.

o Female patients of childbearing potential only. If the patient has missed a menstrual period, she will come into to the clinic immediately to have a urine pregnancy test performed.

p Only patients who have achieved the final height requirement of a change of less than 5 mm between Visit 3 and Visit 11 of the treatment period will be summarized at Visit 11 and will not participate in the safety follow-up addendum.

* All procedures are to be completed prior to next visit.

** Patients who are17 years of age at the time of screening that reach age of majority (as applicable in their country) during the study will be asked to re-consent.

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

¥ Visit 1 may take place in 2 different dates to accommodate the fasting procedure. If a patient comes for visit 1 non-fasting then the site will request the patient return in a fasting state within a week to draw the fasting blood glucose and c-peptide.

‡ Visits 4, 6, 8, and 10 are telephone visits where the LMP is reinforced and all adverse events and concomitant medications will be documented.

† At the unscheduled visit (UV) associated with loss of glycemic control, fasting or non-fasting glucose testing will be done locally, at which time the investigator will decide whether the patient will begin early discontinuation procedures or continue in the trial.

Attachment 2. Protocol GWBQ Clinical Laboratory Tests

Clinical Laboratory Tests[a]

Hematology:
Hemoglobin
Leukocytes (WBC)

Serum Pregnancy Test[b]

Urine Pregnancy Test[f]

Fasting Insulin

Urinalysis:
Specific Gravity
PH
Protein
Glucose
Ketones
Bilirubin
Urobilinogen
Blood

Clinical Chemistry
Serum Concentrations of:
Alanine aminotransaminase (ALT/SGPT)
Aspartate aminotransaminase (AST/SGOT)
Creatinine[d]

Fasting Glucose

Hemoglobin A_{1c}

Fasting C-peptide[c]

Antibodies to exenatide[e]

Stored Samples

Islet cell antigen (ICA512) antibodies[c]

Calcitonin

Carcinoembryonic antigen (CEA)

Glutamic acid decarboxylase (GAD65) antibodies[c]

[a] Assayed by designated laboratory.
[b] Will be performed when a urine pregnancy test at any clinic visit is positive.
[c] Screening test only.
[d] Creatinine measurements will be used to calculate patient glomerular filtration rate by the Schwartz equation.
[e] Blood samples will be collected for antibodies to exenatide analysis. Samples that test positive for antibodies to exenatide may be subjected to further immunologic characterization.
[f] Urine pregnancy test will be performed by local lab.

Attachment 3. Protocol GWBQ
American Diabetes Association: Diagnosis of Diabetes Mellitus*

1. Symptoms of diabetes plus casual plasma glucose concentration greater than or equal to 200 mg/dl (11.1 mmol/L).

Casual is defined as any time of day without regard to time since last meal. The classic symptoms of diabetes include polyuria, polydipsia, and unexplained weight loss.

OR

2. Fasting plasma glucose greater than or equal to 126 mg/dl (7mmol/L).

Fasting is defined as no caloric intake for at least 8 hours.

OR

3. 2-h Plasma glucose greater than or equal to 200 mg/dl (11.1 mmol/L) during an OGTT.

The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75g anhydrous glucose dissolved in water.

NOTE:

In the absence of unequivocal hyperglycemia, in order to make a diagnosis of diabetes mellitus, these criteria should be confirmed by repeat testing on a different day.

The OGTT is not recommended for routine clinical use, but may be required in the evaluations of patients with impaired fasting glucose or when diabetes is still suspected despite a normal FPG.

The use of the hemoglobin A1c (A1C) for the diagnosis of diabetes is *not* recommended at this time.

*ADA's Clinical Practice Recommendations 2007

Attachment 4. Protocol GWBQ Lifestyle Modification Program

A simplified lifestyle modification program (LMP) will be recommended for all patients participating in study GWBQ. The LMP consists of a diet and exercise component suggested to be followed throughout the duration of the study. This program will address the dietary and physical activity needs of the individual. A qualified person (i.e.) Registered Dietitian (RD) or Certified Diabetes Educator (CDE) will meet with the patient and parent or guardian at each scheduled clinic visit. The LMP will be reinforced at each visit.

The study LMP for sites located in the U.S. will be based on the "MyPlate Plan", a program designed by the United States Department of Agriculture and available to the public at www.ChooseMyPlate.gov. The qualified person at each site will enter each patient's age, gender, weight and height into the SuperTracker program calculator. The program will calculate the total daily calories recommended to be consumed to promote at least minimal weight loss and to meet growth needs. The MyPlate Plan will also be used to calculate the number of daily meal servings from each food group in the plan.

The qualified person can individualize the MyPlate Plan using clinical judgment to promote compliance with the meal plans and physical activity throughout the study. At each clinic visit, individualized tools can be given to the patient with a copy retained by the qualified person.

For countries other than the US, the study LMP will be based on the "MyPlate Plan" or other locally applicable plan.

Visit 2 (Beginning of the placebo lead-in period)

The qualified person will meet with the patient and parent or guardian beginning at Visit 2 of the study. The qualified person will introduce and review the MyPlate with the patient and parent/guardian, explaining the recommended number of calories, food groups, portion sizes, and individualizing the plan to aid patient compliance. The patient will be given at least three food and exercise worksheets. The patient will be instructed to complete a minimum of one of the worksheets with at least two weekdays and one weekend day of food consumption and exercise. The patient will be instructed to complete the worksheet prior to Visit 3 and bring the worksheet with them to the next clinic visit.

The qualified person will instruct the patients on the importance of a minimum of 60 minutes of daily exercise (walking, jogging, biking, hiking, sport activity, etc) and limiting sedentary activities (watching TV, video games) to one hour or less daily.

Visit 3 (Randomization) through Visit 10

The qualified person will meet with the patient and parent/guardian to collect and review the food and exercise worksheets, during clinic visits. The qualified person will evaluate adherence to the LMP and address any areas of concern. The patient's weight will be noted at each clinic

visit to help assess diet and exercise compliance. The qualified person will re-instruct patient on problem areas, as appropriate. The qualified person will reinforce positive changes and encourage the patient to adhere to both the diet and exercise recommendations. The patient will be given at least three food and exercise worksheets. The patient will be instructed to complete a minimum of two of the worksheets with at least two weekdays and one weekend day of food consumption and exercise. The patient will be instructed to complete the worksheets prior to the clinic visit and bring the worksheets with them to the next clinic visit. During the phone visits the patient may speak with the qualified person on the LMP if requested.

Visit 11 (End of study treatment)

The qualified person will meet with the patient and parent/guardian and collect the food and exercise worksheets. The patient should be encouraged to maintain a healthy lifestyle after the patient ends study treatment and enters the safety follow-up period, at the discretion of the investigator.

Footnote: Failure to return food and exercise worksheets will not, at any time, be considered a protocol violation.

Attachment 5. Protocol GWBQ Estimated Glomerular Filtration Rate

Note: The central laboratory applies the formula and reports the value in its calculated form.

Standard Schwartz Formula for Estimated Glormerular Filtration Rate (GFR)[a]

For glomerular filtration rate in mL/min/1.73 m^2

GFR = k^b × height(cm)/serum creatinine (mg/dL)

[a] Schwartz GJ et al, 1976; Schwartz et al, 1984; Schwartz et al, 1985.

[b] k= 0.55 in male children aged 2 -12 years and all female children and adolescents up to age 17 years ; k= 0.65 for adolescent males aged 13-17 years.

Modification of Diet in Renal Disease (MDRD) Formula for Estimated Glomerular Filtration Rate (GFR) in Adults

- GFR (mL/min/1.73 m^2) = 175 x (serum creatinine)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.212 if African American)

CKD-EPI Formula for Estimated Glomerular Filtration Rate (GFR) in Adults

GFR (mL/min/1.73 m^2) = 141 x min(Scr/k,1)[a] x max(Scr/k,1) $^{-1.209}$ x_ 0.993^{Age} x_[1.018 if female] x 1.159 if black]

Amendment (a) to Protocol Addendum H8O-MC-GWBQ(3) Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

Exenatide (LY2148568)

Amylin Pharmaceuticals, LLC
San Diego, California USA 92121

Protocol Addendum (3) Approved by Lilly: 01-Feb-2011 GMT
Amendment (a) to Protocol Addendum (3) Approved by Amylin/AZ: 16 May 2013

This addendum is to be performed in addition to all procedures required by protocol H8O-MC-GWBQ or any subsequent amendments to that protocol.

Amendment (a) to Protocol Addendum H8O-MC-GWBQ(3) Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

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Rationale for Addendum

To provide a thorough quantification of the pharmacokinetic (PK) disposition of exenatide in adolescents and allow assessment of safety endpoints relative to maximum plasma exenatide concentrations observed in adolescent patients, additional PK samples will be collected. Optimal design analysis has demonstrated that data from a limited number of subjects in the current study, combined with existing PK data from Amylin Study 2993-124, will provide a robust characterization of exenatide PK in adolescents. At least 36 subjects (12 from each treatment arm) enrolled in Study H8O-MC-GWBQ will be incorporated into the population PK analyses.

- Group A: PK samples will be collected once at Visit 3 at 2 hours post dose. This group will consist of at least 24 subjects, evenly divided among treatment groups (placebo twice daily: 8 subjects, exenatide 5 mcg twice dailly: 8 subjects, and exenatide 10 mcg twice daily: 8 subjects). This is to allow for the assessment of C_{max} in the adolescent population.
- Group B: PK samples will be collected twice during Visit 3: once at 30 minutes post dose and once at 4 hours post dose. This group will consist of at least 12 subjects, evenly divided among treatment groups (placebo twice daily: 4 subjects, exenatide 5 mcg twice daily: 4 subjects, and exenatide 10 mcg twice daily: 4 subjects).

Protocol Additions

Laboratory Tests

Pharmacokinetic Sampling

Additional PK sampling will be performed at Visit 3 in a subset of subjects. At least 36 subjects, from the US, will be chosen from select sites and randomly assigned to 1 of 2 groups:

- Group A: PK samples will be collected once at Visit 3 at 2 hours post dose. This group will consist of at least 24 subjects, evenly divided among treatment groups (placebo twice daily: 8 subjects, exenatide 5 mcg twice daily: 8 subjects, and exenatide 10 mcg twice daily: 8 subjects).
- Group B: PK samples will be collected twice during Visit 3: once at 30 minutes post dose and once at 4 hours post dose. This group will consist of at least 12 subjects, evenly divided among treatment groups (placebo twice daily: 4 subjects, exenatide 5 mcg twice daily: 4 subjects, and exenatide 10 mcg twice daily: 4 subjects).

Dosing of subjects on the PK addendum at Visit 3 will be altered from that in the main protocol. Subjects will administer their first dose of the assigned therapy at Visit 3 (approximately 15 min before receipt of first meal at the clinic)

Subjects participating in the PK addendum are not to take their evening dose on the day of Visit 3.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 2 years following last patient visit for the study.

At the visits and times specified in the Study Schedule, venous blood samples (Attachment 1) will be collected (Attachment 2). Blood samples will be used to determine the plasma concentrations of LY2148568. The actual date and time (24-hour clock time) of each sampling will be recorded.

A maximum of 2 samples may be drawn at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor.

Attachment 1. Protocol Addendum GWBQ (3) Study Schedule for PK Samples

Study Schedule for PK Samples, Protocol Addendum H8O-MC-GWBQ(3)

CRF Visit No.:	V3
Time relative to V3 (baseline) - days	0
Procedure	
PK informed consent signed	X
Venous blood PK samples[a,b]	X

[a] PK samples must be collected only after the subject signs the PK informed consent document.

[b] Group A: PK samples will be collected once at Visit 3 at 2 hours post dose. This group will consist of 24 subjects, evenly divided among treatment groups (placebo twice daily: 8 subjects, exenatide 5 mcg twice daily: 8 subjects, and exenatide 10 mcg twice daily: 8 subjects).

- Group B: PK samples will be collected twice during Visit 3: once at 30 minutes post dose and once at 4 hours post dose. This group will consist of 12 subjects, evenly divided among treatment groups (placebo twice daily: 4 subjects, exenatide 5 mcg twice daily: 4 subjects, and exenatide 10 mcg twice daily: 4 subjects)..

Attachment 2. Protocol Addendum GWBQ (3) Sampling Summary

This table summarizes the maximum number of venipunctures samples and volumes for all PK sampling during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol H8O-MC-GWBQ Sampling Summary

Purpose	Sample Type	Maximum Amount per Sample	Maximum Number Samples	Maximum Total Amount
Drug concentration: Group A: PK samples	Blood	4 mL	1 +2 additional samples if warranted	12 mL
Drug Concentration Group B: PK samples	Blood	4 mL	2+2 additional samples if warranted	16mL

Revised Protocol Addendum Sections

Global change: References to Eli Lilly and Company as Sponsor for this study have been replaced with Amylin Pharmaceuticals, LLC (Amylin).

1. Amendment (a) to Protocol Addendum H8O-MC-GWBQ(4) Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

Exenatide (LY2148568)

Amylin Pharmaceuticals, LLC
San Diego, California USA 92121

Protocol Addendum (4) Electronically Signed and Approved by Lilly: 29 May 2012
Amendment (a) to Protocol Addendum (4) Approved by Amylin/AZ: 16 May2013

This addendum is to be performed in addition to all procedures required by protocol H8O-MC-GWBQ or any subsequent amendments to that protocol.

2. Table of Contents

Amendment (a) to Protocol Addendum H8O-MC-GWBQ(4) Safety and Efficacy of Exenatide as Monotherapy and Adjunctive Therapy to Oral Antidiabetic Agents in Adolescents with Type 2 Diabetes

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3. Rationale for Addendum

In response to a request from the European Medicines Agency Paediatric Committee, patients will be observed in a long-term safety follow-up period following discontinuation of study drug administration. Patients will return to the clinic every 6 months for evaluation on safety measures. Patients will be followed for up to 3 years after the completion of the treatment period, or until the difference between 2 consecutive height measurements at 6-month intervals is less than 5 mm (whichever occurs first). Patients who have achieved the final height requirement of a change of less than 5 mm between Visit 3 and Visit 11 of the treatment period will be excluded from the safety follow-up period. Patients who do not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication will enter the safety follow-up period. Long-term follow-up of patients will allow observation of ongoing development and growth on an individual patient basis and a description of the occurrence of selected adverse events (AEs) in pediatric patients in the absence of study drug treatment following up to 28 weeks of study drug administration.

4. Protocol Additions

4.1. Long-Term Safety Follow-Up Objective

The objectives of the safety follow-up period are as follows:

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

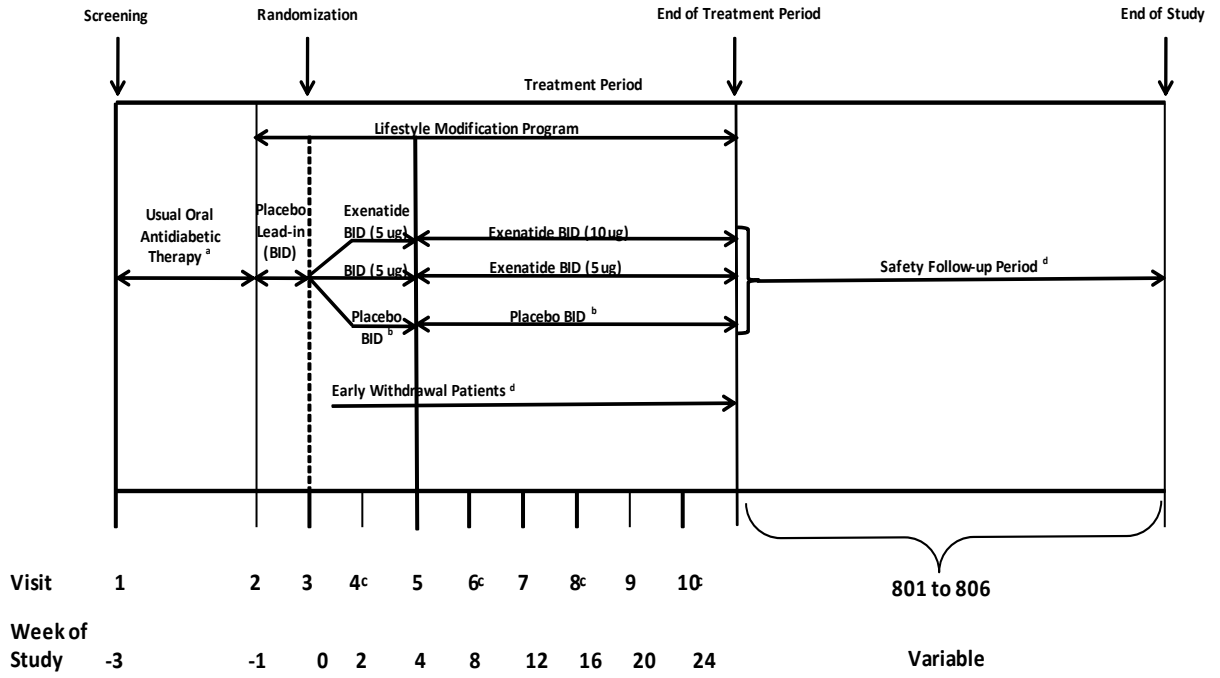
4.2. Summary of Study Design

Following discontinuation of study drug administration, patients with a height difference of at least 5 mm between Visit 3 and Visit 11 will enter the safety follow-up period. Patients who discontinue study drug administration prior to Visit 11 will also enter the safety follow-up period. During this 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 5 mm (whichever comes first). Patients who do not have height assessments at study-site visits over a 6-month interval prior to discontinuation of study medication will enter the safety follow-up period. Patients will not receive any study drug but may be treated with a diabetes treatment regimen deemed appropriate by the investigator or healthcare provider. During the safety follow-up period, the following will occur: AESIs and ongoing prescription medications will be reviewed; height, weight, and Tanner pubertal stage will be assessed; and CEA and calcitonin concentrations will be measured. Refer to the Study Schedule (Attachment 1) for more information.

Patients who have achieved the final height requirement of a change of less than 5 mm between Visit 3 and Visit 11 of the treatment period will be excluded from the safety follow-up period.

Patients who completed the protocol prior to this addendum will be evaluated for inclusion in the safety follow-up period where possible (Section 4.2.1.1).

The entire study design including the safety extension period is illustrated in Figure GWBQ(4) 1.



Abbreviations: BID = twice a day

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

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

[c] Scheduled telephone visit.

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

Figure GWBQ(4) 1. Illustration of study design for Protocol Addendum H8O-MC-GWBQ(4).

4.2.1. Safety Follow-Up Period (Visits 801 to 806)

During the safety follow-up period, patients may return to the study site at 6-month intervals (±2 weeks) for a period of up to 36 months (up to 6 clinic visits). The first visit (Visit 801) during the safety follow-up period is to occur 6 months after discontinuation of study drug administration or Visit 11, whichever comes first. Fasting is not required prior to any of the study visits during the safety follow-up period.

All patients will undergo the following procedures during each safety follow-up period visit:

- Review of ongoing prescription medications
- Review of AESIs (see 4.5.1) will be conducted using an AESI questionnaire and will be recorded in the electronic case report form [eCRF])
- Assessment of body weight and height

- Assessment of Tanner pubertal stage
- Blood samples will be collected to assess the following:
  - Calcitonin
  - CEA concentration

Patients will discontinue participation in the safety follow-up period after 3 years or once they have a height difference of less than 5 mm between two 6-month interval visits.

Study procedures will be performed at Visits 801 to 806 according to the Study Schedule (Attachment 1).

4.2.1.1. Patients Previously Completing the Protocol or Early Withdrawal

Patients who previously completed the protocol or withdrew early from the study will be evaluated for participation in the safety follow-up period. Patients who completed the 28-week study and grew less than 5 mm during the treatment period (between Visits 3 and 11) will be excluded, while early withdrawal patients will be included in the safety follow-up period. Patients who are eligible to participate in the safety follow-up will be contacted to return to the clinic and parent or legal guardian informed consent and patient assent will be obtained. Patients will be observed until either they achieve the height requirement or it has been 3 years since their last dose in the treatment period. Patients will not receive study drug during the 3-year follow-up period and will be allowed to go on any diabetes treatment regimen deemed appropriate by the investigator or healthcare provider.

4.3. Exclusion Criteria

[34] Patients who completed the 28-week study and grew less than 5 mm during the treatment period (between Visits 3 and 11) will be excluded from participation in the safety follow-up period.

4.4. Treatments Administered

No study drug treatment will be administered during the safety follow-up period.

4.5. Concomitant Therapy

During the safety follow-up period, patients will be treated at the discretion of their healthcare provider, with no medication restrictions.

4.5.1. Safety Evaluations

Assessment of body weight, height, vital signs, Tanner pubertal stage, calcitonin concentration, and CEA concentration in the safety follow-up period will be performed as described in the main protocol.

Review of medications during the safety follow-up period will focus on ongoing prescription medications.

Adverse events of special interest will be assessed at all visits during the safety follow-up period, and the eCRF will be completed if it is determined that the patient has experienced 1 or more of the listed AESIs. The AESIs are as follow:

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

This list may be updated if additional AESIs are identified.

Other serious and non-serious adverse events will be done through routine postmarketing spontaneous reporting and according to the relevant medication(s) the patient is receiving (which may or may not include exenatide). Pregnancies that occur during the safety follow-up period should be reported and followed to term.

4.6. Statistical and Analytical Plans

4.6.1. General Considerations

Safety data will be listed for the safety follow-up population, which will consist of all patients who participate in at least 1 safety follow-up period visit.

Data collected in the safety follow-up period is for descriptive purposes and is not associated with a predefined hypothesis or test. Missing data will not be imputed.

Attachment 1. Addendum GWBQ(4) Study Schedule Safety Follow-Up Period

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

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

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

a All procedures are to be completed prior to next visit.

b Required only for patients previously completing the protocol who have returned to the clinic for evaluation.

c Patients will continue to return to the clinic at 6-month intervals for safety evaluation for up to 3 years or until the difference between 2 consecutive height measurements is less than 5 mm (whichever occurs first).

d Patient's height will be measured without shoes, with a wall-mounted stadiometer.

e Assayed by Sponsor-designated laboratory.

f Patient Summary will be completed at the visit where the difference between 2 consecutive height measurements is less than 5 mm if this criterion occurs before the 3-year period ends.

Revised Protocol Addendum Sections

Global change: References to Eli Lilly and Company as Sponsor for this study have been replaced with Amylin Pharmaceuticals, LLC (Amylin).