Protocol H9X-MC-GBGC(e)

Randomized, Double-Blind Study with an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Pediatric Patients with Type 2 Diabetes Mellitus (AWARD-PEDS: Assessment of Weekly AdministRation of LY2189265 in Diabetes-PEDiatric Study)

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Approval Date: 15-Oct-2020

1. Protocol H9X-MC-GBGC(e)
A Randomized, Double-Blind Study with an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Pediatric Patients with Type 2 Diabetes Mellitus

(AWARD-PEDS: Assessment of Weekly AdministRation of LY2189265 in Diabetes-PEDiatric Study)

Dulaglutide (LY2189265)

Study H9X-MC-GBGC is a Phase 3, randomized, double-blind, placebo-controlled trial with an open-label extension that investigates the effect of the addition of dulaglutide (0.75 and 1.5 mg/week) or placebo weekly to metformin and/or basal insulin on change from baseline in hemoglobin A1c at 26 weeks in children and adolescents with type 2 diabetes mellitus.

Eli Lilly and Company
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2. Synopsis

Study Rationale

The purpose of Study H9X-MC-GBGC (GBGC) is to evaluate the use of once weekly dulaglutide (0.75 and 1.5 mg) compared with placebo in pediatric patients with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control despite diet and exercise, with or without metformin and/or basal insulin.

The placebo-controlled, double-blind portion of Study GBGC is 26 weeks in duration, followed by 26 weeks of open-label therapy where all patients will receive dulaglutide (0.75 or 1.5 mg).

Clinical Protocol Synopsis: Study H9X-MC-GBGC

Name of Investigational Product:
Dulaglutide (LY2189265)

Title of Study: A Randomized, Double-Blind Study with an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Pediatric Patients with Type 2 Diabetes Mellitus (AWARD-PEDS: Assessment of Weekly AdministRation of LY2189265 in Diabetes-PEDiatric Study)

Number of Planned Patients:	**Phase of Development:** 3
Entered: 750 Enrolled/Randomized: 150 Completed: 120 Number of patients dependent on sample size re-estimation up to approximately 189 randomized with approximately 150 completers.	

Length of Study: Approximately 61 months
Estimated first patient visit: JAN 2017 Estimated last patient visit: JAN 2022

Objectives: The primary objective of this study is to test the hypothesis that dulaglutide (0.75 mg and 1.5 mg, pooled) given subcutaneously (SC) once a week for 26 weeks to children and adolescents with type 2 diabetes mellitus (T2DM) who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin, is superior to placebo in the treatment of T2DM, as measured by baseline to Week 26 change in hemoglobin A1c (HbA1c).

The key secondary efficacy objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters:

- Change in HbA1c between baseline and Week 26 (individual doses only)
- Change in fasting blood glucose (FBG) between baseline and Week 26
- Percentage of patients with HbA1c <7.0% at Week 26
- Change in body mass index (BMI) between baseline and Week 26

The other secondary efficacy objectives are to assess the 2 dulaglutide treatment groups (individually and pooled) with respect to the following parameters:

- Change in HbA1c between baseline and Week 52
- Change in FBG between baseline and Week 52
- Percentage of patients with HbA1c <7.0% at Week 52
- Change in BMI between baseline and Week 52

The secondary safety objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters at 26 weeks, and to assess the following parameters in the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) at Week 52:

- Glucose management-related safety assessed by the incidence of self-reported hypoglycemic events and the incidence of patients requiring rescue for severe, persistent hyperglycemia
- Pancreatic safety assessed by the incidence of cases of pancreatitis confirmed by adjudication and the effect on pancreatic enzymes
- Thyroid-related safety assessed by the incidence of cases of thyroid treatment-emergent adverse events (TEAEs) and effect on serum calcitonin
- Immune system-related safety, including the incidence of dulaglutide anti-drug antibodies (ADAs), and the incidence of allergic, hypersensitivity, and injection site reactions

The secondary pharmacokinetics/pharmacodynamics (PK/PD) objective is:

- Characterization of the PK of dulaglutide and the relationship between dulaglutide exposure and key safety and efficacy measures

Objectives:

Exploratory objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters at 26 weeks, and to assess the following parameters in the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) at Week 52 (unless otherwise specified):

- Percentage of patients with HbA1c ≤6.5% at Weeks 26 and 52
- Change in HbA1c between baseline and Week 13
- Percentage of patients having HbA1c <7.0% without severe, documented symptomatic (<70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Percentage of patients having HbA1c ≤6.5% without severe, documented symptomatic (<70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Change in weight between baseline and Weeks 26 and 52
- Change in hormone-related safety assessed by the effect on morning serum prolactin, insulin-like growth factor-1 (IGF-1), estradiol, testosterone (males only), luteinizing hormone (LH), and cortisol between baseline and Weeks 26 and 52
- Change in serum lipids between baseline and Weeks 26 and 52
- Change in Tanner staging between baseline and Weeks 26 and 52
- Change in BMI standard deviation score (SDS) between baseline and Weeks 26 and 52
- Change in height and height SDS between baseline and Weeks 26 and 52
- Change in waist circumference between baseline and Weeks 26 and 52
- Change in the EQ-5D Youth version (EQ-5D-Y) visual analogue scale (VAS) score between baseline and Weeks 26 and 52
- Percentage of patients reporting each level of problem on each dimension of the EQ-5D-Y at baseline, weeks 26 and 52
- Assess the effect of dulaglutide on measures of insulin resistance, beta cell function, and serum adiponectin at Weeks 13 and 26
- Change in basal insulin dose from baseline to Week 26 and from baseline to Week 52

Study Design: Study H9X-MC-GBGC (GBGC) is a Phase 3, randomized, double-blind, placebo-controlled, parallel-arm, multicenter superiority trial with an open-label extension to investigate the efficacy, safety, PK and PD in T2DM pediatric patients receiving dulaglutide compared to placebo, who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin.

Two doses of dulaglutide (0.75 mg/week and 1.5 mg/week) and placebo will be used in the 26-week double-blind period of the trial. Following this, during the 26-week open-label extension, patients who received dulaglutide will remain on the same dose they received in the double-blind period, while patients on placebo during the double-blind period will receive dulaglutide 0.75 mg/week. After completion of the open-label extension, patients will return 4 weeks later for safety follow-up.

Diagnosis and Main Criteria for Inclusion and Exclusions: Male and female children and adolescents aged 10 to <18 years, who have been diagnosed with T2DM (Global International Diabetes Foundation/International Society for Pediatric and Adolescent Diabetes [IDF-ISPAD 2011; IDF (WWW)] criteria), with a screening HbA1c >6.5% and ≤11.0% (or >6.5% to ≤9.0% for newly diagnosed patients) will be included. Treatment of T2DM at the time of randomization may include lifestyle measures (standardized diet and exercise program), with or without metformin ≥1000 mg/day, and/or basal insulin; doses of metformin and basal insulin must have been stable for at least 8 weeks prior to the screening visit. Patients should not have received bolus insulin within 6 weeks of the screening visit, except as rescue treatment for management of acute medical conditions for a maximum of 14 days. Any other antihyperglycemic drugs must be discontinued for at least 3 months prior to screening. The BMI must be >85% percentile of the general age- and gender-matched population for that country or region at screening, and body weight ≥50 kg.

Investigational Product, Dosage, and Mode of Administration: Dulaglutide 0.75 mg and 1.5 mg, administered via SC injection once weekly during the double-blind portion of the trial and 0.75 mg and 1.5 mg during the open-label portion of the trial.

Reference Therapy, Dose, and Mode of Administration or Comparative Intervention: Placebo, administered via SC injection once weekly during the double-blind portion of the trial only (baseline to Week 26).

Planned Duration of Treatment: 52 weeks
Screening period: up to 4 weeks
Treatment period: 26-week double-blind treatment period
Open-label safety extension: 26-week open-label treatment period
Safety follow-up: 30 days after last dose of study drug

Criteria for Evaluation:

Efficacy: The primary efficacy measure is change from baseline in HbA1c at 26 weeks for the pooled dulaglutide doses.

Additional secondary efficacy endpoints are the following:

- Change in FBG between baseline and Week 26 and Week 52
- Percentage of patients achieving a target HbA1c <7.0% at Week 26 and Week 52
- Change in BMI from baseline to Week 26 and Week 52
- Change in HbA1c measured in the central laboratory from baseline to Week 26 and Week 52

Safety: Secondary safety endpoints include:

- Incidence of hypoglycemic episodes and the need for rescue due to hyperglycemia at Weeks 26 and 52
- Incidence of pancreatitis and change from baseline in pancreatic enzymes to Weeks 26 and 52
- Incidence of thyroid TEAEs and change from baseline in serum calcitonin to Weeks 26 and 52
- Incidence of dulaglutide ADAs and the incidence of allergic, hypersensitivity, and injection site reactions at Weeks 26 and 52

Pharmacokinetics: Venous blood samples to measure the plasma concentrations of dulaglutide using validated bioanalytical assays.

Pharmacodynamics: Endpoints may include, but are not necessarily limited to, endpoints for efficacy (HbA1c, glucose) and safety (blood pressure, heart rate). The relationship between dulaglutide dose and/or concentration and safety and efficacy measures and patient or study factors that may influence PK or PD responses will be performed using all available patient data.

Health Outcomes: To compare the effect of dulaglutide compared to placebo on health status, as measured by the change from baseline to Week 26 and to assess the following at Week 52 in the validated patient-reported outcome (PRO) measure, EQ-5D-Y.

Statistical Methods:

Determination of Sample Size:

A sample size of approximately 150 will be enrolled (50 patients per arm), in order to obtain 120 completers at 26 weeks. This sample size provides at least 90% power for demonstrating superiority of the pooled dulaglutide 0.75 mg and 1.5 mg arms compared to placebo (primary objective), with a mean difference in change from baseline in HbA1c of -0.65% and standard deviation of 1%, assuming a dropout rate of 20%. Under the same assumptions, each individual dulaglutide arm will have at least 80% power to demonstrate superiority over placebo. The screen failure rate is estimated as 80%. Among the completers, there will be no more than 25% of patients who, at baseline, were treated with diet and exercise only and who are metformin naïve.

While the above assumptions are believed to be reasonable estimates, Eli Lilly and Company (Lilly) may consider an information-based approach to sample size re-estimation to select a larger sample size of up to approximately 189 enrolled (63 patients per arm), in order to obtain 150 completers. This sample size provides at least 80% power for demonstrating superiority of the pooled dulaglutide 0.75 mg and 1.5 mg arms compared to placebo, assuming the standard deviation is 1.3%. Using these assumptions, each individual dulaglutide arm will have at least 69% power to demonstrate superiority over placebo. Lilly will decide on whether to conduct a sample size re-estimation after taking into consideration the study enrollment rate after 100 patients have been enrolled. If it is performed, the Statistical Analysis Center's (SAC) recommendation of sample size adjustment may or may not be implemented by Lilly.

Statistical Methods:

Efficacy Analyses:

There will be 2 primary estimands to compare the placebo and the pooled dulaglutide arms in terms of the primary measure of HbA1c change from baseline to 26 weeks. One primary estimand will be an efficacy estimand, which will not use post-rescue data; the other primary estimand will be a treatment regimen estimand, which will use post-rescue data. The efficacy estimand measures the benefit of treatment when taken as directed, and the treatment regimen estimand measures the benefit of treatment as actually taken. Each estimand will be tested at the full significance level of 0.05.

The primary analysis population for the European Medicines Agency (EMA) will be the intention-to-treat (ITT) population, excluding those patients treated with diet and exercise only who are metformin naïve.

For the efficacy estimand, the primary analysis model for HbA1c will be a mixed-model for repeated measures (MMRM) using restricted maximum likelihood (REML) with treatment, insulin usage, metformin usage, visit, and treatment-by-visit as fixed effects, and baseline HbA1c as a covariate.

Analyses on other secondary efficacy measures that are continuous will be performed using MMRM on the ITT population (without post-rescue data). For percentages of patients achieving the target HbA1c of <7.0% and ≤6.5%, longitudinal logistic regression with repeated measures will be applied.

For the treatment-regimen estimand, the primary analysis model for primary and key secondary efficacy measures that are continuous will be an analysis of covariance (ANCOVA) model with multiple imputation for missing data in the ITT population (with post-rescue data). For percentages of patients achieving the target HbA1c of <7.0%, logistic regression will be applied. Missing data at the endpoint will be imputed as not achieving the target.

The primary and key secondary analyses will follow a graphical approach for multiple comparisons to strongly control the overall Type I error rate in the trial at a 2-sided α level of 0.05.

Safety Analyses:

Listings and summaries of safety data will be generated. Summary statistics will be provided for TEAEs, serious adverse events (SAEs), and study discontinuation due to adverse events (AEs) or death during the treatment period. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

For continuous laboratory analytes, the change from baseline to endpoint will be analyzed using an analysis of variance (ANOVA) on the rank-transformed data, with treatment as a fixed effect. Last observation carried forward will be used to impute missing postbaseline values. For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using Fisher's exact test.

Treatment differences in incidence of hypoglycemic episodes will be assessed by Fisher's exact test. Treatment differences in rates of hypoglycemic episodes will be assessed by a likelihood-based approach for repeated measures with a negative binomial distribution. The model will include treatment, HbA1c strata (<8.0%, ≥8.0%), metformin use, insulin use, visit, and treatment-by-visit interaction.

Pharmacokinetics/Pharmacodynamics:

Population PK (PopPK) analyses will be conducted using dosing data and dulaglutide concentrations obtained from all patients participating in the main protocol, as well as the PK addendum via commonly accepted pharmacostatistical methods (for example, nonlinear mixed-effects modeling), and covariate screening. The relationship between dulaglutide dose and/or concentration and key safety (such as heart rate and blood pressure) and efficacy measures (such as fasting blood glucose and HbA1c) will be assessed graphically or through modeling. In addition, if positive antibody titers to dulaglutide are observed, the relationship between dulaglutide PK and antibody titer will be evaluated.

3. Table of Contents

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4. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
assent	Agreement from a child or other individual who is not legally capable of providing consent, but who can understand the circumstances and risks involved in participating in a study (required by some ethical review boards [ERBs]).
AST	aspartate aminotransferase
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).
AWARD-PEDS	Assessment of Weekly AdministRation of LY2189265 in Diabetes-PEDiatric Study
blinding	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when Lilly is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or Lilly staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CI	confidence interval
CIOMs	Council for International Organizations of Medical Sciences

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, 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 Lilly 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.
CRF/eCRF	case report form/electronic 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.
CRP	Lilly clinical research physician: Lilly individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer employed by or designated by, Lilly.
CSR	clinical study report
CT	computed tomography
DMC	data monitoring committee: An independent group external to Lilly whose primary goal is to ensure the safety of all participants randomized in the trial.
DPP-IV inhibitor	dipeptidyl peptidase-IV inhibitor: A class of oral hypoglycemic drugs used to treat patients with T2DM.
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate: A measure of kidney function.
efficacy	The ability of a treatment to achieve a beneficial intended result under controlled conditions.
EMA	European Medicines Agency
end of study (trial)	The date of the last visit or last scheduled procedure shown in the Study Schedule for the last patient.
enroll	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.
enter	Patients entered into this trial are those who sign the assent form and whose parent or legal guardian signs the informed consent form.
EQ-5D-Y	EQ-5D-Youth version questionnaire
EQ VAS	EQ visual analogue scale

ERB	ethical review board: A board or committee (institutional, regional, or national) composed of medical and nonmedical members whose responsibility is to verify that the safety, welfare, and human rights of the patients participating in a clinical study are protected.
ET	early termination
EU	European Union
EuroQol	European Quality of Life
FBG	fasting blood glucose
GAD65	glutamic acid decarboxylase 65 autoantibodies: A marker of type 1 diabetes mellitus (T1DM).
GCP	good clinical practice
GLP-1 RA	glucagon-like peptide-1 receptor agonist: A class of injectable hypoglycemic drugs approved to treat adult patients with T2DM.
HbA1c	hemoglobin A1c
IA2	tyrosine phosphatase-like insulinoma antigen 2 autoantibodies: A marker of T1DM.
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IDF	Global International Diabetes Foundation
IDMS	isotope dilution mass spectrometry
IGF-1	insulin-like growth factor-1
informed consent	A process by which a pediatric patient and their parent or legal guardian voluntarily confirm their willingness for the patient to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form signed by the parent or legal guardian and an assent form signed by the patient.
interim analysis	An analysis of clinical study data, separated into treatment groups, that is conducted before the complete reporting database is created/locked for the primary endpoint.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.

investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
ISPAD	International Society for Pediatric and Adolescent Diabetes
ITT	intention to treat: 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 patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	Interactive Web-Response System
legal representative	An individual, judicial, or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
LH	luteinizing hormone
LOCF	last observation carried forward
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MEN 2A or 2B	multiple endocrine neoplasia type 2A or type 2B
MMRM	mixed-model for repeated measures
MNAR	missing not at random
MRI	magnetic resonance imaging
NPH	Neutral Protamine Hagedorn insulin
open-label	A study in which there are no restrictions on knowledge of treatment allocation; therefore, the investigator and the study participant are both aware of the drug therapy received during the study.
patient	A study participant who has the disease or condition for which the investigational product is targeted.
PD	pharmacodynamics
PG	plasma glucose
PK	pharmacokinetics
pMI	placebo multiple imputation
PopPK	population pharmacokinetics

PP	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.
PRO	Patient-Reported Outcomes
randomize	The process of assigning patients to an experimental group on a random basis.
REML	restricted maximum likelihood
rescreen	To screen a patient who was previously declared a screen failure for the same study.
SAC	Statistical Analysis Center: A group that serves the logistics needs of and provides analyses to the DMC.
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneously
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 study. In this study, screening involves 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.
SDP	single-dose pen
SGLT-2	sodium-glucose co-transporter 2: A class of oral hypoglycemic drugs approved to treat adult patients with T2DM.
SMBG	self-monitored blood glucose
SmPC	Summary of Product Characteristics (of a drug): A legal document approved by the European Medicines Agency as part of the marketing authorization of each medicine, which is the basis of information for healthcare professionals on how to use the medicine.
SSR	sample size re-estimation
subject	An individual who is or becomes a participant in clinical research, either as a recipient of the investigational product(s) or as a control. A subject may be either a healthy human or a patient.
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that either occurs or worsens at any time after treatment baseline and that does not necessarily have to have a causal relationship with this treatment.

TPO	third-party organization
TZD	thiazolidinedione: A class of oral hypoglycemic drugs approved to treat adult patients with T2DM.
ULN	upper limit of normal
US	United States
USPI	United States prescribing information (for a drug)
VAS	Visual analogue scale

A Randomized, Double-Blind Study with an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Pediatric Patients with Type 2 Diabetes Mellitus

5. Introduction

Type 2 diabetes mellitus (T2DM) is a disease primarily diagnosed in adults, and the risk of the disease increases with age (CDC 2014 [WWW]). However, there has been a significant relative increase in T2DM in adolescents and children in recent years, although type 1 diabetes mellitus (T1DM) remains the most common type of diabetes in youth (Dabelea et al. 2014).

In adults and children with T2DM, the pathophysiology of the disease is similar and is characterized by insulin resistance in the peripheral tissues and the liver, decreased insulin secretion by pancreatic β-cells , and increased glucagon secretion by pancreatic α-cells (Baggio and Drucker 2007; D'Adamo and Caprio 2011). In adolescents, puberty is known to be a time of increased insulin resistance (Caprio and Tamborlane 1994).

In the United States (US) and the European Union (EU), children and adolescents at highest risk for T2DM are minority or immigrant youths who are pubertal or post-pubertal (i.e., ≥10 years of age) living in urban environments (Pinhas-Hamiel and Zeitler 2005; Copeland et al. 2011). Virtually all children with T2DM are obese or overweight (SEARCH 2007). In the US, among youth with T2DM, studies have shown that minority children and adolescents with the disease (i.e., African Americans, Hispanics, American Indians, and Asian/Pacific Islanders) have poorer glycemic control than non-Hispanic whites, even after adjustment for all other variables (Petitti et al. 2009).

Unlike adults with T2DM, children and adolescents with T2DM have few approved glucose-lowering treatment options. Until recently, metformin and insulin were the only agents approved in the US and EU for the treatment of children and adolescents with T2DM (Tamborlane and Klingensmith 2013). In 2019, liraglutide was approved for use in adolescents with T2DM based on the results of the Phase 3 ELLIPSE study (Tamborlane et al. 2019). While therapy with metformin is effective and safe in pediatric patients (Jones et al. 2002), once metformin monotherapy is insufficient to achieve glycemic goals, glycemic control tends to deteriorate rapidly (Badaru et al. 2014). Therefore, there is an important need for additional approved agents to treat children and adolescents with T2DM that are safe and effective in this population.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown in adults to improve several of the central pathophysiological abnormalities of T2DM, including glucose-dependent insulin secretion, glucagon secretion, and obesity (Drucker and Nauck 2006). In children with T2DM, the short-acting GLP-1 RA exenatide showed reductions in postprandial glucose after a single dose (n=13; Malloy et al. 2009), while pediatric T2DM patients taking the once daily GLP-1 RA liraglutide showed improvements in hemoglobin A1c (HbA1c) after 5 weeks (n=19; Klein et al. 2014). In these small trials, the GLP-1 RAs were well tolerated, with pharmacokinetic (PK) profiles similar to adults. In the ELLIPSE Phase 3 trial, liraglutide was

shown to be superior to placebo when added to metformin, with or without basal insulin, with respect to glycemic control in children and adolescents, with gastrointestinal adverse events (AEs) being more common in the liraglutide group (Tamborlane et al. 2019). According to publicly available trial information (ClinicalTrials.gov), enrollment in the Phase 3 trials has been lengthy and challenging, probably due to the relatively small number of pediatric patients with T2DM worldwide and the increasing number of trials enrolling pediatric T2DM patients.

Dulaglutide is a long-acting GLP-1 RA. In 6 Phase 3 studies in adults, once weekly dulaglutide (both 0.75 mg and 1.5 mg) was associated with clinically relevant long-term decreases in glucose concentration (as measured by HbA1c) and body weight, low risk of hypoglycemia, low risk of immunogenicity, and no new safety observations compared to the approved agents from the GLP-1 RA class (Edwards and Minze 2015).

Because of the pathophysiological similarities between T2DM in adults and youth, it is hypothesized that dulaglutide will also have efficacy in the pediatric population with a similar safety profile.

The goals of this randomized, double-blind, placebo-controlled, multicenter, Phase 3 superiority clinical trial with an open-label extension are to investigate the safety, efficacy, and pharmacokinetics/pharmacodynamics (PK/PD) of 2 doses of dulaglutide in a pediatric T2DM population who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin. The double-blind portion of the clinical trial will last for 26 weeks and will test placebo against dulaglutide 0.75 and 1.5 mg/week (both of which are approved for the treatment of adults with T2DM in the US and the EU). This will be followed by the 26-week open-label portion of the clinical trial where all patients will receive either dulaglutide 0.75 mg/week or 1.5 mg/week, which will be followed by a 30-day safety follow-up period.

More detailed information about the known and expected benefits and risks of dulaglutide may be found in the US prescribing information (USPI) or the Summary of Product Characteristics, EU (SmPC).

6. Objectives

6.1. Primary Objective

The primary objective of this study is to test the hypothesis that dulaglutide (0.75 mg and 1.5 mg, pooled) given subcutaneously (SC) once a week for 26 weeks to children and adolescents with T2DM who have inadequate glycemic control, despite diet and exercise, with or without metformin and/or basal insulin is superior to placebo in the treatment of T2DM, as measured by baseline to Week 26 change in HbA1c.

6.2. Secondary Objectives

The secondary objectives of the study are to assess the efficacy, safety, PK and pharmacodynamics (PD) in patients.

The key secondary efficacy objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters:

- Change in HbA1c between baseline and Week 26 (individual doses only)
- Change in fasting blood glucose (FBG) between baseline and Week 26
- Percentage of patients with HbA1c <7.0% at Week 26
- Change in body mass index (BMI) between baseline and Week 26

The other secondary efficacy objectives are to assess the 2 dulaglutide treatment groups (individually and pooled) with respect to the following parameters:

- Change in HbA1c between baseline and Week 52
- Change in FBG between baseline and Week 52
- Percentage of patients with HbA1c <7.0% at Week 52
- Change in BMI between baseline and Week 52

The secondary safety objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters at 26 weeks, and to assess the following parameters in the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) at Week 52:

- Glucose management-related safety assessed by the incidence of self-reported hypoglycemic events and the incidence of patients requiring rescue for severe, persistent hyperglycemia
- Pancreatic safety assessed by the incidence of cases of pancreatitis confirmed by adjudication and the effect on pancreatic enzymes
- Thyroid-related safety assessed by the incidence of cases of thyroid treatment-emergent adverse events (TEAEs) and effect on serum calcitonin
- Immune system-related safety, including the incidence of dulaglutide anti-drug antibodies (ADAs), and the incidence of allergic, hypersensitivity, and injection site reactions.

The secondary PK/PD objective is:

- Characterization of the PK of dulaglutide and the relationship between dulaglutide exposure and key safety and efficacy measures.

6.3. Exploratory Objectives

The exploratory objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters at 26 weeks, and to assess the following parameters in the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) at Week 52 (unless otherwise specified):

- Percentage of patients with HbA1c ≤6.5% at Weeks 26 and 52
- Change in HbA1c between baseline and Week 13
- Percentage of patients having HbA1c <7.0% without severe, documented symptomatic (<70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Percentage of patients having HbA1c ≤6.5% without severe, documented symptomatic (<70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Change in weight between baseline and Weeks 26 and 52
- Change in hormone-related safety assessed by the effect on morning serum prolactin, insulin-like growth factor-1 (IGF-1), estradiol, testosterone (males only), luteinizing hormone (LH), and cortisol between baseline and Weeks 26 and 52
- Change in serum lipids between baseline and Weeks 26 and 52
- Change in Tanner staging between baseline and Weeks 26 and 52
- Change in BMI standard deviation score (SDS) between baseline and Weeks 26 and 52
- Change in height and height SDS between baseline and Weeks 26 and 52
- Change in waist circumference between baseline and Weeks 26 and 52
- Change in the EQ-5D-Y VAS score between baseline and Weeks 26 and 52
- Percentage of patients reporting each level of problem on each dimension of the EQ-5D-Y at baseline, weeks 26 and 52
- Assess the effect of dulaglutide on measures of insulin resistance, beta cell function, and serum adiponectin at Weeks 13 and 26
- Change in basal insulin dose from baseline to Week 26 and from baseline to Week 52

7. Investigational Plan

7.1. Summary of Study Design

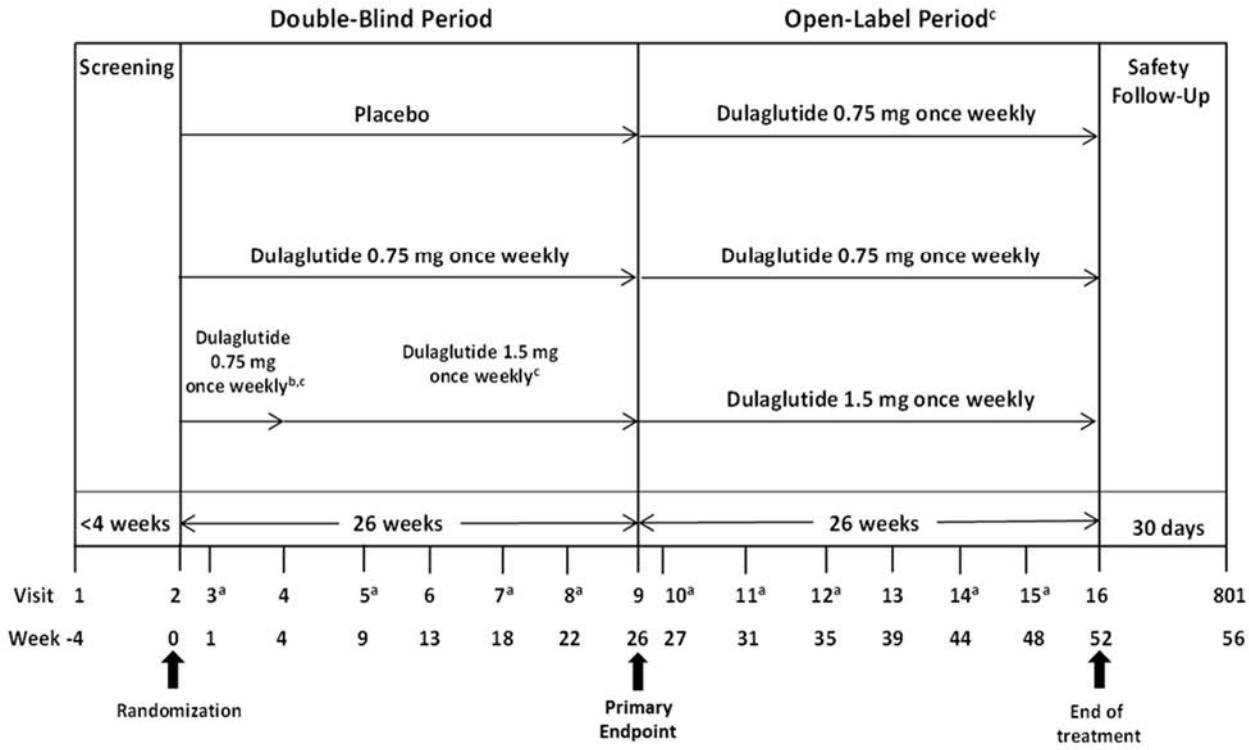
Study H9X-MC-GBGC (GBGC) is a Phase 3, multicenter, randomized, double-blind, parallel-arm, placebo-controlled superiority trial with an open-label extension. Approximately 150 male and female children and adolescents (ages 10 to <18 years) with T2DM and inadequate glycemic control on diet and exercise alone or diet and exercise plus metformin and/or basal insulin will be enrolled. Randomization will be stratified by the patient's background therapy, and screening HbA1c. There will be a limitation on the number of patients with inadequate glycemic control managed by diet and exercise alone who have not previously received metformin so that these patients constitute no more than 25% of the total number of completers. The sponsor may place limitations on the patients enrolled depending on their demographics to meet regulatory expectations.

The main study has 4 periods: (1) a screening period lasting up to 4 weeks; (2) a double-blind treatment period lasting 26 weeks; (3) an open-label extension period lasting 26 weeks; and (4) a 30-day safety follow-up period. The end of trial is the date of the last visit or last scheduled procedure shown in the Study Schedule (Attachment 1) for the last patient.

One of the following measures will be offered to reduce pain associated with venipuncture: anesthetic creams, anesthetic patches, or high pressure anesthetic delivery system immediately before venipuncture.

Patients are discouraged from donating blood or blood products during the trial and for 30 days thereafter.

Figure GBGC.1 illustrates the study design.



a Phone visits.

b Patients who tolerate the 0.75 mg/week dose in the opinion of the investigator will be changed to dulaglutide 1.5 mg/week at Week 4.

c If patients do not tolerate the higher dose, they will be allowed to go back to the previous dose.

Figure GBGC.1. Illustration of study design for Clinical Protocol H9X-MC-GBGC.

Screening period: Patients may be rescreened twice for any reason. At the screening visit, during which patients may be in the non-fasted state, the parent or legal guardian will sign the informed consent form (ICF) and the patient will sign the assent form. If the patient has reached the age of majority per local country regulations, a separate assent document may not be required, as the patient is eligible to sign the ICF. The patients will then undergo assessments related to the inclusion and exclusion criteria.

Week -4: Screening Visit

At this visit, the following will be performed:

- A complete medical history will be taken along with full date of birth.
- Vital signs will be measured, along with height and weight, and BMI will be calculated.
- The patient's concomitant medications will be documented, including diabetes medications.
- Blood will be collected and sent to the central laboratory (see the Study Schedule, Attachment 1).
- Females of childbearing potential will have documentation of the date of their last menstrual period and a serum pregnancy test will be performed. A local urine pregnancy

test may be performed if pregnancy is suspected (see the Study Schedule, Attachment 1). If either test is positive, the patient will be excluded from the trial.

- Females of childbearing potential will undergo questioning about the use of effective contraception (see Attachment 4).
- For those patients who are not immediately excluded, both the patient and parent or legal guardian may be trained on how to use the dulaglutide single-dose pen (SDP) using the demonstration pen, which has no needle and contains no medication.

The patient and parent or legal guardian will be given an appointment to return to the clinic within 4 weeks (±7 days), in the fasted state, for the randomization visit, assuming the patient meets all inclusion and no exclusion criteria at that time.

Double-blind treatment period: This treatment period will last for 26 weeks. With the exception of a telephone visit scheduled 1 week after randomization, study visits will occur approximately monthly: face-to-face visits in the clinic will occur at 1 month (Week 4), 3 months (Week 13), and 6 months (Week 26) and telephone visits will occur in between the face-to-face visits (Weeks 9, 18, and 22). Any phone visit may be converted to a face-to-face visit if deemed medically necessary by study personnel. Optional visits may occur between regularly scheduled visits if deemed medically necessary. If a patient misses a face-to-face visit, every effort must be made to reschedule the visit as soon as possible. If a patient misses a phone visit, the visit should be rescheduled as soon as possible. If the patient misses several visits, every effort must be made to get the patient to return to the clinic, even if it is only for the last visit. A parent or legal guardian should accompany the patient to each clinic visit—whether the parent/legal guardian must be present at each phone visit should be determined by the parent/legal guardian and study personnel.

At the randomization visit (Week 0), for those patients taking background diabetes medication, the metformin and basal insulin doses will be established. Generally, background diabetes medication should not be increased more than 15% during the double-blind period, though it may be decreased at any time if the patient experiences hypoglycemia (see Section 9.8; for the definition of hypoglycemia, see Section 10.4.1.2.1).

During the entire trial, patients should perform self-monitoring of blood glucose (SMBG) in the fasted state and at 1 other time each day, as well as at any time they have symptoms suggestive of hypoglycemia. For each hypoglycemic episode, patients should record their blood glucose level (if available), associated symptoms, and treatment in the study diaries provided. For this study, a hypoglycemic episode should be noted as having occurred any time a patient feels that (s)he is experiencing a sign or symptom associated with hypoglycemia OR has a blood glucose level <70 mg/dL (<3.9 mmol/L), even if asymptomatic. The time and date of all SMBG readings must be recorded in the study diaries as well as the date and time of weekly study drug administration.

If pregnancy is suspected at any time in females of childbearing potential, a local urine pregnancy test will be performed and a serum pregnancy test will be sent to the central

laboratory. If the patient is pregnant, she must be permanently discontinued from study drug and the study.

Week 0: Randomization

At this visit, the patient will return to the clinic in the fasted state. The following will be performed:

- All inclusion and exclusion criteria must be reviewed to ensure that the patient qualifies for the trial.
- A physical examination by a physician will be performed which includes Tanner staging.
- Vital signs will be measured, along with height, weight, and waist circumference, and BMI will be calculated.
- Blood and urine will be collected for baseline laboratory tests and sent to the central laboratory.
    - A local urine pregnancy test must be performed for all females of childbearing potential prior to randomization. If positive, the patient will not be randomized.
- An electrocardiogram (ECG) will be performed.
- Concomitant medications will be documented.
- The baseline background diabetes medication dose (for those patients taking metformin and/or basal insulin) will be established. Generally, once this dose is established, it should not be increased more than 15% during the double-blind period, although it may be decreased at any time if the patient experiences hypoglycemia (see Section 9.8).
- Females of childbearing potential will have documentation of the date of their last menstrual period and will be questioned about the use of effective contraception (see Attachment 4).
- The patient will complete the EQ-5D-Y health outcomes questionnaires.
- The patient will receive:
    - Study diaries for the recording of glycemic and other information and instructions on how to fill them out.
    - A glucometer and supplies, as well as any training needed to use the glucometer.
    - Diet and exercise instruction for their T2DM.
    - Training for the patient and parent or legal guardian on how to use the SDP using the demonstration pen.
    - A supply of study drug (after the investigator uses the Interactive Web-Response System [IWRS] to get the study drug assignment).

At the conclusion of this visit, the patient, caregiver, or study personnel (whichever is deemed most appropriate by study personnel) will inject the patient with the first dose of study drug, noting the time and date of injection in the study diary. This day now becomes the patient's day of study drug administration.

The patient will be sent home with appointments for 1 telephone visit, which will occur in 1 week (Week 1) and for a clinic visit in 4 weeks (Week 4) in the non-fasted state.

Week 1: Telephone Visit (Visit Window up to ± 3 days)

At this visit, the following will be performed:

- The contents of the study diary for the previous week will be reviewed:
  - Self-monitoring of blood glucose results
  - Hypoglycemia events
  - Adverse event information
  - The date and time of all study drug injections
  - Any new concomitant medications or change in metformin or insulin dose
  - Females: The date of the last menstrual period

Week 4: Clinic Visit (Visit Window up to ±7 days)

At this visit, the patient will return to the clinic in the non-fasted state. The following will be performed:

- A symptom-directed physical examination by a physician will be performed.
- Vital signs will be measured, along with height and weight.
- Concomitant medication information will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- Study diaries will be collected and the following reviewed:
  - Self-monitoring of blood glucose results
  - Hypoglycemia events
  - Adverse event information
  - The date and time of all study drug injections
  - Females: The date of the last menstrual period
- A local urine pregnancy test will be performed for all females of childbearing potential.
- The patient will receive:
  - Study diaries
  - Glucometer supplies
  - Diet and exercise instruction for their T2DM
  - Study drug. (At this visit, those patients who were assigned in a blinded fashion to 1.5 mg dulaglutide will be titrated from 0.75 mg/week to 1.5 mg/week. Therefore, prior to dispensing study drug to any patient, the physician will confirm via IWRS that the patient tolerated the previous 4 weeks of blinded study drug.)

The patient will be sent home with appointments for 1 telephone visit, which will occur in 5 weeks (Week 9) and for a clinic visit in 9 weeks (Week 13) in the fasted state.

Week 9: Telephone Visit (Visit Window up to ±7 days)

At this visit, the following will be performed:

- Concomitant medication information will be documented
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- The contents of the study diaries for the previous month will be reviewed:
    - Self-monitoring of blood glucose results
    - Hypoglycemia events
    - Adverse event information
    - The date and time of all study drug injections
    - Females: The date of the last menstrual period

Week 13: Clinic Visit (Visit Window up to ±7 days)

At the half-way point in the double-blind portion of the clinical trial, the patient will return to the clinic in the fasted state. This visit must occur on the date of the patient's usual weekly injection of study drug, and before injection of study drug, as the patient will undergo collection of blood for a pre dose PK level at this visit, inject study drug and have a post dose PK level drawn. The following will be performed:

- Blood will be collected for a predose PK level, noting the exact date and time.*
- This will be followed by injection of study drug, noting the exact date and time.
- A symptom-directed physical exam by a physician will be performed.
- Vital signs will be measured, along with height, weight, and waist circumference.
- Concomitant medication information will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- Study diaries will be collected and the following reviewed:
    - Self-monitoring of blood glucose results
    - Hypoglycemia events
    - Adverse event information
    - The date and time of all study drug injections
    - Females: The date of the last menstrual period
- The patient will receive:
    - Study diaries
    - Glucometer supplies
    - Diet and exercise instruction for their T2DM
    - Study drug
- The visit will conclude with another collection of blood for PK (this post dose PK level must be drawn at least 1 hour and up to 12 hours after study drug injection) noting the exact date and time and the elapsed time since study drug injection.*

The patient will be sent home with appointments for 2 telephone visits, which will occur in 5 and 9 weeks (Weeks 18 and 22), and a clinic visit in 13 weeks (Week 26) in the fasted state for the final double-blind visit.

*All other laboratories required to be collected at this visit (including ADAs) may be collected with either the first or the second blood draw. In females of childbearing potential, the laboratories will include a serum pregnancy test (a local urine pregnancy test must also be performed).

Weeks 18 and 22: Telephone Visits (Visit Window up to ±7 days)

At these visits, the following will be performed:

- Concomitant medication will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- The contents of the study diaries for the previous month will be reviewed:
    - Self-monitoring of blood glucose results
    - Hypoglycemia events
    - Adverse event information
    - The date and time of all study drug injections
    - Females: The date of the last menstrual period

Week 26: Final Double-Blind Visit (Visit Window up to ±6 days)

At the final visit for the double-blind portion of the trial, patients will return to the clinic in the morning in the fasted state. This visit must occur on the date of the patient's usual weekly injection of study drug and before the patient has injected study drug, as blood will be collected for a pre-dose PK level prior to study drug injection.

The following will be performed:

- A physician will perform a physical exam and Tanner staging.
- Vital signs will be measured, along with height, weight, and waist circumference.
- Concomitant medication information will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- Study diaries will be collected and the following reviewed:
    - Self-monitoring of blood glucose results
    - Hypoglycemia events
    - Adverse event information
    - The date and time of all study drug injections
    - Females: The date of the last menstrual period
- As this is the end of the double-blind period, the dose of background diabetes medication (i.e., metformin and basal insulin) may be re-adjusted as needed.
- Blood for PK (pre dose) and other scheduled laboratories will be collected and sent to the central laboratory.
    - A local urine pregnancy test and a serum pregnancy test must be performed for all females of childbearing potential.
- An electrocardiogram (ECG) will be performed.
- The patient will complete the EQ-5D-Y health outcomes questionnaire.

- The patient will receive:
  - Study diaries
  - Glucometer supplies
  - Diet and exercise instruction for their T2DM
- After the site processes the visit in the IWRS, patients will be dispensed the appropriate open-label study drug.
- As it is the patient's dosing day, at the conclusion of this visit, if desired, the patient's first dose of open-label study drug may be administered.

The patient will be sent home with appointments for 3 telephone visits, which will occur in 1 week (Week 27), 5 weeks (Week 31), and 9 weeks (Week 35), and with a clinic visit in 13 weeks (Week 39) in which the patient should return in the non-fasted state.

Open-label period:
This treatment period will last for 26 weeks. With the exception of a telephone visit scheduled 1 week after the open-label period begins, study visits will occur approximately monthly: face-to-face visits in the clinic will occur approximately every 3 months (Week 39 and Week 52) and telephone visits will occur in between the face-to-face visits (Weeks 31, 35, 44, and 48).

If pregnancy is suspected at any time in females of childbearing potential, a local urine pregnancy test will be performed and a serum pregnancy test will be sent to the central laboratory. If the patient is pregnant, she must be permanently discontinued from study drug and the study.

Weeks 27, 31, and 35: Telephone Visits (Visit Window up to ±7 days [+7 days for Week 27])
At these visits, the following will be performed:

- Concomitant medication will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- The contents of the study diaries for the previous month will be reviewed:
  - Self-monitoring of blood glucose results
  - Hypoglycemia events
  - Adverse event information
  - The date and time of all study drug injections (Note: Date and time of first dose of open-label study drug, which should be administered after the Week 26 visit [Visit 9] is completed, will be recorded on the exposure form at the Week 27 visit [Visit 10])
  - Females: The date of the last menstrual period

Week 39: Clinic Visit (Visit Window up to ±7 days)

At the half-way point in the open-label portion of the clinical trial, the patient will return to the clinic in the non-fasted state on their usual dosing day or up to 2 days later. The following will be performed:

- If it is the patient's dosing day, and the patient has not yet taken their weekly dose, the patient's study drug will be administered.
- A symptom-directed physical exam by a physician will be performed.
- Vital signs will be measured, along with height and weight.
- Concomitant medication information will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- Study diaries will be collected and the following reviewed:
    - Self-monitoring of blood glucose results
    - Hypoglycemia events
    - Adverse event information
    - The date and time of all study drug injections
    - Females: The date of the last menstrual period
- Blood will be collected and sent to the central laboratory. If it is the patient's dosing day, the blood may be collected any time after the patient's dose has been administered.
    - Collection of blood for PK taken any time up to 2 days post dose
    - A local urine pregnancy test and a serum pregnancy test must be performed for all females of childbearing potential.
- The patient will receive:
    - Study diaries
    - Glucometer supplies
    - Diet and exercise instruction for their T2DM
    - A supply of study drug.

The patient will be sent home with appointments for 2 telephone visits, which will occur in 5 weeks (Week 44) and 9 weeks (Week 48), and a clinic visit in 13 weeks (Week 52) in the fasted state for the final open-label visit.

Weeks 44 and 48: Telephone Visits (Visit Window up to ±7 days)

At these visits, the following will be performed:

- Concomitant medication will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- The contents of the study diaries for the previous month will be reviewed:
    - Self-monitoring of blood glucose results
    - Hypoglycemia events
    - Adverse event information
    - The date and time of all study drug injections
    - Females: The date of the last menstrual period

Week 52: Final Open-label Visit (Visit Window up to ±7 days)

At the final visit for the open-label portion of the trial, patients will return to the clinic in the morning in the fasted state. The following will be performed:

- A physician will perform a physical exam (and Tanner staging, if appropriate).
- Vital signs will be measured, along with height and weight.
- Concomitant medication information will be documented.
- If a female is of childbearing potential, the use of effective contraception will be discussed (see Attachment 4).
- Study diaries will be collected and the following reviewed:
    - Self-monitoring of blood glucose results
    - Hypoglycemia events
    - Adverse event information
    - The date and time of all study drug injections
    - Females: The date of the last menstrual period
- Blood and urine will be collected and sent to the central laboratory.
    - Collection of blood for PK any time during this visit
    - A local urine pregnancy test and a serum pregnancy test must be performed for all females of childbearing potential.
    - The patient will complete the EQ-5D-Y health outcomes questionnaire.
- An ECG will be performed.
- The patient will receive:
    - Study diaries
    - Glucometer supplies
    - Diet and exercise instruction for their T2DM
- As this is the end of the open-label period and the patient will stop taking dulaglutide, the patient's background diabetes medication must be adjusted.
    - Glucagon-like peptide-1 receptor agonists (including, but not limited to, exenatide, liraglutide, albiglutide, and lixisenatide) and dipeptidyl peptidase-IV (DPP-IV) inhibitors (including, but not limited to, sitagliptin, vildagliptin, saxagliptin, linagliptin, anagliptin, teneligliptin, and alogliptin) are not allowed during the next 30 days.

The patient will be sent home with an appointment for a final visit, which will occur in 30 days in the non-fasted state (safety follow-up visit; Visit 801).

Safety follow-up period: Approximately 30 days after completion of the 26 weeks of open-label treatment, patients will return in the non-fasted state to complete a safety follow-up visit (Visit 801).

Week 56: Safety Follow-Up Visit (Visit Window up to ±7 days)

The patient will return to the clinic in the non-fasted state. At this visit, the following will be performed.

- Vital signs will be measured, along with height and weight.
- Concomitant medication information will be documented.
- Blood will be drawn and sent to the central laboratory.
    - Collection of blood for PK any time during this visit.
- Study diaries and their contents will be collected:

  - Adverse event information
  - Females: The date of the last menstrual period
- Patients must return any remaining study equipment to the investigative site.

Patients discontinuing the study early should have this visit approximately 30 days after the early termination visit. Patients who discontinue the study before randomization do not need to complete this visit.

7.2. Discussion of Design and Control

This is a superiority study, the main objective of which is to compare the effects of dulaglutide 0.75 and dulaglutide 1.5 mg/week (pooled), added to diet and exercise, with or without metformin and/or basal insulin, to those of placebo on glycemic control (defined as change in HbA1c) in pediatric patients with T2DM over a 26-week period.

The efficacy measure, HbA1c, was chosen as the primary objective because it is an accepted endpoint in glycemic trials in pediatric patients with T2DM.

The use of placebo for 26 weeks during the double-blind portion of the trial was considered appropriate, as no results of Phase 3 trials with dulaglutide (or any other GLP-1 RA) had been reported in the pediatric population at the time of protocol development. Thus, a placebo comparator is necessary to understand dulaglutide's true safety and effectiveness. In order to protect the safety of the patients enrolled in both arms of this trial, the double-blind period is relatively short, there are clear rescue criteria for patients with severe, persistent hyperglycemia (see Section 8.3.4) and patients are allowed to decrease basal insulin or metformin as needed if hypoglycemia occurs (for the definition of hypoglycemia, see Section 10.4.1.2.1).

The doses of dulaglutide for this trial were chosen by PK simulations (see Section 9.4).

The background therapies of diet and exercise, with or without metformin and/or basal insulin, are considered appropriate, as these are approved treatments for pediatric patients with T2DM in the US, EU, and many countries around the world.

In adults, dulaglutide has been shown to be effective in lowering HbA1c with consistent safety in the monotherapy setting (diet and exercise only) and when added to metformin and other oral anti-diabetes agents and/or short-acting or basal insulin. The decision not to maximize the doses of metformin and basal insulin was considered appropriate, as metformin at a dose of ≥1000 mg/day is considered an effective dose in pediatric patients. For patients using basal insulin, up-titration of insulin during the double-blind period would reduce the trial's ability to perceive a difference between the placebo and dulaglutide treatment arms and therefore is not allowed (see Section 9.8). Temporary increases in insulin dose are allowed during the trial and appropriate rescue methods exist in the protocol to ensure that patients do not continue in the double-blind portion of the trial with poor glycemic control. Patients may decrease doses of background diabetes medications at any time if hypoglycemia is noted.

According to the visit schedule, patients will be seen by physicians in the clinic approximately every 3 months, with monthly telephone visits in between the clinic visits. This is considered appropriate, as pediatric patients with T2DM are usually seen in the clinic every 3 months.

There is uncertainty in the correct sample size to have sufficient power for this study. This is due to a number of reasons: lack of experience with T2DM pediatric patients receiving GLP-1 RAs; a wide range of baseline HbA1c values; and the inclusion of patients potentially using both metformin and basal insulin in this trial. These factors will influence the variability of the treatment difference for the primary endpoint, which is mean change from baseline in HbA1c at 26 weeks. An underestimate of the variability could lead to an inconclusive study. An overestimate of the treatment variability could expose more patients than necessary to placebo and could lead to unnecessary enrollment challenges. As a consequence, an information-based sample size re-estimation may be implemented to mitigate against an inconclusive study.

To optimize statistical power to detect a meaningful treatment difference, there will be treatment group comparisons at the 26-week primary endpoint based on the pooled dulaglutide arms compared to placebo.

8. Study Population

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened up to 2 times. The interval between re-screenings should be at least 8 weeks. Each time rescreening is performed, the individual must sign a new ICF, and will be assigned a new identification number.

Entered patients who meet all of the Inclusion Criteria and are not excluded by Exclusion Criteria will proceed to Visit 2 (randomization).

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, are not permitted.

8.1. Inclusion Criteria

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

[1] Are male or female children and adolescents aged 10 to <18 years at randomization.

[2] Have T2DM as diagnosed by Global International Diabetes Foundation/International Society for Pediatric and Adolescent Diabetes (IDF-ISPAD; IDF 2011 [WWW]) criteria (see Attachment 5).

[3] Have T2DM treated at the time of randomization with lifestyle measures (standardized diet and exercise program), with or without metformin (≥1000 mg/day, unless the patient has documented intolerance of metformin, in which case the highest tolerated dose will be used, and not more than the locally approved dose), and/or basal insulin therapy. Doses of metformin and basal insulin must have been stable (±15%) for at least 8 weeks prior to screening visit. Lifestyle measures must have been in place for at least 8 weeks prior to the screening visit.

[4] Have HbA1c >6.5% to ≤11.0% at screening visit, unless a patient is newly diagnosed and only treated with lifestyle measures, in which case the HbA1c should be >6.5% to ≤9.0%.

[5] Have BMI >85% percentile of the general age- and gender-matched population for that country or region and body weight ≥50 kg.

[6] Both the child or adolescent with T2DM and a parent or legal guardian are able to understand and fully participate in the activities of the clinical trial and sign their assent and consent, respectively.

8.1.1. Disease Diagnostic Criteria

For the purposes of this study, patients with T2DM are defined by the IDF-ISPAD (IDF 2011 [WWW]) criteria (see Attachment 5), the absence of diabetes-associated autoantibodies for T1DM (glutamic acid decarboxylase 65 [GAD65] autoantibodies and tyrosine phosphatase-like

insulinoma antigen 2 [IA2] antibodies), and BMI >85% percentile of the general age- and gender-matched population for that country or region at screening.

8.2. Exclusion Criteria

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

[7] Have known T1DM.

[8] Have a history of diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome.

[9] Have diabetes-associated autoantibodies (GAD65 or IA2), historically or at screening.

[10] Have a clinically significant gastric emptying abnormality, in the opinion of the investigator, or previous gastric bypass.

[11] Have prior chronic, recurrent, or idiopathic pancreatitis; known gallbladder disease; or clinical hypertriglyceridemia associated with pancreatitis, i.e., >11.2 mmol/L (>1000 mg/dL), historically or at screening.

[12] Have a known self or family history of multiple endocrine neoplasia (MEN) type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.

[13] Have a serum calcitonin ≥20 pg/mL at screening, as determined by the central laboratory.

[14] Have an estimated glomerular filtration rate (eGFR) <60 mL/min at screening.

[15] Have recurrent severe hypoglycemia or hypoglycemic unawareness as judged by the investigator.

[16] Have blood pressure above the 99th percentile for age and gender in children OR systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mmHg at screening.

[17] Have an active or treated malignancy.

[18] Have a hemoglobinopathy or other disorder that interferes with the accurate determination of the primary endpoint, including, but not limited to, patients with the following hemoglobin variants: HbS, HbC, HbE, HbSC, and elevated HbF.

[19] For females of childbearing potential: Are sexually active and not on either 1 highly effective form of contraception or 2 effective forms of contraception (see Attachment 4).

[20] For females of childbearing potential: Are pregnant or intending to become pregnant.

[21] For females of childbearing potential: Are breastfeeding.

[22] Are known to or are suspected of chronically abusing alcohol or drugs/narcotics.

[23] Have any clinically significant disorder, other than T2DM, that, in the investigator's opinion, would preclude participation in the trial.

[24] Are currently taking a class of antihyperglycemic medication other than biguanides (metformin) and/or basal insulin including but not limited to bolus insulin, a sulfonylurea, alpha-glucosidase inhibitor, DPP-IV inhibitor, GLP-1 RA, thiazolidinedione (TZD), glinide, and sodium-glucose co-transporter 2 (SGLT-2) inhibitor. Except for bolus insulin, these medications must have been stopped at least 3 months before the screening visit. Patients should not have received bolus insulin within 6 weeks of the screening visit, except as rescue treatment for management of acute medical conditions for a maximum of 14 days.

[25] Are currently using inhaled steroids at a dose equal to or above 1000 mcg Flovent® (fluticasone propionate) daily.

[26] Have used chronic (>14 consecutive days) oral steroids within the last 60 days or more than 20 days use within the past year.

[27] If currently taking medications indicated to treat a psychiatric condition (including, but not limited to depression, anxiety, bipolar disease, attention deficit hyperactivity disorder [ADHD], and schizophrenia); and if doses have not been stable (±10%) for at least 3 months prior to screening, and/or if there is an intention to change or add new medications during the trial.

[28] Have used any prescription weight loss medication(s) within 30 days of screening or intend to use chronically during the clinical trial. These include, but are not limited to, the following: Contrave® (naltrexone/bupropion), Saxenda® (liraglutide), Xenical® (orlistat), Meridia® (sibutramine), Acutrim® (phenylpropanolamine), Sanorex® (mazindol), Adipex® (phentermine), BELVIQ® (lorcaserin), Qsymia™ (phentermine/topiramate combination), or similar over-the-counter medications (e.g., allī®).

[29] Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[30] Are Lilly employees or are employees of third-party organizations (TPOs) involved in the study who require exclusion of their employees.

[31] Are currently enrolled in any other clinical trial involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study.

[32] Have participated within the last 30 days in a clinical trial involving an IP other than the IP used in this study. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed.

[33] Have previously completed or withdrawn from this study or any other study investigating dulaglutide. This exclusion criterion does not apply to patients who are rescreened prior to randomization.

8.2.1. Rationale for Exclusion of Certain Study Candidates

Exclusion Criteria [7] to [9] eliminate patients with T1DM or those in whom HbA1c cannot be accurately assessed.

Exclusion Criteria [10] to [17] eliminate patients with conditions that may pose a risk for morbidity or mortality.

Exclusion Criterion [18] eliminates patients with conditions that interfere with the assessment of the primary endpoint.

Exclusion Criteria [19] to [21] eliminate female patients at risk for becoming pregnant or who are nursing.

Exclusion Criteria [22] to [23] eliminate patients with conditions making them more likely to not complete the clinical trial.

Exclusion Criteria [24] to [28] eliminate patients taking drugs that may interfere with assessment of the primary endpoint.

Exclusion Criteria [29] to [33] reduce the potential bias that may be introduced at the study site.

8.3. Discontinuations

8.3.1. Discontinuation of Inadvertently Enrolled Patients

The criteria for enrollment must be followed explicitly. If Lilly or the investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical research physician (CRP) or designee and the investigator to determine if the patient may continue in the study, with or without study drug. The investigator must obtain documented approval from the Lilly CRP (or designee) to allow the inadvertently enrolled patient to continue in the study with or without treatment with study drug.

In general, inadvertently enrolled patients must continue in the study, with or without study drug, unless they withdraw their informed consent, are lost to follow-up, have T1DM, have a hemoglobinopathy or other disorder that interferes with the accurate determination of the primary endpoint, or are pregnant or breastfeeding.

Study drug will be continued if the Lilly CRP (or designee) and the investigator agree that it is acceptable for a patient to continue to receive study drug. Patients with significant safety concerns will not be continued on study drug. For patients continuing on study drug, a clinical justification will be provided. If the Lilly CRP (or designee) believes that it is inappropriate for the patient to continue to receive study drug, it will be discontinued, but the patient will remain in the study, and attend all scheduled visits, and be evaluated for all efficacy and safety endpoints for the duration of the study.

8.3.2. Discontinuation of Investigational Product

Patients will be discontinued from study drug if they are confirmed to have the following Exclusion Criteria:

- [7] to [9]—T1DM (the patient will also be discontinued from the trial)
- [11] to [12]—safety concerns, for example, patients will be discontinued from study drug if they develop confirmed pancreatitis (if not confirmed, study drug may be restarted) (see Section 10.4.1.2.2).
- [18]—unable to assess primary endpoint (the patient will also be discontinued from the trial)
- [19] to [21]—pregnancy or breastfeeding (the patient will also be discontinued from the trial)
- [29] to [33]—potential bias.

The patient should be discontinued from study drug for abnormal liver tests when the patient meets 1 of the following conditions (and after consultation with the Lilly CRP or designee):

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >6×upper limit of normal (ULN)
- ALT or AST >5×ULN for more than 2 weeks
- ALT or AST >3×ULN and total bilirubin level >2×ULN or prothrombin time >1.5×ULN
- ALT or AST >3×ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).
- Alkaline phosphatase (ALP) >3×ULN
- ALP >2.5×ULN and total bilirubin >2×ULN
- ALP >2.5×ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

The most common AEs experienced by patients receiving dulaglutide are gastrointestinal symptoms known to be associated with GLP-1 RA therapy. These symptoms may be self-limited. Patients judged by the investigator unable to tolerate study drug (e.g., intractable nausea, vomiting and diarrhea) should temporarily (or permanently) discontinue study drug, but remain in the study.

Patients unable to tolerate the study drug after a potential dosage change at Week 4 may temporarily go back to the previously assigned study drug. However, they should be encouraged to take their assigned study drug, if possible.

Study drug should be temporarily discontinued in any individual suspected of having a severe or serious allergic reaction to study drug or other serious safety concerns. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator.

Patients who permanently discontinue the study drug early will receive another glucose-lowering intervention and continue to attend all scheduled visits and undergo all scheduled procedures as shown in the Study Schedule (Attachment 1). The new glucose-lowering intervention must not be another GLP-1 receptor antagonist or DPP-IV inhibitor.

8.3.3. Patient Discontinuation from the Study

Patients will be discontinued from the study under the following circumstances:

- Patient Decision
    - The patient (and/or parent or legal guardian) withdraws his/her/their consent
- Lost to Follow-Up
    - A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.
        - Site personnel are expected to make diligent, repeated attempts to contact patients who fail to return for a scheduled visit or who were, otherwise, unable to be followed up by the site. Site personnel, or an independent third party, may attempt to collect the vital status of the patient within legal and ethical boundaries for all patients randomized, including those who did not get study drug.
- Inadvertent Enrollment
    - Patients found to have T1DM, a hemoglobinopathy or other disorder that interferes with the accurate determination of the primary endpoint, or are pregnant or breastfeeding at the time of enrollment, will be discontinued.
- Pregnancy and Breastfeeding
    - Patients found to be pregnant or breastfeeding during the trial will be discontinued.

Patients who discontinue the study early will have end-of-study procedures performed as shown in the Study Schedule (Attachment 1) and will also have a follow-up safety visit 30 days after study discontinuation (Visit 801).

8.3.4. Rescue for Hyperglycemia

Patients will be considered for rescue treatment in the following circumstances:

- Weeks 0-6: average FBG >15 mmol/L (270 mg/dL) over at least a 2-week period (at least 4 values/week must be available)
- Weeks 7-12: average FBG >13.3 mmol/L (240 mg/dL) over at least a 2-week period (at least 4 values/week must be available)
- Weeks 13-26: average FBG >11.1 mmol/L (200 mg/dL) over at least a 2-week period (at least 4 values/week must be available)
- Weeks 26-52: average FBG >11.1 mmol/L (200 mg/dL) over at least a 2-week period (at least 4 values/week must be available)

If the patient does not meet the above criteria, an investigator may rescue a patient if there is other documented evidence that the patient is experiencing severe, persistent hyperglycemia over at least 2 weeks.

Rescue therapy will consist of approved therapy for T2DM pediatric patients (i.e., metformin and/or insulins). The use of GLP-1 RAs and DPP-IV inhibitors for rescue therapy is not allowed.

Patients may be treated with short-term (up to 2 weeks) of unlimited metformin or insulin therapy with continuation of study drug (see Section 9.8). This will not constitute rescue.

During the double-blind period (Weeks 0-26), in patients not previously rescued, rescue will have occurred if:

- A patient treated with lifestyle + study drug at baseline receives metformin and/or insulin for more than 2 weeks
- A patient treated with metformin + study drug at baseline receives treatment with >15% more metformin and/or insulin at any dose for more than 2 weeks
- A patient treated with basal insulin + study drug at baseline receives treatment with >15% more basal insulin and/or another type of insulin at any dose for more than 2 weeks

During the open label period, (Weeks 27-52), in patients not previously rescued, rescue will have occurred if there is addition of a new medication as described below and not with changes in dosing of already administered medication(s):

- A patient treated with lifestyle + dulaglutide at Week 26 receives metformin and/or insulin at any dose for more than 2 weeks
- A patient treated with metformin + dulaglutide at Week 26 receives treatment with insulin at any dose for more than 2 weeks
- A patient treated with basal insulin + dulaglutide at Week 26 receives treatment with another type of insulin at any dose for more than 2 weeks

If patients undergo rescue for hyperglycemia, they will remain on study drug, and will continue in the trial, unless the investigator believes they should be discontinued from study drug.

8.3.5. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ethical review board (ERB) of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP).

8.3.6. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

9. Treatment

9.1. Treatments Administered

This study involves a comparison of dulaglutide 0.75 mg and 1.5 mg administered SC once weekly by single-dose pen (SDP) with placebo. All patients in the open-label period will receive either dulaglutide 0.75 mg or 1.5 mg SC once weekly. Table GBGC.9.1 summarizes the study treatments in the randomized, double-blind period, and the open-label period.

Table GBGC.9.1. Study Treatments in the Double-Blind and Open-Label Periods

Name of Drug	Dosage	Frequency	Drug Formulation	Route of Administration
26-Week Double-Blind Period				
Investigational Compound				
Dulaglutide	0.75 mg	Once weekly	Single-dose pen	Subcutaneous injection
Dulaglutide	1.5 mg	Once weekly	Single-dose pen	Subcutaneous injection
Comparator				
Placebo	Placebo	Once weekly	Single-dose pen	Subcutaneous injection
26-Week Open-Label Period				
Dulaglutide	0.75 mg	Once weekly	Single-dose pen	Subcutaneous injection
Dulaglutide	1.5 mg	Once weekly	Single-dose pen	Subcutaneous injection

The investigator or his/her designee is responsible for the following:

- explaining the correct use of the investigational agent(s) to the patient and site personnel
- training the patient and parent or legal guardian in the appropriate use of the SDP
- verifying that instructions are followed properly
- maintaining accurate records of study drug dispensing and collection
- returning all unused medication to Lilly or its designee at the end of the study.

Note: In some cases, sites may destroy the material if, during the investigator site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical trial materials.

Patients will be instructed to contact the investigator as soon as possible if they have a complaint or problem with the study drug or SDP so that the situation can be assessed.

9.2. Materials and Supplies

Lilly will provide dulaglutide and placebo in SDPs, which will be dispensed via an IWRS. Each SDP (0.75 mg dulaglutide in 0.5 mL OR 1.5 mg dulaglutide in 0.5 mL OR placebo in 0.5 mL) is packaged in cartons of 4 pens. Each carton contains a 4-week supply, as each pen is a week's dose. The specified labeling information is provided on the package and on the SDP. The study site must store the SDP cartons in a locked and secure environment. The SDPs must be refrigerated (not frozen) at 2°C to 8°C. Dry ice should not be used for cooling. Patients will be provided with cartons containing 4 dulaglutide or placebo SDPs, as required, at clinic visits according to the Study Schedule (Attachment 1). The patients will receive insulated bags with cooling gel packs for use in transporting the SDP carton(s) from the site to the home. Study drug in each participating country will be labeled according to the country's regulatory requirements.

Commercial metformin and basal insulin may be made available during the treatment period to patients who entered the trial on these agents. Appropriate use and storage information will be available by referring to the package insert.

9.3. Method of Assignment to Treatment

After the ICF and assent are signed and dated, a patient is considered "entered" in the study and will be assigned a patient number. Entered patients who meet all inclusion criteria and no exclusion criteria at screening will be randomized at Visit 2 (baseline). Patients who are randomized to the study treatment are "enrolled." Patients will be randomized to 1 of 3 treatment arms (dulaglutide 0.75 mg/week, dulaglutide 1.5 mg/week, or placebo/week) at Visit 2 in a 1:1:1 ratio according to a computer generated random sequence using an IWRS. Patients will be stratified by HbA1c at Visit 1 (screening) (<8.0%, ≥8.0%), metformin use ("yes" versus "no"), and insulin use ("yes" versus "no") to mitigate against confounding the effects of the treatments with severity of disease or treatment with these agents. The number of patients who are treated with lifestyle only and who are metformin naïve will be tracked, and when the number of these patients reaches approximately 25% of the total planned enrollment, IWRS will not allow further randomization of such patients. Site personnel will confirm that they have located the correct carton by entering a confirmation number found on the carton into the IWRS.

The second phase of the study is considered "open-label." At 26 weeks, all patients on placebo will be dispensed 0.75 mg dulaglutide at that study visit assignment via the IWRS system. All patients previously on dulaglutide will continue on their previously assigned therapy.

9.4. Rationale for Selection of Doses in the Study

Pharmacokinetic simulations were conducted to compare the dulaglutide exposure range in this pediatric age group with that of the approved doses in adult patients. It was found that the median exposure of a 10-year-old child with a BMI of 23 kg/m^2 (approximate weight of 40 kg) is close to the 95th percentile exposure of the 0.75-mg dose, and still reaches the median exposures from the 1.5 mg dose. Hence, a dose of 0.75 mg once-weekly is anticipated to be well tolerated across the overall pediatric population and yet not exceed the adult exposure range for the 1.5 mg once weekly dose for pediatric patients at the lower end of the BMI and age inclusion criteria. However, since patients are required to be at least 50 kg in weight at the beginning of this study, they are expected to be in a similar weight range as adult T2DM patients where the 1.5 mg once weekly dose has been demonstrated to be safe and efficacious. Therefore, this dose may also be appropriate for use in the pediatric population. Both doses will be tested in this study.

9.5. Selection and Timing of Doses

Dulaglutide and placebo will be injected SC once weekly.

Prior to each weekly injection, the patient will remove an SDP from the refrigerator, check the label to make sure that the right medication is being used, and check the SDP to make sure that it is not damaged, and the medication is clear in color.

The patient should choose an injection site. The medication may be injected into the abdominal area or thigh. If the medication is administered by another person, the injection may be given in the upper arm.

The patient should uncap the SDP (making sure it is locked) by pulling the base cap straight off and discarding it. The patient should place the clear base flat and firmly against the skin at the injection site (and keep it there until the injection is complete), unlock by turning the lock ring, and press and hold the injection button; they will hear a loud click. They should continue holding the SDP against the skin until a second click is heard in 5-10 seconds. They should then remove the SDP from the skin and discard the entire SDP in a sharps container. Patients should rotate their injection site each week; they may use the same area of the body, but should choose a different injection site in that area.

Each weekly dose of study drug should be administered on the same day of the week at approximately the same time of day. Study drug can be administered at any time of day, with or without food. The date and exact time of study drug administration should be noted in the study diary.

If a dose is missed, patients should administer it as soon as possible if there are at least 3 days (72 hours) until the next scheduled dose. If fewer than 3 days remain before the next scheduled dose, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

The day of weekly administration can be changed, if necessary, as long as the last dose was administered 3 or more days before.

9.6. Continued Access to Investigational Product

Dulaglutide will not be made available to patients after conclusion of the study.

9.7. Blinding

The first 26 weeks of this trial is double-blind.

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the 26-week double-blind study is complete.

The second 26 weeks of the trial is open-label.

Emergency unblinding for AEs may be performed through the IWRS, 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 IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded during the double-blind portion of the clinical trial, the patient will continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the Lilly CRP or designee prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of a patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

9.8. Concomitant Therapy

The only allowed concomitant chronic diabetes therapies are metformin and basal insulin.

Use of metformin:

- Either metformin immediate release or metformin extended release may be used during the study if indicated for the treatment of children in the local geography; however, the type of metformin should remain the same throughout the study, if possible. If a change in type of metformin (i.e., conversion of extended release to immediate release or vice versa) is required, the investigator should determine the most appropriate clinically equivalent metformin dose.
- The dose of metformin must remain stable during the double-blind period of the trial unless:
    - The patient stops tolerating metformin.
    - The patient develops an absolute or relative contraindication to metformin use (according to the local metformin label).
    - The patient experiences hypoglycemia (for the protocol definition of hypoglycemia, see Section 10.4.1.2.1).
- During the double-blind period, in the event of acute illness with hyperglycemia, the dose of metformin may be increased >15% of the baseline dose for 2 weeks and/or unlimited insulin therapy may be used with metformin for up to 2 weeks. After that period, the metformin dose should be back to the baseline dose and insulin therapy should be stopped. This does not constitute rescue.

Use of basal insulin:

- Basal insulin may include: Neutral Protamine Hagedorn (NPH) insulin, insulin detemir, insulin glargine, or any insulin whose labeling states that it is long-acting and used once or twice a day as basal insulin.
- The type of basal insulin should remain the same throughout the study, if possible.
- During the double-blind phase (Weeks 0-26), the dose of basal insulin should remain no higher than the dose at randomization (Visit 2) +15%.
    - The dose may be decreased if the patient has experienced hypoglycemia. In that case, the patient's basal insulin dose will be decreased until hypoglycemia is absent.

  - If the patient experiences acute illness with hyperglycemia, unlimited insulin therapy may be used for up to 2 weeks. After that time, the patient's basal insulin dose should be at the baseline dose (+15%) and other insulins (if used) should be stopped. This does not constitute rescue.
- In patients on basal insulin, especially those who are in good glycemic control (HbA1c <7.0%), investigators should pay close attention as to whether hypoglycemia is occurring and whether the basal insulin dose needs to be reduced.
- A suggested scheme for adjusting basal insulin in response to hypoglycemia is given below.

If patient has 2 FBGs in a week of:	Adjust basal insulin dose:
≤50 mg/dL (<2.8 mmol/L)	Decrease by at least 8 units or 10%, whichever is greater
>51-70 mg/dL (>2.8-3.9 mmol/L)	Decrease by 5 units or 5%, whichever is greater
>71-80 mg/dL (>3.9-4.4 mmol/L)	Decrease by 5 units
>80 mg/dL (>4.4 mmol/L)	No adjustment

As a reminder, during the double-blind period, if a patient is experiencing severe, persistent hyperglycemia, the patient should be considered for rescue (Section 8.3.4). Patients who are rescued will continue in the study and will continue to take study drug (unless the investigator determines that they should not).

With the exception of prescription weight loss medications, all non-diabetes concomitant therapies that are part of routine medical care that the patient requires are allowed and can be used during the study. High-dose inhaled or oral steroids should be used only as long as medically necessary. Doses of psychiatric medication should remain stable.

Although efforts should be made not to change the basal insulin dose more than 15% during the double-blind period, during the open-label period (as this period is primarily assessing safety) if basal insulin must be increased, it may be, without calling it "rescue." For patients taking basal insulin, rescue will be defined as adding another type of insulin. During the open-label period, patients who are rescued will continue in the study and will continue to take study drug (unless the investigator determines that they should not).

9.9. Treatment Compliance

Patient compliance with study medication will be assessed. Compliance will be assessed by comparing the study drug doses actually taken and the prescribed drug doses.

Patients who are noncompliant should be counseled to increase their compliance, as long as this does not jeopardize the patient's safety. A patient will be considered noncompliant if he or she misses doses of study drug or is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

10. Efficacy, Health Outcome/Quality of Life Measure, 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).

10.1. Efficacy Measures

10.1.1. Primary Efficacy Measure

The primary efficacy measurement in this study is change in HbA1c from baseline to 26 weeks for the pooled dulaglutide doses, as determined by the central laboratory. Blood samples for HbA1c measurements will be collected at specific clinic visits as summarized in the Study Schedule (Attachment 1).

10.1.2. Secondary Efficacy Measures

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

- Change in FBG from baseline to Week 26 and Week 52.
- Percentage of patients achieving a target HbA1c <7.0% at Week 26 and Week 52.
- Change in BMI from baseline to Week 26 and Week 52. Each patient's height and weight should be measured according to a standardized protocol (Attachment 6).
- Change in HbA1c measured in the central laboratory from baseline to Week 26 and Week 52.

10.1.3. Exploratory Efficacy Measures

- Percentage of patients with HbA1c ≤6.5% at Weeks 26 and 52
- Change in HbA1c between baseline and Week 13
- Percentage of patients having HbA1c ≤6.5% without severe, documented symptomatic (<70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Percentage of patients having HbA1c <7.0% without severe, documented symptomatic (<70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Change in weight from baseline to Week 26 and Week 52
- Change in waist circumference from baseline to Week 26 and Week 52
- Measures of insulin resistance and beta cell function (HOMA-IR, HOMA-%B, 1/fasting insulin) and estimated insulin sensitivity score at Weeks 0, 13, and 26

10.2. Health Outcome/Quality of Life Measure

The questionnaire will be administered by the investigator according to the study schedule in countries where the questionnaire has been translated into the native language of the region and linguistically validated.

EQ-5D-Youth Version

The EQ-5D is a standardized generic measure of health status developed by the EuroQol Group. The EQ-5D-Y consists of the EQ-5D-Y descriptive system and the EQ VAS. The descriptive system comprises the same 5 dimensions as the EQ-5D 3 level (EQ-5D-3L), but using a child-friendly wording (mobility; looking after myself; doing usual activities; having pain or discomfort; and feeling worried, sad or unhappy). Each dimension has 3 levels: no problems, some problems, or a lot of problems. The EQ VAS records the respondent's self-rated health on a vertical, EQ VAS where the endpoints are labeled, "The best health you can imagine," and, "The worst health you can imagine." This VAS information can be used as a quantitative measure of the perception of their overall health by the individual respondents.

The EQ-5D-Y will be administered at baseline, Week 26, and Week 52 (or early termination [ET]), as per the Study Schedule (Attachment 1). The Week 26 and Week 52 EQ-5D-Y is an objective in the study.

Details about scoring the PRO instrument can be found in the EQ-5D-Y User Guide (www.euroqol.org).

10.3. Pharmacokinetics and Pharmacodynamics

Pharmacokinetics: For population PK (PopPK) and exposure-response analyses, 6 blood samples will be collected from all patients (see Attachment 1).

Together with the 3 additional PK samples to be collected from each patient in the PK/PD addendum, these PK samples will provide information for PopPK and exposure-response modeling purposes, as well as be utilized for the interpretation of immunogenicity data and whether it has any impact on dulaglutide PK. Collectively, PK sample size and sampling times in the main protocol and PK addendum have been optimized using a standard PK optimal sampling approach.

Pharmacodynamics: Additionally, blood for fasting insulin, C-peptide, glucose, and adiponectin will be taken to assess the effect of dulaglutide on insulin resistance, beta cell function, and adiponectin.

10.4. Safety Evaluations

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly 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.

The investigator remains responsible for following, through an appropriate healthcare option, AEs that are serious or otherwise medically important, considered related to the study treatment or the study, or that caused the patient to discontinue study drug before completing the study. The patient should be followed until the event is resolved or is reasonably explained. Frequency of follow-up evaluation is left to the discretion of the investigator.

10.4.1. Adverse Events

Lilly has standards for reporting AEs that are to be followed regardless of applicable regulatory requirements that may be less stringent.

Lack of drug effect is not an AE in clinical studies because the purpose of the clinical study is to establish drug effect.

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

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

The investigator will record all relevant AE/SAE information in the CRF. After the ICF and assent are signed, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs. All AEs related to protocol procedures are reported to Lilly or its designee.

In addition, all AEs occurring after the patient receives the first dose of study drug must be reported to Lilly or its designee via CRF.

Any clinically significant findings from labs or vital sign measurements that result in a diagnosis should be reported to Lilly or its designee.

Investigators must report to Lilly or its designee their assessment of the potential relatedness of each AE to protocol procedure or studied disease state, study drug, and/or drug delivery system via CRF.

The investigator decides whether he or she interprets the observed AEs as either related to disease, the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terminologies are defined:

- **Related:** a direct cause-and-effect relationship between the study treatment and the AE is likely.
- **Possibly related:** a cause-and-effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible.
- **Unrelated:** without question, the AE is definitely not associated with the study treatment.

As per Lilly's standard operating procedures, all "related" and "possibly related" AEs and serious adverse events (SAEs) will be defined as related to the study drug.

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

10.4.1.1. Serious Adverse Events

Serious adverse event collection begins after the patient and parent or legal guardian have signed informed consent and assent, respectively, and the patient has received study drug. If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be reported as serious unless the investigator feels the event may have been caused by a protocol procedure.

Planned surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a Lilly-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

An SAE is any AE from this study that results in 1 of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (i.e., 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 on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent 1 of the outcomes listed in this definition.

When a condition related to the drug delivery system (i.e., the SDP) 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 up to and including the patient's last study visit will be collected, regardless of the investigator's opinion of causation, in the clinical data collection database and the pharmacovigilance system at the sponsor.

The investigator does not need to actively monitor patients for AEs once the trial has ended, unless provided otherwise in the protocol. However, if an investigator becomes aware of SAEs occurring to a patient after the patient's participation in the trial has ended, the investigator

should report the SAEs to the sponsor, regardless of the investigator's opinion of causation, and the SAEs will be entered in the pharmacovigilance system at the sponsor.

Information on SAEs expected in the study population independent of drug exposure and that will be assessed by Lilly in aggregate periodically during the course of the trial may be found in the Investigator's Brochure (IB).

10.4.1.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study drug or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

10.4.1.2. Adverse Events of Interest

10.4.1.2.1. Hypoglycemia

Patients and their parents or legal guardians will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information in the study diary according to the Study Schedule (Attachment 1).

Hypoglycemia will be classified as follows (the plasma glucose [PG] values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips) (ADA 2005, 2020):

- Documented symptomatic hypoglycemia is defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of <70 mg/dL (<3.9 mmol/L).
- Asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG of <70 mg/dL (<3.9 mmol/L).
- Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by a PG concentration of <70 mg/dL [<3.9 mmol/L]).
- Severe hypoglycemia is defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration.
- Nocturnal hypoglycemia is defined as any hypoglycemic event that occurs between bedtime and waking.

Cases of relative hypoglycemia, defined as symptomatic events during which the person reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but with a measured PG concentration of ≥70 mg/dL (≥3.9 mmol/L), will also be collected.

Certain categories of hypoglycemia will also be evaluated using a PG cutoff <54 mg/dL (<3.0 mmol/L)(International Hypoglycaemia Study Group 2017).

If a hypoglycemic event meets the criteria of severe, it needs to be recorded as serious on the AE CRF and reported to Lilly as an SAE.

10.4.1.2.2. Pancreatitis

Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

1. Abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiating to the back in approximately half the cases [Banks and Freeman 2006; Koizumi et al. 2006]; the pain is often associated with nausea and vomiting)
2. Serum amylase (total and/or pancreatic) and/or lipase ≥3×ULN
3. Characteristic findings of acute pancreatitis on imaging, such as contrast-enhanced computed tomography (CT) scan, or less commonly, magnetic resonance imaging (MRI), or transabdominal ultrasound.

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of amylase [total and pancreatic] and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with (or without) contrast, MRI, or ultrasound (transabdominal or endoscopic), should be performed as appropriate. If evaluation supports the diagnosis of acute pancreatitis, the patient must permanently discontinue therapy with study drug. The most appropriate diabetes therapeutic regimen will be decided on by the investigator, based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug.

In addition to the diagnostic assessment in patients who develop symptoms of acute pancreatitis, each patient will have measurements of amylase (total and pancreatic) and lipase during the trial to assess any potential effects of dulaglutide on the exocrine pancreas (refer to the Study Schedule, Attachment 1). Further diagnostic assessment per the Lilly algorithm for the assessment of asymptomatic elevated pancreatic enzymes will be required whenever lipase and/or amylase (pancreatic and/or total) are ≥3×ULN at any time during the study.

All AEs of acute or chronic pancreatitis, as well as cases of lipase or amylase values that are confirmed ≥3×ULN, will be adjudicated by a group of physicians external to Lilly. In addition,

AEs of severe or serious abdominal pain of unknown origin will also be submitted for adjudication to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute pancreatitis, those with severe or serious abdominal pain of unknown origin, and those that undergo additional assessments due to confirmed elevated pancreatic enzymes will be entered into a specifically designed electronic CRF or eCRF page by study site or Lilly staff. The adjudicators will enter the results of adjudication in a corresponding eCRF page.

10.4.1.2.3. Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Individuals with a known personal or family history of MEN 2A or 2B, thyroid C-cell hyperplasia, medullary thyroid carcinoma, or a serum calcitonin ≥20 pg/mL at screening will be excluded from the study (see Section 8.2). The assessment of thyroid safety during the trial will include reporting of thyroid TEAEs and measurements of serum calcitonin according to the Study Schedule (Attachment 1) at screening, baseline, and periodically throughout the study. The purpose of serum calcitonin measurements is to assess the potential of dulaglutide versus other background medications to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Patients who develop serum calcitonin increases ≥50% of the baseline value AND an absolute value ≥20 pg/mL and <35 pg/mL at Visit 9 (Week 26) or Visit 16 (Week 52) will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be recommended to undergo additional endocrine assessment and longer term follow-up by an endocrinologist to exclude a serious adverse effect on the gland. Patients with an increase in serum calcitonin ≥50% of the baseline value AND an absolute value ≥35 pg/mL at Visit 9 (Week 26) or Visit 16 (Week 52) will be recommended to immediately undergo additional endocrine assessments and longer term follow-up by an endocrinologist.

10.4.1.2.4. Allergic/Hypersensitivity Reactions and Injection Site Reactions

All allergic or hypersensitivity reactions or injection site reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to study drug via a CRF created for this purpose. Study drug should be temporarily discontinued in any individual suspected of having a severe or serious allergic reaction to study drug (Section 8.3.2) or severe injection site reaction. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug is permanently discontinued, the patient will continue in the trial (Section 8.3.2).

10.4.1.2.5. Nausea and Vomiting

Nausea and vomiting are among the most common gastrointestinal AEs associated with dulaglutide administration in adults.

In patients participating in placebo-controlled trials, gastrointestinal adverse reactions occurred more frequently among patients receiving dulaglutide than placebo (placebo 21.3%; dulaglutide 0.75 mg 31.6%; dulaglutide 1.5 mg 41.0%). More patients receiving dulaglutide 0.75 mg (1.3%) and dulaglutide 1.5 mg (3.5%) discontinued treatment due to gastrointestinal adverse reactions than patients receiving placebo (0.2%). Investigators graded the severity of gastrointestinal

adverse reactions occurring on dulaglutide 0.75 mg and 1.5 mg as "mild" in 58% and 48% of cases, respectively, "moderate" in 35% and 42% of cases, respectively, or "severe" in 7% and 11% of cases, respectively. The incidence of gastrointestinal symptoms peaks during the first 2 weeks after dulaglutide therapy is begun.

If an event involving nausea and vomiting meets the criteria of serious, it will be recorded as serious on the AE CRF and reported as an SAE.

10.4.1.2.6. Renal Impairment

In patients treated with GLP-1 RAs, there have been postmarketing reports of acute renal failure and worsening of chronic renal failure, which sometimes required hemodialysis. Some of these events were reported in patients without known underlying renal disease. A majority of reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.

Renal function will be monitored in the clinical trial. Consideration should be given to temporarily discontinuing study drug in any individual suspected of having significant renal impairment. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator. If study drug is permanently discontinued, the patient will continue in the trial (Section 8.3.2).

10.4.2. Other Safety Measures

10.4.2.1. Blood Pressure and Heart Rate

After sitting quietly (not speaking and not engaged in any activities) for at least 5 minutes, sitting blood pressure (BP) and heart rate will be measured at each clinic visit, using the site's existing equipment. If possible, the same arm and the same equipment should be used to measure BP and heart rate at each visit. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of BP measurements. The arm used for the BP measurement should be supported at heart level. If pulse is measured manually, it will be assessed for a full minute. The measurements of BP and heart rate will be taken in order to assess patient safety during the trial.

10.4.2.2. Body Weight, Body Mass Index, Height, and Waist Circumference

Body weight, height, and waist circumference will be measured at prespecified time points (see Study Schedule, Attachment 1). Each patient's weight, height, and waist circumference should be measured according to standardized guidelines (Attachment 6). Body mass index will be computed from the patient's weight and height.

10.4.2.3. Assessment of Pubertal Progression

Patients' pubertal progression will be assessed throughout the trial. Tanner staging will be performed at baseline, 26 weeks and 52 weeks: those patients who have reached Tanner stage 5 will not be evaluated again. Morning hormone levels (estradiol, testosterone in males, LH, IGF-1, cortisol, and prolactin) will be performed at baseline, 26 weeks, and 52 weeks.

10.4.2.4. Electrocardiograms

For each patient, 12-lead digital ECGs will be collected according to the Study Schedule (Attachment 1) as single ECGs for overread. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high quality records.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the patient meets entry criteria and for immediate patient management, should any clinically relevant findings be identified.

After enrollment, if a clinically significant increase in the QT/corrected QT (QTc) interval from baseline, or other clinically significant quantitative or qualitative change from baseline is present, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) and to determine if the patient can continue in the study. The investigator (or qualified designee) is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of evaluation.

All digital ECGs will be electronically transmitted to a designated central ECG laboratory. A cardiologist at the central ECG laboratory will then conduct a full overread on the ECG (including all intervals); a report based on data from this analysis will be issued to the investigative site. All data from the overreads will be placed in the Lilly database for analytical and study report purposes.

When there are differences in ECG interpretation between the investigator (or qualified designee) and the cardiologist at the central ECG laboratory, the investigator's (or qualified designee's) interpretation will be used for study entry and immediate patient management. Interpretations from the cardiologist at the central ECG laboratory will be used for data analysis and report writing purposes.

The investigator (or qualified designee) must document his/her review of the ECG printed at the time of evaluation, the final overread ECG report issued by the central ECG laboratory, and any alert reports.

10.4.3. Safety Monitoring

The Lilly CRP (or designee) will monitor safety data throughout the course of the study and will periodically review evolving aggregate safety data within the study by appropriate methods.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly CRP will, as is appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist, and periodically review, in a blinded fashion:

- Trends in safety data
- Laboratory analytes including ADAs

- Adverse events including monitoring of gastrointestinal AEs including pancreatitis, allergic and hypersensitivity reactions, hypoglycemia, and thyroid TEAEs.

If a study patient experiences elevated ALT or AST≥3×ULN, elevated total bilirubin ≥2×ULN, ALP ≥2×ULN, or acute hepatitis, clinical and laboratory monitoring should be initiated by the investigator (see Attachment 3). Details for hepatic monitoring depend on the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and comply with regulatory guidance, the investigator is to consult with the Lilly CRP or designee regarding collection of specific recommended clinical information and follow-up laboratory tests. As described in Section 8.3.2, study drug may be discontinued if a patient meets 1 of several conditions.

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 board (an advisory group for this study formed to protect the integrity of data; refer to Section 12.2.11) can conduct additional analyses of the safety data.

10.4.4. Complaint Handling

Lilly collects product complaints on IPs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Patients will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP or drug delivery system (SDP) so that the situation can be assessed.

Complaints related to unblinded concomitant drugs (basal insulin and metformin) are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

For blinded studies like this, all product complaints associated with material packaged, labeled, and released by Lilly or its delegate should be reported.

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:

- Providing a complete description of the product complaint and any associated AEs using the study-specific complaint forms provided for this purpose
- Faxing the completed product complaint form within 24 hours to Lilly or its designee.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint form with the product.

10.5. Sample Collection and Testing

Attachment 1 lists the schedule for sample collections in this study.

Attachment 2 lists the laboratory tests that will be performed for this study.

Attachment 3 lists additional laboratory tests that may be required for patients discovered to have a treatment-emergent abnormality in hepatic laboratory tests.

10.5.1. Samples for Study Qualification and Health Monitoring

Blood and urine samples will be collected to determine whether patients meet inclusion/exclusion criteria, to determine efficacy endpoints, and to monitor patient safety and health.

Investigators must document their review of each laboratory safety report by signing and dating each of the report pages.

Laboratory results that could unblind the study (i.e., drug levels and anti-drug antibodies) will not be reported to investigative sites or other blinded personnel until the study has been unblinded. Sites will also not receive hormone levels (prolactin, cortisol, IGF-1, LH, estradiol and testosterone) as they are not required for patient care. Sites will receive all other laboratory tests.

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. When scientific circumstances warrant, however, it is acceptable to retain samples to batch the tests run, or to retain the samples until the end of the study to confirm that the results are valid. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

10.5.2. Samples for Immunogenicity Research

The samples from patients in both treatment groups will be tested for the development of dulaglutide ADAs. A blood sample will be collected at specific study visits at the same time or within 30 minutes of each PK sample according to the Study Schedule (Attachment 1).

Positive (or treatment-emergent) dulaglutide ADA samples will be evaluated for their ability to neutralize the activity of assigned treatment (dulaglutide neutralizing antibodies). Positive dulaglutide ADA samples may also be tested for cross-reactivity with native GLP-1, and if positive, for neutralizing antibodies against native GLP-1.

If a patient develops a positive antibody titer, appropriate medical management will be utilized at the discretion of Lilly and the investigator, if deemed necessary.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if regulations and ERBs impose shorter time limits, at a facility selected by Lilly or its designee. The duration allows Lilly to respond to regulatory requests related to the study drug.

10.5.3. Samples for Drug Concentration Measurements Pharmacokinetics/Pharmacodynamics

At the visits and times specified in the Study Schedule, venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of dulaglutide. Six blood samples will be collected from each patient according to the Study Schedule (Attachment 1), in order to determine plasma concentration of dulaglutide in dulaglutide-treated patients. The date

and time of all study drug injections (especially the most recent injection administered prior to collecting the sample) must be recorded on the eCRF from the study diary. The date and time that each sample was drawn must be recorded on the laboratory accession page.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded. Refer to Section 12.2.11.3 for details of early access to PK/PD data.

Bioanalytical samples collected to measure study drug concentration and metabolism and/or protein binding will be retained for a maximum of 2 years following last patient visit for the study.

10.6. Appropriateness of Measurements

Efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to the efficacy and safety assessments in individuals and populations with T2DM.

11. Data Quality Assurance

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

- Provide instructional material to the study sites, as appropriate.
- Lilly start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, 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 CRF data and use standard computer edits to detect errors in data collection.
- Conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly 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 Lilly, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

11.1. Data Capture System

An electronic data capture system will be used in this study. Case report form data will be encoded and stored in a clinical study database. The site maintains a separate source for the data entered by the site into the Lilly-provided electronic data capture system. Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system. Data will subsequently be transferred from the central vendor to the Lilly generic labs system. Any data for which the eCRF (including electronic capture of blood glucose, electronic or paper documentation provided by the patient) will serve as the source document and will be identified and documented by each study site in the site's study file. Paper documentation provided by the patient may include, for example, a diary to collect SMBG measurements, hypoglycemia events, AEs, the last menstrual period (for females), concomitant medication, and other items.

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

12. Sample Size and Statistical Methods

12.1. Determination of Sample Size

A sample size of approximately 150 patients will be enrolled (50 patients per arm), in order to obtain 120 completers. This provides at least 90% power for demonstrating superiority of the pooled dulaglutide 0.75 mg and 1.5 mg arms to placebo (primary objective), with a difference in mean change from baseline in HbA1c of -0.65% and standard deviation of 1% assuming a dropout rate of 20%. Under the same assumptions, each individual dulaglutide arm will have at least 80% power to demonstrate superiority over placebo. Among the completers, there will be no more than 25% of patients who, at baseline, were treated with diet and exercise only and who are metformin naïve.

Because of the high degree of uncertainty regarding the appropriate sample size, the Statistical Analysis Center (SAC), may perform a sample size re-estimation after approximately 100 patients have been enrolled. Based on treatment variability only (not treatment effect), the SAC may advise an increase in sample size up to approximately 189 patients enrolled (63 per arm), in order to obtain 150 completers. This new sample size would provide at least 80% power for demonstrating superiority of the pooled dulaglutide 0.75 mg and dulaglutide 1.5 mg arms compared to placebo with a difference in mean change from baseline in HbA1c of -0.65% and standard deviation of 1.3% assuming a dropout rate of 20%. Under the same assumptions, each individual dulaglutide arm will have at least 69% power to demonstrate superiority over placebo.

Because of the anticipated difficulties in enrollment and the necessity for meeting regulatory timelines, Lilly will ultimately decide whether to conduct this sample-size re-estimation after taking into consideration the study enrollment rate and other factors. The SAC will document the exact procedure for the calculation. This calculation will not require input from the DMC. The SAC will provide a brief communication to the Lilly Study Team indicating only the recommended sample size (up to approximately 189 patients) with at least 80% power based on the predefined algorithm. Lilly will then have the ability to adopt the recommended sample size or keep it fixed if it is determined to be too challenging to enroll or there are other feasibility concerns. No alpha adjustment is necessary for this analysis, as it does not increase type 1 error (Mehta et al. 2001; Pritchett et al. 2011).

The screen failure rate is estimated as 80%. Approximately 750 patients will be screened, depending on the total enrolled. Based on regulatory feedback, the sample size re-estimation was performed in 2019 and confirmed the original sample size estimation suggesting that approximately 150 patients be enrolled.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods

described in the protocol, and the justification for making the change, will be described in a revised Statistical Analysis Plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

The primary analysis population will be the intention-to-treat (ITT) population, defined as all patients randomized who have received at least 1 dose of study drug. The primary analyses will be performed in this population for the treatment regimen estimand with post-rescue data and for the efficacy estimand without post-rescue data (Section 12.2.6). Analyses of other efficacy measures and hypoglycemia will be evaluated in this population after censoring the data following administration of any rescue medication. The Safety population will be the ITT population, including post-rescue data.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided.

For subgroup analyses, all tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

The baseline visit will be Visit 2. For all variables, including HbA1c, baseline measurement is defined as the last nonmissing value taken prior to the first dosing of study drug. Baseline HbA1c value will be used to define HbA1c strata for analyses. .

Continuous measures, unless otherwise noted, will be analyzed with a mixed-model for repeated measures (MMRM) analysis using restricted maximum likelihood (REML) with treatment, insulin usage, metformin usage, visit, and treatment-by-visit as fixed effects, HbA1c strata ($<8.0\%$, $\geq 8.0\%$), and baseline as a covariate. An unstructured covariance structure will be used to model the within-patient errors. If this model fails to converge, the following covariance structures will be tested in order:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity, by visit,
- Compound symmetry with heterogeneous variances, by visit,
- Toeplitz,
- Autoregressive,
- Compound symmetry without heterogeneous variances, by visit.

The first covariance structure that converges will be used. If none of the models converge then an analysis of covariance (ANCOVA) using last observation carried forward (LOCF) imputation with similar terms as in the MMRM model (except no terms that include visit) will be used in its place. This applies to the subgroup analyses as well. This approach to analyzing continuous data will be referred to as the standard approach in the SAP.

Summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum for both the actual and change from baseline measurements. Least-squares mean and standard errors derived from the MMRM model described above will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the

treatment difference least-squares mean and the 95% CIs for the treatment differences (dulaglutide – placebo), along with p-values for the treatment comparisons.

Unless otherwise specified, for categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test will be used for treatment comparisons.

For data after Week 26 (Visit 9), the efficacy and safety data will be summarized by treatment group sequence (placebo:dulaglutide 0.75 mg, dulaglutide 0.75 mg:dulaglutide 0.75 mg, and dulaglutide 1.5 mg:dulaglutide 1.5 mg), but no inferences will be made.

12.2.2. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

Frequency counts and percentages of all patients entered, randomized/enrolled, completing, and/or discontinuing from the study early will be presented for each of the treatment groups. The reasons for discontinuation from the study will be summarized by treatment group.

The overall percent discontinued comparisons among the treatment groups will be performed using Fisher's exact test.

12.2.3. Patient Characteristics

Demographic and baseline characteristics will be summarized for both treatment arms. For continuous measures, summary statistics will include sample size, mean, median, maximum, minimum, and standard deviations. Means will be analyzed using analysis of variance (ANOVA). For categorical measures, summary statistics will include sample size, frequency, and percent. Frequencies will be analyzed using Fisher's exact test.

12.2.4. Concomitant Therapy

Patients using metformin and/or basal insulin will be allowed to enter the study and stay on their medication as a background therapy. Stratification will be used to ensure a balance across treatment arms of patients using these medications. These stratification factors will be included in all analysis models to further adjust the treatment effect estimates for background usage of metformin and/or insulin usage.

Concomitant medications, including previous therapy for diabetes, will be summarized by treatment. Frequencies will be analyzed using Fisher's exact test.

12.2.5. Treatment Compliance

Treatment compliance will be determined for each study period. Overall compliance will also be determined. The compliance calculation will be detailed in the SAP. The investigator will advise the patient that injections should be given at approximately the same time of the day, on the same day of the week. Compliance will be summarized by all treatment arms, by study period, and overall. Listings will also be produced.

12.2.6. Primary Outcome and Methodology

There will be 2 primary estimands to compare the placebo and the pooled dulaglutide arms in terms of the primary measure of HbA1c change from baseline to 26 weeks. One primary estimand will be an efficacy estimand which will not use post-rescue data; the other primary estimand, requested by the US Food and Drug Administration (FDA), will be a treatment regimen estimand which will use post-rescue data. The efficacy estimand measures the benefit of treatment when taken as directed, and the treatment regimen estimand measures the benefit of treatment as actually taken. Each estimand will be tested at the full significance level of 0.05.

Analyses will be performed for both the efficacy estimand and the treatment regimen estimand.

12.2.6.1. Primary Analysis for the Primary Outcome

For the efficacy estimand, the primary analysis model will be an MMRM for HbA1c change from baseline to 26 weeks (Visit 9) with treatment, insulin usage, metformin usage, visit, treatment-by-visit as fixed effect, and baseline HbA1c as a covariate. The HbA1c strata [<8.0%, ≥8.0%] will not be included in this model as they may be confounded with baseline HbA1c as a covariate. In addition, the actual HbA1c will be analyzed using the same model for plotting purposes. For the treatment regimen estimand, the primary analysis model will be an ANCOVA model with multiple imputation for missing data.

The primary analysis population for the European Medicines Agency (EMA) will be the ITT population excluding those patients treated with diet and exercise only who are metformin naïve. The efficacy estimand is of interest, and post-rescue data will be censored.

The primary analysis population for the FDA will be the ITT population regardless of adherence to treatment, use of rescue therapy, or early termination from the study.

The primary analysis population for the other regulatory agencies and disclosures will be the ITT population by censoring the post-rescue data.

12.2.6.1.1. Multiple Imputation for Missing Data

For the treatment regimen estimand only, an ANCOVA, with missing endpoints imputed using the copy reference approach will be conducted. The reference is from those patients in the placebo arm who had the measurement for the primary endpoint. The reference response will be imputed for all missing data within each treatment group. The ANCOVA model includes baseline HbA1c as a covariate, stratification factors and treatment as fixed effects.

12.2.7. Secondary Efficacy Analyses

Changes from baseline for HbA1c, FBG, and BMI will be analyzed using MMRM and ANCOVA models on the ITT population. The MMRM and ANCOVA models will include the model terms given for the previously described primary analysis models.

For percentages of patients achieving target HbA1c of <7.0% at 26 weeks, for the efficacy estimand, longitudinal logistic regression with repeated measurements will be used. The model will include the independent variables treatment, insulin usage, metformin usage, visit, treatment-by-visit, and baseline HbA1c as a covariate. Post-rescue data for this analysis will be

considered missing. For the treatment regimen estimand, this analysis will be performed on the ITT population of HbA1c target achievement (<7.0% at 26 weeks) via a logistic regression, where patients who have no endpoint data will be imputed as not having achieved the target.

12.2.7.1. Multiple Imputation for Missing Data

In the treatment regimen estimand, the ANCOVA model coupled with the copy reference approach mentioned in Section 12.2.6.1 will be fitted by replacing the baseline HbA1c with baseline HbA1c strata, and adding the corresponding baseline measure as a covariate to assess the treatment effect on the 26-week FBG and BMI change from baseline.

12.2.7.2. Multiplicity

A graphical approach for multiple comparisons (Bretz et al. 2009; Bretz et al. 2011) will be used to strongly control the overall Type I error (2-sided alpha of 0.05) for testing the null hypothesis of no treatment effect with respect to the primary and key secondary endpoints. This graphical approach will be conducted separately for the ITT population with post-rescue data (treatment regimen estimand) coupled with the copy reference approach, the ITT population by censoring the post-rescue data (efficacy estimand), and the ITT population by censoring the post-rescue data (efficacy estimand) and excluding those patients treated with diet and exercise only who are metformin naïve. The same scheme will be adopted in each population, and each will be tested at the full significance level of 0.05.

12.2.8. Pharmacokinetic/Pharmacodynamic Analyses

Population PK analyses will be conducted using dosing data and dulaglutide concentrations obtained from all patients participating in the main protocol, as well as the PK addendum via commonly accepted pharmacostatistical methods (for example, nonlinear mixed-effects modeling), and covariate screening. The relationship between dulaglutide dose and/or concentration and key safety (such as heart rate and blood pressure) and efficacy measures (such as fasting glucose and HbA1c) will be assessed graphically or through modeling. Endpoints may include but are not necessarily limited to those listed above.

In addition, if positive antibody titers to dulaglutide are observed, the relationship between dulaglutide PK and antibody titer will be evaluated.

12.2.9. Safety Analyses

The safety analyses will include measurements of AEs, SAEs, AEs of interest (hypoglycemic episodes, pancreatitis, C-cell hyperplasia, and C-cell neoplasms, allergic/hypersensitivity reactions and injection site reactions, nausea and vomiting, renal impairment), rescue for hyperglycemia, vital signs, and laboratory analytes. Unless otherwise specified, the ITT population (including post-rescue data) will be used for analyses of safety measurements.

12.2.9.1. Study Drug Exposure

Exposure to each study treatment will be calculated for each patient and summarized by treatment group. The time points for exposure summaries will be defined in the SAP.

12.2.9.2. Adverse Events

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported in preferred term and system organ class. Selected notable AEs of interest may be reported using high-level terms if deemed appropriate. All AEs and TEAEs, defined as postbaseline events that are new events or preexisting conditions that become worsened in severity after randomization, will be listed by patient and visit. Information on treatment, actual term, preferred term, severity, seriousness, and relationship to study drug will also be reported

Summary statistics will be provided of TEAEs, SAEs, and study discontinuation due to AEs or death during the treatment period. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

12.2.9.2.1. Adverse Events of Interest

12.2.9.2.1.1. Hypoglycemic Episodes

Treatment differences in incidence of hypoglycemic episodes will be assessed by Fisher's exact test. Treatment differences in rates of hypoglycemic episodes will be assessed by the likelihood-based repeated measures model with negative binomial distribution. The model will include treatment, HbA1c strata (<8.0%, ≥8.0%), metformin use, insulin use, visit, and treatment-by-visit interaction.

12.2.9.2.1.2. Pancreatitis

Listings and summaries of adjudicated pancreatic events will be provided.

12.2.9.2.1.3. Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Listings and summaries of AEs of interest associated with the thyroid gland (benign and malignant neoplasms) will be produced.

12.2.9.2.1.4. Allergic/Hypersensitivity Reactions and Injection Site Reactions

Listings of patients experiencing allergic and hypersensitivity reactions including injection site reactions will be produced.

12.2.9.2.1.5. Nausea and Vomiting

Because gastrointestinal AEs, such as nausea and vomiting, are among the most common events reported in patients treated with dulaglutide, summaries and analyses for time to onset, duration, and severity of nausea and vomiting will be provided. The planned reports will be further described in the SAP.

12.2.9.2.1.6. Renal Impairment

Listing of AEs suggestive of acute kidney failure will be provided. Other reports may be generated if deemed appropriate.

12.2.9.3. Laboratory Analytes

Laboratory measurements will be listed by patient and visit.

Laboratory measurements will also be summarized. For continuous (numeric) laboratory analytes, the change from baseline to endpoint will be analyzed using an ANOVA on the rank-transformed data, with treatment as fixed effects. Last observation carried forward will be used to impute missing postbaseline values.

For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using Fisher's exact test.

12.2.9.4. Dulaglutide Anti-Drug Antibodies

If dulaglutide ADAs are detected, listings of antibody titers and antibody types by patient will be provided. A summary of incidence of treatment-emergent antibodies by antibody types will also be presented.

12.2.10. Subgroup Analyses

A subgroup analysis will be performed on the primary endpoint using the efficacy estimand and the same model as the primary analysis model with an added term for the 3-way interaction visit-by-treatment-by-<subgroup>, 2-way interaction of treatment-by-<subgroup>, and visit-by-<subgroup>. The 2-way interaction of treatment-by-<subgroup> at the primary time point of 26 weeks will be evaluated to assess an interaction in the treatment effect with the subgroup levels. Significance will be evaluated at alpha=0.1. The following are candidate subgroups that might be analyzed. This list is not necessarily all-inclusive:

- Gender
- Age (≤14 years old, >14 years old)
- Race
- Ethnicity
- Region (US, non-US)
- Duration of diabetes at baseline (<median duration and ≥median duration)
- Baseline BMI (<median and ≥median)
- Baseline weight (<median and ≥median)
- Metformin usage ("yes" or "no")
- Baseline HbA1c (<8.0%, ≥8.0%)
- Insulin usage ("yes" or "no")
- Monotherapy ("yes" or "no")
- Metformin and insulin usage ("yes" or "no")

When analyzing baseline HbA1c (<8.0%, ≥8.0%) as a subgroup, the baseline HbA1c will not be included as a covariate to avoid confounding.

A descriptive summary of the change from baseline to Week 26 in HbA1c, FBG, and BMI, and HbA1c target of <7.0% at Week 26 will be presented by age group, categorized by (10-14 years) and (>14 years).

A descriptive summary for the key clinically important safety endpoints may be presented for the aforementioned age group.

12.2.11. Interim Analyses

No formal interim analysis is planned for this study.

An independent DMC will have the responsibility to review the interim results in order to monitor the safety of the patients in the study up until the last patient completes the Week 26 visit (Visit 9). An SAC will perform the data analysis for the DMC. Unblinding details are specified in the unblinding plan section of the SAP.

Only the DMC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

There may be 2 database locks for this study. A primary database lock may be conducted for all data accumulated through the time when all randomized patients have completed 26 weeks of treatment (Visit 9, primary objective endpoint). The final database lock will be conducted for all data accumulated through the time when all patients have completed the 4-week Safety Follow-Up Period (through Visit 801). Following the primary database lock, the sponsor will be unblinded to analyze and report the data.

12.2.11.1. Safety Analysis

The DMC will conduct a safety interim analysis approximately every 6 months until all patients have reached the primary endpoint at 26 weeks as soon as a total of 50 patients are enrolled. The number of interims may be adjusted by the actual enrollment rate.

12.2.11.2. Sample Size Re-Estimation

After 100 patients have been enrolled, an information-based sample size re-estimation (SSR) calculation may be conducted by the SAC. Only the variability of the primary endpoint will be used in this calculation. No alpha adjustment is needed. The details of the SSR are included in the SAP.

12.2.11.3. Initiation of Pharmacokinetic Analyses

A limited number of pre-identified individuals may gain access to the unblinded data prior to the primary database lock at Week 26, in order to initiate the PopPK/PD model development processes. After the final database lock, PK and PK/PD data may be analyzed graphically or used to refresh the PopPK and PK/PD models developed at primary database lock. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

13. Informed Consent, Ethical Review, and Regulatory Considerations

13.1. Informed Consent

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

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

The ICF will be used to explain the potential risks and benefits of study participation to the parent or legal guardian and patient in simple terms before the patient is entered into the study, and to document that the parent or legal guardian is satisfied with his or her understanding of the risks and benefits of their child participating in the study and desires the child to participate in the study.

In addition to the ICF that must be signed by a legal representative (parent or legal guardian), the patient will be required to give documented assent in a separate document if they have not reached the age of majority per local country regulations. If the patient has reached the age of majority per local country regulations at the time of screening, a separate assent document may not be required, as the patient is eligible to sign the ICF. If the patient reaches age of majority per local country regulations during their participation in the trial, they will be required to sign an ICF at the next clinic visit.

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

13.2. Ethical Review

Lilly or its representatives must approve all ICFs and assents before they are used at investigative site(s). All ICFs must be compliant with the International Conference on Harmonisation (ICH) guideline on GCP.

The investigator must give assurance that the ERB was properly constituted and convened as required by ICH guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF and Assent Form must be provided to Lilly before the study may begin at the investigative site(s). The ERB(s) will review the protocol as required.

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

- The current USPI or SmPC and updates during the course of the study

- Informed Consent Form and Assent Form
- Relevant curricula vitae.

13.3. Regulatory Considerations

This study will be conducted in accordance with:

1) Consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
2) The ICH GCP Guideline [E6] and ICH Guideline [E11]
3) Applicable laws and regulations.

The investigator or designee will promptly submit the protocol to applicable ERB(s).

Some of the obligations of Lilly will be assigned to a TPO.

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 AEs and/or other trial-related data.

13.3.1. Investigator Information

Licensed physicians with a specialty in pediatric endocrinology, pediatrics, endocrinology, internal medicine, or family practice will participate as investigators in this clinical trial.

13.3.2. Protocol Signatures

Lilly's responsible medical officer will approve the protocol, confirming that, to the best of his or her knowledge, the protocol accurately describes the planned design and conduct of the study.

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

13.3.3. Final Report Signature

The CSR coordinating investigator will sign the final CSR 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 CSR coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the CSR coordinating investigator.

Lilly's responsible medical officer and statistician will approve the final CSR 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 GBGC Study Schedule

Study Schedule, Protocol H9X-MC-GBGC
Perform procedure as indicated.

	Double-Blind Period									Open-Label Period								Safety
	Screen	Random-ization	Phone visit	Clinic visit	Phone visit	Clinic visit	Phone visit	Phone visit	Clinic visit	Phone visit	Phone visit	Phone visit	Clinic visit	Phone visit	Phone visit	Clinic visit	Clinic visit	Clinic visit
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ET	V16	V801
Week	-4	0	1	4	9	13	18	22	26	27	31	35	39	44	48		52	56
Allowed Visit Intervals (D)	±7	0	±3	±7	±7	±7	±7	±7	±6	+7	±7	±7	±7	±7	±7		±7	±7
Fasting visit		X				X			X								X	
Informed consent and assent	X																	
Evaluation of inclusion and exclusion criteria	X	X																
Complete history/preexisting conditions	X																	
Physical exam by physician (w/Tanner staging)		X							X							X	X	
Symptom-directed physical exam by physician				X[a]		X							X					
Vital signs	X	X		X		X			X				X			X	X	X
Height and weight[b]	X	X		X		X			X				X			X	X	X
Calculation of BMI	X	X																
Waist circumference (cm)[b]		X				X			X									
ECG		X							X							X	X	
Adverse events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Establish basal insulin dose[c]		X							X									
Discussion of effective contraception[d]	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Collect information from study diary[e]	X[f]	X[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[f]
Distribute new study diaries		X		X		X			X				X			X	X	
Distribute SMBG supplies[g]		X		X		X			X				X			X	X	
Lifestyle management instruction (ie, diet and exercise)		X		X		X			X				X				X	
Injection training[h]	X	X																
Use IWRS to get study drug assignment[i]		X		X					X									
Distribute study drug		X	X[j]	X	X[j]	X	X[j]	X[j]	X	X[j]	X[j]	X[j]	X	X[j]	X[j]			
Study drug injection		X		X[a]		X							X[k]					
Return study devices																X		X

Study Schedule, Protocol H9X-MC-GBGC

	Double-Blind Period									Open-Label Period								Safety
	Screen	Random-ization	Phone visit	Clinic visit	Phone visit	Clinic visit	Phone visit	Phone visit	Clinic visit	Phone visit	Phone visit	Phone visit	Clinic visit	Phone visit	Phone visit	Clinic visit	Clinic visit	Clinic visit
Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	V13	V14	V15	ET	V16	V801
Week	-4	0	1	4	9	13	18	22	26	27	31	35	39	44	48		52	56
Allowed Visit Intervals (D)	±7	0	±3	±7	±7	±7	±7	±7	±6	+7	±7	±7	±7	±7	±7		±7	±7
Fasting visit		X				X			X								X	
Islet cell Ab (IA2)	X																	
Anti-GAD Ab (GAD65)	X																	
Standard clinical chemistries and hematology[l]	X	X				X			X				X			X	X	
Random blood glucose	X												X			X		X
Fasting blood glucose		X				X			X								X	
HbA1c	X	X				X			X				X			X	X	X
Amylase, (P) amylase, lipase	X	X				X			X				X			X	X	X
Serum calcitonin	X	X				X			X				X			X	X	X
Serum hormones[m]		X							X							X	X	
Urinalysis		X							X							X	X	
Spot urine ACR		X							X							X	X	
Serum pregnancy test[d]	X					X			X				X			X	X	
Urine pregnancy test	X[n]	X	X[n]	X	X[n]	X	X[n]	X[n]	X	X[n]	X[n]	X[n]	X	X[n]	X[n]	X	X	
Fasting insulin		X				X			X									
Fasting C-peptide		X				X			X									
Fasting adiponectin		X				X			X									
LY2189265 plasma concentrations[o]						X, X			X				X			X	X	X
Anti-LY antibodies[p]		X				X			X				X			X	X	X
EQ-5D-Youth instrument		X							X							X	X	

Study Schedule, Protocol H9X-MC-GBGC

Abbreviations: Ab = antibodies; ACR = albumin/creatinine ratio; ADA = anti-drug antibodies; AE = adverse event; BMI = body mass index; D = days; ECG = 12-lead electrocardiogram; ET = early termination; GAD65 = glutamic acid decarboxylase 65 autoantibodies; HbA1c = hemoglobin A1c; HO = health outcomes; IA2 = tyrosine phosphatase-like insulinoma antigen 2 autoantibodies; IGF-1 = insulin-like growth factor -1; IWRS = Interactive Web-Response System; LH = luteinizing hormone; LY = dulaglutide; PK = pharmacokinetics; QOL = quality of life; SMBG = self-monitored blood glucose; V = visit; V801 = safety follow-up visit; W = week.

[a] At Visit 4, the physician will determine whether the patient tolerated the first 4 weeks of study drug. If the patient tolerated the study drug, they will be given their assigned study drug.

[b] Height, weight, and waist circumference are measured per Attachment 6.

[c] The metformin and basal insulin doses established at Visit 2 should not vary more than 15% during the double-blind period (until Visit 9). Patients may receive unlimited insulin for hyperglycemia for up to 2 weeks and it will not be deemed "rescue." The basal insulin dose may be recalculated at Visit 9 and may be increased as needed during the open-label period. Metformin and basal insulin may be decreased at any time if the patient has hypoglycemia.

[d] In females of childbearing potential. If pregnancy is suspected, a local urine pregnancy test should be performed and a serum pregnancy test sent to the central laboratory.

[e] Includes SMBG results, hypoglycemic events, AE information, date, and exact time of every study drug injection and date of last menstrual period (for females).

[f] At Visits 1 and 2, collect last menstrual period only. At Visit 801, collect AEs and last menstrual period only.

[g] Glucometer, blood glucose test strips, lancets, alcohol swabs, and lancing device as needed. Patients may be trained at screening and will be trained at randomization. Additional training may occur as needed.

[h] Using the demonstration pen, which does not have a needle and is filled with air. Training at Visit 1 is recommended but not required. Training at Visit 2 is required.

[i] Complete baseline assessments before using IWRS.

[j] Optional dispensing visit for investigational product.

[k] If it is the patient's dosing day, study drug will be administered prior to performing other visit procedures.

[l] Standard blood chemistries and hematology are shown in Attachment 2. They include eGFR, which will be calculated by the central laboratory.

[m] Serum hormones should be drawn in the morning (fasting) and include: cortisol, IGF-1, prolactin, LH, estradiol (females and males) and testosterone (males only).

[n] The patient should come to the clinic to have this performed if pregnancy is suspected. If a local urine pregnancy test is performed, draw blood for serum pregnancy test at the same time and send to central laboratory.

[o] Includes both pre- and postdose blood draws. At Week 13 (Visit 6), one PK sample is to be taken predose and then study drug should be administered. Later in the visit, one PK sample should be taken between 1 to 12 hours after administration of the Week13 dose. At Week 26 (Visit 9), the PK sample is to be taken predose. At Week 39 (Visit 13), the PK sample can be taken up to 2 days postdose. At Week 52 (Visit 16), the PK sample can be taken at any time during the visit. At Week 56 (Visit 801) and early discontinuation, the sample can be taken at any time during the visit.

[p] When a PK sample is drawn, an ADA sample should also be drawn at the same time or within 30 minutes of the PK sample (see footnote n), with the exception of the randomization visit, where an ADA sample is drawn but not a PK sample.

Attachment 2. Protocol GBGC Clinical Laboratory Tests

Clinical Laboratory Tests

Standard Hematology:	**Standard Clinical Chemistries:**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	ALT
Neutrophils, segmented	AST
Lymphocytes	BUN
Monocytes	Creatinine[b]
Eosinophils	Cystatin C
Basophils	Uric acid
Platelets	Calcium
	Glucose, random
Urinalysis:	Glucose, fasting
Specific gravity	Albumin
pH	Total cholesterol, HDL, LDL, triglycerides
Protein	CK
Glucose	
Ketones	
Blood	**Hemoglobin A1c**
Urine leukocyte esterase	
	Hepatic monitoring (as appropriate)
Urine:	
Spot urine for albumin/creatinine ratio	**Hormones (serum):**
	Calcitonin
Pregnancy Tests [a]	Prolactin
Urine pregnancy test (performed locally)	Cortisol
Serum pregnancy test	IGF-1
	LH
LY2189265 levels	Estradiol (females and males)
	Testosterone (males only)
Antibodies:	
GAD65	
IA2	**Pancreatic enzymes:**
Anti-LY2189265 antibodies	Lipase
	Amylase
Serum insulin, fasting	P-amylase
Serum C-peptide, fasting	
Serum adiponectin, fasting	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CK = creatine kinase; GAD65 = glutamic acid decarboxylase 65 autoantibodies; HDL = high-density lipoprotein cholesterol; IA2 = tyrosine phosphatase-like insulinoma antigen 2 autoantibodies; IGF-1 = insulin-like growth factor-1; LDL = low-density lipoprotein cholesterol; LH = luteinizing hormone; P-amylase = pancreatic amylase; RBC = red blood cells; WBC = white blood cells.

[a] Performed in females of childbearing potential only.

[b] eGFR to be performed by central laboratory and reported.

Note: All laboratories are assayed by the Lilly-designated central laboratory unless otherwise indicated.

Attachment 3. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with the Lilly, or its designee, clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalised ratio; RBC = red blood cells; WBC = white blood cells.

a Assayed by Lilly-designated or local laboratory.

b Reflex/confirmation dependent on regulatory requirements and/or testing availability.

Attachment 4. Definitions of Highly Effective and Effective Contraception

Participants of childbearing age who are sexually active should be counseled to use either 1 highly effective method of contraception or 2 effective methods of contraception combined for the duration of the trial and for 30 days after (until Visit 801). Childbearing potential is usually considered from menarche to menopause. Menarche should be considered if the female participant is close to the average age for menarche in her country or shows signs of puberty beyond Tanner stage 1. Any past bleeding or spotting, no matter how little, should be considered a potential menarche.

1. Highly effective methods of contraception (use 1 form)
    a. Combined oral contraceptive pill and mini-pill
    b. NuvaRing®
    c. Implantable contraceptives
    d. Injectable contraceptives (such as Depo-Provera®)
    e. Intrauterine device (such as Mirena® and ParaGard®)
    f. Contraceptive patch – ONLY women <198 pounds or 90 kg
    g. Total abstinence[1]
    h. Vasectomy – for men in clinical trials

2. Effective methods of contraception (use 2 forms combined)
    a. Male condom with spermicide
    b. Female condom with spermicide
    c. Diaphragm with spermicide
    d. Cervical sponge
    e. Cervical cap with spermicide

For patients using oral contraceptive pills, if vomiting occurs, advise the patient to use a supplemental barrier method of contraception.

Females who have undergone or who have the following will not be considered of childbearing potential:

a. Female sterilization
b. Hysterectomy
c. Mullerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome [also referred to as congenital absence of the uterus and vagina])

[1]Total abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject (CTFG 2014).

Attachment 5. Protocol GBGC IDF-ISPAD Criteria for the Diagnosis of Diabetes

Criteria for the diagnosis of diabetes mellitus[a]

1. Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/L (200 mg/dL)[a]. Casual is defined as any time of day without regard to time since last meal.

or

2. Fasting plasma glucose ≥7.0 mmol/L (≥ 126 mg/dL)[b].
   Fasting is defined as no caloric intake for at least 8 hours.

or

3. 2-hour postload glucose ≥11.1 mmol/L (≥200 mg/dL) during an oral glucose tolerance test (OGTT).
   The test should be performed as described by World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g (2).
4. HbA1c ≥ 6.5.
   However, there are difficulties with assay standardization and individual variation in the relationship between blood glucose and HbA1c, which may outweigh the convenience of this test.

[a] Corresponding values are ≥10.0 mmol/L for venous whole blood and ≥ 11.1 mmol/L for capillary whole blood.

[b] Corresponding value is ≥ 6.3 mmol/L for both venous and capillary whole blood.

Reference: IDF [WWW]

Attachment 6. Measurement of Height, Body Weight, and Waist Circumference during the Trial

Use the same method of measuring height and weight throughout the trial.

Measuring Height
Measure height using a validated stadiometer, not a height bar on a beam scale or other informal method.

- Ask the patient to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the patient at every clinic visit when their height is measured).
- Ask the patient to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the back board or the stadiometer or the wall.
- Ask the patient to look straight ahead without tilting their head up.
- Ask the patient to breathe in and stand tall. Move the device's measurement arm gently down onto the top of the patient's head. Record the patient's height in centimeters (cm).

Measuring Weight
Measure weight using a validated scale (i.e., balance beam scale, digital scales, but not a bathroom scale).

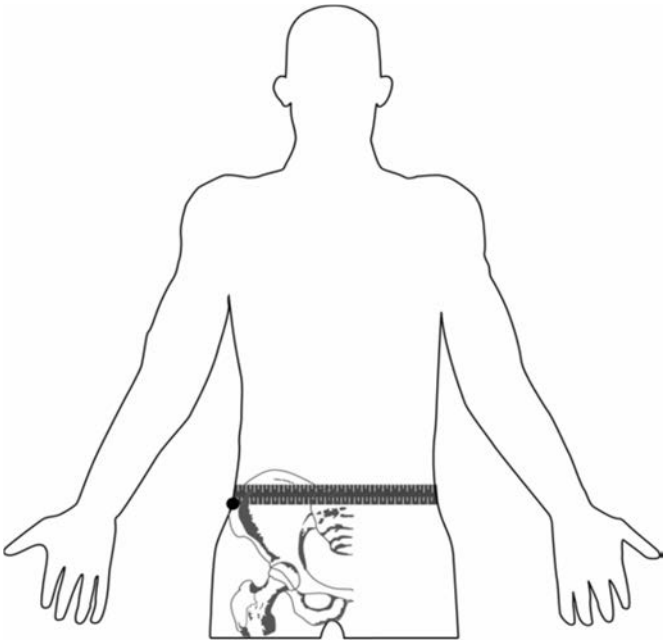
- Body weight measurements should be done in a consistent manner using a calibrated scale (mechanical or digital scales are acceptable). All weights for a given patient should be measured using the same scale, whenever possible, after the patient has emptied their bladder. Patients should be lightly clothed but not wearing shoes while their weight is measured.
- Ask the patient to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the patient at every clinic visit when their weight is measured).
- Make sure the scale is placed on a firm, flat, even surface (not on carpet or on a sloping surface or a rough uneven surface).
- Ask the patient to step onto the scale with 1 foot on each side of the scale.
- Ask the patient to stand still with their arms by their sides and then record their weight in kilograms (kg).

This has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO WWW).

Measuring Waist Circumference (CDC 2007):

Waist circumference will be measured with a steel (or non-stretchy) tape measure at the uppermost lateral border of the hip crest (ilium).

1. Instruct the participant to cross the arms and place the hands on opposite shoulders.
2. Palpate the hip area to locate the right ilium of the pelvis (see figure below). With the cosmetic pencil draw a horizontal line just above the uppermost lateral border of the right ilium. Cross this mark at the midaxillary line, which extends from the armpit down the side of the torso.
3. Extend the measuring tape around the waist. Position the tape in a horizontal plane at the level of the measurement mark. If available, use a wall mirror to ensure the horizontal alignment of the tape. Check that the tape sits parallel to the floor and lies snug but does not compress the skin.
4. Take the measurement to the nearest 0.1 cm at the end of the participant's normal expiration. Record the result.



Attachment 7. Protocol Amendment H9X-MC-GBGC(e) Summary – A Randomized, Double-Blind Study with an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Pediatric Patients with Type 2 Diabetes Mellitus (AWARD-PEDS: Assessment of Weekly AdministRation of LY2189265 in Diabetes-PEDiatric Study)

Overview

Protocol H9X-MC-GBGC, A Randomized, Double-Blind Study with an Open-Label Extension Comparing the Effect of Once-Weekly Dulaglutide with Placebo in Pediatric Patients with Type 2 Diabetes Mellitus (AWARD-PEDS: Assessment of Weekly AdministRation of LY2189265 in Diabetes-PEDiatric Study), has been amended. The new protocol is indicated by amendment (e) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for changes made to this protocol are as follows:

- In the Synopsis, updated the estimated last patient visit date and overall duration of the study based on current enrollment projections; removed sensitivity analyses of analysis of covariance (ANCOVA) with last observation carried forward (LOCF), since it was not mentioned in the body of the protocol and not included in current statistical approaches used for other dulaglutide studies; and updated all other content to align with changes made in the body of the protocol.
- In Section 4, Abbreviations and Definitions, revised the definition of 'interim analysis' to distinguish it from the primary lock analysis planned for when all patients complete the Week 26 visit (primary endpoint visit).
- In Section 4, Abbreviations and Definition, revised abbreviation for the EQ-5D-Y as meaning "EQ-5D-Youth Version" and revised this abbreviation throughout the protocol to align with established naming conventions for the EQ-5D instrument (Brooks et al., 2020).
- In Section 5, Introduction, and Section 7.2, Discussion of Design and Control, updated certain statements that are no longer accurate to align with current information (for example, in Section 5, added liraglutide to medications approved for the treatment of adolescents with type 2 diabetes mellitus [T2DM]).
- In Section 6.2, Secondary Objectives:
    - For the secondary objective of percentage of patients achieving hemoglobin A1c (HbA1c) goal at 26 weeks, updated the threshold level of HbA1c from ≤6.5% to <7.0% for consistency with current clinical practice guidelines for adolescents with T2DM (Zeitler et al. 2018). Moved percentage of patients achieving ≤6.5% at 26 weeks to the exploratory objectives.

  - Added change in fasting blood glucose between baseline and Week 52 to other secondary objectives, as this objective was inadvertently omitted from prior versions of the protocol.
- In Section 6.3, Exploratory Objectives:
  - Added percentage of patients with HbA1c ≤6.5% at Week 26 as an exploratory objective.
  - Updated definition of hypoglycemia from plasma glucose (PG) ≤70 mg/dL to PG <70 mg/dL in exploratory objectives assessing composite endpoints to align with revisions to hypoglycemia definition made in Section 10.4.1.2.1 described below.
  - Added change in standard deviation scores for body mass index and height between baseline and Weeks 26 and 52 to exploratory objectives, as these are standard methods for assessing growth and development parameters in pediatric populations by normalizing measurements to population reference values.
  - Added change in waist circumference between baseline and Weeks 26 and 52 to exploratory objectives to align with the measurement of waist circumference that was added in GBGC protocol amendment (b).
  - Revised the exploratory objective regarding the EQ-5D-Y to specify assessment of both change in VAS and the percentage of patients reporting each level of problem on each dimension of the EQ-5D-Y. These changes reflect the anticipation that an EQ-5D-Y index formula will not be available at the time of primary database lock.
  - Added change in basal insulin dose from baseline to Week 26 and from baseline to Week 52 to exploratory objectives to align with the statistical analysis plan (SAP) where this was added as an exploratory measure of interest in Version 4.
- In Sections 7.1, Summary of Study Design, and 12.1, Determination of Sample Size, updated the projected sample size from a minimum of 150 to approximately 150 based on the results of the sample size re-estimation.
- In Section 7.1, Summary of Study Design, updated Figure GBGC.1 to add 'Primary Endpoint' label to Visit 9/Week 26 to reflect addition of the primary database lock at Week 26.
- In Section 10.1, Efficacy Measures, updated secondary and exploratory efficacy measures to align with revisions to efficacy objectives discussed above.
- In Section 10.2, Health Outcome/Quality of Life Measure, revised the description of how the EQ-5D-Y will be analyzed, deleted content regarding conversion to a single index value since an EQ-5D-Y index formula will likely not be available at the time of primary database lock, and deleted outdated statement that an EQ-5D-Y index formula is anticipated to be available in 2016.
- In Section 10.4.1.2.1, Hypoglycemia:
  - Revised upper threshold of hypoglycemia definition from PG ≤70 mg/dL (≤3.9 mmol/L) to PG <70 mg/dL (<3.9 mmol/L) to align with current hypoglycemia definitions (International Hypoglycaemia Study Group 2017; ADA 2020); added updated references and made corresponding updates throughout the protocol.

  - Revised PG threshold in definition of relative hypoglycemia from >70 mg/dL (>3.9 mmol/L) to ≥70 mg/dL (≥3.9 mmol/L) to align with revised definition of hypoglycemia above.
  - Changed statement that certain categories of hypoglycemia may be evaluated using a PG cutoff <54 mg/dL (<3.0 mmol/L) from 'may' to 'will' to align with published recommendations (International Hypoglycaemia Study Group 2017).
- In Section 12.2, Statistical and Analytical Plans, changed 'ITT estimand' to 'treatment regimen estimand' to align with the SAP where this naming convention was changed in Version 4.
- In Section 12.2.1, General Considerations:
  - Removed the sensitivity analyses for the PP population and Completers populations, since these analyses have little relevance to clinical or regulatory decision making.
  - Updated baseline measurement definition to align with the SAP where the definition was updated in Version 4 and clarified that the baseline HbA1c value will be used to define HbA1c strata for analyses, since baseline HbA1c is more relevant to postrandomization changes than the screening value.
- Removed chi-square test from analyses throughout the protocol; only Fisher's exact test will be used, which aligns with current statistical approaches used for other dulaglutide studies.
- In Section 12.2.2, Patient Disposition, removed summary of discontinuations by visit to align with current statistical approaches used for other dulaglutide studies.
- In Section 12.2.6, Primary Outcome and Methodology:
  - Updated the primary analysis model for the treatment regimen estimand from MMRM to ANCOVA with multiple imputation for missing data to align with FDA-recommended analysis.
  - Removed sensitivity analyses using tipping point approach to align with current statistical approaches used for other dulaglutide studies.
  - Updated the reference group in the 'copy reference' approach to 'patients in the placebo arm who had measurement at primary endpoint,' since review of blinded study data suggest there are too few patients receiving rescue medication and/or stopping study medication and having a primary endpoint measurement to result in a meaningful analysis.
- In Section 12.2.7, Secondary Efficacy Analyses:
  - For HbA1c target, for the efficacy estimand, removed the interaction term of baseline HbA1c by visit from longitudinal logistic regression, and for the treatment regimen estimand, updated the analysis to a logistic regression with missing endpoint data being imputed as not achieving the target to align with current statistical approaches used for other dulaglutide studies.
  - Added efficacy estimand excluding metformin naïve patients to conduct the graphical approach to align with the population for the EMA that was added in GBGC protocol amendment (b).

- In Section 12.2.8, Pharmacokinetic/Pharmacodynamic Analyses, clarified the PK analysis to be performed.
- In Section 12.2.9.2.1.3, Thyroid C-Cell Hyperplasia and C-Cell Neoplasms, deleted the phrase '… as well as a listing of biopsy reports' because this information is not being collected on an eCRF and will not be available in the reporting database.
- In Section 12.2.10, Subgroup Analyses:
    - Added 2-way interaction of treatment-by-<subgroup> and visit-by-<subgroup> to the model, to align with the SAP where this was added to reflect the correct model in Version 4.
    - Removed 'Patients with missing HbA1c and those who received rescue medication will be categorized as not reaching the HbA1c target of ≤6.5%' from the description summary for primary/key secondary objectives by age subgroup, since more details will be provided in SAP.
- Added text to Section 12.2.11, Interim Analyses, to provide for 2 database locks: a primary lock when all patients have completed the 26-week primary endpoint visit and a final lock when all patients have completed the trial.
- Revised Section 12.2.11.3, Initiation of Pharmacokinetic Analyses, to align with addition of a primary 26-week database lock.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Synopsis

Length of Study: Approximately ~~66~~ 61 months
Estimated first patient visit: JAN 2017 Estimated last patient visit: ~~JUN~~JAN 2022

Objectives:

…

The key secondary efficacy objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters:

- Change in HbA1c between baseline and Week 26 (individual doses only)
- Change in fasting blood glucose (FBG) between baseline and Week 26
- Percentage of patients with HbA1c ~~≤6.5~~<7.0% at Week 26
- Change in body mass index (BMI) between baseline and Week 26

The other secondary efficacy objectives are to assess the 2 dulaglutide treatment groups (individually and pooled) with respect to the following parameters:

- Change in HbA1c between baseline and Week 52
- Change in FBG between baseline and Week 52
- Percentage of patients with HbA1c ~~≤6.5~~<7.0% at Week 52
- Change in BMI between baseline and Week 52

…

Exploratory objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters at 26 weeks, and to assess the following parameters in the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) at Week 52 (unless otherwise specified):

- Percentage of patients with HbA1c ~~<7.0~~≤6.5% at Weeks 26 and 52
- Change in HbA1c between baseline and Week 13
- Percentage of patients having HbA1c <7.0% without severe, documented symptomatic (≤≤70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Percentage of patients having HbA1c ≤6.5% without severe, documented symptomatic (≤≤70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Change in weight between baseline and Weeks 26 and 52

- Change in hormone-related safety assessed by the effect on morning serum prolactin, insulin-like growth factor-1 (IGF-1), estradiol, testosterone (males only), luteinizing hormone (LH), and cortisol between baseline and Weeks 26 and 52
- Change in serum lipids between baseline and Weeks 26 and 52
- Change in Tanner staging between baseline and Weeks 26 and 52
- Change in BMI standard deviation score (SDS) between baseline and Weeks 26 and 52
- Change in height and height SDS between baseline and Weeks 26 and 52
- Change in waist circumference between baseline and Weeks 26 and 52
- Change in the ~~European Quality of Life (EuroQOL) Five Dimension (~~EQ-5D~~)~~ Youth version (EQ-5D-Y) visual analogue scale (VAS) score between baseline and Weeks 26 and 52
- Percentage of patients reporting each level of problem on each dimension of the EQ-5D-Y at baseline, weeks 26 and 52
- Assess the effect of dulaglutide on measures of insulin resistance, beta cell function, and serum adiponectin at Weeks 13 and 26
- Change in basal insulin dose from baseline to Week 26 and from baseline to Week 52

Criteria for Evaluation:

Efficacy: The primary efficacy measure is change from baseline in HbA1c at 26 weeks for the pooled dulaglutide doses.

Additional secondary efficacy endpoints are the following:

- Change in FBG between baseline and Week 26 and Week 52
- Percentage of patients achieving a target HbA1c ~~≤6.5~~<7.0% at Week 26 and Week 52
- …

…

Health Outcomes: To compare the effect of dulaglutide compared to placebo on health status, as measured by the change from baseline to Week 26 and to assess the following at Week 52 in the validated patient-reported outcome (PRO) measure, EQ-5D-Y~~outh version~~.

Statistical Methods:

Determination of Sample Size:

A ~~minimum~~ sample size of approximately 150 will be enrolled (50 patients per arm), in order to obtain 120 completers at 26 weeks. This sample size provides at least 90% power for demonstrating superiority of the pooled dulaglutide 0.75 mg and 1.5 mg arms compared to placebo (primary objective), with a mean difference in change from baseline in HbA1c of -

0.65% and standard deviation of 1%, assuming a dropout rate of 20%. Under the same assumptions, each individual dulaglutide arm will have at least 80% power to demonstrate superiority over placebo. The screen failure rate is estimated as 80%. Among the completers, there will be no more than 25% of patients who, at baseline, were treated with diet and exercise only and who are metformin naïve.

While the above assumptions are believed to be reasonable estimates, Eli Lilly and Company (Lilly) may consider an information-based approach to sample size re-estimation to select a larger sample size of up to approximately 189 enrolled (63 patients per arm), in order to obtain 150 completers. This sample size provides at least 80% power for demonstrating superiority of the pooled dulaglutide 0.75 mg and 1.5 mg arms compared to placebo, assuming the standard deviation is 1.3%. Using these assumptions, each individual dulaglutide arm will have at least 69% power to demonstrate superiority over placebo. Lilly will decide on whether to conduct a sample size re-estimation after taking into consideration the study enrollment rate after 100 patients have been enrolled. If it is performed, the Statistical Analysis Center's (SAC) recommendation of sample size adjustment may or may not be implemented by Lilly. ~~If the sample size re-estimation is not implemented, then the target enrollment will be 150 patients (50 patients per arm).~~

Efficacy Analyses:

There will be 2 primary estimands to compare the placebo and the pooled dulaglutide arms in terms of the primary measure of HbA1c change from baseline to 26 weeks. One primary estimand will be an efficacy estimand which will not use post-rescue data; the other primary estimand will be ~~an intent-to-treat (ITT)~~ a treatment regimen estimand which will use post-rescue data. The efficacy estimand measures the benefit of treatment when taken as directed, and the ~~ITT~~ treatment regimen estimand measures the benefit of treatment as actually taken. ~~Both estimands will use the same primary analysis model and each~~ Each estimand will be tested at the full significance level of 0.05.

The primary analysis population for the European Medicines Agency (EMA) will be the intention-to-treat (ITT) population, excluding those patients treated with diet and exercise only who are metformin naïve.

For the efficacy estimand, ~~T~~the primary analysis model for HbA1c will be a mixed-model for repeated measures (MMRM) using restricted maximum likelihood (REML) with treatment, insulin usage, metformin usage, visit, and treatment-by-visit as fixed effects, and baseline HbA1c as a covariate. ~~An unstructured covariance structure will be used to model the within patient errors. An analogous analysis of covariance (ANCOVA) will be conducted as supportive analysis. Missing endpoints will be imputed with the last (postbaseline) observation carried forward (LOCF). Multiple imputation for missing data will also be conducted on the primary analysis model in the ITT population (with and without post-rescue data) as supportive analyses to evaluate the situation when data is not missing at random. The primary analysis model, MMRM, will be repeated using the Per Protocol (PP) population to check the sensitivity of the analysis.~~

Analyses on other secondary efficacy measures that are continuous will be performed using MMRM on the ITT population (~~with and~~ without post-rescue data). For percentages of patients achieving the target HbA1c of <7.0% and ≤6.5%, longitudinal logistic regression with repeated measures will be applied.

For the treatment-regimen estimand, the primary analysis model for primary and key secondary efficacy measures that are continuous will be an analysis of covariance (ANCOVA) model with multiple imputation for missing data in the ITT population (with post-rescue data). For percentages of patients achieving the target HbA1c of <7.0%, logistic regression will be applied. Missing data at the endpoint will be imputed as not achieving the target.

The primary and key secondary analyses will follow a graphical approach for multiple comparisons to strongly control the overall Type I error rate in the trial at a 2-sided α level of 0.05.

Safety Analyses:

Listings and summaries of safety data will be generated. Summary statistics will be provided for TEAEs, serious adverse events (SAEs), and study discontinuation due to adverse events (AEs) or death during the treatment period. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and ~~chi square or~~ Fisher's exact test~~s~~ will be used to compare the treatment groups.

For continuous laboratory analytes, the change from baseline to endpoint will be analyzed using an analysis of variance (ANOVA) on the rank-transformed data, with treatment as a fixed effect. Last observation carried forward will be used to impute missing postbaseline values. For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using ~~chi square or~~ Fisher's exact test~~s~~.

Treatment differences in incidence of hypoglycemic episodes will be assessed by ~~a chi square or~~ Fisher's exact test. Treatment differences in rates of hypoglycemic episodes will be assessed by a likelihood-based approach for repeated measures with a negative binomial distribution….

Pharmacokinetics/Pharmacodynamics:

… The relationship between dulaglutide dose and/or concentration and key safety (such as heart rate and blood pressure) and efficacy measures (such as fasting glucose and HbA1c) will be ~~performed~~ assessed graphically or through modeling.

4. Abbreviations and Definitions

interim analysis	An analysis of clinical study data, separated into treatment groups, that is conducted before the ~~final~~complete reporting database is created/locked for the primary endpoint.
EQ-5D-~~Y~~outh ~~Version~~	~~European Quality of Life (EuroQoL) Five Dimension~~EQ-5D-Youth version questionnaire
VAS	Visual analogue scale

5. Introduction

…

Unlike adults with T2DM, children and adolescents with T2DM have few approved glucose-lowering treatment options. Until recently, ~~M~~metformin and insulin ~~are~~ were the only agents approved in the US and EU for the treatment of children and adolescents with T2DM (Tamborlane and Klingensmith 2013). In 2019, liraglutide was approved for use in adolescents with T2DM based on the results of the Phase 3 ELLIPSE study (Tamborlane et al. 2019). While therapy with metformin is effective and safe in pediatric patients (Jones et al. 2002), once metformin monotherapy is insufficient to achieve glycemic goals, glycemic control tends to deteriorate rapidly (Badaru et al. 2014) ~~and the only available approved next step is exogenous insulin therapy~~. Therefore, there is an important need for additional approved agents to treat children and adolescents with T2DM that are safe and effective in this population.

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) have been shown in adults to improve several of the central pathophysiological abnormalities of T2DM, including glucose-dependent insulin secretion, glucagon secretion, and obesity (Drucker and Nauck 2006). In children with T2DM, the short-acting GLP-1 RA exenatide showed reductions in postprandial glucose after a single dose (n=13; Malloy et al. 2009), while pediatric T2DM patients taking the once daily GLP-1 RA liraglutide showed improvements in hemoglobin A1c (HbA1c) after 5 weeks (n=19; Klein et al. 2014). In these small trials, the GLP-1 RAs were well tolerated, with pharmacokinetic (PK) profiles similar to adults. In the ELLIPSE Phase 3 trial, liraglutide was shown to be superior to placebo when added to metformin, with or without basal insulin, with respect to glycemic control in children and adolescents, with gastrointestinal adverse events (AEs) being more common in the liraglutide group (Tamborlane et al. 2019). ~~Phase 3 trials in T2DM pediatric populations are underway with both exenatide and liraglutide using the doses approved for adults (ClinicalTrials.gov NCT00658021, NCT01541215, respectively).~~ According to publicly available trial information (ClinicalTrials.gov), enrollment in the Phase 3 trials has been lengthy and challenging, probably due to the relatively small number of pediatric patients with T2DM worldwide and the increasing number of trials enrolling pediatric T2DM patients.

6.2. Secondary Objectives

The secondary objectives of the study are to assess the efficacy, safety, PK and pharmacodynamics (PD) in patients.

The key secondary efficacy objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters:

- Change in HbA1c between baseline and Week 26 (individual doses only)
- Change in fasting blood glucose (FBG) between baseline and Week 26
- Percentage of patients with HbA1c ~~≤6.5~~<7.0% at Week 26
- Change in body mass index (BMI) between baseline and Week 26

The other secondary efficacy objectives are to assess the 2 dulaglutide treatment groups (individually and pooled) with respect to the following parameters:

- Change in HbA1c between baseline and Week 52
- Change in FBG between baseline and Week 52
- Percentage of patients with HbA1c ~~≤6.5~~<7.0% at Week 52
- Change in BMI between baseline and Week 52

6.3. Exploratory Objectives

The exploratory objectives are to compare the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) to placebo with respect to the following parameters at 26 weeks, and to assess the following parameters in the dulaglutide 0.75 mg and dulaglutide 1.5 mg arms (individually and pooled) at Week 52 (unless otherwise specified):

- Percentage of patients with HbA1c ~~<7.0~~≤6.5% at Weeks 26 and 52
- Change in HbA1c between baseline and Week 13
- Percentage of patients having HbA1c <7.0% without severe, documented symptomatic (≤≤70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Percentage of patients having HbA1c ≤6.5% without severe, documented symptomatic (≤≤70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Change in weight between baseline and Weeks 26 and 52
- Change in hormone-related safety assessed by the effect on morning serum prolactin, insulin-like growth factor-1 (IGF-1), estradiol, testosterone (males only), luteinizing hormone (LH), and cortisol between baseline and Weeks 26 and 52
- Change in serum lipids between baseline and Weeks 26 and 52
- Change in Tanner staging between baseline and Weeks 26 and 52
- Change in BMI standard deviation score (SDS) between baseline and Weeks 26 and 52
- Change in height and height SDS between baseline and Weeks 26 and 52
- Change in waist circumference between baseline and Weeks 26 and 52
- Change in the ~~European Quality of Life Five Dimension (~~EQ-5D-Y~~) Youth version~~ VAS score between baseline and Weeks 26 and 52
- Percentage of patients reporting each level of problem on each dimension of the EQ-5D-Y at baseline, weeks 26 and 52
- Assess the effect of dulaglutide on measures of insulin resistance, beta cell function, and serum adiponectin at Weeks 13 and 26
- Change in basal insulin dose from baseline to Week 26 and from baseline to Week 52

7.1. Summary of Study Design

Study H9X-MC-GBGC (GBGC) is a Phase 3, multicenter, randomized, double-blind, parallel-arm, placebo-controlled superiority trial with an open-label extension. ~~A minimum of~~Approximately 150 male and female children and adolescents (ages 10 to <18 years) with T2DM and inadequate glycemic control on diet and exercise alone or diet and exercise plus metformin and/or basal insulin will be enrolled…

…

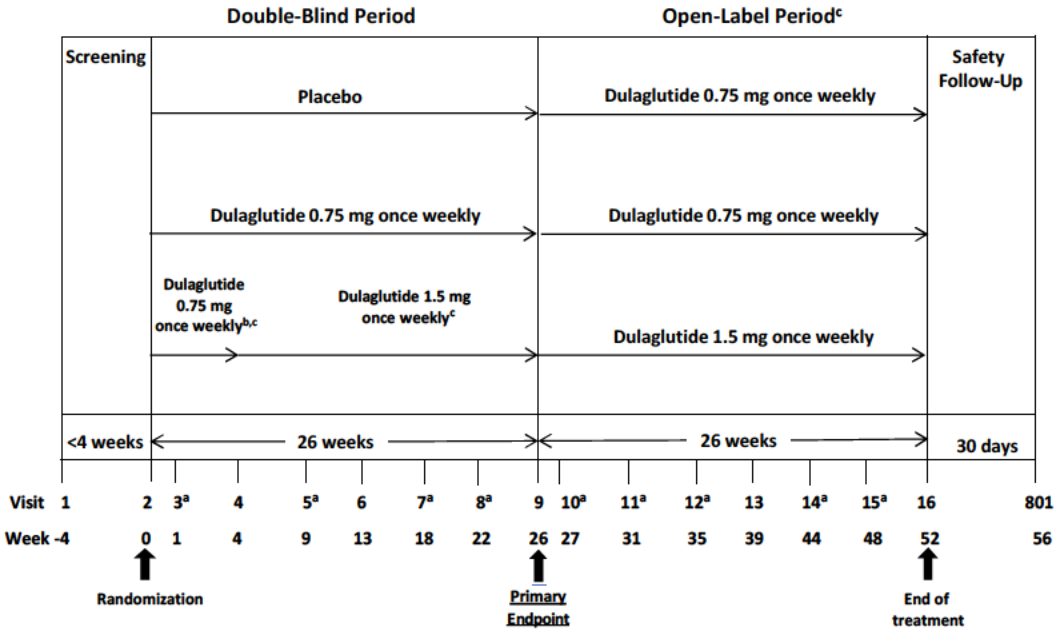


Figure GBGC.1. Illustration of study design for Clinical Protocol H9X-MC-GBGC.

…

Double-blind treatment period:

…

During the entire trial, patients should perform self-monitoring of blood glucose (SMBG) in the fasted state and at 1 other time each day, as well as at any time they have symptoms suggestive of hypoglycemia. For each hypoglycemic episode, patients should record their blood glucose level (if available), associated symptoms, and treatment in the study diaries provided. For this study, a hypoglycemic episode should be noted as <u>having</u> occurred any time a patient feels that (s)he is experiencing a sign or symptom associated with hypoglycemia OR has a blood glucose level <u><</u>70 mg/dL (<u><</u>3.9 mmol/L), even if asymptomatic…

…

Week 0: Randomization

At this visit, the patient will return to the clinic in the fasted state. The following will be performed:

- …
- The patient will complete the EQ-5D-Y~~outh version~~ health outcomes questionnaires.
- …

…

Week 26: Final Double-Blind Visit (Visit Window up to ±6 days)

…

-
- The patient will complete the EQ-5D-Y~~outh~~ health outcomes questionnaire.
- …

…

Week 52: Final Open-label Visit (Visit Window up to ±7 days)

- …
- The patient will complete the EQ-5D-Y~~outh version~~ health outcomes questionnaires.
- …

7.2. Discussion of Design and Control

…

The use of placebo for 26 weeks during the double-blind portion of the trial was considered appropriate, as no results of Phase 3 trials with dulaglutide (or any other GLP-1 RA) ~~have~~ had been reported ~~to date~~ in the pediatric population at the time of protocol development. …

…

10.1.1. Primary Efficacy Measure

The primary efficacy measurement in this study is change in HbA1c from baseline to 26 weeks for the pooled dulaglutide doses, as determined by the central laboratory. Blood samples for HbA1c measurements will be collected at specific clinic visits as summarized in the Study Schedule (Attachment 1).

10.1.2. Secondary Efficacy Measures

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

- Change in FBG ~~between~~ from baseline ~~and~~ to Week 26 and Week 52.
- Percentage of patients achieving a target HbA1c ~~≤6.5~~<7.0% at Week 26 and Week 52.
- …

10.1.3. Exploratory Efficacy Measures

- Percentage of patients with HbA1c ~~<7.0%:~~≤6.5% at Weeks 26 and 52
  - ~~At Week 26~~
  - ~~At Week 52~~
- Change in HbA1c between baseline and Week 13
- Percentage of patients having HbA1c ≤6.5% without severe, documented symptomatic (~~≤~~<70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52

- Percentage of patients having HbA1c <7.0% without severe, documented symptomatic (≤≤70 mg/dL), or probable hypoglycemic episodes at Weeks 26 and 52
- Change in weight ~~between:~~ from baseline to Week 26 and Week 52
  - ~~Baseline and Week 26~~
  - ~~Baseline and Week 52~~
- ~~Change in height from baseline to Week 26 and Week 52~~
- Change in waist circumference from baseline to Week 26 and Week 52
- Measures of insulin resistance and beta cell function (HOMA-IR, HOMA-%B, 1/fasting insulin) and estimated insulin sensitivity score at Weeks 0, 13, and 26

10.2. Health Outcome/Quality of Life Measure

…

EQ-5D-Youth Version

The ~~EuroQOL Five Dimension (~~EQ-5D~~) Youth version questionnaire~~ is a standardized generic measure of health status developed by the EuroQol Group. The EQ-5D-Y consists of ~~2 pages:~~ the EQ-5D-Y~~outh version~~ descriptive system and the EQ ~~visual analogue scale (~~VAS~~)~~. The descriptive system comprises the same 5 dimensions as the EQ-5D 3 level (EQ-5D-3L), but using a child-friendly wording (mobility; looking after myself; doing usual activities; having pain or discomfort; and feeling worried, sad or unhappy). Each dimension has 3 levels: no problems, some problems, or a lot of problems. The EQ VAS records the respondent's self-rated health on a vertical, EQ VAS where the endpoints are labeled, "The best health you can imagine," and, "The worst health you can imagine." This VAS information can be used as a quantitative measure of the perception of their overall health ~~outcome as judged~~ by the individual respondents.

~~EQ-5D-Youth version health states, defined by the EQ-5D descriptive system, will be converted into a single index value by applying a formula that essentially attaches value (also called weights) to each of the levels in each dimension. The index value is a major feature of the EQ-5D instrument, facilitating the calculation of quality-adjusted life years that are used to inform economic evaluations of healthcare interventions. As of 2015, an EQ-5D-Youth version index formula is not available, but it is anticipated to be available in 2016. Please refer to the EQ-5D-Youth version User Guide for appropriate scoring methodology.~~ The EQ-5D-Y~~outh version~~ will be administered at baseline, Week 26, and Week 52 (or early termination [ET]), as per the Study Schedule (Attachment 1). The Week 26 and Week 52 EQ-5D-Y~~outh version~~ is an objective in the study.

Details about scoring the PRO instrument can be found in the EQ-5D-Y~~outh version~~ User Guide (www.euroqol.org).

10.4.1.2.1. Hypoglycemia

…

Hypoglycemia will be classified as follows (the plasma glucose [PG] values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips) (~~American Diabetes Association~~ ADA 2005, 2020):

- Documented symptomatic hypoglycemia is defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a PG level of ≤≤70 mg/dL (≤≤3.9 mmol/L).
- Asymptomatic hypoglycemia is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG of ≤≤70 mg/dL (≤≤3.9 mmol/L).
- Probable symptomatic hypoglycemia is defined as an event during which symptoms of hypoglycemia are not accompanied by a PG determination (but that was presumably caused by a PG concentration of ≤≤70 mg/dL [≤≤3.9 mmol/L]).
- …

Cases of relative hypoglycemia, defined as symptomatic events during which the person reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but with a measured PG concentration of ~~>~~≥70 mg/dL (~~>~~≥3.9 mmol/L), will also be collected.

Certain categories of hypoglycemia ~~may~~ will also be evaluated using a PG cutoff <54 mg/dL (<3.0 mmol/L)(International Hypoglycaemia Study Group 2017).

…

10.5.3. Samples for Drug Concentration Measurements Pharmacokinetics/ Pharmacodynamics

…

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel until the study has been~~completed and~~ unblinded. Refer to Section 12.2.11.3 for details of early access to PK/PD data.

12.1. Determination of Sample Size

A ~~minimum~~ sample size of approximately 150 patients will be enrolled (50 patients per arm), in order to obtain 120 completers….

…

The screen failure rate is estimated as 80%. Approximately 750 patients will be screened, depending on the total enrolled. ~~The minimum number of patients enrolled will be approximately 150.~~Based on regulatory feedback, the sample size re-estimation was performed in 2019 and confirmed the original sample size estimation suggesting that approximately 150 patients be enrolled.

12.2. Statistical and Analytical Plans

12.2.1. General Considerations

…

The primary analysis population will be the intention-to-treat (ITT) population, defined as all patients randomized who have received at least 1 dose of study drug. The primary analyses will be performed in this population~~,~~ for the ~~ITT~~ treatment regimen estimand with post-rescue data and for the efficacy estimand without post-rescue data (Section 12.2.6). Analyses of other efficacy measures and hypoglycemia will be evaluated in this population after censoring the data following administration of any rescue medication. ~~The primary endpoint measure, HbA1c in change from baseline to Week 26, and key secondary endpoint measures (FBG, percent to goal in HbA1c, and BMI) in change from baseline to Week 26 will also be evaluated in the Per Protocol (PP) population and Completers populations. The PP population will be based on patients who were compliant with study medication, took no concomitant medications that would confound the interpretation of results (such as systemic steroids or non-study glucose-lowering agents used >14 days), and have an HbA1c measurement at the primary visit endpoint. Data post-rescue will be censored for the PP analyses.~~ The Safety population will be the ITT population, including post-rescue data. ~~The Completers population will consist of all patients in the ITT population who completed Week 26 without receiving rescue medication for severe, persistent hyperglycemia and without receiving alternative antihyperglycemic medication following discontinuation of or in addition to study drug. There is no requirement that completers had to have been on study drug for the entire study.~~

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and confidence intervals (CIs) will be calculated at 95%, 2-sided.

For subgroup analyses, all tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

The baseline visit will be Visit 2. For all variables, including HbA1c, baseline measurement is defined as the last nonmissing value taken prior to the first dosing of study drug. Baseline HbA1c value will be used to define HbA1c strata for analyses. ~~if baseline data are missing, the last nonmissing measurement taken prior to this visit will be used for the baseline measurement.~~

…

Unless otherwise specified, for categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test will be used for treatment comparisons~~, unless 80% of cells have an expected value of at least 5, in which case the chi-square test will be used~~.

12.2.2. Patient Disposition

All patients who discontinue from the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

Frequency counts and percentages of all patients entered, randomized/enrolled, completing, and/or discontinuing from the study early will be presented for each of the treatment groups. The reasons for discontinuation from the study will be summarized by treatment group. ~~A summary of discontinuations will also be presented by visit.~~

The overall percent discontinued comparisons among the treatment groups will be performed using ~~a chi-square or~~ Fisher's exact test.

12.2.3. Patient Characteristics

Demographic and baseline characteristics will be summarized for both treatment arms. For continuous measures, summary statistics will include sample size, mean, median, maximum, minimum, and standard deviations. Means will be analyzed using analysis of variance (ANOVA). For categorical measures, summary statistics will include sample size, frequency, and percent. Frequencies will be analyzed using ~~a chi-square or~~ Fisher's exact test.

12.2.4. Concomitant Therapy

…

Concomitant medications, including previous therapy for diabetes, will be summarized by treatment. Frequencies will be analyzed using ~~a chi-square or~~ Fisher's exact test.

12.2.6. Primary Outcome and Methodology

There will be 2 primary estimands to compare the placebo and the pooled dulaglutide arms in terms of the primary measure of HbA1c change from baseline to 26 weeks. One primary estimand will be an efficacy estimand which will not use post-rescue data; the other primary estimand, requested by the US Food and Drug Administration (FDA), will be ~~an ITT~~ a treatment regimen estimand ~~(effectiveness/treatment regimen estimand)~~ which will use post-rescue data. The efficacy estimand measures the benefit of treatment when taken as directed, and the ~~ITT~~ treatment regimen estimand measures the benefit of treatment as actually taken. ~~Both estimands will use the same primary analysis model, and e~~Each estimand will be tested at the full significance level of 0.05.

Analyses will be performed for both the efficacy estimand and the ~~ITT~~ treatment regimen estimand.

12.2.6.1. Primary Analysis for the Primary Outcome

For the efficacy estimand, ~~T~~the primary analysis model will be an MMRM for HbA1c change from baseline to 26 weeks (Visit 9) with treatment, insulin usage, metformin usage, visit, and treatment-by-visit as fixed effect, and baseline HbA1c as a covariate. The HbA1c strata [<8.0%, ≥8.0%] will not be included in this model as they may be confounded with baseline HbA1c as a covariate. In addition, the actual HbA1c will be analyzed using the same model for plotting purposes. For the treatment regimen estimand, the primary analysis model will be an ANCOVA model with multiple imputation for missing data.

…

~~12.2.6.2. Additional Analyses for the Primary Outcome~~

~~The primary analysis model, MMRM, will be repeated using the PP and Completers populations to check the sensitivity of the analysis.~~

12.2.6.1.1. Multiple Imputation for Missing Data

~~To investigate departure from the missing at random (MAR) assumption for the primary analysis that excludes post-rescue data, sensitivity analyses using pattern mixture models with a missing not at random (MNAR) assumption will be performed. For both the efficacy estimand (missing data and post-rescue data both considered as missing), and the ITT estimand (post-rescue data not treated as missing), the same MMRM model coupled with a tipping point approach for data imputation, recommended by National Research Council, will be performed to evaluate the magnitude of the departure from MAR assumption.~~

For the ~~ITT population~~ treatment regimen estimand only, an ANCOVA, with missing endpoints imputed using the copy reference approach will be conducted. The reference is from those patients ~~on the same treatment who received rescue medication and/or stopped study medication, but~~ in the placebo arm who had the measurement for the primary endpoint. The reference response will be imputed for all missing data within each treatment group. The ANCOVA model includes baseline HbA1c as a covariate~~,~~ and stratification factors and treatment as fixed effects.

12.2.7. Secondary Efficacy Analyses

Changes from baseline for HbA1c, FBG, and BMI will be analyzed using MMRM and ANCOVA models on the ITT ~~and PP and Completers~~ population~~s~~. The MMRM and ANCOVA models will include the model terms given for the previously described primary analysis model~~s~~.

For percentages of patients achieving target HbA1c of ~~≤6.5~~<7.0% at 26 weeks, for the efficacy estimand, longitudinal logistic regression with repeated measurements will be used. The model will include the independent variables treatment, insulin usage, metformin usage, visit, treatment-by-visit, ~~baseline HbA1c by visit,~~ and baseline HbA1c as a covariate. ~~For an efficacy estimand, post~~Post-rescue data for this analysis will be considered missing. ~~As an additional effectiveness~~For the treatment regimen estimand, this analysis will be performed on the ITT population of HbA1c target achievement (~~≤6.5~~<7.0% at 26 weeks) via a ~~longitudinal~~ logistic regression, where patients who ~~have been rescued or~~ have no ~~postbaseline~~ endpoint data will be imputed as not having achieved the target~~, while for nonrescued patients the available data will be used~~.

12.2.7.1. Multiple Imputation for Missing Data

In the ~~ITT~~ population treatment regimen estimand, the ANCOVA model coupled with the copy reference approach mentioned in Section 12.2.6.1 will be fitted by replacing the baseline HbA1c with baseline HbA1c strata, and adding the corresponding baseline measure as a covariate to assess the treatment effect on the 26-week FBG and BMI change from baseline.

12.2.7.2. Multiplicity

A graphical approach for multiple comparisons (Bretz et al. 2009; Bretz et al. 2011) will be used to strongly control the overall Type I error (2-sided alpha of 0.05) for testing the null hypothesis of no treatment effect with respect to the primary and key secondary endpoints. This graphical approach will be conducted separately for the ITT population with post-rescue data (treatment regimen estimand)~~, ITT population~~ coupled with the copy reference approach,~~ and~~ the ITT population by censoring the post-rescue data (efficacy estimand), and the ITT population by censoring the post-rescue data (efficacy estimand) and excluding those patients treated with diet and exercise only who are metformin naïve. The same scheme will be adopted in each population, and each will be tested at the full significance level of 0.05.

12.2.8. Pharmacokinetic/Pharmacodynamic Analyses

Population PK analyses will be conducted using dosing data and dulaglutide concentrations obtained from all patients participating in the main protocol, as well as the PK addendum via commonly accepted pharmacostatistical methods (for example, nonlinear mixed-effects modeling), and covariate screening. The relationship between dulaglutide dose and/or concentration and key safety (such as heart rate and blood pressure) and efficacy measures (such as fasting glucose and HbA1c) will be~~ performed~~ assessed graphically or through modeling. Endpoints may include but are not necessarily limited to those listed above.

In addition, if positive antibody titers to dulaglutide are observed, the relationship between dulaglutide PK and antibody titer will be evaluated.

12.2.9.2. Adverse Events

…

Summary statistics will be provided of TEAEs, SAEs, and study discontinuation due to AEs or death during the treatment period. Counts and proportions of patients experiencing AEs will be reported for each treatment group, and~~ chi square~~ Fisher's exact test~~s~~ will be used to compare the treatment groups.

12.2.9.2.1.1. Hypoglycemic Episodes

Treatment differences in incidence of hypoglycemic episodes will be assessed by~~ a chi square or~~ Fisher's exact test.

12.2.9.2.1.3. Thyroid C-Cell Hyperplasia and C-Cell Neoplasms

Listings and summaries of AEs of interest associated with the thyroid gland (benign and malignant neoplasms) will be produced~~, as well as a listing of biopsy reports~~.

12.2.9.3. Laboratory Analytes

…

For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using~~ chi square or~~ Fisher's exact test~~s~~.

12.2.10. Subgroup Analyses

A subgroup analysis will be performed on the primary endpoint using the efficacy estimand and the same model as the primary analysis model with an added term for the 3-way interaction visit-by-treatment-by-<subgroup>, 2-way interaction of treatment-by-<subgroup>, and visit-by-<subgroup>. The 2-way interaction of treatment-by-<subgroup> at the primary time point of 26 weeks will be evaluated to assess an interaction in the treatment effect with the subgroup levels. Significance will be evaluated at alpha=~~10%~~0.1. The following are candidate subgroups that might be analyzed. This list is not necessarily all-inclusive:

- Gender
- Age (≤14 years old, >14 years old)
- Race
- Ethnicity
- Region (US, non-US)
- …

…

A descriptive summary of the change from baseline to Week 26 in HbA1c, FBG, and BMI, and HbA1c target of ~~≤6.5~~<7.0% at Week 26 will be presented by age group, categorized by (10-14 years) and (>14 years). ~~Patients with missing HbA1c and those who received rescue medication will be categorized as not reaching the HbA1c target of ≤6.5%.~~

A descriptive summary for the key clinically important safety endpoints may be presented for the aforementioned age group.

12.2.11. Interim Analyses

…

There may be 2 database locks for this study. A primary database lock may be conducted for all data accumulated through the time when all randomized patients have completed 26 weeks of treatment (Visit 9, primary objective endpoint). The final database lock will be conducted for all data accumulated through the time when all patients have completed the 4-week Safety Follow-Up Period (through Visit 801). Following the primary database lock, the sponsor will be unblinded to analyze and report the data.

12.2.11.3. Initiation of Pharmacokinetic Analyses

A limited number of pre-identified individuals may gain access to the unblinded data prior to the primary database lock at Week 26~~during the open-label phase after the last randomized patient provides the Visit 13 PK sample, as specified in the unblinding plan, prior to the final database lock~~, in order to initiate the PopPK/PD model development processes. After the final database lock, PK and PK/PD data may be analyzed graphically or used to refresh the ~~These~~ PopPK and PK/PD models developed at primary database lock. ~~may be refreshed with locked data after final database lock.~~ Information that may unblind the study during the analyses will not be reported to study sites or blinded study team until the study has been unblinded.

14. References

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