Protocol H9X-JE-GBGK(a)

A Phase 4 Study to Evaluate Glucodynamic Effects of Dulaglutide in Japanese Patients with Type 2 Diabetes Mellitus

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Dulaglutide (LY2189265)

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1. Protocol Synopsis

Title of Study:
A Phase 4 Study to Evaluate Glucodynamic Effects of Dulaglutide in Japanese Patients with Type 2 Diabetes Mellitus.

Rationale:
In the clinical development program of dulaglutide in Japan, meal tolerance test (MTT) after administration of 0.75 mg of dulaglutide in patients with type 2 diabetes mellitus (T2D) was not performed. Furthermore, postprandial glucose metabolic hormones after administration of 0.75 mg of dulaglutide were not assessed. These data are frequently requested by healthcare providers.

Study GBGK will evaluate detailed 4-hour postprandial data at 1, 2, and 4 weeks after starting administration of 0.75 mg of dulaglutide once weekly, and these data will provide information not collected in previous studies for dulaglutide in Japanese patients with T2D.

Objectives/Endpoints:

Objectives	Endpoints
Primary The primary objective of this study is to evaluate glucodynamic effects of dulaglutide 0.75 mg compared with placebo in area under the glucose concentration versus time curve from 0 to 4 hours (glucose AUC[0-4h]) at 4 weeks in Japanese patients with T2D.	• The change from baseline in glucose AUC(0-4h) at 4 weeks
Secondary To evaluate pharmacodynamic (PD) effects of dulaglutide 0.75 mg compared with placebo at 4 weeks.	• The change from baseline in fasting blood glucose at 4 weeks • The change from baseline in postprandial blood glucose at 4 weeks • The change from baseline in insulin at 4 weeks • The change from baseline in c-peptide at 4 weeks • The change from baseline in glucagon at 4 weeks • The change from baseline in triglyceride at 4 weeks
To evaluate safety and tolerability of dulaglutide 0.75 mg for 4 weeks.	• Treatment-emergent adverse events (TEAEs) • Incidence of hypoglycemic episodes

Summary of Study Design:

Study GBGK is a Phase 4, single-center, randomized, cross-over, single-blind, placebo-controlled study to evaluate glucodynamic effects of dulaglutide in Japanese patients with T2D after a standardized test meal.

Treatment Arms and Planned Duration for an Individual Patient:

Two cohorts of dulaglutide 0.75 mg→placebo or placebo→dulaglutide 0.75 mg.

The patient will be randomized in a 1:1 ratio to dulaglutide 0.75 mg→placebo or placebo→dulaglutide 0.75 mg.

Ten- to 28-day screening period.

Cross-over design with 4 weeks' treatment and additional 4 weeks' cross-over treatment after 4 to 6 weeks' washout period.

Number of Patients:
Up to 14 patients may be entered to randomize 12 patients and complete at least 11 patients.

Statistical Analysis:
The PD parameters on Weeks 0, 1, 2, and 4 will be analyzed using a mixed-effects linear model. The PD parameters for glucose, insulin, glucagon, c-peptide, and triglyceride that will be statistically evaluated include area under the curve, fasting and postprandial values at each time point. The model will include treatment, sequence, day, and treatment-by-day interaction as fixed effects, baseline as covariate, and patient as random effect. The baseline is the predose value on Day 1. The least squares means and the 95% confidence intervals (CIs) by treatment group will be tabulated and plotted. Comparisons between dulaglutide and placebo will be performed. Difference of least squares means of dulaglutide to placebo, and the 95% CIs, will be tabulated.

2. Schedule of Activities

Study Schedule Protocol H9X-JE-GBGK(a)

	Screening	CGM Initiation	Period 1 (4 weeks)					Washout (4-6 weeks)	CGM Initiation	Period 2 (4 weeks)					E/T[i]
Visit Number	1	2	3	4	5	6	7		8	9	10	11	12	13	ET
Study Day	-28~-10	-7 or -6	1	8	15	22	29	30~56	50 or 51	57 (1)	64 (8)	71 (15)	78 (22)	85 (29)	
Allowance (days)				±1	±1	±1	±1	+14			±1	±1	±1	±1	
Informed Consent	X														
Medical History	X														
Concomitant Medications	X	X	X	X	X	X	X			X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X		X	X	X	X	X	X	X
Hypoglycemia		X	X	X	X	X	X		X	X	X	X	X	X	X
Height	X														
Weight [a]	X		X				X			X				X	X
Physical Exam	X	X	X	X	X	X	X			X	X	X	X	X	X
Vital Signs (sitting) [b]	X	X	X	X	X	X	X			X	X	X	X	X	X
ECG	X		X							X					
Pregnancy Test [c]	X	X	X							X					
Fasting Blood Glucose [d]	X														
Serology	X														
Hematology, Clinical Chemistry, Endocrinology, HbA1c [d]	X		X				X			X				X	X
Urinalysis, UACR [d]			X				X			X				X	X
MTT [e]			X	X	X		X			X	X	X		X	X[j]
Satiety Evaluation (VAS) [f]			X	X	X		X			X	X	X		X	X[j]
Continuous Glucose Monitoring [g]		←	→						←	→					
Investigational Product Administration [h]			X	X	X	X				X	X	X	X		

Abbreviations: ECG = electrocardiogram; E/T = early termination visit; HbA1c = glycated hemoglobin; UACR = urine albumin/creatinine ratio; MTT = meal tolerance test; VAS = visual analog scale.

[a] Body weight will be measured once in light clothing with shoes removed.

[b] For each parameter (systolic blood pressure, diastolic blood pressure, and pulse rate), 3 measurements will be taken 1 minute apart using the same arm. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of blood pressure (BP) measurements. The arm used for the BP measurement should be supported at heart level. See Appendix 6, Meal Tolerance Test, for details.

[c] Serum pregnancy test will be performed at Visit 1. Urine pregnancy test will be performed at Visit 2, 3, and 9, if applicable.

[d] Fasting condition. See Appendix 2, Clinical Laboratory Tests, and Appendix 6, Meal Tolerance Test, for details.

[e] Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride will occur at 0, 30, 60, 90, 120, 180, and 240 minutes after the standardized test meal. See Appendix 6, Meal Tolerance Test, for details.

[f] Satiety will be assessed at 0, 60, 120, 180, and 240 minutes after the standardized test meal. See Appendix 6, Meal Tolerance Test, for details.

[g] Continuous glucose monitoring will be initiated on Day -7 (or -6) and Day 50 (or 51) and will end on Day 8 and Day 64.

[h] Investigational product will be administered at study site after all examinations, including MTT, are completed. See Appendix 6, Meal Tolerance Test, for details.

[i] Patients discontinuing from the study prematurely for any reason should complete adverse event and other follow-up procedures.

[j] Optional.

3. Introduction

3.1. Study Rationale

In the clinical development program of dulaglutide in Japan, meal tolerance test (MTT) after administration of 0.75 mg of dulaglutide in patients with type 2 diabetes mellitus (T2D) was not performed. Furthermore, postprandial glucose metabolic hormones after administration of 0.75 mg of dulaglutide were not assessed. These data are frequently requested by healthcare providers.

Study GBGK will evaluate detailed 4-hour postprandial data at 1, 2, and 4 weeks after starting administration of 0.75 mg of dulaglutide once weekly, and these data will provide information not collected in previous studies for dulaglutide in Japanese patients with T2D.

In addition, continuous glucose monitoring (CGM) will be performed in each study period in order to evaluate the glucodynamic effects of dulaglutide 0.75 mg during the first week.

3.2. Background

Dulaglutide exhibits glucagon-like peptide-1 (GLP-1) mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss. Preclinical and clinical experience to date support the use of dulaglutide as a once-weekly injection to improve glycemic control in patients with T2D (Tamaki et al. 2015). Dulaglutide received regulatory approval for the treatment of T2D in the United States on 18 September 2014, in the European Union on 21 November 2014, and in Japan on 3 July 2015.

3.3. Benefit/Risk Assessment

This study will assess detailed plasma glucose (PG) profiles, insulin, c-peptide, glucagon, and triglyceride, and satiety after standardized test meal. These outcomes will be supportive data to understand the mechanism of action of dulaglutide, and to answer the frequently asked questions by healthcare providers.

For the patients participating in this study, there is no anticipated therapeutic benefit because of the short treatment period (4 weeks).

No clinically significant safety or tolerability concerns about dulaglutide 0.75 mg have been identified in patients to date.

More detailed information about the known and expected benefits and risks of dulaglutide 0.75 mg may be found in the Package Insert.

4. Objectives and Endpoints

Table GBGK.1 shows the objectives and endpoints of the study.

Table GBGK.1. Objectives and Endpoints

Objectives	Endpoints
Primary The primary objective of this study is to evaluate glucodynamic effects of dulaglutide 0.75 mg compared with placebo in area under the glucose concentration versus time curve from 0 to 4 hours (glucose AUC[0-4h]) at 4 weeks in Japanese patients with T2D.	• The change from baseline in glucose AUC(0-4h) at 4 weeks
Secondary To evaluate pharmacodynamic (PD) effects of dulaglutide 0.75 mg compared with placebo at 4 weeks.	• The change from baseline in fasting blood glucose at 4 weeks • The change from baseline in postprandial blood glucose at 4 weeks • The change from baseline in insulin at 4 weeks • The change from baseline in c-peptide at 4 weeks • The change from baseline in glucagon at 4 weeks • The change from baseline in triglyceride at 4 weeks
To evaluate safety and tolerability of dulaglutide 0.75 mg for 4 weeks	• Treatment-emergent adverse events (TEAEs) • Incidence of hypoglycemic episodes
Tertiary/Exploratory Objectives To evaluate daily glucose variability	• Time course of daily average glucose by CGM during the first week
To evaluate satiety after standardized test meal	• The change from baseline in satiety (full and hungry) in visual analog scale (VAS) at 1, 2, and 4 weeks

5. Study Design

5.1. Overall Design

Study GBGK is a Phase 4, single-center, randomized, cross-over, single-blind, placebo-controlled study to evaluate glucodynamic effects of dulaglutide after standardized test meal in Japanese patients with T2D.

The study includes a 10- to 28-day screening period, a 4-week treatment period (Period 1), a 4- to 6-week washout period, and a 4-week treatment period (Period 2).

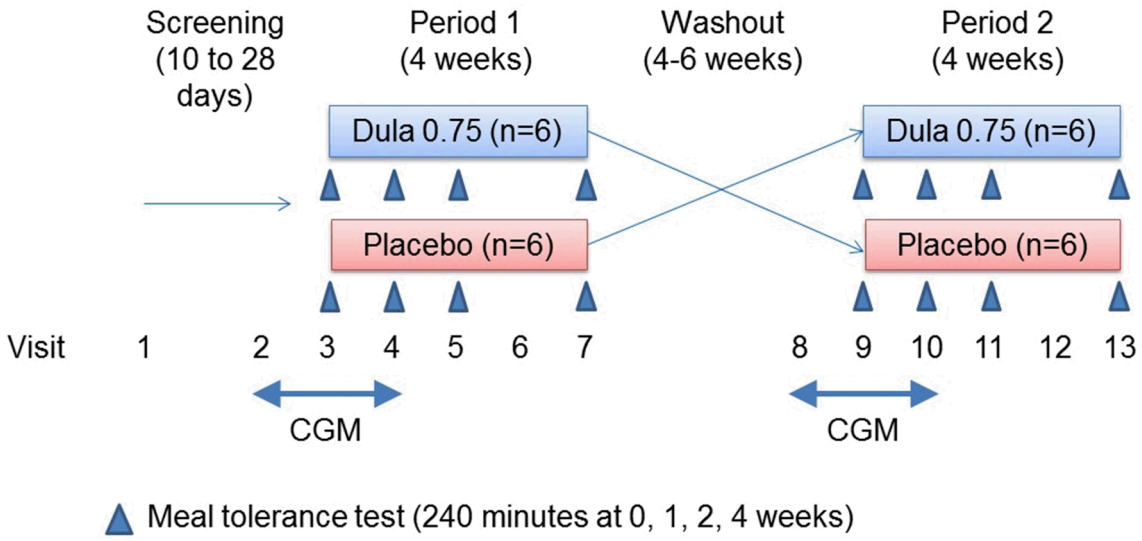
Screening tests will be performed at Visit 1. After confirming eligibility, the patient will be randomized in a 1:1 ratio to dulaglutide 0.75 mg or placebo treatment in Period 1.

Meal tolerance test will be performed at baseline, 1, 2, and 4 weeks for each period. Time points for blood sampling will be 0, 30, 60, 90, 120, 180, and 240 minutes after the start of standardized test meal. Satiety will be also assessed at 0, 60, 120, 180, and 240 minutes after the start of standardized test meal. Detailed schedule of MTT is described in Appendix 6. After completion of Period 1, all patients must have a 4- to 6-week washout period, and then will start Period 2 on the opposite treatment (patients taking dulaglutide will be switched to placebo and patients taking placebo will be switched to dulaglutide).

This is a single-blind study, and the treatment assignments will be blinded to patients until study completion.

Study governance considerations are described in detail in Appendix 3.

Figure GBGK.5.1 illustrates the study design.



Abbreviations: CGM = continuous glucose monitoring; dula = dulaglutide; n = number of patients.

Figure GBGK.5.1. General study design for Protocol H9X-JE-GBGK.

5.2. Number of Participants

Up to 14 patients may be entered to randomize 12 patients and complete at least 11 patients. For the purposes of this study, a patient completes the study when all scheduled procedures shown in the Schedule of Activities have been finished.

5.3. End of Study Definition

End of the study is the date of the last visit or last scheduled procedure shown in the Schedule of Activities (Section 2) for the last patient.

5.4. Scientific Rationale for Study Design

This study is designed to evaluate glucodynamic effects after standardized test meal. Cross-over design was selected to minimize the effect of confounding factors between patients. Placebo will be used to minimize the effect of bias including placebo effects. Duration of washout period (4 to 6 weeks) was set based on the results of Japan Phase 3 monotherapy study (GBDP). In the GBDP study, fasting blood glucose was returned to baseline 4 weeks after discontinuation of study drug. Patients with T2D who have diet and exercise therapy only will be enrolled to exclude background effect of other antidiabetic agents. Japanese standardized test meal (480 kcal, carbohydrate: protein: fat = 2.8:1:1) was selected because that was used in the previous MTTs conducted in Japan (Lee et al. 2010, Yabe et al. 2010, Yabe et al. 2015).

Japanese patients are leaner compared with the Western population and eat rice as their staple diet. As a result, insulin secretion in the Japanese is lower than that in the Western population, and postprandial glucose tends to be increased (Obika and Trence 2010). Therefore, reduction of postprandial glucose is relatively more important for Japanese patients compared with the Caucasian patients. Also, postprandial insulin, c-peptide, glucagon, and triglyceride data will be supportive data to consider the mechanism of action of this drug.

5.5. Justification for Dose

The approved dosage and administration of dulaglutide in Japan is 0.75 mg once weekly, given subcutaneously. The dosage and administration were established based on Phase 2 and 3 studies in Japanese patients with T2D (Terauchi et al. 2014, Araki et al. 2015, Emoto et al. 2015, Miyagawa et al. 2015, Odawara et al. 2016).

6. Study Population

Eligibility of patients for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiogram (ECG).

The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

Screening may occur 10 to 28 days prior to enrollment. Patients who are not enrolled within 28 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

Patients are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] are males or females ages of ≥20 and ≤75 years at Visit 1;

[1a] male patients:

- Men with partners of childbearing potential, for the duration of the study and for 120 days after the last dose of study drug, will either remain abstinent (if this is their preferred and usual lifestyle) or use at least one highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or an effective method of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges). The patient may choose to use a barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.
- Men should refrain from sperm donation for the duration of the study and for 120 days after the last dose of study drug.
- Men who are in exclusively same sex relationships (when it is their preferred and usual lifestyle) are not required to use contraception.

[1b] female patients:

1) Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males.

2) Otherwise, women of childbearing potential participating must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of two effective methods of contraception for the entirety of the study.

   A. Women of childbearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

   B. Either one highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or a combination of two effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The patient may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined.

3) Women not of childbearing potential may participate and include those who are:

   A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation) or congenital anomaly such as mullerian agenesis; or

   B. postmenopausal – defined as either

      i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

         a) cessation of menses for at least 1 year, or

         b) at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or

      ii. A woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

      iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

[2] have T2D (based on the World Health Organization's [WHO] diagnostic criteria) for at least 1 year.

[3] have diet and exercise therapy only (no oral antihyperglycemic medication for at least 3 months prior to Visit 1).

[4] have a fasting blood glucose value of ≥120 and ≤200 mg/dL at Visit 1.

[5] have a screening body weight of ≥50 and ≤80 kg.

[6] are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

[7] are able and willing to give signed informed consent.

6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

[8] are investigative site personnel directly affiliated with this study and their immediate families. Immediate family is defined as a spouse, biological or legal guardian, child, or sibling.

[9] are Lilly employees.

[10] are currently enrolled in a clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

[11] have participated, within the last 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

[12] have previously completed or withdrawn from this study or have previously received dulaglutide within the 3 months prior to Visit 1.

[13] have known allergies to dulaglutide, or other GLP-1 receptor agonists.

[14] have had any of the following cardiovascular conditions within the 3 months prior to Visit 1: acute myocardial infarction, New York Heart Association (NYHA) Class III or Class IV heart failure, or cerebrovascular accident (stroke).

[15] have a known clinically significant gastric emptying abnormality or have undergone gastric bypass surgery or restrictive bariatric surgery.

[16] have acute or chronic hepatitis, signs and symptoms of any other liver disease, or alanine aminotransferase (ALT) level >2.5 times the upper limit of the reference range, as determined by the local laboratory at Visit 1.

[17] have a history of chronic pancreatitis or acute idiopathic pancreatitis, or were diagnosed with any type of acute pancreatitis within the 3 months prior to Visit 1.

[18] have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by the Japanese Society of Nephrology equation, at Visit 1 (eGFR [mL/min/1.73 m^2] = $194 \times Cr^{-1.094} \times Age^{-0.287} \times 0.739$ [if female]).

[19] have any self or family history of type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) in the absence of known C-cell hyperplasia.

[20] have any self or family history of medullary C-cell hyperplasia, focal hyperplasia, or carcinoma (including sporadic, familial, or part of MEN 2A or 2B syndrome).

[21] have serum calcitonin ≥20 pg/mL, as determined by the local laboratory at Visit 1.

[22] Positive human immunodeficiency virus (HIV) antigen and antibody, hepatitis C antibody, hepatitis B surface antigen, or syphilis at Visit 1.

[23] have evidence of a significant, active uncontrolled endocrine or autoimmune abnormality, as judged by the investigator at Visit 1.

[24] have a history of transplanted organ.

[25] are receiving systemic glucocorticoid therapy.

[26] have a history of active or untreated malignancy, or are in remission from a clinically significant malignancy during the 5 years prior to Visit 1.

[27] have donated 400 mL or more blood in the last 12 weeks (males) or in the last 16 weeks (females), or any blood donation (including apheresis) within the last 4 weeks, or total volume of blood donation within 12 months is 1200 mL (males) / 800 mL (females) or more at Visit 1.

[28] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (females and males over 65) at Visit 1. (1 unit = 360 mL of beer; 150 mL of wine; 45 mL of distilled spirits.)

[29] in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.

6.3. Lifestyle and/or Dietary Requirements

Throughout the study, patients may undergo medical assessments and review of compliance with requirements before continuing in the study.

6.3.1. Meals and Dietary Restrictions

Study participants should be instructed to continue diet therapy during study period.

Solid Japanese standardized test meal (480 kcal, carbohydrate: protein: fat = 2.8:1:1) will be supplied for MTT. The menu will be prepared by managerial dietitian at study site. Identical meal will be supplied for each test. Patients should ingest standardized test meal within 15 minutes.

6.3.2. Activity

Study participants should be instructed to continue exercise therapy during study period.

6.3.3. Blood Donation

Study participants should be instructed not to donate blood or blood products during the study or for 4 weeks following the study.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may be re-screened once. The interval between re-screenings should be at least 2 weeks. Each time re-screening is performed, the individual must sign a new informed consent form (ICF) and will be assigned a new identification number.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of dulaglutide 0.75 mg versus placebo administered once weekly as a subcutaneous injection by single-dose pen (SDP).

Investigational product will be injected subcutaneously in the abdomen. Trained site staff will administer the injection.

Table GBGK.2 shows the treatment regimens.

Table GBGK.2. Treatments Administered

Treatment Name	Dulaglutide	Placebo
Dosage Formulation	single-dose pen	single-dose pen
Unit Dose Strength(s)/ Dosage Level(s)	0.75 mg (0.5 mL)	0 mg (0.5 mL)
Route of Administration	subcutaneous injection	subcutaneous injection
Dosing Instructions	once weekly	once weekly

The investigator or his/her designee is responsible for maintaining accurate records of investigational product dispensing and collection.

7.1.1. Packaging and Labeling

The sponsor will provide dulaglutide and placebo in SDPs. Each SDP (0.75 mg dulaglutide in 0.5 mL OR placebo in 0.5 mL) is packaged in cartons of 4 pens.

The investigational product will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized at Visit 3 in a 1:1 ratio to dulaglutide 0.75 mg or placebo. Assignment to treatment groups will be determined by a randomization table.

7.2.1. Selection and Timing of Doses

Investigational product will be administered once weekly. It is recommended that patients receive the investigational product on the same day each week. The doses will be administered at approximately the same times on each day.

The actual time of all dose administrations will be recorded in the patient's case report form (CRF).

7.3. Blinding

Single-blind (patient-blind) is adopted for this study. Glucose data (including CGM data) will not be disclosed to patients during study period.

Blinding will be maintained throughout the conduct of the study as described in the separate Blinding Plan.

7.4. Dose Modification

Dose adjustments are not allowed in this study.

7.5. Special Treatment Considerations

7.5.1. Management of Increased Hypoglycemia Risk

If a hypoglycemic event occurs, the patient should record in the study diary the episode and associated symptoms and/or signs, and rescue treatment (if taken).

Study site personnel will record information related to hypoglycemia such as start and end date and time of the episode, hypoglycemia signs and symptoms present. Following definitions and criteria will be used for categorizing an episode considered to be related to hypoglycemia (the 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 2005):

- **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.

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

7.5.2. Management of Severe Hyperglycemia

If a patient experiences severe hyperglycemia, the patient must discontinue from the study. Severe hyperglycemia is defined as follows: the patient's fasting blood glucose concentrations are >270 mg/dL (>15.0 mmol/L) on two or more occasions.

7.6. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by sponsor, during transit for all investigational product received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational product should be stored in an environmentally controlled and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

7.7. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.8. Concomitant Therapy

Concomitant non-study antidiabetic medication is not allowed in this study. Concomitant systemic glucocorticoid therapy is also not allowed in this study.

Patients on stable concomitant medication other than antidiabetic medication or systemic glucocorticoid therapy at the time of study entry should continue their regular, unchanged dose throughout the study.

In general, additional concomitant medication should be avoided; however, rescue medicine such as acetaminophen (up to 2 g) may be administered at the discretion of the investigator for treatment of headaches etc. Any medication used during the course of the study must be documented.

7.9. Treatment after the End of the Study

Not applicable.

8. Discontinuation Criteria

Patients discontinuing from the study prematurely for any reason should complete AE and other follow-up procedures per Section 2 of this protocol.

8.1. Discontinuation from Study Treatment

Discontinuation of the investigational product for abnormal liver tests **should be considered** by the investigator when a patient meets 1 of the following conditions after consultation with the Lilly designated medical monitor:

- ALT (alanine aminotransferase) or AST (aspartate aminotransferase) >8× ULN (upper limit of normal)
- ALT or AST >5× ULN sustained for more than 2 weeks or
- ALT or AST >3× ULN and total bilirubin level (TBL) >2× ULN or International Normalized Ratio (INR) >1.5 or
- ALT or AST >3× ULN the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP (alkaline phosphatase) >3× ULN
- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%).

In addition, patients will be discontinued from the investigational product in the following circumstances:

- For inadvertently enrolled patients for whom it was determined that continued treatment with investigational product would not be medically appropriate (see Section 8.1.1);
- The patient's fasting blood glucose concentrations are >270 mg/dL (>15.0 mmol/L) on two or more occasions (see Section 7.5.2);
- The patient becomes pregnant during the study, in which case, the patient must discontinue the study immediately and Lilly or its designee is to be informed immediately;
- The patient is diagnosed with acute pancreatitis or acute hepatitis (see Section 9.2.2.1);
- The patient develops Exclusion Criterion [18] (eGFR <30 mg/min/1.73m^2);
- The patient is diagnosed with C-cell hyperplasia or medullary thyroid carcinoma;
- The patient uses or needs to use additional antidiabetic medication or prohibited medication (systemic glucocorticoids).

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist and the

investigator to determine if the patient may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist to allow the inadvertently enrolled patient to continue in the study with or without continued treatment with investigational product.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- Investigator Decision
    - the investigator decides that the patient should be discontinued from the study
    - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Patient Decision
    - the patient, or legal representative, requests to be withdrawn from the study.

8.3. Patients Lost to Follow-up

A patient will be considered lost to follow-up if he or 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 attempts to contact patients who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

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

Appendix 5 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

Appendix 6 provides a summary of MTT procedures.

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

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

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.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the patient to discontinue the investigational product before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

After the ICF is signed, study site personnel will record, via CRF, the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a potential cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via CRF.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above
- when a condition related to the investigational device (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.

Study site personnel must alert the Lilly clinical research physician (CRP)/clinical pharmacologist, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-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.

Although all AEs are recorded in the CRF after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, AND is considered reasonably possibly related to a study procedure then it MUST be reported.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued from and/or completed the study (the patient summary CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a patient has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

Pregnancy (maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the investigator's brochure and that the investigator reports as related to investigational product or procedure. 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.

9.2.2. Adverse Events of Interest

9.2.2.1. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with dulaglutide, including this trial. 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 radiates 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; or
3. Characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of amylase [total and pancreatic] and lipase) should be obtained via the local laboratory. Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with investigational product and will also be discontinued from the study. The most appropriate diabetes therapeutic regimen will be decided 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 case of 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 investigational product.

In addition to the diagnostic assessment in patients who develop symptoms of acute pancreatitis, each patient will have measurements of total amylase and lipase at Visit 3, 7, 9, 13, and early termination visit to assess any potential effects of dulaglutide on the exocrine pancreas (refer to the Schedule of Activities, Section 2). Further diagnostic assessment per Lilly algorithm for assessment of asymptomatic pancreatic hyperenzymemia will be required whenever lipase and/or total amylase are ≥3× ULN at any time during the study. If this situation occurs at Visit 13, the

patient will undergo this additional work, and the data will be collected in the clinical trial database.

9.2.2.2. C-Cell Hyperplasia and C-Cell Neoplasms

Individuals with personal or family history of certain thyroid or nonthyroid endocrine abnormalities or certain preexisting laboratory and genetic characteristics will be excluded from the study (see Section 6.2). The assessment of thyroid safety during the trial will include reporting of thyroid TEAEs and measurements of calcitonin according to the Study Schedule (Section 2) at Visit 3, 7, 9, 13, and ET visit. The purpose of calcitonin measurements is to assess the potential of dulaglutide versus placebo to affect the thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Patients who develop serum calcitonin increases ≥50% of the mean of the baseline and screening values AND an absolute value ≥20 pg/mL and <35 pg/mL at Visit 13 will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be recommended that he or she 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 mean of the baseline and screening values AND an absolute value ≥35 pg/mL at Visit 13 will be recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

9.2.3. Complaint Handling

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

Patients should be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

For the purposes of this study, an overdose of dulaglutide is considered any dose higher than the dose assigned through randomization.

Effects of overdose with dulaglutide in clinical studies have included gastrointestinal disorders and hypoglycemia. In the event of overdose, appropriate supportive treatment (including frequent PG monitoring) should be initiated according to the patient's clinical signs and symptoms.

Refer to the dulaglutide Japan Package Insert.

9.4. Safety

9.4.1. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2).

9.4.2. Vital Signs

Systolic blood pressure, diastolic blood pressure, and pulse rate should be measured in triplicate in a sitting position.

For each patient, vital signs measurements should be conducted according to the Schedule of Activities (Section 2).

Vital signs should be taken before collection of blood samples for laboratory testing. For each parameter, 3 measurements will be taken 1 minute apart using the same arm. An appropriately sized cuff (cuff bladder encircling at least 80% of the upper arm) should be used to ensure the accuracy of blood pressure measurements. The arm used for the blood pressure measurement should be supported at heart level. Each measurement of sitting heart rate and blood pressure is to be recorded in the CRF.

9.4.3. Electrocardiograms

For each patient, a single 12-lead ECG will be obtained according to the Study Schedule (Section 2). The patient must be supine for approximately 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms must be recorded before collecting any blood for safety tests. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

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 finding is identified (including but not limited to changes in QT/corrected QT [QTc] interval from baseline), the investigator will 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 collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Other Tests

9.4.4.1. Continuous Glucose Monitoring

The [redacted] system ([redacted]) will be used for CGM in this study. Continuous Glucose Monitoring will be performed in each study period. Continuous Glucose Monitoring will be initiated on Day -7 (or -6) and Day 50 (or 51) and will last until Day 8 and Day 64.

This CGM data will complement the evaluation of the glucodynamic effects of dulaglutide 0.75 mg during the first week.

9.4.4.2. Patient Reported Outcomes

9.4.4.2.1. Satiety after Standardized Test Meal

A perception of satiety (full and hungry) VAS should be performed by patients every hour for 4 hours following the standardized test meal on each MTT day.

9.4.5. Safety Monitoring

The Lilly clinical pharmacologist or CRP/scientist will monitor safety data throughout the course of the study.

Lilly will review SAEs within time frames mandated by company procedures. The Lilly clinical pharmacologist will periodically review the following data:

- trends in safety data
- laboratory analytes
- AEs, including hypoglycemia

When appropriate, the Lilly clinical pharmacologist will consult with the functionally independent Global Patient Safety therapeutic area physician or clinical research scientist.

9.4.5.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase (GGT), and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly clinical pharmacologist. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

Additional safety data should be collected if 1 or more of the following conditions occur:

- elevation of serum ALT to ≥ 5× ULN on two or more consecutive blood tests
- elevated serum TBL to ≥ 2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥ 2× ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests

- hepatic event considered to be an SAE.

9.5. Pharmacokinetics

This section is not applicable for this study.

9.6. Pharmacodynamics

At times specified in the Schedule of Activities (Section 2), venous blood samples will be collected and used to determine the PD effects of dulaglutide. Blood will be collected by venipuncture in order to evaluate fasting blood glucose, postprandial blood glucose, insulin, c-peptide, glucagon, and triglyceride.

The sample(s) will be stored until testing is complete at a facility selected by the sponsor.

9.6.1. Primary Measure

The primary measure of PD is change from baseline in glucose AUC(0-4h) at 4 weeks.

9.6.2. Secondary Measures

The following secondary measures of PD will be evaluated:

- The change from baseline in fasting blood glucose at 1, 2, and 4 weeks
- The change from baseline in postprandial blood glucose (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in glucose AUC(0-4h) at 1 and 2 weeks
- The change from baseline in insulin (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in insulin AUC(0-4h) at 1, 2, and 4 weeks
- The change from baseline in c-peptide (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in c-peptide AUC(0-4h) at 1, 2, and 4 weeks
- The change from baseline in glucagon (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in glucagon AUC(0-4h) at 1, 2, and 4 weeks
- The change from baseline in triglyceride (30, 60, 90, 120, 180, and 240 minutes) at 1, 2, and 4 weeks
- The change from baseline in triglyceride AUC(0-4h) at 1, 2, and 4 weeks

9.7. Genetics

No samples for pharmacogenetic test will be collected for this study.

9.8. Biomarkers

No samples for non-pharmacogenetic biomarker will be collected for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

Up to 14 patients may be entered to randomize 12 patients and complete at least 11 patients. Patients will be randomized in a 1:1 ratio to one of two sequences. Assuming one dropout, the sample size of 11 patients would provide 93% power to demonstrate superiority of dulaglutide to placebo. This computation assumes the true treatment difference in glucose AUC(0-4h) is 190 mg*hr/dL, a common standard deviation of 140 mg*hr/dL, intra-patient correlation of 0.3, and a one-sided significance level of 0.025.

Patients who are randomized but do not complete study treatment may be replaced at the discretion of the investigator and Lilly clinical pharmacologist.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of patients' disposition will be provided at the end of the study.

10.2.2. Study Participant Characteristics

The patients' age, sex, weight, height, or other demographic characteristics will be summarized and may be used in the PD and safety analyses as quantitative or classification variables.

10.3. Statistical Analyses

Statistical analysis of this study will be the responsibility of Eli Lilly and Company or its designee.

Pharmacodynamic analyses will be conducted on data from all patients who receive at least one dose of the investigational product and have evaluable PD.

Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

Additional exploratory analyses of the data will be conducted as deemed appropriate.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology.

The incidence of symptoms for each treatment will be presented by severity and by association with investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the medical regulatory dictionary.

The number of investigational product-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety laboratory parameters and vital signs will be listed, and summarized using standard descriptive statistics. Additional analysis may be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

This section is not applicable for this study.

10.3.3. Pharmacodynamic Analyses

10.3.3.1. Pharmacodynamic Parameter Estimation

Pharmacodynamic parameters will be calculated for glucose, insulin, glucagon, c-peptide, and triglyceride data following the standardized test meal at Weeks 0, 1, 2, and 4. The AUC(0-4h) will be calculated using the linear-trapezoidal method. This analysis will be performed for both original data and adjusted data with the predose value at each period. The parameters AUC(0-1h), AUC(0-2h), and AUC(0-3h) may also be calculated.

All PD parameters will be summarized and tabulated by treatment group and day. Summary statistics will be provided. The individual observed and mean time profile will be plotted by treatment group.

10.3.3.2. Pharmacodynamic Statistical Inference

The PD parameters on Weeks 0, 1, 2, and 4 will be analyzed using a mixed-effects linear model. The PD parameters for glucose, insulin, glucagon, c-peptide, and triglyceride that will be statistically evaluated include AUC, fasting and postprandial values at each time point. The model will include treatment, sequence, day, and treatment-by-day interaction as fixed effects, baseline as covariate, and patient as random effect. The baseline is the predose value on Day 1. The least squares means and the 95% CIs by treatment group will be tabulated and plotted. Comparisons between dulaglutide and placebo will be performed. Difference of least squares means of dulaglutide to placebo, and the 95% CIs, will be tabulated.

10.3.4. Other Analyses

Daily average, daily standard deviation, and daily mean amplitude of glycemic excursion (MAGE) from glucose data collected by a CGM device by treatment and day will be summarized. Individual (by patient) or mean by treatment of glucose data will be plotted, if deemed appropriate.

Satiety after standardized test meal (full and hungry) in VAS will be summarized by treatment and time after standardized test meal.

10.3.5. Data Review During the Study

Particular data review during the study is not planned for this study.

10.3.6. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly clinical pharmacologist, CRP/investigator, or designee will consult with the appropriate medical director or designee to determine if it is necessary to amend the protocol.

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Appendix 1. Abbreviations and Definitions

Term	Definition
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 AE 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
AST	aspartate aminotransferase
AUC(0-4h)	area under the concentration versus time curve from time zero to 4 hours
blinding	A procedure in which one or more parties to the study 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 the sponsor 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 sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received
CGM	continuous glucose monitoring
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 study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that 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	case report form
CRP	clinical research physician
CT	computed tomography
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate

enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GLP-1	glucagon-like peptide-1
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study 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.
INR	International Normalized Ratio
Investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, 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.
Legal Representative	An individual or 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.
MAGE	mean amplitude of glycemic excursion
MEN	multiple endocrine neoplasia
MRI	magnetic resonance imaging
NYHA	New York Heart Association
Non-investigational product (non-IP)	A product that is not being tested or used as a reference in the clinical study, but is provided to patients and used in accordance with the protocol, such as: concomitant or rescue/escape medication for preventative, diagnostic, or therapeutic reasons, medication to ensure adequate medical care, and/or products used to induce a physiological response.
randomize	the process of assigning patients to an experimental group on a random basis

PD	pharmacodynamic
PG	plasma glucose
QTc	corrected QT interval
SAE	serious adverse event
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.
SDP	single-dose pen
SUSARs	suspected unexpected serious adverse reactions
T2D	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
ULN	upper limit of normal
VAS	visual analog scale
WHO	World Health Organization

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests [a]

Hematology
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Platelets

Differential WBC [%] of:
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Urinalysis
- Protein
- Glucose
- Ketones
- Blood

Urine albumin/creatinine ratio (UACR)

Serum pregnancy test [if applicable] [b]

Urine pregnancy test [if applicable]

Serology [b]
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antigen and antibody
- Syphilis

Clinical Chemistry
- Sodium
- Potassium
- Calcium
- Chloride
- Uric acid
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Gamma-glutamyl transferase (GGT)
- Blood urea nitrogen (BUN)
- Creatinine
- Creatine kinase (creatine phosphokinase)
- Total cholesterol
- Low-density lipoprotein (LDL) cholesterol
- High-density lipoprotein (HDL) cholesterol
- Triglyceride

HbA1c

Meal tolerance test
- Glucose
- Insulin
- c-peptide
- Glucagon
- Triglyceride

Endocrinology
- Total amylase
- Lipase
- Calcitonin

Abbreviations: HIV = human immunodeficiency virus; HbA1c = glycated hemoglobin; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by local laboratory.

[b] Performed at screening only.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the patient understands the nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. 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 investigational product.
- answering any questions the patient may have throughout the study and sharing in a timely manner any new information that may be relevant to the patient's willingness to continue his or her participation in the study.
- providing a copy of the ICF to the participant or the participant's legal representative and retaining a copy on file.

Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on GCP.

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

- the package labeling and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

This study will be conducted in accordance with the protocol and 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) applicable ICH GCP Guidelines
3) applicable laws and regulations

Some of the obligations of the sponsor will be assigned to a third party organization.

Protocol Signatures

The sponsor'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, the principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

Final Report Signature

The investigator or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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

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.
- provide 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/or 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 and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to the original source documents.

Data Collection Tools/Source Data

An electronic data capture system will be used in this study. The site must define and retain all source records and must maintain a record of any data where source data are directly entered into the data capture system.

Data Protection

Data systems used for the study will have controls and requirements in accordance with local data protection law.

The purpose and use of patient personal information collected will be provided in a written document to the patient by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

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

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.

Appendix 4. 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 Lilly or its designee CRP.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils	
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
Conjugated bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	**Alkaline Phosphatase Isoenzymes[a]**
GGT	**Anti-smooth muscle antibody (or anti-actin**
CPK	**antibody)[a]**

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

a Assayed by local laboratory.

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

Appendix 5. Blood Sampling Summary

This table summarizes the approximate number of venipunctures and blood volumes for all blood sampling (screening, safety laboratories, and bioanalytical assays) during the study.

Protocol H9X-JE-GBGK Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Hematology, clinical chemistry, endocrinology [a]	8	5	40
HbA1c	2	4	8
Serology tests	6	1	6
Serum pregnancy test	2	1	2
Fasting blood glucose	2	1	2
MTT (glucose, insulin, c-peptide, glucagon, and triglyceride)	6	56	336
Total			394

Abbreviations: HbA1c = glycated hemoglobin; MTT = meal tolerance test.

[a] Additional samples may be drawn if needed for safety purposes.

Appendix 6. Meal Tolerance Test

Time	Procedure
-120 min	Physical exam, vital signs (sitting) Weight (only Day 1, Day 29, Day 57, and Day 85) ECG (only Day 1 and Day 57)
	Urine sampling for pregnancy test (only Day 1 and Day 57, if needed) Urinalysis and UACR (only Day 1, Day 29, Day 57, and Day 85)
	Blood sampling for hematology, clinical chemistry, endocrinology, HbA1c (only Day 1, Day 29, Day 57, and Day 85)
	Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride (for 0 min) Satiety evaluation (VAS) (for 0 min)
0 min	Start standardized test meal [a]
30 min	Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride
60 min	Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
90 min	Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride
120 min	Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
180 min	Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
240 min	Blood sampling for glucose, insulin, c-peptide, glucagon, and triglyceride Satiety evaluation (VAS)
After MTT	Dose of dulaglutide 0.75 mg or placebo (except Days 29 and 85)

Abbreviations: HbA1c = glycated hemoglobin; min = minutes; MTT = meal tolerance test; UACR = urine albumin/creatinine ratio; VAS = visual analog scale.

[a] Japanese standard test meal (480 kcal, carbohydrate: protein: fat = 2.8:1:1) should be ingested within 15 min.

Appendix 7. Protocol Amendment H9X-JE-GBGK(a) Summary: A Phase 4 Study to Evaluate Glucodynamic Effects of Dulaglutide in Japanese Patients with Type 2 Diabetes Mellitus

Overview

Protocol H9X-JE-GBGK(a) A Phase 4 Study to Evaluate Glucodynamic Effects of Dulaglutide in Japanese Patients with Type 2 Diabetes Mellitus has been amended. The new protocol is indicated by Amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

Section 7.5.1:
The detailed method of a hypoglycemic event is added.

Section 9.2.2.1:
Pancreatitis adjudication by an independent committee of expert physicians is removed.

Appendix 2:
The detailed item of the seerum pregnancy test is removed.

Appendix 6:
Time window before the meal tolerance test (MTT) is changed .

Minor editorial changes were made for accuracy, consistency and clarity.

Revised Protocol Sections

Note:	All deletions have been identified by ~~strikethroughs~~. All additions have been identified by the use of underscore.

The numbering system used for inclusion and exclusion criteria provides a unique number for each criterion and allows for efficiency in data collection.

In case an amendment to the protocol adds a criterion, that criterion will receive the next available number, regardless of whether it is an inclusion or exclusion criterion.

6.2. Exclusion Criteria

[22] Positive human immunodeficiency virus (HIV) antigen and antibody, hepatitis C antibody, hepatitis B surface antigen, or syphilis at Visit 1.

7.5. Special Treatment Considerations

7.5.1 Management of Increased Hypoglycemia Risk

If a hypoglycemic event occurs, the patient should record in the study diary the episode and associated symptoms and/or signs, and rescue treatment (if taken).

~~Investigator should use~~ Study site personnel will record information related to hypoglycemia such as start and end date and time of the ~~following~~ episode, hypoglycemia signs and symptoms present. Following definitions and criteria ~~when diagnosing and~~ will be used for categorizing an episode considered to be related to hypoglycemia (the 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 2005):

9.2.2. Adverse Events of Interest

9.2.2.1. Pancreatitis

~~All AEs of acute or chronic pancreatitis, as well as cases of confirmed lipase or amylase values ≥3× ULN, will be adjudicated by an independent committee of expert physicians. In addition, AEs of severe or serious abdominal pain of unknown origin will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis, those with severe or serious abdominal pain, and those that undergo additional assessments due to confirmed hyperenzymemia will be entered into a specifically designed CRF page by study site or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding CRF page.~~

9.4.2. Vital Signs

Vital signs should be taken before collection of blood samples for laboratory testing. For each parameter, 3 measurements will be taken 1 minute apart using the same arm. An appropriately sized cuff (cuff bladder encircling at least 80% of the upper arm) should be used to ensure the accuracy of blood pressure measurements. The arm used for the blood pressure measurement should be supported at heart level. Each measurement of sitting heart rate and blood pressure is to be recorded in the CRF.

9.4.4. Other Tests

9.4.4.1. Continuous Glucose Monitoring

The CCI system (CCI [WWW])) will be used for CGM in this study. Continuous Glucose Monitoring will be performed in each study period. Continuous Glucose Monitoring will be initiated on Day -7 (or -6) and Day 50 (or 51) and will last until Day 8 and Day 64.

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests [a]

Urine albumin/creatinine ratio (UACR)	Meal tolerance test
	Glucose
Serum pregnancy test [if applicable] [b]	Insulin
~~Follicle stimulating hormone~~	c-peptide
Urine pregnancy test [if applicable]	Glucagon
	Triglyceride
Serology [b]	
Hepatitis B surface antigen	Endocrinology
Hepatitis C antibody	Total amylase
HIV antigen and antibody	Lipase
Syphilis	Calcitonin

Abbreviations: HIV = human immunodeficiency virus; HbA1c = glycated hemoglobin; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by local laboratory.

[b] Performed at screening only.

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[a] Additional samples may be drawn if needed for safety purposes.

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Abbreviations: HbA1c = glycated hemoglobin; min = minutes; MTT = meal tolerance test; UACR = urine albumin/creatinine ratio; VAS = visual analog scale.