

H9X-JE-GBGF (b) Protocol

A Phase 4 Study of Efficacy and Safety of Dulaglutide When Added to Insulin Treatment With or Without Oral Antidiabetic Medication in Patients with Type 2 Diabetes

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Approval Date: 11-Jul-2016

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Added to Insulin Treatment With or Without Oral Antidiabetic  
Medication in Patients with Type 2 Diabetes**

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**Dulaglutide (LY2189265)**

Study H9X-JE-GBGF is a Phase 4, randomized, placebo-controlled, double-blind (16 weeks) and subsequent open-label (36 weeks) study to assess the efficacy and safety of dulaglutide 0.75 mg in Japanese patients with type 2 diabetes who have inadequate glycemic control on insulin therapy with or without 1 or 2 oral antidiabetic medications.

Eli Lilly Japan K.K.  
Kobe, Hyogo Japan

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## 1. Synopsis

### Title of Study:

A Phase 4 Study of Efficacy and Safety of Dulaglutide When Added to Insulin Treatment With or Without Oral Antidiabetic Medication in Patients with Type 2 Diabetes

### Rationale:

Study H9X-JE-GBGF (GBGF) will assess the efficacy and safety of once-weekly dulaglutide added to insulin therapy (basal insulin, premixed insulin, or basal/mealtime insulin) with or without 1 or 2 oral antidiabetic (OAD) medications.

This study will provide data for combination therapy with dulaglutide and insulin in Japanese patients with type 2 diabetes (T2D). This study will assess hemoglobin A1c (HbA1c), fasting serum glucose, 7-point self-monitored plasma glucose profile, and other aspects of diabetes management, such as hypoglycemia risk and body weight changes. These outcomes will enable appropriate clinical characterization of the combination regimen.

### Objectives/Endpoints:

Objectives	Endpoints
<p><b>Primary</b> To show superiority of the addition of once-weekly dulaglutide 0.75 mg compared to the addition of once-weekly placebo to insulin treatment with or without 1 or 2 OADs, on change from baseline in HbA1c after 16 weeks of treatment in Japanese patients with T2D.</p>	<ul style="list-style-type: none"> <li>• The change in HbA1c from baseline to 16 weeks</li> </ul>
<p><b>Secondary</b> For efficacy, to compare dulaglutide 0.75 mg to placebo at 16 weeks</p> <p>For safety, to compare dulaglutide 0.75 mg to placebo for 16 weeks</p>	<ul style="list-style-type: none"> <li>• Percentage of patients achieving HbA1c target values of &lt;7.0% or ≤6.5% at 16 weeks</li> <li>• The change in FSG (central laboratory) from baseline to 16 weeks</li> <li>• The change in PG from 7-point SMPG profiles from baseline to 16 weeks</li> <li>• The change in body weight from baseline to 16 weeks</li> <li>• The change in insulin dose from baseline to 16 weeks</li> <li>• TEAEs</li> <li>• Incidence and rate of hypoglycemic episodes</li> <li>• Adjudicated cardiovascular and pancreatic AEs</li> <li>• Thyroid neoplasm AEs</li> <li>• Allergic/hypersensitivity AEs</li> <li>• Laboratory parameters of hematological safety and biochemical abnormalities</li> </ul>

Objectives	Endpoints
<p>To describe long-term efficacy of dulaglutide 0.75 mg in combination with insulin therapy up to 52 weeks.</p> <p>To describe long-term safety of dulaglutide 0.75 mg in combination with insulin therapy up to 56 weeks (to include the follow-up period).</p>	<ul style="list-style-type: none"> <li>• Efficacy parameters described above</li> <li>• Safety parameters described above</li> </ul>

Abbreviations: AE = adverse event; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; OAD = oral antidiabetic; PG = plasma glucose; SMPG = self-monitored plasma glucose; T2D = type 2 diabetes; TEAE = treatment-emergent adverse event.

### Summary of Study Design:

Study GBGF is a Phase 4, randomized, placebo-controlled, double-blind (16 weeks) and subsequent open-label (36 weeks, 52 weeks total) study to assess the efficacy and safety of once-weekly dulaglutide 0.75 mg in Japanese patients with T2D who have inadequate glycemic control on insulin therapy with or without 1 or 2 OADs.

### Treatment Arms and Duration:

After completing Visit 1, and, if necessary, a 12-week washout period (dipeptidyl peptidase-4 inhibitors, sulfonylurea, and glinides will be washed out), patients will be randomized in a 3:1 ratio to a weekly injection of dulaglutide 0.75 mg or placebo, in combination with stable doses of insulin (with or without 1 or 2 OADs). Study participants will be treated for 16 weeks after randomization in the double-blind manner, after which all patients will be treated with 0.75 mg dulaglutide in combination with insulin for 36 weeks in the open-label extension.

### Number of Patients:

A total of approximately 160 patients (dulaglutide: 120 patients; placebo: 40 patients) will be randomized to have approximately 136 completers (dulaglutide : 102 patients; placebo: 34 patients) to show dulaglutide is superior to placebo with more than 99% power assuming a treatment difference of 1% in HbA1c reduction, standard deviation = 1.0%, and dropout rate of 15%. The screen failure rate is estimated as 20%. Approximately 200 patients will be screened.

### Statistical Analysis:

The primary analysis model will be mixed-model repeated measure (MMRM) analysis using restricted maximum likelihood with treatment, insulin regimen (basal insulin, premixed insulin, or basal/mealtime insulin), visit, and treatment-by-visit as fixed effects, a covariate of baseline value, and patient as a random effect. For analyses of variables other than HbA1c, the HbA1c stratum (<8.5%, ≥8.5%) will be included in the model. An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data. The secondary analysis for the primary endpoint will be analysis of covariance using a similar model as described above with treatment, and insulin regimen (basal insulin, premixed insulin, or basal/mealtime insulin) as fixed effects and baseline HbA1c as a covariate, with missing endpoints imputed with the last (postbaseline) observation carried forward. All secondary efficacy measures that are continuous variables (changes from baseline) will be analyzed using MMRM. Repeated measures logistic regression with generalized linear mixed model will be used to analyze for percentage of patients achieving HbA1c targets of <7.0% or ≤6.5%. Analyses for other secondary efficacy categorical measurements will use the repeated measures logistic regression with generalized linear mixed model, unless otherwise noted.

The primary analysis population will be the full analysis set, defined as all patients who received at least 1 dose of study treatment and have at least 1 measurement of HbA1c after study treatment. The safety population will include all patients who received at least 1 dose of study treatment. The primary efficacy measure (HbA1c) will also be evaluated in the Per-Protocol population.

## 2. Schedule of Activities

Study Schedule, Protocol H9X-JE-GBGF

Study Visit	Screening and Lead-in <sup>a</sup>		Primary Treatment					Extension Treatment					ET	Follow-up
			Fixed Insulin Dose					Flexible Insulin Dose						
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	ET <sup>b</sup>	13 <sup>c</sup>
Week of Treatment	-4 or -14 <sup>d</sup>	-2 <sup>e</sup>	0	4	8	12	16	20	28	36	44	52	—	56
Visit Window (days)	±7	±7	—	±7	±7	±7	±7	±7	±7	±7	±7	±7	—	±7
<b>Informed Consent and Randomization</b>														
Informed consent	X													
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization			X											
<b>Clinical Assessments</b>														
Medical history	X	X												
Demographics	X	X												
Previous diabetes therapy	X	X												
Physical exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X													
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs <sup>f</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X
Preexisting conditions and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemic events		X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG <sup>g</sup>	X													
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Laboratory Assessments</b>														
Serum Pregnancy test <sup>h</sup>	X		X											
Hematology, Chemistry panel	X		X				X			X		X	X	X
Urinalysis	X		X				X			X		X	X	X
Fasting serum glucose <sup>i</sup>			X	X	X	X	X	X	X	X	X	X	X	X
Lipid panel <sup>i</sup>			X				X			X		X	X	X
HbA1c	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Pancreatic Enzymes			X				X			X		X	X	X
Calcitonin	X		X				X			X		X	X	
<b>Stored Sample</b>														
Pharmacogenomics sample (Stored)			X											
<b>Patient Education, Supplies, and SMPG</b>														
Dispensing of SMPG meter/supplies		X	X	X	X	X	X	X	X	X	X	X	X	
SMPG meter training		X												

Study Schedule, Protocol H9X-JE-GBGF

	Screening and Lead-in <sup>a</sup>		Primary Treatment					Extension Treatment					ET	Follow-up
			Fixed Insulin Dose					Flexible Insulin Dose						
Study Visit	1	2	3	4	5	6	7	8	9	10	11	12	ET <sup>b</sup>	13 <sup>c</sup>
Week of Treatment	-4 or -14 <sup>d</sup>	-2 <sup>e</sup>	0	4	8	12	16	20	28	36	44	52	—	56
Visit Window (days)	±7	±7	—	±7	±7	±7	±7	±7	±7	±7	±7	±7	—	±7
<b>Patient Education, Supplies and SMPG (cont)</b>														
SMPG values review			X	X	X	X	X	X	X	X	X	X	X	X
Daily fasting SMPG measurement <sup>j</sup>			X	X	X	X	X	X	X	X	X	X	X	X
7-point SMPG measurement <sup>k</sup>			X				X						X	
Dispensing study diary and instruct in use		X	X	X	X	X	X	X	X	X	X	X	X	
Study diary review			X	X	X	X	X	X	X	X	X	X	X	X
Dispensing of investigational product and injection supplies			X	X	X	X	X	X	X	X	X			
Subcutaneous injection training/injection site inspection/review of technique		X	X	X	X	X	X	X	X	X	X	X	X	
Return of used investigational product containers, unused study medication and study diary				X	X	X	X	X	X	X	X	X	X	X
Assessment of investigational product compliance				X	X	X	X	X	X	X	X	X	X	
<b>Health Outcome Questionnaires/Other Evaluation</b>														
DTR-QOL, DTSQs			X				X					X	X	
Dietary Evaluation			X				X					X		
Questionnaire for device							X					X	X	

Abbreviations: DPP-4 = dipeptidyl peptidase-4; DTR-QOL = Diabetes Therapy-Related Quality of Life Questionnaire; DTSQs = Diabetes Treatment Satisfaction Questionnaire status; ECG = electrocardiogram; ET = early termination visit; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; IWRS = interactive web response system; SMPG = self-monitored plasma glucose; SU = sulfonylurea.

- a A telephone visit (T/V1; or site visit if preferred) will occur at Week -12 after screening results are available. An optional telephone visit (T/V2; or site visit if preferred) may occur between Weeks -8 and 0.
- b Early termination (ET) visit is conducted within 14 days after the decision of discontinuation.
- c Visit 13 should occur 28 days after Visit 12 or the day on which the decision of early termination is made.
- d Visit 1 should occur 4 weeks prior to Visit 3 for patients who have not been receiving DPP-4 inhibitors, SU, or glinides. Visit 1 should occur 14 weeks prior to Visit 3 for patients who have been receiving DPP-4 inhibitors, SU, or glinides (to include 12 weeks of washout).
- e Visit 2 should be 2 weeks prior to Visit 3

**Study Schedule, Protocol H9X-JE-GBGF**

- f For each parameter, 3 measurements will be taken 30 seconds 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.
- g A single 12-lead ECG will be performed locally and recorded, after the patient has been lying supine for 5 minutes. If the subject has a single 12-lead ECG record which was performed within 3 months prior to Visit 1, the data can be used as a baseline measurement.
- h Serum pregnancy test to be performed by the central lab at Visits 1 and 3 for women of childbearing potential only. Subsequent pregnancy tests can be performed as required at local laboratories. A local (urine) pregnancy test may additionally be performed at the investigator's discretion during the study.
- i Fasting laboratory samples must be obtained after a fast of 8 hours or more without eating, drinking (except for water), or performing any significant physical activity.
- j Patients are required to measure their fasting (pre-breakfast) plasma glucose (FPG) concentration at least once every 2 to 3 days at approximately the same time of day after Visit 3. By the investigator's decision, the frequency of measurement of FPG could be increased.
- k 7-point SMPG profiles (blood glucose measurements before breakfast, lunch, dinner, and bedtime and 2 hours after breakfast, lunch, and dinner) should be performed on 2 days within the 2 weeks prior to Visit 3 (Week 0), Visit 7 (Week 16), and ET visit (only when the patient discontinued before Week 16).

### 3. Introduction

It has been approximately 6 years since liraglutide received marketing approval as the first glucagon-like peptide-1 (GLP-1) receptor agonist in Japan. Additional GLP-1 receptor agonists (exenatide twice daily, exenatide once weekly, and lixisenatide) have been launched since then, and these have all become important treatment options for patients with type 2 diabetes (T2D) (Japan Diabetes Society 2013; ADA 2015).

Dulaglutide is a long-acting GLP-1 receptor agonist that mimics the effects of endogenous GLP-1 (Glaesner et al. 2010). It has been approved and launched in the United States and the European Union at once weekly doses of 0.75 mg and 1.5 mg (Trulicity USPI, 2015; Trulicity SmPC, 2015) and in Japan at a once weekly dose of 0.75 mg (Trulicity Japan Prescribing Information, 2015). In Phase 3 studies in Japanese patients with T2D, once weekly dulaglutide 0.75 mg has shown superiority to insulin glargine (in a randomized, 26-week, open-label study of dulaglutide in combination with sulfonylureas [SU] and/or biguanides) and noninferiority to liraglutide 0.9 mg/day (in a randomized monotherapy study in which dulaglutide was compared to placebo [double-blind] and to liraglutide 0.9 mg/day [open-label]; the study had a 26-week primary endpoint and a 52-week treatment period) in hemoglobin A1c (HbA1c) changes (Araki et al. 2015; Miyagawa et al. 2015; Odawara et al. 2016). Also, in a nonrandomized, open-label, long-term (52-week) Phase 3 safety study in Japanese patients with T2D, once weekly dulaglutide 0.75 mg was well-tolerated overall in combination with a single oral antidiabetic (OAD; SU, biguanides,  $\alpha$ -glucosidase inhibitors [ $\alpha$ -GI], thiazolidinediones [TZD], or glinides) (Emoto et al. 2015).

Glucagon-like peptide-1 receptor agonist is frequently used in combination with insulin and in combination with OADs. Beneficial effects of the combination of GLP-1 receptor agonist and insulin including greater HbA1c reduction, less weight gain, and lower incidence of hypoglycemia associated with a smaller dose of insulin have been reported (Balena et al. 2013; Eng et al. 2014). The combination of dulaglutide and insulin has been investigated in global studies. Dulaglutide in combination with mealtime insulin was tested in the AWARD-4 study (Blonde et al. 2015) and in combination with basal insulin in the AWARD-9 study (ClinicalTrials.gov [WWW]).

It is known that the daily dose of insulin in Japanese diabetic patients is lower than that in Western patients because of lean body mass. In clinical studies in Japanese patients, average insulin doses in patients with T2D were 10 to 15 IU for basal insulin (Kawamori et al. 2003a; Inagaki et al. 2012; Odawara et al. 2012) and in patients with type 1 diabetes or T2D, 40 to 50 IU for basal/mealtime insulin (Kawamori et al. 2003b; Kobayashi et al. 2007; Iwamoto et al. 2013). Because it is difficult to adopt Western data for Japanese patients, efficacy and safety data for the combination treatment of dulaglutide and insulin in Japanese patients will be beneficial information for clinical use of dulaglutide in Japan.

Study H9X-JE-GBGF (GBGF) will assess the efficacy and safety of once weekly dulaglutide in combination with insulin therapy (basal insulin, premixed insulin, or basal/mealtime insulin) with or without 1 or 2 OADs. The primary objective is to show superiority of dulaglutide to

placebo in HbA1c change from baseline after 16 weeks of treatment, and the secondary objectives are to compare the efficacy and safety of the combination to placebo up to 16 weeks and to describe the long-term efficacy up to 52 weeks and safety up to 56 weeks (including the follow-up period). Dulaglutide will be administered per label in this Phase 4 study.

### **3.1. Study Rationale**

Study GBGF will provide data for combination therapy with dulaglutide and insulin in Japanese patients with T2D. This study will assess HbA1c, fasting serum glucose (FSG), 7-point self-monitored plasma glucose (SMPG) profile, and other aspects of diabetes management, such as hypoglycemia risk and body weight changes. These outcomes will enable appropriate clinical characterization of the combination regimen in Japanese patients with T2D.

### **3.2. Background**

Dulaglutide is a biosynthetic fusion protein molecule produced using mammalian cell cultures, and consists of 2 identical, disulphide-linked chain, each containing an N-terminal GLP-1 analogue sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain by a small peptide linker. These structural features of the dulaglutide molecule (1) decrease the rate of clearance, (2) increase the duration of pharmacologic activity, (3) may reduce the immunogenic potential, and (4) may decrease unwanted antibody-mediated effector function (Tamaki et al. 2015).

Dulaglutide exhibits 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**

More information about the known and expected benefits, risks, serious adverse events (SAEs) and reasonably anticipated adverse events (AEs) of dulaglutide are to be found in the Japan prescribing information (JPI) and interview form.

## 4. Objectives and Endpoints

Table GBGF.4.1 shows the objectives and endpoints of the study.

**Table GBGF.4.1. Objectives and Endpoints**

Objectives	Endpoints
<p><b>Primary</b> To show superiority of the addition of once-weekly dulaglutide 0.75 mg compared to the addition of once-weekly placebo to insulin treatment with or without 1 or 2 OADs, on change from baseline in HbA1c after 16 weeks of treatment in Japanese patients with T2D.</p>	<ul style="list-style-type: none"> <li>• The change in HbA1c from baseline to 16 weeks</li> </ul>
<p><b>Secondary</b> For efficacy, to compare dulaglutide 0.75 mg to placebo at 16 weeks.</p> <p>For safety, to compare dulaglutide 0.75 mg to placebo for 16 weeks.</p> <p>To describe long-term efficacy of dulaglutide 0.75 mg in combination with insulin therapy up to 52 weeks.</p> <p>To describe long-term safety of dulaglutide 0.75 mg in combination with insulin therapy up to 56 weeks (to include the follow-up period).</p>	<ul style="list-style-type: none"> <li>• Percentage of patients achieving HbA1c target values of &lt;7.0% or ≤6.5% at 16 weeks</li> <li>• The change in FSG (central laboratory) from baseline to 16 weeks</li> <li>• The change in PG from 7-point SMPG profiles from baseline to 16 weeks</li> <li>• The change in body weight from baseline to 16 weeks</li> <li>• The change in insulin dose from baseline to 16 weeks</li> <li>• TEAEs</li> <li>• Incidence and rate of hypoglycemic episodes</li> <li>• Adjudicated cardiovascular and pancreatic AEs</li> <li>• Thyroid neoplasm AEs</li> <li>• Allergic/hypersensitivity AEs</li> <li>• Laboratory parameters of hematological safety and biochemical abnormalities</li> <li>• Efficacy parameters described above</li> <li>• Safety parameters described above</li> </ul>
<p><b>Exploratory</b> Exploratory objectives are to assess the health outcomes variables at 16 and 52 weeks.</p>	<ul style="list-style-type: none"> <li>• Diabetes Treatment Satisfaction Questionnaire status (DTSQs)</li> <li>• Diabetes Therapy Related Quality of Life (DTR-QOL)</li> <li>• Device Questionnaire</li> <li>• Dietary Evaluation</li> </ul>

**Objectives and Endpoints**

Abbreviations: AE = adverse event; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; OAD = oral antidiabetic; PG = plasma glucose; SMPG = self-monitored plasma glucose; T2D = type 2 diabetes; TEAE = treatment-emergent adverse event.

## 5. Study Design

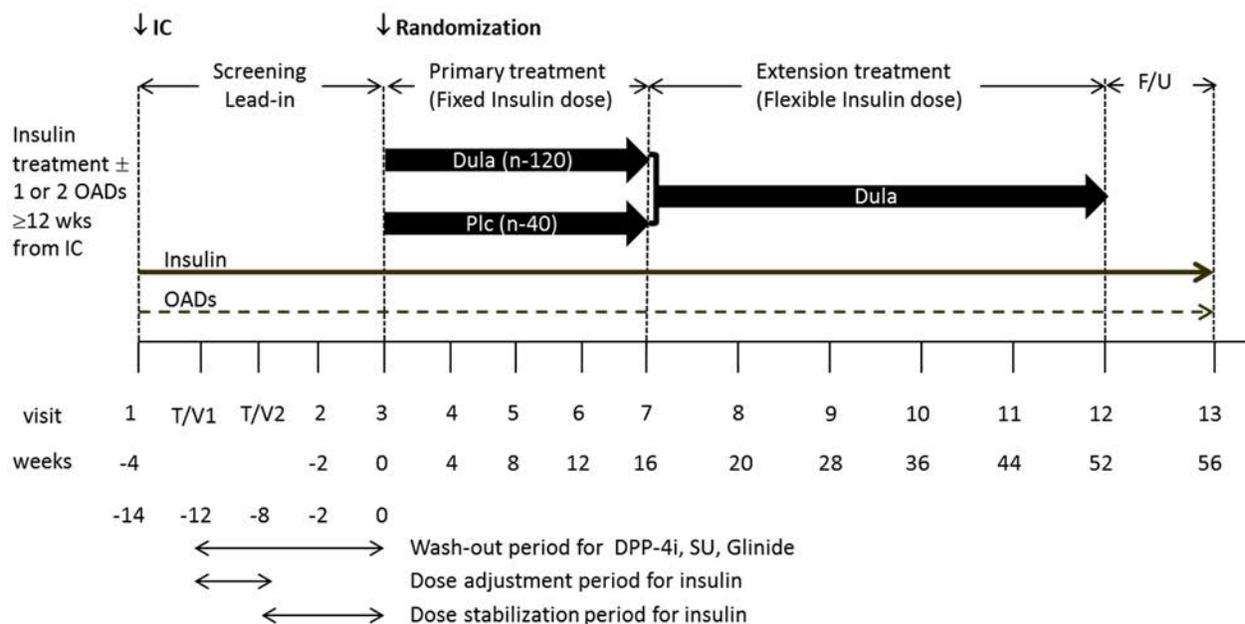
### 5.1. Overall Design

Study GBGF is a Phase 4, randomized, placebo-controlled, double-blind (16 weeks) and subsequent open-label (36 weeks, 52 weeks total) study to assess the efficacy and safety of once-weekly dulaglutide 0.75 mg in Japanese patients with T2D who have inadequate glycemic control on insulin therapy with or without 1 or 2 OADs. The insulin regimen in this study includes basal insulin, premixed insulin, and basal/mealtime insulin for basal-bolus therapy, with enrollment target percentages of 60%, 20%, and 20% for the insulin regimens, respectively. Also, 20% or more of the patients enrolled in this study will be on insulin therapy without OADs (including OAD washout). The sponsor will closely monitor enrollment status to achieve these enrollment target percentages.

The study includes a 4- or 14-week screening and lead-in with or without washout period, a 16-week double-blind primary treatment period, followed by a 36-week open-label extension treatment period, and a 4-week safety follow-up visit.

Laboratory tests will be performed at Visit 1. A telephone visit (T/V1; or site visit if preferred by the patient) at Week -12 will occur after Visit 1 laboratory results are available, and eligible patients on dipeptidyl peptidase-4 (DPP-4) inhibitors, SU, or glinides will begin a 12-week washout period during which the insulin dose may be uptitrated for up to 4 weeks, with an 8 week-stabilization ( $\pm$  20% adjustment) prior to Visit 3. During Weeks -8 through 0 (the insulin dose stabilization period), a second telephone visit (T/V2; or site visit, if preferred) may occur. The insulin dose should remain unchanged for the 16-week primary treatment period, unless hypoglycemia occurs (see Section 7.4.1.2). In addition, for patients treated with 1 or 2 OADs other than DPP-4 inhibitors, SU, or glinide prior to Visit 1, the dosage and administration of OADs should not be changed during the 16-week primary treatment period. Eligible patients not on DPP-4 inhibitors, SU, or glinides can proceed to Visit 2. At Visit 2, HbA1c will be measured and eligibility will be reconfirmed. At Visit 3, approximately 160 patients will be randomized in a 3:1 ratio to dulaglutide 0.75 mg or placebo. After 16 weeks of primary treatment period, patients taking placebo will be switched to dulaglutide for an additional 36 weeks of extension treatment period. After the extension treatment period, dulaglutide must be discontinued and restart is not allowed during the follow-up period. To preserve the blinding of the study, the treatment assignments in the double-blind primary treatment period will be blinded to patients and investigators until study completion.

Figure GBGF.1 illustrates the study design.



Abbreviations: DPP-4i = dipeptidyl peptidase-4 inhibitors; Dula = dulaglutide; F/U = follow-up; IC = informed consent; n = number of patients; OAD = oral antidiabetic; Plc = placebo; SU = sulfonylurea; T/V = telephone visit; wks = weeks.

Note: A telephone visit (T/V1; or site visit if preferred) will occur at Week -12 after screening results are available. An optional telephone visit (T/V2; or site visit if preferred) may occur between Weeks -8 and 0. Telephone visits or site visits may occur anytime during the study, as needed.

**Figure GBGF.1. Illustration of study design for Clinical Protocol H9X-JE-GBGF.**

For each study period and each visit, study procedures are provided in the Schedule of Activities (Section 2).

### 5.2. Number of Participants

Approximately 200 patients will be screened to achieve approximately 160 randomized (dulaglutide: 120 patients; placebo: 40 patients) and approximately 136 patients completing the study (dulaglutide: 102 patients; placebo: 34 patients).

### 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 was planned based on the Japanese guideline for clinical evaluation of hypoglycemic agents (Draft version, Ministry of Health, Labour and Welfare, 2014). This guideline requests 2

points; the first is to confirm efficacy of study drug compared with placebo in combination with stable insulin dose for 12 to 24 weeks, and the second is to confirm long-term (up to 52 weeks) efficacy and safety of the combination of study drug and insulin. In this study, we divided treatment into 16 weeks for the primary treatment period and a 36-week extension treatment period. Since HbA1c reduction was stable after 14 weeks in Japanese Phase 3 studies, 16 weeks is appropriate to assess efficacy.

For the insulin regimen, this study allows basal insulin, premixed insulin, and basal/mealtime insulin. These insulin regimens are frequently used in Japanese patients with T2D.

In the screening period, DPP-4 inhibitors, SU, and glinides will be washed out. Both dulaglutide and DPP-4 inhibitors decrease blood glucose via the GLP-1 receptor. Dulaglutide in combination with DPP-4 inhibitors has not been investigated for efficacy or safety in clinical studies. Sulfonylureas and glinides will be washed out because these drugs increase the risk of hypoglycemia in combination with dulaglutide (Emoto et al. 2015).

In the 16-week primary treatment period, dulaglutide will be compared with placebo using a fixed insulin dose to evaluate the efficacy of dulaglutide only. In the 36-week extension treatment period, the insulin dose will be adjusted to achieve target glucose levels ( $\leq 110$  mg/dL preprandial, and  $\leq 140$  mg/dL at bedtime), and efficacy and safety of the combination therapy of dulaglutide and insulin will be assessed.

### **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

The planned patient population includes Japanese adult patients with T2D who have inadequate glycemic control with insulin therapy with or without OADs.

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 to be included in the study only if they meet all of the following criteria at Visit 1 except criterion [4]:

- [1] have T2D (based on the World Health Organization's [WHO] diagnostic criteria [[Appendix 5](#)]);
- [2] have been treated with insulin therapy (basal insulin [once or twice daily], premixed insulin [twice or 3 times daily], or basal/mealtime insulin [4 or 5 times daily] regimen) with or without 1 or 2 OADs at stable dose for at least 3 months prior to Visit 1;
- [3] doses of daily insulin must be stable ( $\pm 20\%$  versus the most commonly used dose for the period) and more than 10 units per day during the 3-month period prior to Visit 1;
- [4] have an HbA1c value  $\geq 7.0\%$  and  $\leq 10.5\%$  at Visit 1 if the patient is washing out OADs (DPP-4 inhibitors, SU, or glinides) or  $\geq 7.5\%$  and  $\leq 10.5\%$  at Visit 1 if the patient is not washing out OADs. At Visit 2, have an HbA1c  $\geq 7.5\%$  and  $\leq 10.5\%$  (values at Visit 1 and Visit 2 as assessed by the central laboratory);
- [5] have stable weight ( $\pm 5\%$ )  $\geq 3$  months prior to Visit 1;
- [6] have body mass index (BMI) of 18.5 to 35 kg/m<sup>2</sup> at Visit 1;
- [7] Japanese men or nonpregnant, nonbreastfeeding Japanese women aged  $\geq 20$  years at Visit 1;
- [8] are females of childbearing potential who must:
  - [a] test negative for pregnancy at Visit 1;
  - [b] agree to remain abstinent, use 1 highly effective method of contraception (ie, combined oral contraceptive pill and mini-pill, Nuva-Ring, implantable contraceptives, injectable contraceptives, intrauterine device, contraceptive patch [ONLY women <90 kg], or partner with vasectomy) or use a combination of 2 effective methods (ie, condom with spermicide, diaphragm with spermicide, female condom with spermicide, cervical sponge, cervical cap with spermicide) for the entire study. Abstinence or contraception must continue following completion of investigational product administration for 4 weeks following the last dose of investigational product.

[c] not be breastfeeding.

Women not of childbearing potential may participate and are defined as:

- a) infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
- b) postmenopausal woman  $\geq 50$  years of age with an intact uterus, who has not taken hormones or oral contraceptives within 1 year, AND
  - i) who has had either cessation of menses for at least 1 year, OR
  - ii) 6 months of spontaneous amenorrhea with follicle-stimulating hormone  $>40$  mIU/mL.

[9] have given written informed consent to participate in the study in accordance with local regulations and the ethical review board (ERB) governing the study site.

## 6.2. Exclusion Criteria

Patients will be excluded from study enrollment if they meet any of the following criteria at Visit 1:

- [10] have type 1 diabetes (based on WHO diagnostic criteria);
- [11] have previously received therapy with a GLP-1 receptor agonist within 3 months prior to Visit 1;
- [12] have been previously treated with dulaglutide prior to Visit 1;
- [13] have been treated with 2 of the following at Visit 1: DPP-4 inhibitor, SU, and glinide (ie, DPP-4 inhibitor and SU, or DPP-4 inhibitor and glinide);
- [14] have been treated with continuous subcutaneous insulin infusion at Visit 1;
- [15] have been treated with drugs that promote weight loss within the 3 months prior to Visit 1;
- [16] are receiving chronic ( $>14$  days) systemic glucocorticoid therapy (excluding topical, intraocular, or intranasal preparations) or have received such therapy within the 4 weeks prior to Visit 1;
- [17] have 1 or more episodes of severe hypoglycemia within the 6 months prior to Visit 1;
- [18] have 1 or more episodes of diabetic ketoacidosis within the 6 months prior to Visit 1;
- [19] have had any of the following cardiovascular conditions within the 3 months prior to Visit 1: acute myocardial infarction (MI), New York Heart Association (NYHA) Class III or Class IV heart failure, or cerebrovascular accident (stroke);

- [20] have a known clinically significant gastric emptying abnormality or have undergone gastric bypass surgery or restrictive bariatric surgery;
- [21] 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 central laboratory at Visit 1;
- [22] 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;
- [23] have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m<sup>2</sup>, calculated by the Japanese Society of Nephrology equation, as determined by the central laboratory; for participants on metformin, have moderate renal disease or renal dysfunction (for example, eGFR <60 mL/min/1.73 m<sup>2</sup>) at Visit 1;
- [24] 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;
- [25] 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);
- [26] have serum calcitonin  $\geq$ 20 pg/mL, as determined by the central laboratory at Visit 1;
- [27] have evidence of a significant, active uncontrolled endocrine or autoimmune abnormality, as judged by the investigator at Visit 1;
- [28] have a history of transplanted organ;
- [29] 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;
- [30] have a history of any other condition which, in the opinion of the investigator, may preclude the participant from following and completing the protocol;
- [31] have any hematologic condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle-cell disease);
- [32] are currently enrolled in any other clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
- [33] have participated, within the last 30 days in a clinical trial involving an investigational product. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed;
- [34] have previously completed or withdrawn from this study or any other study investigating dulaglutide;

[35] 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;

[36] are Lilly employees;

[37] are unable and/or unwilling to provide written informed consent, make themselves available for the duration of the study, or abide by study procedures and restrictions.

### **6.3. Lifestyle Restrictions**

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 not be rescreened.

## 7. Treatments

### 7.1. Treatments 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) in patients with T2D who are already treated with insulin with or without 1 or 2 OADs. [Table GBGF.7.1](#) summarizes study treatments and concomitant medications during the primary treatment period, and the extension treatment period.

**Table GBGF.7.1. Study Treatments and Concomitant Medications**

Name of Drug	Dose <sup>a</sup>	Frequency <sup>a</sup>	Drug Formulation	Route of Administration
<b>16-Week Primary Treatment Period</b>				
<b>Investigational Compound</b>				
Dulaglutide	0.75 mg	Once weekly	Single-dose pen	Subcutaneous injection
<b>Comparator</b>				
Placebo	Placebo	Once weekly	Single-dose pen	Subcutaneous injection
<b>Concomitant Insulin for Both Treatment Arms</b>				
Basal, mixed, or mealtime insulin	Fixed	Fixed	Pen type device/Vial and syringe	Subcutaneous injection
<b>Oral Antidiabetic Medications for Both Treatment Arms</b>				
Biguanides, TZD, $\alpha$ -GI, SGLT2i	Fixed	Fixed	Tablet	Oral
<b>36-Week Extension Treatment Period</b>				
Dulaglutide	0.75 mg	Once weekly	Single-dose pen	Subcutaneous injection
Basal, mixed, or mealtime insulin	Flexible	Fixed	Pen type device/Vial and syringe	Subcutaneous injection
Biguanides, TZD, $\alpha$ -GI, SGLT2i	Fixed <sup>b</sup>	Fixed <sup>b</sup>	Tablet	Oral

Abbreviations:  $\alpha$ -GI = alpha-glucosidase inhibitor; CRP = clinical research physician; CRS = clinical research scientist; OAD = oral antidiabetic; SGLT2i = sodium-glucose co-transporter 2 inhibitor; TZD = thiazolidinedione.

<sup>a</sup> Dose and frequency refer to investigational compound and concomitant medications within a patient.

<sup>b</sup> The investigator is to consult with the Lilly CRP or CRS if the dosage of OADs is changed.

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

- explaining the correct use of the investigational agent(s) to the patient or patient representative, and SDP training with a demonstration device
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection

#### 7.1.1. Packaging and Labeling

The sponsor will provide dulaglutide and placebo in SDPs, which will be dispensed via an interactive web-response system (IWRS). Each SDP (0.75 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 weekly dose.

Investigational products 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 to double-blind treatment at Visit 3. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign cartons containing double-blind investigational product to each patient. Site personnel will confirm that they have located the correct cartons by entering a confirmation number found on the carton label into the IWRS.

Randomization will be stratified by insulin regimen (basal insulin, premixed insulin, or basal/mealtime insulin) and HbA1c at Visit 2 ( $<8.5\%$ ,  $\geq 8.5\%$ ) to achieve between-group comparability.

### **7.2.1. Selection and Timing of Doses**

Details of the dosing strategy and administration timing for injectable investigational product, insulin, and concomitant OADs are provided in the following sections.

#### **7.2.1.1. Dulaglutide or Placebo Injections**

All patients will inject investigational product subcutaneously in the abdomen or thigh using the injection supplies provided; a caregiver may administer the injection in the patient's upper arm. A new SDP will be used for each injection.

Investigational product will be administered once weekly. It is recommended that patients inject the investigational product on the same day each week. If the injection is not given on the scheduled day, the missed dose should be given as soon as possible after the scheduled day if there are at least 3 days (72 hours) until the next injection. If fewer than 3 days remain before the next scheduled injection, the missed dose should be skipped and the next dose given at the regularly scheduled time and day.

#### **7.2.1.2. Insulin Treatment**

During the screening period, eligible patients on DPP-4 inhibitor, SU, or glinide will begin a 12-week washout of those medications; these patients may uptitrate their insulin dose for up to 4 weeks, followed by an 8-week stabilization ( $\pm 20\%$  adjustment) of insulin dose prior to Visit 3. For the patients who do not need to wash out, the insulin dose will remain unchanged during the screening and lead-in period.

After completion of the screening and lead-in period, the insulin dose at randomization will be fixed for the 16-week primary treatment period, except for patients who experience repeated or severe hypoglycemia (Section 7.4.1.2). During the 36-week extension treatment period in which all patients will be on dulaglutide and insulin therapy, the investigator will adjust the patient's insulin dose to achieve target blood glucose values (Table GBGF.7.2).

During the whole study period (16-week primary treatment period and 36-week extension treatment period), if repeated hypoglycemia (SMPG  $\leq 70$  mg/dL or symptomatic hypoglycemia) occurs, and it is considered to be related to the pharmacological therapy, the investigator can decrease the dose of insulin any time. If at least 1 episode meets the criteria for severe hypoglycemia (events requiring assistance to administer therapy) or is associated with SMPG  $< 54$  mg/dL recorded during the assessment period, the investigator should decrease the dose of insulin.

**Table GBGF.7.2. Target Blood Glucose Values**

<b>Insulin Therapy</b>	<b>Assess Blood Glucose Value</b>	<b>Target Blood Glucose</b>	<b>Adjust Insulin Dose</b>
Basal Insulin	Pre-Morning Meal	$>70$ and $\leq 110$ mg/dL	Basal Insulin
Mixed Insulin	Pre-Morning Meal	$>70$ and $\leq 110$ mg/dL	Mixed Insulin (Pre-Evening Meal)
	Pre-Evening Meal	$>70$ and $\leq 110$ mg/dL	Mixed Insulin (Pre-Morning Meal)
Mealtime Insulin	Pre-Midday Meal	$>70$ and $\leq 110$ mg/dL	Mealtime Insulin (Pre-Morning Meal)
	Pre-Evening Meal	$>70$ and $\leq 110$ mg/dL	Mealtime Insulin (Pre-Midday Meal)
	Pre-Bedtime	$>70$ and $\leq 140$ mg/dL	Mealtime Insulin (Pre-Evening Meal)

### 7.2.1.3. Concomitant Oral Antidiabetic Medications

The use of 1 or 2 of the OADs (biguanides, TZD,  $\alpha$ -GI, and sodium-glucose co-transporter 2 inhibitors [SGLT2i]) is permitted during the study, provided the dose is stable for at least 3 months prior to Visit 1. These drugs must be used based on label information. Patients should remain on their prestudy OAD regimen for the screening and lead-in, and treatment periods. Patients who are taking concomitant OADs and who develop a condition that is a contraindication will be considered ineligible and must be discontinued from the study before randomization. No change in dosage or administration of OADs is allowed during the 16-week primary treatment period. During the 36-week extension treatment period, the investigator is to consult with the Lilly Clinical Research Physician (CRP) or Clinical Research Scientist (CRS) if the dosage or administration of OADs is changed.

## 7.3. Blinding

This study includes a 16-week double-blind (dulaglutide versus placebo) primary treatment period, and a 36-week open-label extension treatment period.

To preserve the blinding of the study, the treatment assignments in the double-blind period will be blinded to patients and investigators until study completion.

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 actions resulting in an unblinding event are recorded and reported by the IWRS.

If an investigator, site personnel performing assessments, or patient is unblinded, the patient must be discontinued from the study. In cases where there are ethical reasons to have the patient remain in the study, the investigator must obtain specific approval from a Lilly CRP or CRS for the patient to 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 CRS prior to unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, Lilly must be notified immediately.

## **7.4. Dosage Modification**

The dosage of investigational product (dulaglutide or placebo) cannot be adjusted (see Section 7.2.1.1).

During the 16-week primary treatment period, the patient's insulin dose is to remain fixed. The insulin dose may be adjusted to maintain target glucose values during the 36-week extension treatment period (Section 7.2.1.2). For patients treated with 1 or 2 OADs prior to Visit 1, no change is allowed during the 16-week primary treatment period; during the 36-week extension treatment period, the investigator is to consult with the Lilly CRP or CRS if the dosage or administration of OADs is changed (7.2.1.3).

### **7.4.1. Special Treatment Considerations**

#### **7.4.1.1. Standards of Medical Care**

Maintenance of adequate glycemic control in study participants may be enhanced but should not be compromised due to trial participation. Investigators and other study team members are expected to treat patients according to the nationally established standard of care for diabetes management (Japan Diabetes Society, 2013), except where that treatment would be in conflict with the protocol-provided treatment requirements.

This section provides guidance on management of hypoglycemic events and episodes of severe, persistent hyperglycemia. For effective implementation of measures described here, it is important that patients, and their caregivers, if applicable, be well-educated about the signs and symptoms of hypoglycemia (for example, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders) and hyperglycemia (for example, severe thirst, dry mouth, frequent micturition, or dry skin). Patients should be instructed to contact the investigative site in the event of severe hypoglycemia or severe, persistent hyperglycemia (Section 7.4.1.3) between study visits.

#### **7.4.1.2. Management of Increased Hypoglycemia Risk**

If a hypoglycemic event occurs, the patient should record in the study diary the plasma glucose (PG) level measured during the episode and, prior to administration of treatment (if taken), associated symptoms, and treatment administered. Site personnel should educate and encourage

patients to measure and record PG values during the symptoms of hypoglycemia in their study diaries. Patients should be instructed to call the investigative site as soon as possible if they experience a hypoglycemic event that requires assistance to administer treatment.

Investigators should use the following definitions and criteria when diagnosing and 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) (ADA 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  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).
- **Asymptomatic hypoglycemia** is defined as an event not accompanied by typical symptoms of hypoglycemia but with a measured PG of  $\leq 70$  mg/dL ( $\leq 3.9$  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  $\leq 70$  mg/dL [ $\leq 3.9$  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.

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

#### 7.4.1.3. Management of Severe, Persistent Hyperglycemia

During the 16-week primary treatment period, if a patient experiences severe, persistent hyperglycemia, the patient must discontinue from study. Severe, persistent hyperglycemia is defined as follows; the patient's fasting SMPG concentrations are consistently above the fasting plasma glucose threshold (see below) for at least 2 weeks.

Week of Study Treatment	Weeks 0-4	Weeks 5-16
Average Fasting Plasma	$>15.0$ mmol/L	$>13.3$ mmol/L
Glucose for 2 weeks	$>270$ mg/dL	$>240$ mg/dL

### **7.5. Preparation/Handling/Storage/Accountability**

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 until use. Dry ice should not be used for cooling. Patients will be provided with cartons containing 4 dulaglutide or placebo SDPs, as required, at clinical visits per the Schedule of Activities (Section 2). They will receive insulated bags with cooling gel packs for use in transporting the SDP carton from the site to home. Investigational products will be labeled according to Japan's regulatory requirements.

Dulaglutide demonstration pens will be provided for subcutaneous injection training at the site; these pens do not have needles and do not contain investigational product.

Patients will also be provided with a commercially available PG meter and test strips to use during the study. Sufficient investigational product and glucose testing supplies will be dispensed, as needed, at each visit.

Study site staff must regularly assess whether the patient is correctly administering the assigned investigational product and storing the investigational product according to the provided instructions.

### **7.6. Treatment Compliance**

Patient compliance with study medication will be assessed at each visit by the investigator, based on the patient's adherence to the visit schedule and compliance with the study medication assessed by study diaries. Initially, patients considered as poorly compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and be reminded of the importance of complying with the protocol.

Overall treatment compliance is defined as taking at least 75% of the required doses of investigational product. Compliance is further defined as not missing more than 2 consecutive weekly injections of dulaglutide or >14 consecutive daily injections of insulin. Similarly, a patient will be considered significantly noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

### **7.7. Concomitant Therapy**

Patients are permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the investigational product.

Investigative site staff will inform patients that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study, except when initiated for treatment of medical emergencies. Any additional medication initiated during the course of the study (including over-the-counter [OTC] drugs, such as paracetamol or aspirin) must be documented, and the name of the drug, the dosage (OADs only), and the date(s) of administration must be recorded in the patient's diary and on the "Concomitant Medications" section of the eCRF.

Nonstudy medications taken by patients who are screened but not randomized will not be reported to Lilly unless the medication is associated with an SAE or AE that the investigator believes may have been caused by a study procedure.

If the following prohibited drugs are used by a patient, the patient must discontinue from the study.

### **7.7.1. Oral Antidiabetic Medications**

In the screening and lead-in period, DPP-4 inhibitors, SU, and glinides will be washed out, and are not permitted during the treatment period. Dulaglutide and DPP-4 inhibitors decrease blood glucose via the GLP-1 receptor; this combination has not been investigated for efficacy and safety in clinical studies. Sulfonylureas and glinides increase the risk of hypoglycemia in combination with dulaglutide (Emoto et al. 2015).

### **7.7.2. Nonstudy Glucagon-Like Peptide-1 Receptor Agonists**

Nonstudy GLP-1 receptor agonists (for example, liraglutide or exenatide) are not allowed at any time during the study.

### **7.7.3. Systemic Glucocorticoids**

Systemic glucocorticoid therapy for >14 consecutive days (with the exception of topical, intraocular, or intranasal preparations) within 4 weeks prior to Visit 1 is exclusionary, and is not allowed at any time during the study. Patients who require >14 days of therapy with these medications at any time during the treatment period must immediately be discontinued from the study.

### **7.7.4. Medications that Promote Weight Loss**

Medications that promote weight loss are not allowed at any time during the study.

## **7.8. Treatment after the End of the Study**

### **7.8.1. Continued Access**

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

## 8. Discontinuation Criteria

### 8.1. Discontinuation from Study Treatment

Investigational product may be interrupted temporarily or discontinued permanently. Those patients who stop the investigational product permanently will also be immediately discontinued from the study.

#### 8.1.1. *Permanent Discontinuation from Study Treatment and Study*

Patients will be permanently discontinued from investigational product and from the study 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 8.1.3);
- The patient misses more than 2 consecutive weekly injections of investigational product or more than 14 consecutive daily injections of insulin;
- The patient's fasting SMPG concentrations are consistently above the fasting plasma glucose threshold for at least 2 weeks (see Section 7.4.1.3)
- 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;
- The patient develops Exclusion Criterion [23] (eGFR <30 mg/min/1.73m<sup>2</sup>);
- 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 (for example, weight loss medication; see Section 7.7);
- The patient requires >14 days of therapy with systemic glucocorticoids;
- Enrollment in any other clinical trial involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study;
- Sponsor decision
  - Sponsor stops the study or stops the patient's participation in the study 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 requests to be withdrawn from the study

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 CRP or CRS:

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

Patients who discontinue investigational product and the study early will complete the early termination (ET) visit and safety follow-up visit as shown in the Schedule of Activities (Section 2), unless the patient withdraws consent. At the ET visit, the investigator will prescribe an appropriate antihyperglycemia regimen and SMPG monitoring plan to be followed after completion of the study.

### **8.1.2. Temporary Interruption of Study Treatment**

In certain situations after randomization, the investigator may need to temporarily discontinue (interrupt) investigational product (for example, due to an AE or a clinically significant laboratory value). If investigational product discontinuation is due to an AE, the event is to be documented and followed according to the procedures in Section 9.2 of this protocol.

### **8.1.3. Discontinuation of Inadvertently Enrolled Patients**

If the sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the sponsor CRP or CRS 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 sponsor CRP or CRS to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product.

## **8.2. Discontinuation from the Study**

Patients who discontinue investigational product must discontinue from the study (see Section [8.1.1](#)).

## **8.3. 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, with the study procedures and their timing (including tolerance limits for timing).

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

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. 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

#### 9.1.1. Primary Efficacy Assessments

The primary efficacy measure is change in HbA1c from baseline at 16 weeks.

#### 9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be evaluated at 16 and 52 weeks:

- Change from baseline in HbA1c (52 weeks)
- Percentage of patients achieving HbA1c targets of  $<7.0\%$  or  $\leq 6.5\%$ , as measured at the central laboratory
- Changes from baseline in FSG measured at the central laboratory
- Changes from baseline in PG from 7-point SMPG profiles
- Changes from baseline in body weight
- Changes from baseline in insulin dose

#### 9.1.3. Exploratory Health Outcome/Quality of Life Measures

The following health outcomes and dietary measures listed below will be assessed according to the Schedule of Activities (Section 2); these are considered exploratory objectives of the study. The questionnaires will be given to the patient by the investigator or site staff and self-completed by the patient during the visit. The investigator or site staff will be responsible for checking for missing responses before the patient leaves the site. The questionnaires should be completed before any other study procedures, if the patient is not adversely affected by the fasting condition, or completed after the patient has sufficiently recovered from the visit procedures.

- The Diabetes Therapy Related-Quality of Life (DTR-QOL) is a disease-specific, self-administered questionnaire to assess the influence of diabetes treatment on patient quality of life, regardless of treatment method. The DTR-QOL consists of “burden on social activities and daily activities” (13 items), “anxiety and dissatisfaction with treatment” (8 items), “hypoglycemia” (4 items), and “satisfaction with treatment” (4 items). Each

question is rated on a 7-point scale, with higher scores indicating higher quality of life (4 scores in “satisfaction with treatment” must be reversed).

- The Diabetes Treatment Satisfaction Questionnaire status (DTSQs) is a patient-reported assessment of treatment satisfaction (6 questions) and perceived frequency of severe hypoglycemia and hyperglycemia (2 questions). Each question is rated on a 7-point scale from 0 to 6, with higher scores indicating either greater treatment satisfaction or greater perceived frequency of hypoglycemic or hyperglycemic events.
- The Device Questionnaire is a self-administered questionnaire to assess the usability and preference of Ateos (the name of device for Trulicity in Japan) compared to the insulin device the patient has been using so far. The questionnaire consists of 2 sections. In the first section, patients will respond to 12 items about usability and preference using a 5-point scale (from “Strongly Agree” to “Agree” in insulin device, both devices are the same, and from “Strongly Agree” to “Agree” in Ateos). In the second section, patients are asked whether each procedure to prepare and inject was cumbersome or not for Ateos (3 procedures) and insulin device (6 items). The patients’ response is chosen from rarely, sometimes, or always cumbersome in each procedure. This questionnaire was developed by the study team based on the previous research (Bailey et al. 2011; Oyer et al. 2011).
- The Dietary Evaluation will explore the relationship between meal preference and efficacy of dulaglutide in Japanese patients with T2D. Patients are required to complete a meal record (picture and record sheet) on 2 days during the 2-week period immediately before: Visit 3 (Week 0), Visit 7 (Week 16), or Visit 12 (Week 52). The timing of the meal record should be on the same date as 7-point SMPG measurements (except for 52 weeks). The Lilly designated vendor will calculate the total fats, total carbohydrates, total protein, and caloric intake amount based on the meal record.

#### **9.1.4. Appropriateness of Assessments**

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 T2D.

## **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.

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

After the informed consent form (ICF) is signed, study site personnel will record via eCRF the occurrence and nature of each patient's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to study procedure, investigational product, and study device via eCRF.

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 cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions 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 eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

### **9.2.1. Serious Adverse Events**

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 (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- considered significant by the investigator for any other reason: important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious, based upon appropriate medical judgment.

Although all AEs occurring after signing the ICF are recorded in the eCRF, SAE reporting begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, it needs to be reported ONLY if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly 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.

Pregnancy (during 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.

Investigators are not obligated to actively seek AEs or SAEs in patients once they have discontinued 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.

Requirements for the reporting of severe hypoglycemia episodes, AEs of pancreatitis, and AEs of systemic hypersensitivity as SAEs are found in Section 9.2.2.

#### **9.2.1.1. Suspected Unexpected Serious Adverse Reactions**

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the package insert and that the investigator identifies as related to investigational product 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.

### **9.2.2. Adverse Events of Interest**

#### **9.2.2.1. Hypoglycemia**

Patients will collect information on episodes of hypoglycemia between Visit 2 and the last study visit (Visit 13 or ET visit). For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia in the study diary (see Section 7.4.1.2) according to the Schedule of Activities (Section 2). Site personnel will enter this information into the eCRF at each visit after Visit 1.

### 9.2.2.2. 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  $\geq 3 \times \text{ULN}$ ; 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 central laboratory (and locally, if needed). 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 supports 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, lipase, and trypsin at Visit 3 (Week 0), Visit 7 (Week 16), Visit 10 (Week 36), Visit 12 (Week 52), and the 4-week safety follow-up 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 amylase (pancreatic and/or total) are  $\geq 3 \times \text{ULN}$  at any time during the study. If this situation occurs at Visit 12 (Week 52), the patient will undergo this additional work-up, and the data will be collected in the clinical trial database.

All AEs of acute or chronic pancreatitis, as well as cases of confirmed lipase or amylase values  $\geq 3 \times \text{ULN}$ , 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 eCRF page by study site or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

#### **9.2.2.3. 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 treatment-emergent adverse events (TEAEs) and measurements of calcitonin according to the Schedule of Activities (Section 2) at Visit 1, Visit 3 (Week 0), Visit 7 (Week 16), Visit 10 (Week 36), and Visit 12 (Week 52). 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  $\geq 50\%$  of the mean of the baseline and screening values AND an absolute value  $\geq 20$  pg/mL and  $< 35$  pg/mL at Visit 12 (Week 52) will be asked to repeat the measurement within 1 month. If this repeat value is increasing ( $\geq 10\%$  increase), it will be recommended that the patient 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  $\geq 50\%$  of the mean of the baseline and screening values AND an absolute value  $\geq 35$  pg/mL at Visit 12 (Week 52) will be recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

#### **9.2.2.4. Cardiovascular Events**

Deaths and nonfatal cardiovascular (CV) AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. The nonfatal CV AEs to be adjudicated include: MI; hospitalization for unstable angina; hospitalization for heart failure; coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack (TIA).

#### **9.2.2.5. Allergic/Hypersensitivity Reactions**

All allergic or hypersensitivity 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 investigational product via a CRF created for this purpose. Investigational product should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to investigational product (Section 8.1.2). Investigational product may be restarted when/if it is safe to do so, in the opinion of the investigator. If investigational product is permanently discontinued, the patient will be discontinued from the trial (Section 8.1.1).

### **9.2.3. Complaint Handling**

Lilly collects product complaints on investigational products 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 investigational product so that the situation can be assessed.

## **9.3. Treatment of Overdose**

Investigational product overdose will be reported as an AE. In the event of overdose, refer to the Product Label.

## **9.4. Safety**

### **9.4.1. Electrocardiograms**

For each patient, a single 12-lead electrocardiogram (ECG) will be obtained according to the Schedule of Activities (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/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.

### **9.4.2. Vital Signs**

Sitting blood pressure (BP) and pulse rate (PR) will be measured according to the Schedule of Activities (Section 2), using the site's existing equipment. Vital sign measurements should be taken before obtaining an ECG tracing, at visits where required (see Schedule of Activities, Section 2), and before collection of blood samples for laboratory testing. For each parameter, 3 measurements will be taken 30 seconds 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 BP measurements. The arm used for the BP measurement should be supported at heart level. Each

measurement of sitting BP and PR is to be recorded in the eCRF. Any AE related to changes in BP and PR should be reported, per requirements provided in Section 9.2.

### **9.4.3. Laboratory Tests**

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of investigational product should be reported to Lilly or its designee as an AE via eCRF.

### **9.4.4. Body Weight and Body Mass Index**

Body weight will be measured at prespecified time points (see Schedule of Activities, Section 2). Each patient's weight should be measured according to a standardized protocol ([Appendix 6](#)). Body mass index will be computed from the patient's weight and height.

### **9.4.5. Safety Monitoring**

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods.

In addition, specific safety measures are included in the protocol to ensure appropriate monitoring of pancreatic, thyroid, and liver safety. Laboratory findings that trigger pancreatic and thyroid safety monitoring per Lilly standards are provided in Sections 9.2.2.2 and 9.2.2.3, respectively. If a study patient/subject experiences elevated ALT  $\geq 3X$  ULN, ALP  $\geq 2X$  ULN, or elevated TBL  $\geq 2X$  ULN, clinical and laboratory monitoring should be initiated by the investigator. Details for hepatic monitoring depend upon the severity and persistence of observed laboratory test abnormalities. To ensure patient safety and to comply with regulatory guidance, the investigator is to consult with the Lilly CRP or CRS regarding collection of specific recommended clinical information and follow-up laboratory tests (see [Appendix 4](#)).

## **9.5. Pharmacokinetics**

Not applicable.

## **9.6. Pharmacodynamics**

Not applicable.

## **9.7. Pharmacogenomics**

### **9.7.1. Whole Blood Sample for Pharmacogenetic Research**

A whole blood sample will be collected for pharmacogenetic analysis as specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to dulaglutide and to

investigate genetic variants thought to play a role in T2D and related complications. Assessment of variable response may include evaluation of AEs or differences in efficacy.

All samples will be coded with the patient number. These samples and any data generated can be linked back to the patient only by the investigator site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and/or ethical review boards (ERBs)/investigational review boards (IRBs) impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of dulaglutide.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of technology utilized genotyping data generated will be used only for the specific research scope described in this section.

### **9.8. Biomarkers**

Not applicable.

### **9.9. Health Economics**

Not applicable.

## 10. Statistical Considerations

### 10.1. Sample Size Determination

A total of approximately 160 patients (dulaglutide: 120 patients; placebo: 40 patients) will be randomized to have approximately 136 completers (dulaglutide : 102 patients; placebo: 34 patients) to show dulaglutide is superior to placebo with more than 99% power assuming a treatment difference of 1% in HbA1c reduction, standard deviation (SD) = 1.0%, and dropout rate of 15%. The screen failure rate is estimated as 20%. Approximately 200 patients will be screened.

### 10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
All Randomized Patients	All patients randomized to 1 of the 2 treatments
Full Analysis Set (FAS)	All patients who received at least 1 dose of study treatment and have at least 1 measurement of HbA1c after study treatment
Per Protocol	All patients in the FAS who meet the following criteria: <ul style="list-style-type: none"> <li>• Have no important protocol deviations that could impact the assessment of the primary objective (see SAP)</li> <li>• At least 75% compliant with investigational product</li> <li>• Complete the treatment phase (16 weeks [Visit 7]) for primary endpoint</li> <li>• Not missing more than 2 consecutive weekly injections of investigational product or more than 14 consecutive daily injections of insulin</li> </ul>
Safety Population	All patients who received at least 1 dose of study treatment

Abbreviations: HbA1c = hemoglobin A1c; SAP = Statistical Analysis Plan.

### 10.3. Statistical Analyses

#### 10.3.1. General Statistical 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 the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Statistical tests will only be conducted for the 16-week primary treatment period. Summary statistics will be provided for the observed value and change from baseline value based on mixed-model for repeated measures (MMRM) (note: statistical comparison will not be conducted) during the entire study period for each arm.

Unless otherwise specified, listings will include all randomized patients. Efficacy analyses will be conducted using the full analysis set (FAS) which is defined as all patients who received at

least 1 dose of study treatment and have at least 1 measurement of HbA1c after study treatment. The primary efficacy measure (HbA1c) will also be evaluated in the Per Protocol (PP) population. Also, safety analyses will be conducted on the safety population which is defined as all patients who received at least 1 dose of study treatment.

Unless otherwise specified, 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. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10.

The baseline will be Visit 3. For all variables, including HbA1c, if baseline data are missing, the last nonmissing measurement taken prior to this visit will be used for the baseline measurement. The measurement for the primary analysis is defined as the change from baseline in HbA1c to Week 16 (Visit 7).

The primary analysis model will be MMRM analysis using restricted maximum likelihood (REML) (Section 10.3.3.1). An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data. If this analysis 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. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Significance tests will be based on least squares (LS) means using Type III sum of squares.

The secondary analysis for the primary endpoint will be analysis of covariance (ANCOVA) (Section 10.3.3.2). Missing endpoints will be imputed with the last observation carried forward (LOCF), using only postbaseline data. If there are no data after the date of randomization, the endpoint will be considered missing.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-squares mean and standard errors derived from the model will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences (dulaglutide – placebo), along with the p-values for the treatment comparisons.

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. Multiplicity will not be adjusted for efficacy and health outcome endpoints in this study.

### **10.3.2. Treatment Group Comparability**

#### **10.3.2.1. Patient Disposition**

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

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.

#### **10.3.2.2. Patient Characteristics**

Patients' age, sex, weight, height, and other demographic characteristics will be recorded.

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 SDs. Means will be displayed. For categorical measures, summary statistics will include sample size, frequency, and percent.

#### **10.3.2.3. Concomitant Therapy**

Concomitant medications, including previous therapy for diabetes, will be summarized by treatment.

#### **10.3.2.4. Treatment Compliance**

Overall treatment compliance is defined as taking at least 75% of the required doses of investigational product. Compliance is further defined as not missing more than 2 consecutive weekly injections of dulaglutide or >14 consecutive daily injections of insulin. Similarly, a patient will be considered significantly non-compliant if he/she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication. Compliance will be summarized by treatment arm, by visit, and overall. Listings will also be produced.

### **10.3.3. Efficacy Analyses**

#### **10.3.3.1. Primary Analyses**

The primary analysis model will be an MMRM for HbA1c change from baseline to 16 weeks (Visit 7) using REML with treatment, insulin regimen (basal insulin, premixed insulin, or basal/mealtime insulin), visit, and treatment-by-visit as fixed effects, baseline HbA1c as a covariate, and patient as a random effect.

#### **10.3.3.2. Secondary Analyses**

The primary analysis model, MMRM, will be repeated using the PP population to check the sensitivity of the analysis. If the conclusion differs from that of the FAS, the data and analyses will be further investigated. The secondary analysis for the primary endpoint will be an ANCOVA for HbA1c change from baseline to the Week 16 endpoint with treatment, and insulin regimen (basal insulin, premixed insulin, or basal/mealtime insulin) as fixed effects and baseline HbA1c as a covariate, with missing endpoints imputed with LOCF using postbaseline data only.

All secondary efficacy measures that are continuous variables (changes from baseline) other than HbA1c will be analyzed using MMRM on the FAS. There will be no multiplicity adjustment for pairwise treatment comparisons. The MMRM and ANCOVA models will include treatment, baseline HbA1c ( $<8.5\%$ ,  $\geq 8.5\%$ ), and insulin regimen (basal insulin, premixed insulin, or basal/mealtime insulin) as fixed effects and a covariate of baseline value.

Repeated measures logistic regression with generalized linear mixed model will be used to analyze for percentage of patients achieving HbA1c targets of  $<7.0\%$  or  $\leq 6.5\%$ .

#### **10.3.4. Safety Analyses**

The safety analyses will include measurements of AEs, SAEs, hypoglycemic episodes, laboratory analytes, vital signs, and ECGs. The safety analyses will be conducted by treatment for 2 periods; primary treatment period and entire study period (including primary, extension, and follow-up periods). Unless otherwise specified, the Safety Population will be used for analyses of safety measurements. P-values provided from all safety analyses will be used for guidance purposes only.

##### **10.3.4.1. Study Drug Exposure**

Exposure to each study treatment will be calculated for each patient and summarized by treatment group.

##### **10.3.4.2. 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 (SOC). Selected notable AEs of interest may be reported using high-level terms. All AEs and TEAEs, defined as events that are newly reported after the first dose of investigational product or reported to worsen in severity from baseline, will be listed by patient and visit. Information on treatment, actual term, preferred term, severity, seriousness, and relationship to investigational product will also be reported.

Summary statistics will be provided for 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 tests will be used to compare the treatment groups.

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 Statistical Analysis Plan (SAP).

Listings of patients experiencing allergic and hypersensitivity reactions, as well as those discontinuing the study due to AEs, will be produced.

### **10.3.4.3. Hypoglycemic Episodes**

Section 7.4.1.2 contains definitions of categories of hypoglycemia. A listing of individual hypoglycemic episodes by patient will be presented. Summary reports will include both incidence and rates of hypoglycemia for the Safety Population. Hypoglycemia will be analyzed as “documented symptomatic,” “asymptomatic,” “probable,” “severe,” or “nocturnal” and for all events combined, “total hypoglycemia.” Other categories, including the categories above defined with differing PG thresholds, may also be included in these analyses when deemed appropriate.

Hypoglycemia rates will be summarized for periods of 1 year, 30 days, and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical method (details will be described in the SAP). For each of the other categories of hypoglycemia, the number of hypoglycemia events during a specific period (rate) after randomization (for example, 0-16 weeks of treatment period) will be analyzed by using a negative binomial regression model. The model will include treatment and the baseline hypoglycemia rate (measured during lead-in) as a covariate. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days (or 30 days) will be included in the model to estimate the rate of hypoglycemia per year (or per 30 days). The proportion of subjects with at least 1 hypoglycemic event in each category (incidence) during a specific period after randomization will be analyzed using a logistic regression model including treatment and baseline hypoglycemia rate value in the model.

### **10.3.4.4. Severe, Persistent Hyperglycemia**

Time to study discontinuation due to severe, persistent hyperglycemia will be analyzed. The incidence and percentage of patients discontinuing the study due to severe, persistent hyperglycemia will be analyzed using Fisher’s exact test. A listing of patients who discontinue the study due to severe, persistent hyperglycemia will be provided.

### **10.3.4.5. Special Safety Topics**

#### **10.3.4.5.1. Pancreas Safety**

Listings and summaries of adjudicated pancreatic events will be provided.

#### **10.3.4.5.2. Cardiovascular Safety**

Listings and summaries and adjudicated CV events will be provided. Pulse rate and systolic and diastolic BP from vital signs will also be summarized.

#### **10.3.4.5.3. Thyroid Safety**

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

#### **10.3.4.5.4. Allergic/Hypersensitivity Reactions**

Summaries and listings of allergic and other hypersensitivity AEs will be provided.

### **10.3.4.6. Laboratory Analyses**

Laboratory measurements will be listed by patient and visit. An additional listing will be presented for laboratory measurements that are outside the normal range.

Laboratory measurements and vital signs will also be summarized.

For subjective (qualitative) laboratory analytes, counts and percentages of patients with normal and abnormal values will be analyzed using chi-square tests.

### **10.3.5. Health Outcomes Variables**

- **DTR-QOL (Diabetes Therapy Related-Quality of Life)**  
Summary statistics for each dimension and total score by visit and change from baseline values will be provided.
- **DTSQs (Diabetes Treatment Satisfaction Questionnaire status)**  
Summary statistics for each dimension and total score by visit and change from baseline values will be provided.
- **Device Questionnaire**  
In the first section, frequency and percentage of sum of “Strongly Agree” and “Agree” for Ateos, sum of “Strongly Agree” and “Agree” for Insulin Device, and “Both Devices are the same” will be presented. Also, the overall preference for Ateos versus Insulin Device, which was evaluated by a percentage of sum of “Strongly Agree” and “Agree” for Ateos will be presented. This was tested by the use of a one-sample binomial test using an exact method at each visit. The null hypothesis was that the preference for Ateos was equal to 50%, against the hypothesis that it was different from 50%.  
  
In the second section, the frequency and percentage of each category (ie, “Rarely,” “Sometimes,” and “Always”) will be presented by device at each scheduled visit.

### **10.3.6. Other Exploratory Variables**

- **Dietary Evaluation**  
Summary statistics for total fats, total carbohydrates, total protein, and caloric intake amount (actual) by visit and change from baseline values will be provided.

### **10.3.7. Subgroup Analyses**

Population subgroups of interest will be analyzed for the variable of HbA1c, body weight, and hypoglycemia rate. Other variables may also be evaluated.

The following are candidate subgroups that might be analyzed. This list is not necessarily all-inclusive:

- Baseline HbA1c (<8.5%, ≥8.5%)
- Insulin regimen (basal insulin, premixed insulin, or basal/mealtime insulin).

For the subgroup analysis of insulin regimen, an analysis will be performed using an MMRM model that includes the same effects given for primary or secondary efficacy measures plus subgroup, subgroup-by-treatment interaction, subgroup-by-visit interaction, and subgroup-by-treatment-by-visit interaction. For the subgroup analysis of baseline HbA1c strata (<8.5%, ≥8.5%), baseline HbA1c will not be included as a covariate. The interaction effect will be evaluated using a significance level of 0.10, unadjusted.

**10.3.8. Interim Analyses**

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly CRP or CRS, or designee, will be consulted to determine whether it is necessary to amend the protocol.

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## 12. Appendices

## Appendix 1. Abbreviations and Definitions

Term	Definition
<b>AE</b>	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.
<b>α-GI</b>	alpha-glucosidase inhibitor
<b>ALP</b>	alkaline phosphatase
<b>ALT</b>	alanine aminotransferase
<b>ANCOVA</b>	analysis of covariance
<b>AST</b>	aspartate aminotransferase
<b>blinding/masking</b>	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.
<b>BP</b>	blood pressure
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>complaint</b>	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.
<b>CI</b>	confidence interval
<b>CRF/eCRF</b>	case report form/electronic case report form
<b>CRP</b>	clinical research physician: 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.
<b>CRS</b>	clinical research scientist
<b>CSR</b>	clinical study report
<b>CT</b>	computed tomography
<b>CV</b>	cardiovascular
<b>DPP-4</b>	dipeptidyl peptidase-4

<b>DTR-QOL</b>	Diabetes Therapy Related-Quality of Life
<b>DTSQs</b>	Diabetes Treatment Satisfaction Questionnaire status
<b>ECG</b>	electrocardiogram
<b>eGFR</b>	estimated glomerular filtration rate
<b>enroll</b>	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.
<b>enter</b>	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>ERB</b>	ethical review board
<b>ET</b>	early termination
<b>FAS</b>	full analysis set
<b>FSG</b>	fasting serum glucose
<b>GCP</b>	good clinical practice
<b>GLP-1</b>	glucagon-like peptide-1
<b>HbA1c</b>	hemoglobin A1c
<b>ICF</b>	informed consent form
<b>ICH</b>	International Conference on Harmonisation
<b>investigational product</b>	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.
<b>IWRS</b>	interactive web-response system
<b>LOCF</b>	last observation carried forward
<b>LS mean</b>	least-squares mean
<b>MEN</b>	multiple endocrine neoplasia
<b>MI</b>	myocardial infarction
<b>MMRM</b>	mixed-model repeated measures
<b>MRI</b>	magnetic resonance imaging
<b>OAD</b>	oral antidiabetic

<b>PG</b>	plasma glucose
<b>PP</b>	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.
<b>PR</b>	pulse rate
<b>QTc</b>	corrected QT interval
<b>REML</b>	restricted maximum likelihood
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>screen</b>	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.
<b>SD</b>	standard deviation
<b>SDP</b>	single-dose pen
<b>SGLT2i</b>	sodium-glucose co-transporter 2 inhibitor
<b>SMPG</b>	self-monitored plasma glucose
<b>SmPC</b>	summary of product characteristics
<b>SU</b>	sulfonylurea
<b>SUSARs</b>	suspected unexpected serious adverse reactions
<b>T2D</b>	type 2 diabetes
<b>TBL</b>	total bilirubin level
<b>TEAE</b>	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, which and does not necessarily have to have a causal relationship with this treatment.
<b>T/V</b>	telephone visit
<b>TZD</b>	thiazolidinedione
<b>ULN</b>	upper limit of normal
<b>USPI</b>	United States prescribing information
<b>WHO</b>	World Health Organization

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## Appendix 2. Clinical Laboratory Tests

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### Clinical Laboratory Tests (to be collected centrally)<sup>a</sup>

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#### Hematology

Hemoglobin  
 Hematocrit  
 Erythrocyte count (RBC)  
 Mean cell volume (MCV)  
 Mean cell hemoglobin concentration (MCHC)  
 Leukocytes (WBC)  
 Neutrophils  
 Lymphocytes  
 Monocytes  
 Eosinophils  
 Basophils  
 Platelets

#### Urinalysis

Protein  
 Glucose  
 Ketones  
 Blood  
 Urine leukocyte esterase  
 Microscopic<sup>b</sup>

#### Albumin/creatinine ratio (urine)<sup>c</sup>

#### Lipid panel

Total cholesterol  
 High-density lipoprotein-cholesterol (HDL-C)  
 Low-density lipoprotein-cholesterol (LDL-C)<sup>d</sup>  
 Triglycerides

#### Stored Samples

Pharmacogenomics sample

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Abbreviations: CK-MB = creatine kinase-MB; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; RBC = red blood cells; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cells.

<sup>a</sup> All tests will be performed by the Lilly-designated central laboratory.

<sup>b</sup> Microscopic evaluation to be performed if any of the listed analytes are positive.

<sup>c</sup> Urinary albumin and creatinine are measured; ratio is calculated.

<sup>d</sup> Direct LDL-C is measured.

<sup>e</sup> Japanese eGFR equation defined by the Japanese Society of Nephrology is used to estimate glomerular filtration rate.

<sup>f</sup> CK-MB is to be assayed if creatine kinase result >1000 IU/L.

#### Clinical Chemistry

Sodium  
 Potassium  
 Chloride  
 Bicarbonate  
 Total bilirubin  
 Direct bilirubin  
 Alkaline phosphatase (ALP)  
 Alanine aminotransferase (ALT/SGPT)  
 Aspartate aminotransferase (AST/SGOT)  
 Gamma-glutamyl transferase (GGT)  
 Blood urea nitrogen (BUN)  
 Creatinine<sup>e</sup>  
 Creatine kinase (creatine phosphokinase)<sup>f</sup>  
 Uric acid  
 Calcium  
 Albumin

#### Pregnancy test (serum)<sup>g</sup>

#### HbA1c

#### Glucose, fasting

#### Calcitonin

#### Pancreas (exocrine)

Total amylase  
 Lipase  
 Trypsin

- g A serum pregnancy test will be performed at Visit 1 and Visit 3 for women of childbearing potential only and will be analyzed at a central laboratory. Pregnancy tests may be repeated at any time during the study and analyzed locally at the investigator's discretion.

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**Appendix 3. Study Governance Considerations**

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## **Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process**

### ***Appendix 3.1.1. Informed Consent***

The investigator is responsible for ensuring:

- that the patient understands the potential risks and benefits of participating in the study
- that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (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 trial.

### ***Appendix 3.1.2. Ethical Review***

The investigator must give assurance that the ethical review board (ERB) was properly constituted and convened as required by International Conference on 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, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (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

### ***Appendix 3.1.3. Regulatory Considerations***

This study will be conducted in accordance with:

- 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
- applicable ICH GCP Guidelines
- applicable laws and regulations

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

**Appendix 3.1.4. Investigator Information**

Physicians with a specialty in diabetes/endocrinology, internal medicine, or family medicine will participate as investigators in this clinical trial.

**Appendix 3.1.5. 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, each principal investigator will sign the protocol signature page and send a copy of the signed page to a Lilly representative.

**Appendix 3.1.6. Final Report Signature**

The Clinical Study Report (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.

The sponsor'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.

**Appendix 3.2. 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
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (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.

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 ethical review boards (ERBs) with direct access to original source documents.

#### ***Appendix 3.2.1. Data Capture System***

An electronic data capture system will be used in this study. The site maintains a separate source for the data entered by the site into the sponsor-provided electronic data capture system.

Case report form data will be encoded and stored in a clinical trial database. 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 data warehouse.

Any data for which paper documentation provided by the patient will serve as the source document will be identified and documented by each site in that site's study file. Paper documentation provided by the patient may include, for example, a paper diary to collect patient-reported outcome (PRO) measures (for example, health outcome measures), dosing information, or an event diary.

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

### **Appendix 3.3. Study and Site Closure**

#### ***Appendix 3.3.1. Discontinuation of Study Sites***

Study site participation may be discontinued if Lilly, 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.

#### ***Appendix 3.3.2. Discontinuation of the Study***

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

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## Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

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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, CRP.

### Hepatic Monitoring Tests

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#### Hepatic Hematology<sup>a</sup>

Hemoglobin  
 Hematocrit  
 RBC  
 WBC  
 Neutrophils, segmented  
 Lymphocytes  
 Monocytes  
 Eosinophils  
 Basophils  
 Platelets

#### Hepatic Chemistry<sup>a</sup>

Total bilirubin  
 Direct bilirubin  
 Alkaline phosphatase  
 ALT  
 AST  
 GGT  
 CPK

#### Haptoglobin<sup>a</sup>

#### Hepatic Coagulation<sup>a</sup>

Prothrombin Time  
 Prothrombin Time, INR

#### Hepatic Serologies<sup>a,b</sup>

Hepatitis A antibody, total  
 Hepatitis A antibody, IgM  
 Hepatitis B surface antigen  
 Hepatitis B surface antibody  
 Hepatitis B Core antibody  
 Hepatitis C antibody  
 Hepatitis E antibody, IgG  
 Hepatitis E antibody, IgM

#### Anti-nuclear antibody<sup>a</sup>

#### Alkaline Phosphatase Isoenzymes<sup>a</sup>

#### Anti-smooth muscle antibody (or anti-actin antibody)<sup>a</sup>

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

<sup>a</sup> Assayed by Lilly-designated laboratory.

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

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## **Appendix 5. Protocol GBGF World Health Organization Classification of Diabetes and Diagnostic Criteria**

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**Type 1 Diabetes Mellitus (T1DM):** Type 1 diabetes mellitus is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death.

**Type 2 Diabetes Mellitus (T2DM):** Type 2 diabetes mellitus, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in type 2 diabetes but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with type 2 diabetes later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

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## Appendix 6. Protocol GBGF World Health Organization Standardized Protocols for the Measurement of Height and Weight

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The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2008).

### Measuring Height

- Step 1 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).
- Step 2 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.
- Step 3 Ask the patient to look straight ahead without tilting their head up.
- Step 4 Ask the patient to breathe in and stand tall. If using a stadiometer or fixed measuring device, 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

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.

- Step 1 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).
- Step 2 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).
- Step 3 Ask the patient to step onto the scale with one foot on each side of the scale.
- Step 4 Ask the patient to stand still with their arms by their sides and then record their weight in kilograms (kg).

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**Appendix 7. Protocol H9X-JE-GBGF(b) Amendment  
Summary  
A Phase 4 Study of Efficacy and Safety of Dulaglutide  
When Added to Insulin Treatment With or Without Oral  
Antidiabetic Medication in Patients with Type 2 Diabetes**

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## **Overview**

Protocol H9X-JE-GBGF, A Phase 4 Study of Efficacy and Safety of Dulaglutide When Added to Insulin Treatment With or Without Oral Antidiabetic Medication in Patients with Type 2 Diabetes, has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

Lilly has made a change as follows:

- Section 6.2: Changed eGFR exclusion threshold for metformin users to comply with metformin package insert.

## Revised Protocol Sections

<b>Note:</b> Deletions have been identified by <del>strike</del> throughs. Additions have been identified by the use of <u>underscore</u> .
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### 6.2. Exclusion Criteria

[23] have an estimated glomerular filtration rate (eGFR)  $<30$  mL/min/1.73 m<sup>2</sup>, calculated by the Japanese Society of Nephrology equation, as determined by the central laboratory; for participants on metformin, have moderate renal disease or renal dysfunction (for example, eGFR  $<45$  ~~60~~ mL/min/1.73 m<sup>2</sup>) at Visit 1;