Protocol H9X-MC-GBGO(a)

A Randomized, Double-Blind Trial Comparing the Effect of the Addition of Dulaglutide 1.5 mg versus the Addition of Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Patients with Type 2 Diabetes (AWARD-CHN3: Assessment of Weekly AdministRation of LY2189265 in Diabetes-CHINA3)

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(AWARD-CHN3: Assessment of Weekly AdministRation of LY2189265 in Diabetes – CHINA3)

Dulaglutide (LY2189265)

Eli Lilly and Company
Indianapolis, Indiana USA 46285

Protocol Electronically Signed and Approved by Lilly on 06 March 2020.
Amendment (a) Electronically Signed and Approved by Lilly on date provided below.

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1. Synopsis

Title of Study:
A Randomized, Double-Blind Trial Comparing the Effect of the Addition of Dulaglutide 1.5 mg versus the Addition of Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Patients with Type 2 Diabetes (T2D).

Rationale:
Glucagon-like peptide-1 (GLP-1) receptor agonists and insulin are often recommended to be used concomitantly in diabetes treatment guidelines, and several studies including AWARD-9 (Study H9X-MC-GBDI) have provided efficacy and safety data of the addition of a GLP-1 receptor agonist to basal insulin (Pozzili et al. 2017).

The purpose of study H9X-MC-GBGO (GBGO) is to evaluate the effects of the addition of once weekly (QW) dulaglutide or the addition of placebo QW to titrated insulin glargine, with metformin and/or acarbose, on glycemic control and safety in adult Chinese patients with T2D.

Objectives:

Objectives	Endpoints
Primary • To show the superiority of the addition of dulaglutide 1.5 mg QW compared to the addition of placebo QW to titrated basal insulin glargine, with metformin and/or acarbose, on change from baseline in hemoglobin A1c (HbA1c) after 28 weeks of treatment in patients with T2D.	• The change in HbA1c from baseline.
Key Secondary (controlled for Type I error) • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for other parameters of glucose control and body weight change after 28 weeks of treatment in patients with T2D.	• Proportion of patients achieving HbA1c target of <7.0% • Change from baseline in body weight • Change from baseline in FSG (central lab)
Additonal Secondary • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for the following parameters after 28 weeks of treatment in patients with T2D.	• Proportion of patients achieving HbA1c target of ≤6.5%; • Proportion of patients achieving HbA1c target of <7.0% and with no weight gain (<0.1 kg) at 28 weeks and without documented symptomatic hypoglycemia (BG <3.0 mmol/L) during the maintenance period (Weeks 12-28); • Proportion of patients achieving HbA1c target of <7.0% at 28 weeks and without documented symptomatic hypoglycemia (BG

	<3.0 mmol/L) during the maintenance period (Weeks 12-28); • Proportion of patients achieving HbA1c target of <7.0% and without weight gain (<0.1 kg); • Changes from baseline in BG from daily self-monitored blood glucose (SMBG) profiles; • Changes from baseline in daily mean insulin glargine doses
Safety: • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for selected safety parameters through 32 weeks in patients with T2D (unless noted otherwise).	• Incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs) and discontinuation of study drug due to adverse events (AEs); • Incidence of adverse event of special interest (AESI) o Occurrence of hypoglycemic episodes; o Incidence of initiation of rescue therapy due to severe, persistent hyperglycemia; o Incidence of adjudicated and confirmed pancreatitis; o Incidence of thyroid neoplasm o Incidence of deaths and nonfatal cardiovascular (CV) events; o Incidence of allergic and hypersensitivity AEs • Change from baseline in electrocardiograms, laboratory and vital sign measurements.

Abbreviations: BG = blood glucose; CV = Cardiovascular; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; SMBG = self-monitored plasma glucose; T2D = type 2 diabetes.

Summary of Study Design:

Study GBGO is a Phase 3b, multicenter, randomized, double-blind, parallel-arm trial that investigates the effect of the addition of dulaglutide 1.5 mg QW or the addition of placebo QW to titrated insulin glargine, with metformin and/or acarbose, on change in HbA1c from baseline in Chinese patients with T2D over a 28-week treatment period.

Treatment Arms and Duration:

Study GBGO will consist of 3 periods: an approximately 3-week screening/lead-in period, followed by a 28 week treatment period, and a 4-week safety follow-up period. Patients will be

randomized in a 1:1 ratio to (1) dulaglutide 1.5 mg QW as add-on to insulin glargine, or (2) placebo QW as add-on to insulin glargine, with metformin and /or acarbose. Patients will be stratified at randomization based on HbA1c (<8.5%, ≥8.5%) and oral antihyperglycemic medications (OAMs) usage (metformin alone, acarbose alone, metformin and acarbose).

Number of Planned Patients:

- Entered: 483
- Enrolled/Randomized: 290
- Completed: 246

Statistical Analysis:

Determination of Sample Size:

A total of approximately 290 patients (145 per group) will be randomized to have approximately 246 completers (123 per group) to show dulaglutide as add-on to titrated insulin glargine is superior to placebo as add-on to titrated insulin glargine with 90% power assuming a treatment difference of 0.5% in HbA1c reduction, standard deviation (SD) = 1.2%, and dropout rate of 15%. The screen failure rate (including lead in failure) is estimated as 40%. Approximately 483 patients will be screened.

Efficacy Analyses:

The primary analysis model for HbA1c will be mixed-model for repeated measures (MMRM) analysis using restricted maximum likelihood (REML) with treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), visit, and treatment-by-visit as fixed effects, baseline as a covariate, and patient as random effect. An unstructured covariance structure will be used to model the within-patient variability and implicitly adjust for missing data.

The primary evaluation of change from baseline for body weight will be performed using MMRM on the intention to treat (ITT) population. The analyses of other secondary efficacy measures that are continuous variables will be performed using MMRM on the ITT population. For percent of patients achieving the target HbA1c of <7.0% and ≤6.5%, repeated measures logistic regression with generalized linear mixed model will be used. The model includes treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), visit, and treatment-by-visit as fixed effects and baseline HbA1c as a covariate.

Safety Analyses:

Listings and summaries of safety data will be generated. 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 Fisher's exact tests will be used to compare the treatment groups.

For continuous laboratory analytes, the change from baseline to endpoint will be analyzed using an analysis of variance (ANOVA) on the rank-transformed data, with treatment as a fixed effect. Last observation carried forward will be used to impute missing postbaseline values. For

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

Treatment differences in incidence of hypoglycemic episodes will be assessed by a Fisher's exact test. Treatment differences in rates of hypoglycemic episodes will be assessed by the generalized linear mixed-effects (GLM) model for negative binomial distribution. The model will include treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), visit, treatment-by-visit interaction, and baseline hypoglycemia rate.

Time to initiation of rescue therapy due to severe, persistent hyperglycemia will be analyzed using the semiparametric proportional hazard Cox model with treatment, and OAM usage (metformin alone, acarbose alone, metformin and acarbose) as fixed effects and baseline HbA1c as a fixed covariate. The proportions of patients initiating rescue therapy due to severe, persistent hyperglycemia will be analyzed using Fisher's exact tests.

2. Schedule of Activities

Table GBGO.1. Schedule of Activities

	Screening/Lead In		Treatment Period																Safety Follow-Up
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**28**		**32**
Allowable Deviation (±Days)	**±7**	**±3**	**0**	**±3**	**±3**	**±4**	**±2**	**±4**	**±2**	**±4**	**±2**	**±7**	**±2**	**±7**	**±2**	**±7**	**±7**		**±7**
Fasting visit[c]			X									X					X	X	
Telephone visit							X		X		X		X		X				
Informed consent	X																		
Randomization			X																
Clinical Assessments																			
Demography[d]	X																		
Medical history	X																		
Previous diabetes therapy	X																		
Physical examination	X																X	X	
Height	X																		
Weight	X		X			X				X		X		X		X	X	X	X
Vital signs (BP and PR[e])	X	X	X	X	X	X		X		X		X		X		X	X	X	X
Electrocardiogram[f]	X																X	X	
Preexisting conditions and adverse events	X	X	X	X	X	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X[g]	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X[h]	X	X	X	X
Review/record hypoglycemic events		-	X	X	X	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X[i]	X	X	X	X
Patient summary																	X	X	X
Patient Education																			
Dietary and exercise counseling and BG management training[j]		X	X																
BG meter and SMBG training		X	X																
SUP training and SoloStar pen training[k]		X	X																
Dispense BG meter/supplies[l]		X	X	X	X	X		X		X		X		X		X			
Dispense study diary, instruct in use		X	X	X	X	X		X		X		X		X		X	X[m]	X	

	Screening/Lead In		Treatment Period																Safety Follow-Up
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**28**		**32**
Allowable Deviation (±Days)	**±7**	**±3**	**0**	**±3**	**±3**	**±4**	**±2**	**±4**	**±2**	**±4**	**±2**	**±7**	**±2**	**±7**	**±2**	**±7**	**±7**		**±7**
Fasting visit[c]			**X**									**X**					**X**	**X**	
Telephone visit							**X**		**X**		**X**		**X**		**X**				
Review and transfer to eCRF/return study diary			X	X	X	X		X		X		X		X		X	X	X	X
Remind patients about 7 point SMBG[n]		X								X						X			
Review/record 7-point SMBG values			X									X					X	X[o]	
Review fasting/4-point BG from SMBG[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review study drug usage			X	X	X	X		X		X		X		X		X	X	X	
Review insulin dose and adjustment per TTT algorithm[q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug and injection supplies			X			X				X				X					
Observe patient inject dulaglutide QW			X																
Patient returns study drug and injection supplies				X	X	X		X		X		X		X		X	X	X	
Assess dulaglutide compliance						X				X		X		X		X	X	X	
Assess compliance with weekly insulin dose adjustment per TTT algorithm				X	X	X		X[r]		X[r]		X[r]		X		X	X	X	
Laboratory tests																			
Serum pregnancy test[s]	X																		
Urine pregnancy test[t]			X														X	X	X
Follicle-stimulating hormone test[u]	X																		
Chemistry panel	X																X[v]	X[v]	
Serum creatinine, eGFR (CKD-EPI)[w]	X		X														X	X	
Urinary albumin/creatinine			X														X	X	
Calcitonin	X		X														X	X	
Hematology	X																X	X	

	Screening/Lead In		Treatment Period																Safety Follow-Up
Visit	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16	17	ET[b]	801
Week of Treatment	-3	-2	0	1	2	4	5	6	7	8	10	12	15	18	21	24	28		32
Allowable Deviation (±Days)	±7	±3	0	±3	±3	±4	±2	±4	±2	±4	±2	±7	±2	±7	±2	±7	±7		±7
Fasting visit[c]			X									X					X	X	
Telephone visit							X		X		X		X		X				
Fasting serum glucose			X									X					X	X	
HbA1c	X		X									X					X	X	
Lipid panel			X														X	X	
Pancreatic enzymes	X		X														X	X	X
Health Outcomes																			
EQ-5D-5L			X									X					X	X	
IW-SP			X									X					X	X	
MDDAB Module 1: SUP Ease of Use								X									X	X	
MDDAB Module 2: SUP Device Features								X									X	X	
MDDAB Module 3a: SUP Experience (interim evaluation)								X											
MDDAB Module 3b: SUP Experience (end of study evaluation)																	X	X	
MDDAB Module 4: Glargine Delivery Device Experience																	X	X	

Abbreviations: 801 = safety follow-up visit; BG = blood glucose; BP = blood pressure; CV = cardiovascular; D = days; eCRF = electronic case report form; EQ-5D-5L = EuroQol 5-dimension questionnaire; ET = early termination; FSH = follicle-stimulating hormone; GAD = glutamic acid decarboxylase; HbA1c = hemoglobin A1c; ICA = islet cell antibodies; IWRS = interactive web response system; IW-SP = Impact of Weight on Self-Perception Scale; MDDAB = Medication Delivery Device Assessment Battery; PR = pulse rate; Rand = randomization; SMBG = Self-Monitored Plasma Glucose; SUP = Single-Use Pen; TTT = treat-to-target.

a. IWRS for randomization should be accessed after all baseline assessments have been completed.

b. Patients who are unable or unwilling to continue in the study for any reason will perform an ET visit. If the patient is discontinuing during an unscheduled visit, that visit should be performed as the ET visit. If the patient is discontinuing during a scheduled visit, that visit should be performed as an ET visit. 801 (Safety Follow-Up Visit) should be performed 4 weeks after the ET visit as the final study visit.

c. Before visits at which laboratory tests will be conducted, patients should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity, and before taking their study drug, metformin and/or

acarbose, and insulin glargine, if administered before breakfast.

d. Demographics include patient birth year, sex.

e. Site should record all results on the eCRF

f. Single tracing, performed locally (see Section 9.4.1).

g. Preexisting conditions and adverse events will be reviewed during telephone contacts but recorded on the eCRF at subsequent office visits.

h. Concomitant medications will be reviewed during telephone contacts but recorded on the eCRF at subsequent office visits.

i. Hypoglycemic events will be reviewed during telephone contacts but recorded on the eCRF at subsequent office visits.

j. Patient training should occur at Visit 2. Additional training can also be performed at Visit 3, when needed. Patient training will include training on TTT insulin dose adjustment algorithm.

k. Retraining and review of device training to be performed as needed.

l. Dispense only as needed.

m Safety data to be captured after discontinuation of study drug during safety follow-up period.

n. Patients will be asked to perform two 7-point SMBG profiles on two nonconsecutive days, in the 2-week period prior to Visit 3, as well as prior to Visit 12 and Visit 17. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime. If 7-point SMBG is not performed, then data from the most recent nonconsecutive 4-point SMBG (3 before each meal and one at bedtime) profiles can be used. If more than 2 SMBG profiles are available, the 2 most recent profiles on nonconsecutive days should be used. In the weeks that the 7-point profiles are performed, the 4-point SMBG profiles will not be needed.

o. Review/record 7-point SMBG profile(s), only if applicable, based on previous study visit.

p. Patients will be encouraged to collect a daily fasting BG and a weekly 4-point SMBG. Missing a fasting BG measurement will not be considered a protocol deviation.

q. Insulin dose assessment and dose adjustment should be done at least 3 days prior to Visit 3 to ensure the collection of at least 3 days of FBG for patient eligibility assessment prior to randomization. The insulin glargine dose should be reduced by 20% at Visit 3 if baseline HbA1c ≤8.0%. Further dose adjustments are to start at Visit 6 per the TTT algorithm, and before that only in certain situations (for details see Section 5.1). The TTT algorithm should be used for dose adjustments until the last visit on randomized treatment (Visit 17 or ET Visit). After discontinuation of study drug, the investigator will decide on the most appropriate therapeutic regimen, and if applicable, the most appropriate insulin dose adjustment schedule. Refer to Protocol Section 7.2.2.2 for complete instructions on insulin dose adjustment.

r. Assessment of the patient's compliance to the TTT algorithm will be collected in the eCRF at Visits 8, 10, and 12 for the period since the previous visit.

s. A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.

t. A urine pregnancy test will be performed at Visit 3, with the result available prior to randomization and first injection of study drug, and at additional visits as shown in the schedule, for women of childbearing potential only. Additional pregnancy tests will be performed at the investigator's discretion or if required per local regulations and/or institutional guidelines during the study.

u. Follicle-stimulating hormone test will be collected at Visit 1 for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL). After Visit 1, additional tests may be performed at the investigator's discretion during the study.

v. For those visits when fasting glucose is required, glucose will not be included in the chemistry panel.

w. Chronic Kidney Disease-Epidemiology (CKD-EPI) equation will be used to estimate the glomerular filtration rate.

3. Introduction

3.1. Study Rationale

Initial pharmacological therapy for T2D is based on stepwise addition of oral antihyperglycemic medications (OAMs) when patients become persistently hyperglycemic despite treatment with lifestyle measures (Inzucchi et al.2012). With further progression of the disease, many patients eventually require injectable therapies, a GLP-1 receptor agonist, or insulin to maintain adequate glycemic control. Basal insulin, such as insulin glargine, is a common choice when initiating injectable therapy, but there are drawbacks to treating patients with T2D with a single injection of basal insulin. For instance, a significant proportion of patients is not able to achieve glycemic targets (Rosenstock et al. 2008; Nichols et al.2012), and hypoglycemia and weight gain are common side effects of therapy with insulin (ADA 2019). To address these issues in basal insulin-treated patients with T2D, addition of a GLP-1 receptor agonist to insulin glargine has been investigated in randomized, clinical trials (Buse et al. 2011; Pozzili et al. 2017). Compared to the titrated basal insulin glargine, the addition of a GLP-1 receptor agonist resulted in improved glycemic control, reduced insulin dose, similar risk of hypoglycemia, and smaller increases or reduction in body weight.

Combination therapy can be administered using separate preparations of each component (flexible-dosing strategy) or using combination preparations containing both agents (fixed-ratio strategy) (Ahmann A et al. 2015; Buse JB et al. 2011; Rosenstock J et al. 2012). Flexible combination therapy requires the patient to administer basal insulin and the GLP-1 receptor agonist subcutaneously separately, using 2 different devices. In order to reduce the number of injections required with flexible dosing (daily injection of basal insulin and separate once or twice daily injection of GLP-1 receptor agonists), a single daily injection of both agents in a fixed-ratio combination has also been investigated and is available in some countries (Gough et al. 2014). Published data of clinical trials assessing the efficacy and safety of fixed-ratio combinations of a GLP-1 receptor agonist and a basal insulin such as the combination of liraglutide with insulin degludec (IDegLira, Xultophy) and lixisenatide with insulin glargine (iGlarlixi/LixiLan) demonstrated a significant HbA1c reduction, with potential weight benefit in patients with T2D failing one or more OAMs (Gough et al. 2014; Aroda et al. 2016). There are several limitations of the fixed-ratio combination, including chronic administration of subtherapeutic doses (drug exposure with no proven glycemic efficacy and unapproved) of GLP-1 receptor agonist in patients who require only a small dose of insulin, and difficulties with insulin dose adjustments in patients who require a greater dose of insulin or have an increased risk of hypoglycemia. The use of GLP-1 receptor agonists with long duration of action, such as dulaglutide, in a flexible combination with basal insulin may overcome these issues. This combination requires once weekly administration of the GLP-1 receptor agonist, with the possibility of daily insulin dose adjustment that more closely matches the needs of patients than is the case with the fixed-dose combination.

3.2. Background

A GLP-1 receptor agonist, dulaglutide is a biosynthetic fusion protein molecule produced using mammalian cell cultures, and consists of 2 identical, disulphide-linked chains, each containing an N-terminal glucagon-like peptide-1 (GLP-1) analogue sequence covalently linked to a modified human immunoglobulin G4 (IgG4) heavy chain by a small peptide linker (Trulicity™ USPI, 2015). These structural features of the dulaglutide molecule (1) decrease the rate of clearance, (2) increase the duration of pharmacologic activity, (3) may reduce immunogenic potential, and (4) decreased unwanted antibody-mediated effector function (Barrington et al. 2011; Trulicity USPI, 2015). The molecular design of dulaglutide makes it suitable for once-weekly dosing.

Dulaglutide exhibits GLP-1 mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss (Trulicity USPI, 2015). Preclinical and clinical experience to date support the use of dulaglutide as a once-weekly injection to improve glycemic control in patients with T2D (Barrington et al. 2011). Dulaglutide received regulatory approval in the United States on 18 September 2014 and in the European Union on 21 November 2014 for treatment of adult patients with T2D, including the combination with insulin. Dulaglutide has been approved in China on 22 February 2019 for use as monotherapy, or in combination with metformin and/or sulfonylurea for treatment of adult patients with T2D.

Insulin glargine, a recombinant human insulin analog, has up to a 24-hour duration of action, and is used as a basal insulin. Designed to have a low aqueous solubility at neutral pH but completely soluble at pH 4, the acidic solution is neutralized after injection into the subcutaneous (SC) tissue. The neutralization leads to formation of microprecipitates from which small amounts of insulin glargine are slowly released. As a result, a relatively constant concentration/time profile over 24 hours is produced when compared to human neutral protamine Hagedorn (NPH) insulin. Such a profile makes it suitable as a once-daily basal insulin. The treat-to-target (TTT) trial demonstrated that the addition of once daily insulin glargine to OAM therapy in patients with T2D results in similar glycemic control and lower risk of hypoglycemia compared to human NPH insulin (Riddle et al. 2003). A meta-analysis of data from 2304 patients with T2D from 4 randomized clinical trials supports these observations (Rosenstock et al. 2005).

Thus, Study H9X-MC-GBGO (GBGO) will assess the effects of the addition of dulaglutide 1.5 mg QW or the addition of placebo QW to titrated insulin glargine, with metformin and/or acarbose, on glycemic control and safety in Chinese patients with T2D. The primary objective is to show superiority of dulaglutide as add-on to titrated insulin glargine to placebo as add-on to titrated insulin glargine for change from baseline in HbA1c after 28 weeks of treatment.

3.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of dulaglutide can be found in the Investigator's Brochure (IB).

In addition, detailed information about the known and expected benefits and risks of dulaglutide can be found in the Trulicity® China Package Insert (2019).

4. Objectives and Endpoints

Table GBGO.2 presents the objectives and endpoints of the study.

Table GBGO.2. Objectives and Endpoints

Objectives	Endpoints
Primary • To show the superiority of the addition of dulaglutide 1.5 mg QW compared to the addition of once weekly placebo to titrated insulin glargine, with metformin and/or acarbose, for change from baseline in HbA1c after 28 weeks of treatment in adult Chinese patients with T2D.	• The change in HbA1c from baseline.
Key Secondary (controlled for Type I error) *Efficacy:* • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for other parameters of glucose control and body weight change after 28 weeks of treatment in patients with T2D.	• Proportion of patients achieving HbA1c target of <7.0% • Change from baseline in body weight • Change from baseline in FSG (central lab)
Additonal Secondary *Efficacy* • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for the following parameters after 28 weeks of treatment in patients with T2D. •	• Prortion of patients achieving HbA1c target of ≤6.5%; • Proportion of patients achieving HbA1c target of <7.0% and with no weight gain (<0.1 kg) at 28 weeks and without documented symptomatic hypoglycemia (BG <3.0 mmol/L) during the maintenance period (Weeks 12-28); • Proportion of patients achieving HbA1c target of <7.0% at 28 weeks and without documented symptomatic hypoglycemia (BG <3.0 mmol/L) during the maintenance period (Weeks 12-28); • Proportion of patients achieving HbA1c target of <7.0% and without weight gain (<0.1 kg) at 28 weeks; • Changes from baseline in BG from daily SMBG profiles; • Changes from baseline in daily mean insulin glargine doses.
Safety: • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for selected safety	• Incidence of TEAEs, SAEs and discontinuation of study drug due to AEs;

parameters through 32 weeks in patients with T2D (unless noted otherwise).	• Change from baseline in electrocardiograms, laboratory and vital sign measurements. • Incidence of AESI o Occurrence of hypoglycemic episodes; o Incidence of initiation of rescue therapy due to severe, persistent hyperglycemia; o Incidence of adjudicated and confirmed pancreatitis; o Incidence of thyroid neoplasm o The incidence of deaths and nonfatal CV events; o Incidence of allergic and hypersensitivity AEs
Exploratory *Efficacy:* • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for exploratory efficacy parameters after 28 weeks of treatment in patients with T2D.	• Frequency of insulin dose adjustments through 28 weeks; • Number of insulin dose assessments per TTT algorithm and compliance with the TTT algorithm at 6, 8, and 12 weeks; • Proportion of patients achieving HbA1c target of <7.0% and with no weight gain (<0.1 kg) at 28 weeks and without documented symptomatic hypoglycemia (BG <3.9 mmol/L) during the maintenance period (Weeks 12-28); • Proportion of patients achieving HbA1c target of <7.0% and without weight gain (<0.1 kg) at 28 weeks; • Proportion of patients achieving HbA1c target of <7.0% at 28 weeks and without documented symptomatic hypoglycemia (BG <3.9 mmol/L) during the maintenance period (Weeks 12-28);
Safety: • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for exploratory safety parameters through 32 weeks in patients with T2D.	• Assessments of time to onset and duration of diarrhea, nausea, abdominal distension and vomiting in dulaglutide-treated patients.
Health Outcome/Quality of Life Measures:	

• To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for the following HO/QoL parameters in patients with T2D.	• Changes from baseline in patient-reported health status as measured by the EuroQol 5-dimension 5-level questionnaire (EQ-5D-5L) at 12 and 28 weeks; • Changes from baseline in patient-reported weight-related self-perception as measured by the Impact of Weight on Self-Perception Scale (IW-SP) at 12 and 28 weeks; • Assessments of patient perceptions regarding use and specific features of the delivery devices using the following modules of the Medication Delivery Device Assessment Battery (MDDAB): o Module 1: Single-Use Pen (SUP) Ease of Use Module (6 and 28 weeks) o Module 2: SUP Device Features Module (6 and 28 weeks) o Module 3a: SUP Experience Module (6 weeks) o Module 3b: SUP Experience Module (28 weeks) o Module 4: Glargine Delivery Device Experience Module (28 weeks).

Abbreviations: BG = blood glucose; CV = Cardiovascular; EQ-5D-5L = EuroQol 5-dimension 5-level questionnaire; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; IW-SP = Impact of Weight on Self-Perception Scale; MDDAB = Medication Delivery Device Assessment Battery; SMBG = self-monitored plasma glucose; SUP = Single-Use Pen; T2D = type 2 diabetes; TTT = treat-to-target.

5. Study Design

5.1. Overall Design

Study GBGO is a multicenter, randomized, double-blind, parallel-arm Phase 3b trial that compares the effect of the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine, with metformin and/or acarbose, on glycemic control and safety in adult Chinese patients with T2D.

Eligible patients are those with HbA1c at screening ≥7.0% and ≤11.0% despite treatment with stable doses of basal insulin glargine, stable doses of metformin and/or acarbose for at least 3 months prior to Visit 1 (See Section 6.1, inclusion criterion [4] for more detail). The primary objective of the study is to show superiority of dulaglutide 1.5 mg as add-on to titrated insulin glargine to placebo as add-on to titrated insulin glargine with regard to change from baseline in HbA1c at 28 weeks. The study will consist of 3 periods: an approximately 3-week screening/lead-in period followed by a 28-week treatment period and a 4-week safety follow-up period.

Patients who meet all inclusion criteria and none of the exclusion criteria will enter a 2-week lead-in period. Only those patients who require further up-titration of the insulin glargine dose per TTT algorithm at the end of lead-in period (FBG ≥5.6 mmol/L in the prior week before Visit 3) will then be randomized to 1 of the following treatment groups at Visit 3: (1) dulaglutide 1.5 mg QW as add-on to insulin glargine or (2) placebo QW as add-on to insulin glargine. Insulin glargine will be titrated using the treat-to-target (TTT) algorithm (Section 7.2.2.2.1). Metformin and/or acarbose dose must be kept unchanged for at least 3 months prior to Visit 1, and the dose should be within the inclusive range of half maximum to maximum approved daily dose per the locally-approved label during this period. Patients will be required to continue pretrial metformin and/or acarbose during the lead-in and treatment periods. Patients will be treated for 28 weeks (a 4-week stabilization period followed by a 24-week titration period); after which patients will be required to complete a safety follow-up visit (801) approximately 4 weeks later.

Figure GBGO.1 illustrates the study design.

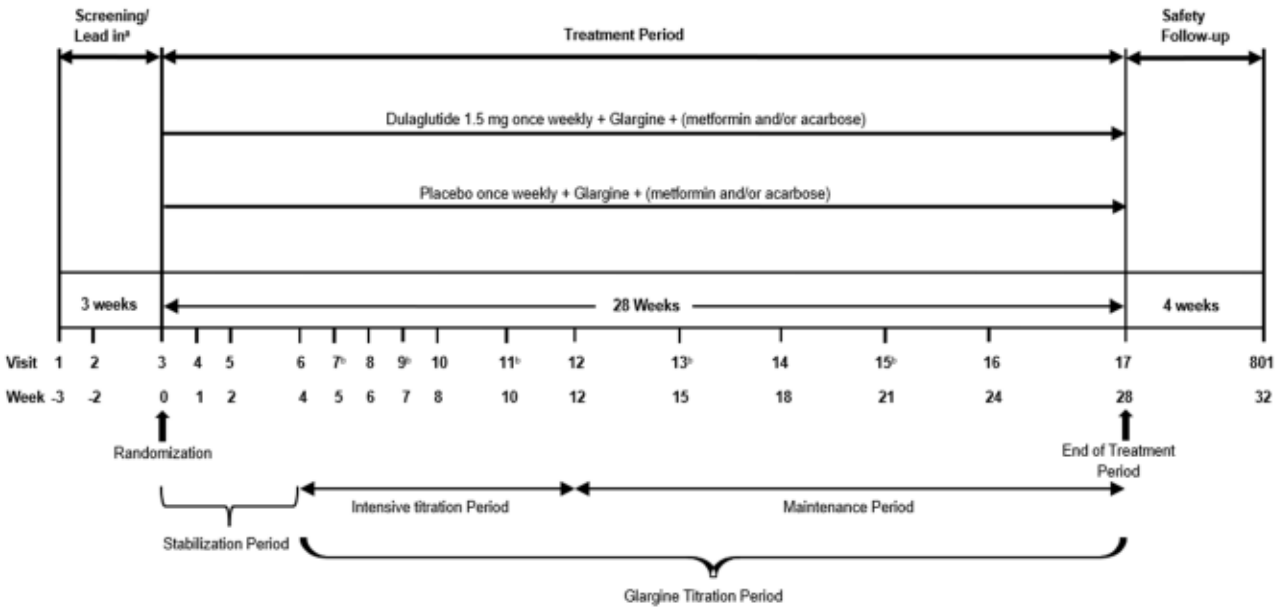

Figure GBGO.1. Illustration of study design for Clinical Protocol H9X-MC-GBGO.

[a] Patients should continue their prestudy regimen and should not change the type of antihyperglycemia medications used or their doses, except when allowed per protocol.

[b] At Weeks 5, 7, 10, 15 and 21 (Visits 7, 9, 11, 13 and 15), study sites will contact patients by telephone and perform procedures per the Schedule of Activities (Section 2).

Stabilization Period = first 4 weeks after randomization, with restricted insulin dose adjustments.

Glargine titration Period = Weeks 4 to 28 (end of treatment), with unrestricted insulin dose adjustments.

- Intensive Titration Period = Weeks 4 to 12, insulin is titrated to reach the optimal dose.
- Maintenance Period = Weeks 12 to 28, the period when basal insulin dose is expected to be stable.

Study Period I (Screening and Lead-In)

Screening (Visit 1)

The purpose of Visit 1 is to initiate the assessment of patient eligibility for participation in the trial. The patient will sign the informed consent form (ICF) and receive a patient identification number before any study procedures are performed. Procedures at this visit will be performed as shown in the Schedule of Activities (Section 2). Patients who meet all applicable inclusion criteria and none of the applicable exclusion criteria (Section 6) at Visit 1 will enter an approximately 2-week lead-in period. During this period, patients will be required to continue stable insulin and OAM treatment .

Lead-in (Visit 2 to Visit 3)

The screening laboratory results will be reviewed at Visit 2, and patient eligibility will be established. Procedures at this visit will be performed as shown in the Schedule of Activities (Section 2).

At Visit 2, patients and their caregiver(s), if applicable, will receive a glucometer and training on how to perform SMBG and how to record BG values in the diaries. Patients will be provided visit-specific diaries and will be trained as appropriate to record BG values, insulin dose assessments per TTT algorithm, insulin doses, hypoglycemic events, medications, and adverse events. After Visit 2, patients will start insulin dose assessments once weekly for the remainder of the lead-in period (the use of the algorithm is restricted during the lead-in and stabilization periods, as described below). If needed, other trainings will be provided, as well, and trainings could be repeated in other visits.

Patients will be requested to perform two 7-point SMBG profiles on two nonconsecutive days before Visit 3 per Schedule of Activities (Section 2).

During the lead-in period, patients should continue their prestudy therapy and should not change the type of OAMs used or their doses in order to allow reliable assessment of HbA1c at baseline (Visit 3). If patients develop a condition that is a contraindication for the use of OAMs, they will be considered ineligible and must discontinue from the trial before randomization. Insulin doses should be adjusted only for the safety of patients (occurrence of hypoglycemia [fasting blood glucose (FBG) <3.9 mmol/L] due to insulin dose or severe hyperglycemia, defined as mean daily BG from 4-point SMBG profile >15 mmol/L or mean weekly FBG >15 mmol/L). In these situations, the insulin dose will be adjusted per the TTT algorithm at the discretion of the investigator (see Section 7.2.2.2.1).

Study Period II (Treatment Period):

Randomization (Visit 3)

At Visit 3, patient should arrive to the clinic in the fasting state, which should last at least 8 hours, without having taken any doses of their study drug, OAMs and insulin glargine. Procedures at this visit will be performed as shown in the Schedule of Activities (Section 2). The questionnaires (EQ-5D-5L and IW-SP) 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 preceding visit procedures.

Investigators will review the diary and assess patient eligibility (Section 6.1 and 6.2). Insulin dose should be kept unchanged for at least 3 days prior to Visit 3, so as to have at least 3 daily FBG values ready for eligibility assessment at Visit 3. Patients who continue to be eligible will be randomized in a 1:1 ratio to one of the following treatment groups: (1) dulaglutide 1.5 mg QW as add-on to insulin glargine or (2) placebo QW as add-on to insulin glargine, with metformin and/or acarbose.

Patients will be instructed on how to use the single-use pen (SUP) and will inject their first dose of study drugs under the supervision of the personnel while in the clinic for Visit 3. Patients will also be trained on how to use the SoloSTAR™ pen and will administer insulin glargine once daily ideally at bedtime. The date and time of the first dosing of study drug should be recorded on the eCRF.

Following randomization, patients will participate in a 28-week treatment period.

Treatment Period – General Considerations

The treatment period starts with a 4-week stabilization period immediately after randomization, followed by a 8-week intensive titration period and a 16-week maintenance period. In the 4 weeks of stailization period (Week 0 to Week 4), randomized study drug (dulaglutide or placebo) will be introduced in a safe manner, and insulin glargine dose will be reduced or remain stable. In the initial 8 weeks of intensive titration period (Week 4 to Week 12), most of the insulin glargine titration should occur, and insulin will be titrated to reach the optimal dose. In the final 16 weeks of maintenance period (Week 12 to Week 28), insulin glargine dose is expected to be stable and optimized.

Throughout the treatment period, patients will collect all data on SMBG, insulin dose assessments, insulin doses administered, dosing dates, hypoglycemic events, AEs, and concomitant medications in the patient diary to be reviewed with the study site personnel at the next office visit. For that purpose, at each office visit, study diaries for the period after the last office visit will be collected, new study diaries will be dispensed, and instructions will be reviewed at each visit. Used and unused study drug and injection supplies will be returned per the Schedule of Activities (Section 2) and according to local requirements. New supplies will be dispensed as needed. At Week 28 or ET visit, all used and unused study drug(s) will be returned.

Results of SMBG and hypoglycemic events will be used by the patient to assess insulin glargine doses per the TTT algorithm. Insulin glargine dose assessments will be required to perform once or twice per week (see Section 7.2.2.2).

Compliance with the dulaglutide administration schedule and compliance with the insulin glargine TTT algorithm will be assessed at every office visit and collected in the eCRF at prespecified visits (Section 7.6). Based on the outcome of these reviews, the site personnelshould discuss additional insulin glargine dose adjustments while the patient is still at the site and provide retraining, if needed. Patients should be instructed to contact the study site for assistance as soon as possible if they experience any difficulties administering their study medication or with the TTT algorithm at any time during the study.

Patients are required to continue using their concomitant OAMs throughout the treatment period. Discontinuation of these medications or dose changes are not permitted, except in certain situations (see Sections 7.7.1 and 7.7.5.2 for details).

Patients will be 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 study treatments (Section 7.7).

Patients who develop severe, persistent hyperglycemia based on prespecified thresholds (see Sections 7.7.5.3 and 9.2.2.1) will receive a new glucose-lowering intervention (“rescue therapy”) and will also continue with study drug. Patients who need hyperglycemic rescue therapy will continue in the trial until they complete all study visits. Patients who permanently discontinue study drug prior to the Safety Follow-Up Period will also be required to continue in the trial and should receive a new glucose-lowering intervention (Section 7.7.1).

Study governance considerations are described in detail in Appendix 3.

Stabilization Period (End of Visit 3 to Visit 6 [Weeks 0 to 4])

The main purposes of this period are to introduce randomized study drug (dulaglutide or placebo) in a safe manner and to ensure regular and correct use of the self-monitoring and insulin dose adjustment procedures and study diaries during the entire study. In an effort to allow appropriate time for dulaglutide to reach steady state, insulin glargine dose adjustments during the 4-week stabilization period should be restricted to patients with significant safety risks due to insulin dose: (1) occurrence of hypoglycemia (FBG <3.9 mmol/L; see Section 7.2.2.2.1); in this case, the insulin glargine dose will be decreased per the TTT algorithm; or (2) development of severe hyperglycemia, defined as mean daily BG from 4-point SMBG profile >15 mmol/L; in this case, insulin dose will be increased per the TTT algorithm. In addition, for patients with baseline HbA1c ≤8.0%, the insulin glargine dose will be decreased by 20% immediately after randomization, and will then remain unchanged during the stabilization period to decrease the risk of hypoglycemia. The insulin glargine dose will remain unchanged during the stabilization period if baseline HbA1c is >8.0%. If the baseline HbA1c value for a patient is not available within the first 7 days after randomization, the study site should immediately consult the responsible Lilly physician (not later than the date of Visit 4) to discuss if an adjustment in insulin dose would be appropriate based on the available clinical data for the patient.

The planned visits for this period, Visits 4, 5, and 6, will take place 1 week (±3 days), 2 weeks (±3 days), and 4 weeks (±4 days) after randomization, respectively. Study procedures will be performed per the Schedule of Activities (Section 2).

Titration Period (End of Visit 6 to Visit 17 [Weeks 4 to 28])

At the beginning of the titration period, the patient will be instructed to start to use the TTT algorithm without restrictions in order to reach the optimal dose of insulin glargine as soon as possible.

The planned office visits during this period (excluding the final visit), Visits 8 through 16, will take place at Week 6 (±4 days), 8 (±4 days), 12 (±7 days), 18 (±7 days), and 24 weeks (±7 days) after randomization. In addition to the office visits, 5 telephone visits will be scheduled at Visit 7 (Week 5), Visit 9 (Week 7), Visit 11 (Week 10), Visit 13 (Week 15), and Visit 15 (Week 21). At each of these visits, procedures will include assessments of SMBG, compliance with insulin titration algorithm, insulin dose, dulaglutide compliance (will be re-assessed at the office visit), hypoglycemic events, concomitant medications, and AEs. The data obtained at these telephone visits will be entered into the eCRFs at the next office visit.

Between Week 4 and Week 8, the insulin glargine dose adjustment will be discussed with the patients and determined by the investigator, and this procedure will be used as preparation and training for implementation of the patient self-titration according to the TTT algorithm (Table GBGO.4). After Week 8, the decision of the titration will be made and implemented by the patient in a weekly manner. Between Week 8 and Week 12, patients will be contacted by the study site personnel every 2 weeks (either telephone or office visit). Investigators or study site

personnel will review the insulin dose adjustment made by the patient at each office visit or telephone visit. From Week 12 , patients will be contacted by the study site personnel every 3-4 weeks (either telephone or office visit), to enable the site to properly monitor patients' usage of the TTT algorithm. Investigators may perform additional telephone visits if necessary, or perform additional office visits if deemed necessary by the investigator. Also, more frequent insulin dose assessments may be requested by the investigator if clinically appropriate.

At Visit 8 (Week 6) only, MDDAB modules 1, 2, and 3a should be completed by the patient 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 preceding visit procedures.

At Visit 12 (Week 12), questionnaires (EQ-5D-5L and IW-SP) 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 preceding visit procedures.

The final office visit, Visit 17, will take place at Week 28 (±7 days). Study procedures at this visit are shown in the Schedule of Activities (Section 2). The EQ-5D-5L, IW-SP, and MDDAB modules 1, 2, 3b, and 4 questionnaires will 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 preceding visit procedures. A final physical examination will be performed, including weight and vital signs (sitting blood pressure [BP] and pulse rate [PR]) measurements and electrocardiogram (ECG) testing using the existing equipment at the site. Study drug will be discontinued and an appropriate diabetes treatment regimen will be prescribed per the investigator's judgment. A patient summary eCRF will be completed.

Study procedures will be performed per the Schedule of Activities (Section 2).

Study Period III (Safety Follow-Up Period):

Safety Follow-Up (801) Visit

All patients who complete the treatment period are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after last visit. Patients discontinuing the study early and performing an early termination (ET) visit will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit. During the safety follow-up period, patients will not receive study drug. Patients may be treated with another glucose-lowering intervention decided upon by the investigator (see Section 7.7.1). Initiation of new antihyperglycemic therapy for the safety follow-up period will not be classified as "rescue therapy". Patients are required to return any remaining study diaries to the study site at the end of this period.

Early Termination Visit (If Necessary)

Every attempt will be made to keep patients in the trial irrespective of their adherence to treatment with study drug. At any time after Visit 3 (randomization), a patient who is to discontinue from the study before Visit 17 will have an early termination (ET) visit conducted. At this visit, procedures will occur as shown in the Schedule of Activities (Section 2). Patients

should be instructed to return any remaining used or unused study drug supplies and patient diaries to the study site at this visit. Study drug will be discontinued, and an appropriate glucose management regimen (Section 7.7.1) will be prescribed by the investigator. Patients will be asked to perform the Safety Follow-Up visit (801) approximately 30 days after the ET visit, so that the Safety Follow-Up visit will be their final visit. If the patient is not able to perform the Safety Follow-Up visit, the ET visit will be the final study visit. A patient summary eCRF will be completed.

5.2. Number of Participants

Approximately 483 patients will be screened to achieve approximately 290 randomized and 246 evaluable patients with an estimated total of 123 evaluable patients in the dulaglutide as add-on to insulin glargine treatment group, and 123 evaluable patients in placebo as add-on to insulin glargine treatment group.

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

Combination therapy of basal insulin and GLP-1 receptor agonist is broadly used and previous studies have demonstrated the efficacy and safety of this combination. In the AWARD-9 clinical trial (Study H9X-MC-GBDI), a significantly greater proportion of patients treated with dulaglutide added to basal insulin with or without metformin (66.7%) achieved HbA1c <7.0% compared to the addition of placebo with further titration of insulin glargine (33.3%). The better glycemic control with the addition of dulaglutide was achieved without increasing the risk of hypoglycemia and with weight benefit (Pozzili et al. 2017).

This study (H9X-MC-GBGO) is designed to compare the benefits and risks of dulaglutide 1.5 mg QW as add-on to titrated insulin glargine with placebo QW as add-on to titrated insulin glargine, with metformin and/or acarbose, in Chinese patients with T2D. The trial design will enable assessment of the effects of these interventions on daily and long-term glycemic control, as well as on safety variables.

Patients selected to participate in this study will be those who require intensification of their current basal insulin regimen due to inadequate glycemic control, as indicated by HbA1c value above the ADA/EASD established target of 7.0%.

To ensure that patients randomized to receive placebo also have the opportunity for effective treatment (ie, basal insulin optimization) during the treatment period, only patients who require insulin glargine dose up-titration will be randomized to continue in the treatment period of this study.

To ensure a valid comparison of the randomized study treatments, it is important that insulin glargine is titrated in an optimal way throughout the entire study. Patients will be required to use a TTT algorithm, which has been shown to be effective in enabling a high proportion of patients

with T2D to achieve their therapeutic targets when treated with insulin glargine (Davies et al. 2005).

The treatment period is 28 weeks, including 4 weeks of stabilization period to introduce randomized study drugs (dulaglutide or placebo), 8 weeks of intensive insulin glargine titration period to reach the optimal insulin dose, and 16 weeks of maintenance period when insulin glargine dose is expected to be stable. The 28-week period was chosen based on experience from AWARD-9 dulaglutide trial. It should enable a sufficient time period for insulin titration and to assess the full effect of study treatments after the majority of the patients reach a stable insulin dosage.

Furthermore, the frequency of postrandomization office and telephone visits is intended to allow patients and investigators to frequently assess study treatments and to make insulin dose adjustments as needed, to attain glycemic goals within a short time period.

5.5. Justification for Dose

The approved Product Information in China for dulaglutide includes 2 approved doses, 0.75 mg and 1.5 mg once weekly (Trulicity® China Package Insert 2019). Dulaglutide 1.5 mg was selected as the optimal dose for the purposes of exploring the safety and efficacy in combination with basal insulin glargine in Study GBDI and other Phase 3 trials. Therefore, dulaglutide 1.5 mg will be used in Study GBGO.

The TTT algorithm (Section 7.2.2.2.1), adapted from Davies et al. (2005), is a broadly accepted approach to insulin glargine dose adjustments and will be used in this study to target a FBG <5.6 mmol/L.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible for enrollment in the study only if they meet **all** of the following criteria:

Type of Patient and Disease Characteristics

[1] have type 2 diabetes (based on the World Health Organization's [WHO] diagnostic criteria Appendix 5);

Patient Characteristics

[2] are men or nonpregnant women aged ≥18 years at Visit 1;

[3] have been treated with basal insulin glargine once daily and metformin and/or acarbose for at least 3 months prior to Visit 1;

[4] doses of once daily insulin glargine and OAMs must be stable during the 3-month period prior to Visit 1. Insulin glargine dose is considered stable when all doses during this period are within the range defined by ±20% of the most commonly used insulin glargine dose during this same period. Doses of metformin and/or acarbose are considered stable when doses are unchanged during the same period, and the doses should be in the inclusive range of the half maximum to maximum approved daily dose per the locally-approved label;

[5] have an HbA1c value ≥7.0% and ≤11.0% as assessed by the central laboratory at Visit 1;

[6] require further insulin glargine dose increase at Visit 3 per the TTT algorithm based on the SMBG data (FBG ≥5.6mmol/L) collected during the prior week;

[7] have stable weight (±5%) ≥3 months prior to Visit 1;

[8] have body mass index (BMI) between ≥19.0 and ≤35.0 kg/m^2 at Visit 1;

[9] are able and willing to administer once weekly randomized therapy;

[10] in the investigator's opinion, are well motivated, capable, and willing to:

[a] perform fingerstick BG monitoring, including scheduled BG profile with up to 7 measurements in 1 day;

[b] learn how to self-inject as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug);

[c] maintain a study diary as required for this protocol;

[11] Women of child-bearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Otherwise, women of child-bearing potential participating must agree to use one highly effective (less than 1% failure rate) method of contraception or use a combination of two effective methods of contraception until plasma concentration equals or is lower than the [*NOAEL* for embryo fetal effects].

[a] Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

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

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

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

[b] post-menopausal – defined as either

i. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
ii. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

Not be breastfeeding.

[40] No male contraception required except in compliance with specific local government study requirements.

Informed Consent

[12] have given written informed consent to participate in this 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 the study if they meet any of the following criteria at Visit 1 (screening), or when indicated below for specific criteria, at Visit 3 (baseline) or at any time during the screening and lead-in periods (Visits 1-3):

Medical Conditions

[13] have type 1 diabetes (T1D);

[14] have a history of ≥1 episode of ketoacidosis or hyperosmolar state/coma;

[15] have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1;

[16] have had any of the following CV conditions within the 2 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);

[17] have a known clinically significant gastric emptying abnormality (eg, severe diabetic gastroparesis or gastric outlet obstruction) or have undergone or plan to have a gastric bypass (bariatric) surgery or restrictive bariatric surgery (eg, Lap-Band®) during the course of the study, or chronically take drugs that directly affect gastrointestinal (GI) motility;

[18] have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >2.5 times the upper limit of the reference range, as determined by the central laboratory at study entry (Visit 1); patients with NAFLD are eligible for participation in this trial only if their ALT level is ≤2.5 times the upper limit of normal (ULN) for the reference range;

[19] 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;

[20] for patients on metformin or metformin and acarbose, have renal disease or renal dysfunction (eGFR [CKD-EPI] <45 mL/min/1.73 m^2), as determined by the central laboratory (Glucophage China PI, 2017; Glucobay China PI, 2018; Trulicity China PI 2019); for patients on acarbose, have renal disease or renal dysfunction (eGFR [CKD-EPI] <25 mL/min/1.73 m^2), as determined by the central laboratory (Glucobay China PI, 2018; Trulicity China PI 2019);

[21] have evidence of a significant, uncontrolled endocrine abnormality (eg, thyrotoxicosis, adrenal crisis), in the opinion of the investigator;

[22] have any self or family history of type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) syndrome in the absence of known C-cell hyperplasia (the only exception for this exclusion will be for patients whose family members with MEN 2A or 2B syndrome have a known RET mutation and the potential patient for the study is negative for the RET mutation);

[23] 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);

[24] have serum calcitonin ≥20 pg/mL at Visit 1, as determined by the central laboratory;

[25] have evidence of a significant, active autoimmune abnormality (eg, lupus, rheumatoid arthritis);

[26] have a history of transplanted organ (corneal transplants [keratoplasty] are allowed), or awaiting an organ transplant;

[27] have a history of active or untreated malignancy, or have been in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years prior to Visit 1;

[28] have a history of any other condition (eg, known drug or alcohol abuse or psychiatric disorder), which, in the opinion of the investigator, may preclude the patient from following and completing the protocol;

[29] have any hematologic condition that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle-cell disease);

Prior/Concomitant Therapy

[30] have been treated with any other antihyperglycemia regimen, other than basal insulin glargine once daily and metformin and/or acarbose, within the 3 months prior to Visit 1 or between Visits 1 and 3;

[31] per the TTT algorithm, do not require insulin glargine dose increase at Visit 3 based on the SMBG data (FBG <5.6mmol/L) collected during the prior week;

[32] have any other condition not listed in this section that is a contraindication for use of insulin glargine, or, for patients using metformin and/or acarbose, have a condition that is a contraindication for the use of metformin and/or acarbose and would require metformin and/or acarbose discontinuation per label;

[33] have been treated with drugs that promote weight loss (e.g.,Saxenda (liraglutide 3.0 mg), Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex®[phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], contrave® [naltrexone/bupropion] or similar other body weight loss medications including over-the-counter [OTC] medications [e.g., allī®]) within the 3 months prior to Visit 1 or between Visits 1 and 3; or current (or within the last 3 months) participation in, or planned intent to initiate within timeframe of the study, an organized diet and/or exercise weight reduction program other than the lifestyle and dietary measures for diabetes treatment;

[34] are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) or have received such therapy within the 4 weeks prior to Visit 1 or between Visits 1 and 3;

Prior/Concurrent Clinical Trial Experience

[35] are currently enrolled in or discontinued within the 30 days prior to Visit 1 from any other clinical study involving an investigational product, or are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study. If the previous investigational product has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed;

[36] have previously screen failed, withdrawn, discontinued from, or completed this study or been randomized in any clinical trial of dulaglutide.

Other Exclusions

[37] 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);

[38] are Lilly employees;

[39] are unwilling or unable to comply with the use of a paper diary to directly record data from the subject.

6.3. Lifestyle Restrictions

Per the Schedule of Activities (Section 2), qualified medical staff will provide diabetes management counseling, which includes instructions on diet and exercise, and education about the signs, symptoms, and treatment of hypoglycemia, should it occur.

Patients should continue their usual exercise habits and generally follow a healthy meal plan (with consistent meal size and time of day) throughout the course of the study. Dietary counseling may be reviewed throughout the study, as needed. Per Exclusion Criterion [33] (Section 6.2), patients should not initiate during the study an organized diet and/or exercise weight reduction program other than the lifestyle and dietary measures for diabetes treatment.

Patients should be instructed not to donate blood or blood products during the study or for 4 weeks following their last study visit.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be re-screened for this study.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of dulaglutide 1.5 mg versus placebo given once weekly as a subcutaneous injection, both as add-ons to titrated basal insulin glargine, with metformin and/or acarbose, on glycemic control and safety in Chinese patients with T2D. Table GBGO.3 summarizes the randomized study treatments and titrated insulin glargine.

Table GBGO.3. Study Treatments and Concomitant Insulin

Name of Drug	Dosage	Frequency	Drug Formulation	Route of Administration
Investigational Compound				
Dulaglutide	1.5 mg	Once weekly	Single-Use Pen[a]	Subcutaneous injection
Comparator				
Placebo	Placebo	Once weekly	Single-Use Pen[a]	Subcutaneous injection
Concomitant insulin for both treatment arms				
Insulin glargine	TTT dosing	Once daily	SoloSTAR™ Pen	Subcutaneous injection

Abbreviation: TTT = treat-to-target.

[a] Prefilled device containing 1 dose of study drug.

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

- Explaining the correct use of the study drug to the patient or patient representative;
- Explaining the correct use of metformin and/or acarbose to the patient, including any contraindications and appropriate dosing per label in China;
- Verifying that treatment instructions described above are followed properly;
- Maintaining accurate records of study drug dispensing and collection;
- Patients should return all unused study drug to the site according to the Schedule of Activities (Section 2). The patients should be instructed to discard all used SUPs and SoloSTAR™ Pens in a closeable, puncture-resistant container, and dispose according to local regulations. Sites may be authorized to destroy used and unused SUPs locally per applicable local or national requirements.

7.1.1. Packaging and Labelling

The sponsor will provide dulaglutide and placebo in single-use pens (SUPs), which will be dispensed via an Interactive Web Response System (IWRS). Each SUP will be packaged in cartons to be dispensed. Each carton contains a 4-week supply, as each pen provides a weekly dose. Injections are to be administered as described in Section 7.2.2.

Commercial insulin glargine will be provided, in 3 mL (100 units/mL) prefilled delivery devices (SoloSTAR™ Pen) during the treatment period, and will also be dispensed via an IWRS.

Clinical study materials will be labeled according to China's regulatory requirements.

7.1.2. Medical Devices

The manufactured medical devices provided for use in the study will be SUPs containing dulaglutide 1.5 mg (0.5 mL at 3.0 mg/mL) or placebo, SoloSTAR™ Pen containing insulin glargine (per TTT dose).

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to 1 of the 2 study treatment arms at Visit 3. Assignment to treatment arms will be determined by a computer-generated random sequence using an IWRS. The IWRS will be used to assign cartons containing double-blind study drug to each patient. Site personnel will confirm that they have located the correct cartons by entering a confirmation number found on the label into the IWRS .

Patients will be randomized in a 1:1 ratio to (1) dulaglutide 1.5 mg QW as add-on to insulin glargineor (2) placebo QW as add-on to insulin glargine, with metformin and/or acarbose. Patients will also be stratified by HbA1c at Visit 1 (screening) (<8.5% *vs*. ≥8.5%) and OAM usage (metformin alone, acarbose alone, metformin and acarbose) at Visit 3 (randomization) to achieve between-group comparability and to mitigate against the confounding effects of the treatments with severity of disease or treatment with metformin and/or acarbose.

7.2.1. Selection and Timing of Doses

Details of the dosing strategy and administration timing for injectable study drug and insulin glargine are provided in the following sections and are designed to achieve HbA1c <7.0%, a standard treatment goal in this population. In order to optimize insulin glargine dose, patients in both groups will be targeting FBG <5.6 mmol/L.

7.2.2. Injecting Study Drug

7.2.2.1. Dulaglutide or Placebo

No adjustment in injectable study drug dose (dulaglutide or placebo) will be allowed. All patients will inject study drug subcutaneously in the skin fold of the left or right abdominal wall or the thigh using the injection supplies provided; a caregiver may administer the injection in the patient's upper arm. A new SUP will be used for each injection.

It is recommended that patients inject the study drug at approximately the same time of day 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 scheduled injection. If less 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. The day of administration can be changed if necessary, as long as the last dose was administered 3 or more days before.

The day and time of all dulaglutide injections will be recorded in the patient's diary and eCRF.

7.2.2.2. Insulin Glargine

Insulin glargine will be injected QD, as a single subcutaneous injection, always at bed time at approximately the same time every night. The dose will be adjusted weekly per TTT algorithm (Table GBGO.4), based on FBG values and recorded hypoglycemic episodes (see below for details). For this purpose, patients will be required to measure their FBG each morning and to collect 4-point SMBG profiles at least once weekly, starting at Visit 2 through the end of the treatment period (Visit 17 [Week 28]).

During the lead-in period (between Visits 2 and 3 [baseline]), insulin doses should be adjusted per TTT algorithm (Table GBGO.4) only when needed to protect the safety of patients (occurrence of hypoglycemia or severe hyperglycemia). Insulin dose assessments during this period will occur once per week (Section 5.1).

During the treatment period, office visits will occur weekly or every other week during the first 2 months and thereafter every 4 to 6 weeks to enable the site to properly monitor patients' usage of the TTT algorithm. After randomization, during the 4-week stabilization period, the basal insulin dose will remain unchanged if the patient's baseline (Visit 3) HbA1c is >8.0%. For patients with baseline HbA1c ≤8.0%, the basal insulin dose will be decreased by 20% immediately after randomization and will then remain unchanged during the stabilization period. Additional insulin dose adjustments during the stabilization period will only be allowed using the TTT algorithm (Table GBGO.4) in case of the occurrence of hypoglycemia or the development of severe hyperglycemia. Patients will be requested to perform insulin dose assessments twice per week during this period.

Following stabilization, patients will be treated for an additional 24 weeks, and they will be required to assess their basal insulin dose once weekly, using the SMBG values for that week. During this period, the insulin dose will be adjusted per the TTT algorithm with no restriction. The main treatment target for basal insulin dose adjustment through the treatment period (28 weeks) is FBG <5.6 mmol/L.

Compliance with the study drug (dulaglutide or placebo) administration schedule and compliance with the basal insulin TTT algorithm (at selected visits; see Schedule of Activities; Section 2) will be assessed and collected in the eCRF.

7.2.2.2.1. Insulin Glargine Dose Titration Algorithm

The decision to adjust insulin glargine doses will be based upon the median of the last 3 daily FBG (SMBG) values (preferably most recent readings) collected after the previous dose assessment. If fewer than 3 values are available for assessment, then the average value will be calculated and used to adjust the dose. If the median or average FBG value is within the target FBG range, then there will be no resulting change in dose. If that value is ≥5.6 mmol/L, the dose will be increased based on the titration algorithm provided in Table GBGO.4 (Davies et al. 2005). In the case of recorded hypoglycemic episodes any time during the period included in the assessment, the criteria provided in Table GBGO.4 should be followed.

Table GBGO.4. Insulin Glargine Treatment-to-Target Algorithm

Median or Average BG Before Breakfast (for Titration of Evening Dose)	Increase in Basal Dose (Units)
<70 mg/dL (<3.9 mmol/L)	Decrease to previous lower dose*
70-<100 mg/dL (3.9-5.6 mmol/L)	No adjustment
100-<120 mg/dL (5.6-6.7 mmol/L)	+1 to +2 U[#]
120-<140 mg/dL (6.7-7.8 mmol/L)	+ 2 U
140-<180 mg/dL (7.8-10.0 mmol/L)	+ 4 U
≥180 mg/dL (>10.0 mmol/L)	+6 to +8 U[#]

* The patient will be administered with the previous lower dose if he/she has documented hypoglycemia or probable symptomatic hypoglycemia.

[#] Insulin glargine dose adjustment will be discussed with the patient and determined by the investigator before Week 8 as preparation and training for implementation of the patient self-titration according to the treatment-to-target algorithm after Week 8 (Section 5.1).

Abbreviations: BG = blood glucose; U = unit(s).

7.3. Blinding

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

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted for medical management of the event. The Patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

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 clinical research physician (CRP) for the patient to continue in the study.

7.4. Dosage Modification

No adjustment in study drug doses will be allowed. Further details about dose administration during the study are described in Section 7.2.1.

Dosing of required concomitant metformin and/or acarbose is discussed in Section 7.7.1.

7.5. Preparation/Handling/Storage/Accountability

The study site must store the SUP cartons in a locked and secure environment. The SUPs 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 SUPs at office visits per the Schedule of Activities (Section 2). They will receive insulated bags with cooling gel packs for use in transporting the SUP carton from the site to home. Prior to self-injection, 1 SUP should be removed from the carton and allowed to sit at room temperature for about 30 minutes before self-injection. Investigational product will be labeled according to the China's regulatory requirements.

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

Study site personnel must regularly assess whether the patient is correctly administering the assigned study drug and storing the study drug according to the provided instructions.

7.6. Treatment Compliance

The assessment of treatment compliance in this study will include assessment of administration of the study drugs (dulaglutide or placebo), the use of the TTT algorithm, administration of insulin glargine doses, and frequency of protocol deviations related to any glucose-lowering medications.

The assessment of treatment compliance with study drug will be determined by the following:

- Information about the administration of once weekly study drug injections will be entered into the patient diary by the patient and reviewed by the site personnel at each study visit; this information will be collected in the eCRF;
- Study drugs accountability will be checked according to the Schedule of Activities (Section 2). For that purpose, patients will be instructed to return the study drug carton at the next visit. They will also be instructed to return any unused study drug at the next study visit;
- Treatment compliance for once weekly study drug is defined as taking at least 75% of the required injections of study drug,
    - Between Visit 3 (randomization) and Visit 6 (Week 4), and
    - Since the previous visit, assessed at Visits 10 (Week 8), 12 (Week 12), 14 (Week 18), 16 (Week 24) and 17 (Week 28)

  Compliance is assessed by site personnel; this information will be entered in the eCRF.

Compliance with the TTT algorithm will be determined by the following:

- The study site will review and document patients' use of the insulin glargine TTT algorithm for appropriate number of assessments, appropriate assessment of the insulin

dose, and subsequent dose adjustments at each visit from randomization to Visit 17. These data will be entered into the eCRF for the period prior to Visits 8 (Week 6), 10 (Week 8), and 12 (Week 12).

Other aspects of compliance with the study treatments will also be assessed at each visit, including the patient's adherence to the visit schedule, compliance with the concomitant metformin and/or acarbose requirements and other medication guidances (Section 7.7), completion of study diaries, results of SMBG, and any other parameters the investigator considers necessary. Patients considered to be poorly compliant with their medication and/or the study procedures (for example, missed visits or specific diagnostic tests) will receive additional training and instructions as required.

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 study drugs.

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. This may not be possible when initiated for treatment of medical emergencies, in which case the patient will inform the investigator or a designated site staff member as soon as possible.

Any additional medication initiated during the course of the study (including OTC drugs, such as paracetamol or aspirin) must be documented, and the name of the drug, the dosage (metformin and/or acarbose) and the date(s) of administration must be recorded in the patient's diary and on the "Concomitant Medications" section of the eCRF.

Non-study 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.

Table GBGO.5 provides a summary of criteria for use of concomitant medications that may interfere with planned assessments during the study.

Table GBGO.5. Criteria for Use of Concomitant Medications that May Interfere with Efficacy and Safety Assessments

Drug Class	Use During Screening/Lead-In	Conditions for Use after Randomization		
		Acute therapy[a]	Rescue therapy	During Safety Follow-Up Period
Drugs with approved weight loss indication[b]	Excluded	N	N/A	N
Systemic glucocorticoid therapy[c]	Excluded[d] except for acute therapy[a]	Y	N/A	N
Antihyperglycemia medications				
Other GLP-1 RAs and related fixed-dose combinations	Excluded	N	N	N

DPP-4 inhibitors and related fixed-dose combinations	Excluded	N	N	N
Pramlintide	Excluded	N	N	N
SGLT2 inhibitors	Excluded	N	Y	Y
Insulins [e]	Excluded	Y	Y	Y
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors[f]	Allowed	N/A	Y[g]	Y
Sulphonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y
Metformin[f]	Allowed	N/A	Y[e]	Y

Abbreviations: DPP-4 = dipeptidyl peptidase-4; GLP-1 RA = glucagon-like peptide-1 receptor agonist; N = no; N/A = not applicable; SGLT2 = sodium-glucose co-transporter 2; Y = yes

[a] Acute therapy = treatment for up to 14 days.

[b] Includes Saxenda® [liraglutide 3.0 mg], Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex®[phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], contrave® [naltrexone/bupropion] or similar other body weight loss medications including over-the-counter [OTC] medications [e.g., allī®] within 3 months prior to Visit 1 or any time during the trial.

[c] Does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

[d] Chronic systemic glucocorticoid therapy (>14 days) should be excluded within 4 weeks prior to Visit 1 or between Visits 1 and 3.

[e] Use of insulin glargine is allowed during screening/lead-in period For acute therapy, rescue therapy and therapy during safety follow-up period, use of other basal insulins will not be allowed in both treatment groups. .

[f] Switching metformin or acarbose manufacturers is allowed as long as the dosage is the same. Changing to a metformin formulation with a different action profile (for example, from short-acting to long-acting metformin) is not permitted.

[g] For rescue therapy, metformin or acarbose dose can be increased if the dose is no more than maximum approved dose per country-specific label and is well tolerated.

7.7.1. Antihyperglycemia Medications

Anti-hyperglycemic medications, other than study drug, metformin and/or acarbose, are not allowed at any time during the study, except those used as rescue therapy, and/or used after early study drug discontinuation or during safety follow-up period, or insulins for short-term use. Rescue therapy with other glucose-lowering agents, including insulin, may be medically indicated in certain situations after randomization due to severe, persistent hyperglycemia or early discontinuation of study treatment. These situations are described in Section 7.7.5.3 and Section 8.1.1, respectively. If any such situation occurs, the patients may be treated with any locally-approved glucose-lowering agents. Other GLP-1 RAs, another basal insulin, or DPP-4 inhibitors, fixed-dose combination with component of GLP-1 receptor agonists or DPP-4 inhibitor, and pramlintide are prohibited medications and are not allowed as rescue therapies.

If any new anti-hyperglycemic medication is initiated after randomization at Visit 3 and prior to Visit 17 (end of Treatment Period), other than study drug, rescue therapy, drugs used after early study drug discontinuation or during safety follow-up period, or insulins for short-term use for medical emergencies, the patient will be required to immediately discontinue the medication and the appropriate study deviation report will be generated. Any such violation of the protocol that

lasts > 14 consecutive days will exclude the patient from the Per-Protocol (PP) Population for analyses.

7.7.2. Medications That Promote Weight Loss

Prescription or OTC medications that promote weight loss are exclusionary if used within the 3 months prior to Visit 1 (study entry), or between study entry and randomization at Visit 3 (see Section 6.2). These medications are not allowed at any time during the treatment period. If started, these medications should be immediately withdrawn. In addition, patients should not receive an intensive diet/exercise program with the intent of reducing body weight at any time during the study, other than the lifestyle and dietary measures for diabetes treatment (see Section 6.3).

Patients who use any medication from these groups during the treatment period will not be included in the PP analyses if the duration of use is >14 days (cumulative).

7.7.3. Systemic Glucocorticoids

Chronic systemic glucocorticoid therapy (>14 consecutive days; excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) is exclusionary if being in use or has been used during the 4-week period before study entry or between study entry and randomization at Visit 3. If glucocorticoid therapy is needed for more than 14 consecutive days during the treatment period, then patients will not be included in the PP analysis.

7.7.4. Antihypertensive Medications

If used, anti-hypertensive therapy should be kept stable throughout the trial to allow assessments of the effect of randomized therapies on BP. However, if adjustments to antihypertensive medications or dosages are needed for patient safety, this information should be recorded in the "Concomitant Medications" section of the patient's eCRF. As with all aspects of medical care, the physician's clinical judgment and the well-being of the patient take precedence in clinical decisions.

7.7.5. Special Treatment Considerations

7.7.5.1. Standards of Medical Care

Investigators and other study team members are expected to treat patients according to the nationally established standards of care for diabetes management (Chinese Diabetes Association 2019) or to international standard (American Diabetes Association 2019) except where the treatment would be in conflict with the protocol-provided treatment requirements.

This section provides guidance on management of episodes of hypoglycemic events and events 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 (eg, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders) and hyperglycemia (eg, 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 between study visits.

7.7.5.2. Management of Increased Hypoglycemia Risk

If a hypoglycemic event occurs, the patient should record in the study diary the BG level measured during the episode and prior to administration of treatment (if taken), as well as associated symptoms and treatment administered. Site personnel will enter this information into the hypoglycemia eCRF at each visit. Patients should be trained about signs and symptoms of hypoglycemia and how to manage hypoglycemia. Patients should first seek acute medical or emergency care if needed, and inform the investigative site as soon as possible after an event of severe hypoglycemia has occurred that required assistance to administer corrective treatment.

Investigators should use definitions and criteria provided in Section 9.2.2.1 to diagnose hypoglycemia. In each case of suspected or confirmed hypoglycemia, it is important that details for each event be recorded on the eCRF as completely and accurately as possible, including information on the date, time, BG value, symptoms, and the nature and outcome of any interventions. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The patient should receive additional education, if deemed appropriate.

In this study, increased risk of hypoglycemia is defined as having a single episode of severe hypoglycemia or having more than 1 episode of documented symptomatic hypoglycemia (<3.0 mmol/L) within a 1-week period at any time during the Treatment Period.

In cases where a patient experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the patient has been fully compliant with the assigned therapeutic regimen and also that there is no evidence of other possible causes of hypoglycemia (eg, omission of meal, unexpected increase in exercise).

Patients fulfilling the definition of increased risk of hypoglycemia should first decrease the insulin glargine dose, followed by discontinuation of insulin glargine, if needed. If increased risk of hypoglycemia persists despite discontinuation of insulin glargine, then dose reduction or discontinuation of OAMs should be considered. No adjustment of the dulaglutide dose should be made.

7.7.5.3. Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period

Investigators will be trained on the application of criteria for deciding when and how to intervene in patients who do not reach glycemic targets. An additional therapeutic intervention should be considered in patients who develop severe, persistent hyperglycemia after randomization based on the following criteria:

a) During the first 12 weeks postrandomization (up to Visit 12): An average daily BG >15 mmol/L (equivalent to HbAlc 11%) [Nathan, et al. 2008] on at least two 4-point SMBG profiles over a consecutive 2-week period

OR

b) Between Week 12 and Week 28 (between Visits 12 and 17): An average daily BG >11 mmol/L (equivalent to HbAlc 8.5%) on at least two 4-point SMBG profiles over a consecutive 2-week period

Persistent hyperglycemia considered of severe intensity by the investigator should be reported on the AE eCRF whenever any of the above criteria are met.

Investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that they do not have an acute condition that is raising their BG. If confirmed, the investigator will initiate an appropriate glucose-lowering intervention (rescue intervention) according to the guidance outlined in Section 7.7.1, and it will be recorded on the eCRF specified for collecting antihyperglycemic medications. Other GLP-1 receptor agonists (including commercial Trulicity), basal insulins, and dipeptidyl peptidase -4 (DPP-4) inhibitors are prohibited medications and must not be included in the rescue intervention. Patients who receive rescue intervention for hyperglycemia management should also continue administering study drug for the remaining period in the trial.

7.8. Treatment after the End of the Study

7.8.1. Continued Access

An appropriate diabetes treatment regimen will be prescribed per the investigator's judgment following the last study visit or an early termination visit. However, during the safety follow-up period patients cannot be prescribed GLP-1 receptor agonists.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Patient Decision**
  - The patient requests to discontinue investigational product.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the electronic case report form (eCRF).
  Discontinuation of the investigational product for abnormal liver tests **should be** considered by the investigator when a patient meets one of the following conditions after consultation with the Lilly designated medical monitor:
  - Alanine aminotransferase (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 >2.5X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

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

- If a patient is inadvertently enrolled and it is determined that continued treatment with study drugs would not be medically appropriate;
- Acute or chronic pancreatitis;
- If a patient is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization;

- If a patient is diagnosed with C-cell hyperplasia or medullary thyroid carcinoma (MTC) after randomization;
- Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken;
- Any significant study drug-related hypersensitivity reaction;
- If a non-study GLP-1 receptor agonist is initiated, and the patient refuses to discontinue this medication;
- If female patient becomes pregnant;
- If a patient is diagnosed with T1D;
- If an investigator, site personnel performing assessments, or patient is unblinded;
- If the investigator or sponsor decides that the patient should be withdrawn from study drug; if the investigator decides to permanently discontinue study treatment because of an SAE or a clinically significant laboratory value, Lilly or its designee should be alerted immediately.
- if the patient or the patient's designee, for example, legal guardian, requests that the patient be withdrawn from study drug

Patients who stop the study drug permanently will receive another glucose-lowering intervention (Section 7.7.1) and will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements.

Patients discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 2 Schedule of Activities, Section 9.2 Adverse Event, and Section 9.4 Safety of this protocol.

8.1.2. Temporary Discontinuation from Study Treatment

In certain situations after randomization, the investigator may need to temporarily discontinue (interrupt) study drug (for example, due to an AE or a clinically significant laboratory value). If study drug interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 9.2 of this protocol. Every effort should be made by the investigator to maintain patients on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so. Investigators should inform the Sponsor that study drug has been temporarily interrupted. The data related to temporary interruption of study treatment will be documented in source documents and entered in the eCRF.

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, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on

study treatment. If the investigator and the sponsor CRP agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Every attempt should be made to keep patients in the trial irrespective of their adherence to treatment with study drug in order to minimize the amount of missing data and to enable assessment of study objectives as planned by the study protocol. Early patient discontinuation from the study may be warranted in the following situations for ethical or legal reasons:

- If a patient is diagnosed with T1D;
- If a female patient becomes pregnant;
- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study;

Patients may also discontinue from the study due to:

- Sponsor or investigator decision
    - participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP);
- Patient decision
    - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study.

Patients who agree to provide information relevant to any trial endpoint at the end of the study are not considered to have discontinued from the study.

A patient who withdraws consent and clearly indicates that there will be no further contact of any kind with the site will be considered to have discontinued from the study.

Prior to early study discontinuation, the patient will discontinue study drug and will have end-of-study procedures (ET visit) performed as shown in the Schedule of Activities (Section 2). During the ET visit, the patient will be prescribed an appropriate glucose-lowering regimen and glucose self-monitoring plan. Visit 801 (safety follow-up visit) should be performed approximately 4 weeks after the ET visit as the final study visit.

Patients discontinuing from the study prematurely for any reason should complete adverse event and other safety follow-up per Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

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 are otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 presents the Schedule of Activities, with the study procedures and their timing (including number of days for allowable visit deviations [visit windows]).

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.

9.1. Efficacy Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy measure will be evaluated at 28 weeks:

- change from baseline in HbA1c.

9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be evaluated at 28 weeks:

- proportion of patients achieving HbA1c target of <7.0% or ≤6.5%;
- proportion of patients achieving HbA1c target of <7.0% and without weight gain (<0.1 kg) and without documented symptomatic hypoglycemia during the maintenance period (Week 12-28);
- proportion of patients achieving HbA1c target of <7.0% and without documented symptomatic hypoglycemia during the maintenance period;
- proportion of patients achieving HbA1c target of <7.0% and without weight gain (<0.1 kg);
- changes from baseline in FSG measured at the central laboratory;
- changes from baseline in BG from daily SMBG profiles;
- changes from baseline in body weight;
- changes from baseline in daily mean insulin glargine doses.

9.1.3. Exploratory Efficacy Measures

The following exploratory efficacy measures will be evaluated:

- frequency of insulin dose adjustments at 28 weeks;
- number of insulin dose assessments per TTT algorithm and compliance with the TTT algorithm at 6, 8, and 12 weeks.

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 patient 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 patient 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 one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization

- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor 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, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (see Section 9.2) 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. Patients with a serious hepatic adverse event should have additional data collected using the eCRF.

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 subjects once they have discontinued and/or completed the study (the patient disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject 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.

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to 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 identification, recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Adverse Event of Special Interest

9.2.2.1. Hypoglycemia

Patients will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (ET visit or 801). 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 according to the Schedule of Activities (Section 2). Site personnel will enter this information into the hypoglycemia eCRF at each visit.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the BG 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) in accordance with the 2020 ADA position statement on glycemic targets:

Level 1 hypoglycemia:

Glucose <70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L): Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel particpants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L): This is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence of absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that **occurs at night** and presumably during sleep.

To avoid duplicate reporting, all consecutive BG values <3.9 mmol/L occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013; ADA. 2020).

In each case of suspected or confirmed hypoglycemia, it is important that the event be properly categorized, the effect of the intervention be assessed, and the frequency of hypoglycemia be evaluated. The role of dietary changes and physical exercise (or any other contributing factor) in the development of an event should be established. The patient should receive additional education, if deemed appropriate. Management of increased risk of hypoglycemia is described in Section 7.7.5.2 and Section 8.1.1. It is important that each case of suspected or confirmed hypoglycemia be properly categorized with respect to severity.

9.2.2.2. Severe, Persistent Hyperglycemia

Severe, persistent hyperglycemia will be collected as an AE during the trial to assess the risk of extreme imbalance in glycemic control, as defined in Section 7.7.5.3. Details of antihyperglycemic medication initiated as rescue therapy for severe, persistent hyperglycemia per these criteria will be collected on the antihyperglycemic concomitant therapy eCRF.

9.2.2.3. 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:

- 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);
- serum amylase (total and pancreatic) and/or lipase ≥3×ULN;
- 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 pancreatic amylase 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 support the diagnosis of acute pancreatitis, the patient must discontinue therapy with investigational product,but will still continue in the study on another glucose-lowering regimen (see Section 7.7.1 and Section 8.1.1 for details on the introduction of new antihyperglycemic interventions). 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 [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug.

Each patient will have measurements of pancreatic amylase and lipase (assessed at the central laboratory) as shown on the Schedule of Activities (Section 2), to assess the effects of the investigational doses of dulaglutide on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck et al. 2017; Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3×ULN) is not mandated, but may be performed based on the investigator's clinical judgement and assessment of the patient's overall clinical condition.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent committee of expert physicians. Only cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication. In addition, AEs of severe or serious abdominal pain of unknown etiology 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 and those with severe or serious abdominal pain 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.

9.2.2.4. 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). Patients with a personal or family history of MTC or personal history of MEN 2 syndrome, or who have serum calcitonin ≥20 pg/mL at study entry as determined by the central laboratory will be excluded. 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). The purpose of calcitonin measurements is to assess the potential of dulaglutide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Patients who develop serum calcitonin increases ≥50% of the screening value AND an absolute value ≥20 pg/mL and <35 pg/mL at Visit 17 (Week 28) will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the patient will be encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude a serious adverse effect on the gland.

Patients with an increase in serum calcitonin ≥50% of screening value AND an absolute value ≥35 pg/mL at Visit 17 (Week 28) will be recommended to immediately undergo additional endocrine assessments and longer term follow-up by an endocrinologist.

For patients who require additional endocrine assessment because of increased calcitonin concentration per criteria provided in this section, data from the follow-up assessment will be collected in the specific section of the eCRF.

9.2.2.5. Cardiovascular Events

Vital signs (PR, SBP, DBP) will be monitored throughout the study, and 12-lead electrocardiograms (ECGs) will be monitored at screening and Visit 17 (Week 28). Any clinically relevant finding from vital signs and ECGs obtained before the first dosing of study drug that results in a diagnosis should be recorded in eCRF as a preexisting condition and medical history. Any clinically relevant finding from vital signs and ECGs that occurs after the first dosing of study drug and results in a diagnosis should be recorded as an AE in eCRF. CV events will be analyzed using preferred terms and abnormal ECG result.

Deaths will be monitored throughout the study. Relevant data from patients who experienced death will be entered into a specifically designed eCRF page by study site.

9.2.2.6. 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 the eCRF for any AEs or SAEs deemed related to study drug by the investigator. Injection site reactions will be collected on an eCRF separate from the hypersensitivity reaction eCRF. Study drug should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug (Section 8.1.2). Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator. It is recommended that patients who experience a systemic hypersensitivity reaction be treated per the local standard of care. In the case of generalized urticaria or anaphylaxis, additional blood samples might be collected per investigator's judgement to diagnose and treat the event at local hospital.

If study drug is permanently discontinued, the patient will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the patient's clinical status, and will continue in the trial to collect all planed efficacy and safety measurements (see Sections 7.7.1 and 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 or drug delivery system so that the situation can be assessed.

9.3. Treatment of Overdose

Study drug overdose will be reported as an AE. In the event of overdose, refer to the IB and/or Product Labels.

9.4. Safety

9.4.1. Electrocardiograms

For each patient, single 12-lead ECG will be conducted at screening and at week 28 per the Schedule of Activities (Section 2). The patient must be supine for approximately 5 to 10 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. Any clinically relevant findings from ECGs obtained *before* the first dose of study drug that result in a diagnosis should be reported as a preexisting condition and medical history.

After enrollment, if a clinically significant finding is identified from the additional ECGs conducted at the discretion of the investigator (including but not limited to changes in QT/QTc interval from baseline), the investigator will determine if the patient can continue on study drug. 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 clinically relevant findings from ECGs that result in a diagnosis and that occur *after* the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via eCRF.

9.4.2. Vital Signs

Sitting BP and PR will be measured using standardized equipment provided by the Sponsor according to the Schedule of Activities (Section 2). Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required (see Schedule of Activities Section 2). The patient should be allowed to sit quietly for 5 minutes before vital sign measurements. 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. At Visit 1 (screening), to determine which arm should be used to collect BP and PR throughout the study. BP and PR will be measured once in each arm and the arm that had the higher BP should be used to collect all 2 measurements of both BP and PR at all study visits. For each parameter (PR, SBP/diastolic blood pressure [DBP]), 2 measurements will be taken using the same arm; the recordings should

be taken at least 1 minute apart. Each measurement of sitting PR and BP is to be recorded in the eCRF. Any AE related to changes in BP and PR should be reported.

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(s) should be reported to Lilly or its designee as an AE via eCRF.

9.4.4. Body Weight, Height, 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. 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.

Specific safety measures are included in the protocol to ensure appropriate monitoring of pancreatic (Section 9.2.2.3), thyroid (Section 9.2.2.4), and liver safety (Section 9.4.5.1).

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring board (an advisory group for this study formed to protect the integrity of data; refer to Interim Analyses section (Section 10.3.8) can conduct additional analyses of the safety data.

9.4.5.1. Hepatic Safety Monitoring

9.4.5.1.1. Close Hepatic Monitoring

Laboratory tests (Appendix 4), including ALT, AST, ALP, TBL, direct bilirubin (D. Bil), gamma-glutamyltransferase (GGT), and creatine kinase (CK), should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur:

If a participant with baseline results of ...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline

TBL ≥1.5x ULN	TBL ≥2x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ULN= upper limit of normal; TBL = total bilirubin

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

9.4.5.1.2. Comprehensive Hepatic Evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms*, or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for patients with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms*, or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for patients with Gilbert's syndrome)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ALP = alkaline phosphatase; ULN= upper limit of normal; TBL = total bilirubin

Note: * Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

9.4.5.1.3. Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the two consecutive blood tests should be at least 2 days.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

Not applicable.

9.8. Biomarkers

Not applicable.

9.9. Health Outcome

The 3 questionnaires listed below will be completed by the patients per 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 personnel and self-completed by the patient during the visit. The investigator or site personnel 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.

9.9.1. EuroQol 5-dimension 5-level (EQ-5D-5L)

Generic HR-QoL will be assessed using the EQ-5D-5L (EQ-5D; EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3251 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. In conjunction with the health state data, it provides a composite picture of the respondent's health status.

The EQ-5D-5L is used worldwide and is available in more than 170 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide (EuroQoL Group 2015).

9.9.2. Impact of Weight on Self-Perception (IW-SP)

The IW-SP questionnaire contains 3 items that assess how often patients body weight affects how happy they are with their appearance and how often they feel self-conscious when out in public (Hayes and DeLozier 2015). Items are scored on a 5-point numeric rating scale, where 5 = never and 1 = always. Overall score is calculated by summing the scores of the 3 items and dividing by the number of items (3). Overall score ranges from 1 to 5. Transformed overall score is obtained by linearly transforming the raw overall score to a 0 to 100 scale. Higher overall score and higher transformed score are indicative of better self-perception.

The IW-SP will be completed by the patients at Visits 3 (Week 0), 12 (Week 12), 17 (Week 28), and ET per the Schedule of Activities (Section 2).

9.9.3. Medication Delivery Device Assessment Battery (MDDAB)

The MDDAB was developed for use in Study H9X-MC-GBDZ (GBDZ) to evaluate patient perceptions regarding use and specific features of the SUP. Modules of the MDDAB that are relevant to the current study and appropriate for administration to an injection-experienced population will be administered:

- Module 1, SUP ease of use: The ease of use module comprises 12 items evaluating overall ease of using the SUP device and ease of using specific SUP device features. Patients will be instructed to complete this module thinking about their *weekly* injection device (ie, the SUP) only. The module will be administered at Visits 8 (Week 6), 17 (Week 28), and ET, as per the Schedule of Activities (Section 2).
- Module 2, SUP device features: The device features module comprises 13 items evaluating the degree to which patients like or dislike specific features of the SUP device. Patients will be instructed to complete this module thinking about their *weekly* injection device (ie, the SUP) only. The module will be administered at Visits 8 (Week 6), 17 (Week 28), or ET, as per the Schedule of Activities (Section 2).
- Module 3a, SUP experience: The SUP experience module (a) comprises 5 items evaluating patient experience with the SUP device; specifically assessing convenience, satisfaction, pain, and confidence. Patients will be instructed to complete this module thinking about their *weekly* injection device (ie, the SUP) only. Module 3a will be administered at Visit 8 (Week 6) only, per the Schedule of Activities (Section 2).
- Module 3b, SUP experience: The SUP experience module (b) comprises 8 items, collectively evaluating patient experience with the SUP device. Module 3b includes the same 5 items as Module 3a plus items pertaining to willingness to continue using the device and willingness to recommend the device to someone else. Patients will be instructed to complete this module thinking about their *weekly* injection device (ie, the SUP) only. Module 3b will be administered at Visit 17 (Week 28) or ET only, per the Schedule of Activities (Section 2).
- Module 4, Glargine delivery device experience: The glargine delivery device experience module is similar to SUP experience module 3b, differing only in its instructions to the patient. This version will instruct patients to complete the questions according to their experience with the daily (ie, glargine) device. Module 4 will be administered at Visit 17 (Week 28) or ET only, as per the Schedule of Activities (Section 2).

At Visit 17 (Week 28) or the ET visit, patient completion of modules 3b and 4 will be arranged to minimize bias; additional details will be provided in the SAP.

10. Statistical Considerations

10.1. Sample Size Determination

A total of approximately 290 patients (145 per group) will be randomized to have approximately 246 completers (123 per group) to show dulaglutide as add-on to titrated insulin glargine is superior to placebo as add-on to titrated insulin glargine with 90% power assuming a treatment difference of 0.5% in HbA1c reduction, standard deviation (SD)=1.2%, dropout rate of 15%, and 2-sided alpha of 0.05. The screen failure rate is estimated as 40%. Approximately 483 patients will be screened.

10.2. Populations for Analyses

Table GBGO.6 defines the populations to be used for analyses.

Table GBGO.6. Populations for Analyses

Population	Description
Entered	All patients who sign informed consent
Randomized	All patients who are randomized to a treatment arm
Nonrandomized	All patients entered, but not randomized to a treatment arm
Intent-to-treat (ITT)	All patients randomized who take ≥1 dose of study medication for assigned treatment arm
Completers	All patients in the ITT population who complete the treatment period (that is, do not discontinue early from the study). Data after initiation of rescue therapy will be censored for the efficacy analyses. • Note: There is no requirement that completers have to be on study drug the entire study.
Per-Protocol (PP)	All patients in ITT and who also meet the following criteria: • Have no protocol deviations expected to impact the primary endpoint for HbA1c; • Complete the treatment period (28 week [Visit 17]) for primary endpoint (that is, do not discontinue from the study drug early)

Abbreviations: HbA1c = hemoglobin A1c.
Note: The full list will be defined in the Trial issue management 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 statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise specified, listings will include all randomized patients. Both efficacy and safety analyses will be conducted using the intention to treat (ITT) population. Unless otherwise

specified, efficacy data from patients who started rescue therapy or discontinued study treatment prematurely will be censored from the point of initiating rescue treatment or premature discontinuation onwards. Selected analyses will also be conducted using the PP and Completers populations. The PP and Completers populations are subsets of the ITT population.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and 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 at the randomization visit (Visit 3). If baseline data are missing, the last nonmissing measurement taken prior to Visit 3 will be used.

The primary and key secondary continuous efficacy measures will be analyzed with mixed-model repeated measures (MMRM) using restricted maximum likelihood (REML) (Section 10.3.3.1). The model will include factors for treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), visit, and treatment-by-visit as fixed effects, baseline as a covariate, and patient as random effect. An unstructured covariance structure will be used to model the within-patient variability. If this model fails to converge, the following covariance structures will be tested in order:

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

The first covariance structure that converges will be used.

The proportion of patients achieving the target HbA1c of <7.0% will be analyzed using a longitudinal logistic regression with repeated measurements (Section 10.3.3.2).

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and change from baseline measurements. Least-squares mean (LS 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 mean and the 95% CIs for the treatment differences along with the p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and proportion. Fisher's exact tests will be used for treatment comparisons .

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

The overall comparison of proportions of patients who discontinued between the treatment groups will be performed using a Fisher's exact test.

10.3.2.2. Patient Characteristics

Demographic and baseline characteristics will be summarized by treatment arms. For continuous measures, summary statistics will include sample size, mean, median, maximum, minimum, and SDs along with an analysis of variance (ANOVA) to compare the means of the 2 treatment groups . For categorical measures, summary statistics will include sample size, frequency, and percent. Frequencies will be analyzed using a Fisher's exact test.

10.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by treatment groups. Proportion of certain categories of concomitant medications will be analyzed using a Fisher's exact test.

10.3.2.4. Treatment Compliance

Treatment compliance defined as taking at least 75% of required injections of study drug during specified study periods (see Section 7.6). Overall compliance is defined as being at least 75% compliant with study drug for at least 75% of the visits. The investigator will advise the patient that injections should be given weekly at approximately the same time of the day, on the same day of the week. Compliance will be summarized by treatment arm, by visit and overall.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary outcome is the difference in HbA1c change from baseline between treatment groups based on the ITT population at the planned end of the treatment period of 28 weeks. The analysis model will be a MMRM for HbA1c change from baseline to 28 weeks (Visit 17) in the ITT population with treatment, OAM use, visit and treatment-by-visit as fixed effects, baseline HbA1c as a covariate, and patient as a random effect.

The analysis model, MMRM, will be repeated using the PP and Completers populations. If the conclusion differs from that of the ITT population, the data and analyses will be further investigated.

10.3.3.2. Secondary Analyses

The key secondary objectives include single endpoint (HbA1c of <7.0% or ≤6.5% at 28 weeks); triple endpoint (HbA1c <7% and with no weight gain [<0.1 kg] at 28 weeks and without documented symptomatic hypoglycemia [<3.0 mmol/L] during the miantenance period [Weeks 12-28]); double endpoint (HbA1c <7% at 28 weeks and without documented symptomatic hypoglycemia [<3.0 mmol/L] during the miantenance period [Weeks 12-28]); and double

endpoint (HbA1c <7% and with no weight gain [<0.1 kg] at 28 weeks). These endpoints will be analyzed using longitudinal logistic regression with repeated measurements. The model will include independent variables of treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), visit, and treatment-by-visit as fixed effects and baseline HbA1c as covariates.

The key secondary continuous efficacy measures (change from baseline in body weight and FBG) will be analyzed using MMRM. The MMRM model will include independent variables of treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), baseline HbA1c stratum (<8.5% vs. ≥8.5%), visit, and treatment-by-visit as fixed effects and baseline dependent variable as covariates.

For analysis of the other continuous secondary efficacy measures (change from baseline in BG, insulin dose), MMRM will be performed using the ITT population. The MMRM models will include the model terms given for the previously described primary analysis model. There will be no multiplicity adjustment for pairwise comparisons.

10.3.3.3. Tertiary/Exploratory Analyses

The number of insulin dose assessments per the TTT algorithm, compliance with the TTT algorithm (number of assessments performed correctly, number of assessments that required dose change, number of assessments for which the outcomes were correctly followed by the patient, and reason the outcomes of assessments were not followed by the patient) and frequency of insulin dose adjustments will be analyzed using an ANOVA model, including treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), and baseline HbA1c stratum.

The other objectives include triple endpoint (HbA1c <7% and no weight gain [<0.1 kg] at 28 weeks, and no documented symptomatic hypoglycemia [BG <3.9 mmol/L] during the maintenance period); double endpoint (HbA1c <7% at 28 weeks and no documented symptomatic hypoglycemia [BG <3.9 mmol/L] during the maintenance period); Proportion of patients achieving HbA1c target <7.0% and without weight gain (<0.1 kg) at 28 weeks.

Furthermore, we will conduct some additional efficacy analysis without censoring the data after rescue therapy or premature treatment discontinuation (whichever occurs first). Missing endpoints will be imputed by jumping to the reference method. Measurements include actual HbA1c, body weight and FSG and frequency counts and percentage of patients achieving the HbA1c target of <7.0% and changes in these measures from baseline. We will analyze HbA1c, body weight and FSG by ANCOVA. Percentages of patients achieving the target of HbA1c <7.0% will be analyzed using longitudinal logistic regression with repeated measurements.

10.3.4. Safety Analyses

The safety analysis will include analysis of AEs, SAEs, hypoglycemic and hyperglycemic episodes, vital signs, electrocardiogram and laboratory analyses. Unless otherwise specified, the ITT population will be used for analyses of safety measures.

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 treatment-emergent adverse events (TEAEs), defined as post-baseline events that are new events or preexisting conditions that worsened in severity after randomization, will be listed by patient and visit. Information on treatment, actual term, preferred term, severity, seriousness, and relationship to study drug will also be reported.

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

Summaries (if appropriate) of AESI defined in Section 9.2.2 will be generated.

10.3.4.3. Hypoglycemic Episodes

Section 9.2.2.1 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 ITT population (with post-rescue data censored). Categories of hypoglycemia for analysis include "documented", "documented symptomatic", "severe hypoglycemia", and "nocturnal".

Hypoglycemic episodes will be analyzed using 2 hypoglycemic thresholds: Level 1 (glucose alert level, <3.9 mmol/L [70 mg/dL] and ≥3.0 mmol/L [54 mg/dL]) and Level 2 (clinically significant hypoglycemia level, <3.0 mmol/L [54 mg/dL]). Other categories, including the categories above defined with different glucose thresholds, may also be included in these analyses when deemed appropriate.

The incidence of hypoglycemic episodes will be summarized by frequencies and proportion for each treatment group, by visit as well as overall. Treatment differences in the incidence of hypoglycemic episodes will be assessed using Fisher's exact tests. Treatment differences in rates of hypoglycemic episodes (episodes/patient/30 days; episodes/patient/year) will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution. The model will include treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), baseline HbA1c stratum (<8.5% vs. ≥8.5%), visit, treatment-by-visit interaction, and baseline hypoglycemia rate. The logarithm of days between visits will be included as an offset to account for possible unequal duration between visits and between patients.

10.3.4.4. Severe, Persistent Hyperglycemia

Listings and summaries (if appropriate) will be provided for patients with at least one event of severe, persistent hyperglycemia.

Time to initiation of rescue therapy due to severe, persistent hyperglycemia will be analyzed using the semiparametric proportional hazard Cox model with treatment, and OAM use as fixed effects and baseline HbA1c as a fixed covariate. The proportions of patients initiating rescue therapy due to severe, persistent hyperglycemia will be analyzed using Fisher's exact tests.

10.3.4.5. Vital Signs

The average value of the 2 sitting vital sign measurements will be used for analyses.

Descriptive statistic for the actual measurements and changes from baseline for SBP, DBP and PR will be presented by treatment and visit on the ITT population.

10.3.4.6. Electrocardiogram

Descriptive statistics for the absolute measurements, changes from baseline, and clinically relevant changes for selected ECG parameters will be defined in the SAP.

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

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

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Evaluation of Immunogenicity

Not applicable.

10.3.7. Other Analyses

10.3.7.1. Health Economics

Continuous measures from the patient reported outcomes (PRO) instruments will be analyzed using the ANCOVA model specified in Section 10.3.1, using on-treatment without rescue data.

Categorical measures from the PRO instruments will be summarized for each treatment.

10.3.7.2. Subgroup Analyses

Subgroup analyses of treatment interaction with important factors may be conducted for the primary endpoint of HbA1c. The model for the primary analysis will be an MMRM utilized by adding addtional factors of subgroup, subgroup by treatment, subgroup by visit and treatment by subgroup by visit when accessing the treatment by subgroup interaction. If the subgroup is one of the stratification variables, then the subgroup will only be included once in the model.

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

- Sex
- Baseline age group (<65 years, ≥65 years)
- Duration of diabetes at baseline (<median duration and ≥median duration)
- BMI at baseline (<median and ≥median))
- Baseline HbA1c (<8.5%, ≥8.5%)
- Baseline fasting glucose (by quartile)
- OAM usage (metformin alone, acarbose alone, metformin and acarbose), if more than 25% of the total patients

10.3.8. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, 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
ADA	American Diabetes Association
adjudication committee	An external committee whose purpose is to evaluate study data and decide whether a study endpoint or other criterion has been met.
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AST	aspartate aminotransferase
BG	blood glucose
blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CI	confidence interval
CK	creatine kinase
CKD-EPI	Chronic Kidney Disease-Epidemiology

complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
CRP	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.
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
D.Bil	direct bilirubin
DBP	diastolic blood pressure
DPP-4	dipeptidyl peptidase-4
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	EuroQol 5-dimension questionnaire
ERB	Ethics Review Board
ET	early termination
fasting	Abstaining from food and drink (except water) for approximately 8 hours (typically, overnight), no significant physical activity and non administration of glucose-lowering agents during this period
FBG	fasting blood glucose
FDA	Food and Drug Administration
FSG	fasting serum glucose
FSH	follicle-stimulating hormone
GAD	glutamic acid decarboxylase

GCP	good clinical practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICA	islet cell antibodies
ICF	informed consent form
ICH	International Conference on Harmonisation
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the complete reporting database is created/locked for the primary endpoint.
investigational product	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.
ITT	intent to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IW-SP	Impact of Weight on Self-Perceptions Questionnaire
IWRS	interactive web-response system
LS mean	least-squares mean
MDDAB	Medication Delivery Device Assessment Battery
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia
MI	myocardial infarction
MMRM	mixed-model repeated measures
MRI	magnetic resonance imaging

MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
NOAEL	no-observed-adverse-effect level
NPH	neutral protamine Hagedorn
OAM	oral antihyperglycemic medication
OTC	over-the-counter
PD	pharmacodynamic
PK	pharmacokinetics
PP	per-protocol set: 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.
PR	pulse rate
PRO	patient reported outcome
QD	once daily
QW	once weekly
REML	restricted maximum likelihood
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SUP	single-use pen
SGLT2	sodium-glucose co-transporter 2
SMBG	self-monitored plasma glucose
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
T1D	type 1 diabetes
T2D	type 2 diabetes

TBL	total bilirubin level
TE	treatment-emergent
TEAE	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, and does not necessarily have to have a causal relationship with this treatment.
TTT	treat-to-target
ULN	upper limit of normal
USPI	United States Prescribing Information
VAS	Visual Analog Scale

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a,c]

Hematology	**Clinical Chemistry**
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Gamma-glutamyl transferase (GGT)
Eosinophils	Blood urea nitrogen (BUN)
Basophils	Creatinine
Platelets	Creatine kinase (creatine phosphokinase; CPK)[d]
	Uric acid
Urinalysis	Calcium
Albumin/creatinine ratio (urine)[b]	Glucose
	Albumin
Endocrine	
Calcitonin	**eGFR (calculated by CKD-EPI equation)**
Lipid Panel	**Fasting glucose**
Total cholesterol	
LDL[g]	**Pancreas (Exocrine)**
HDL	Serum amylase, total and pancreatic
VLDL	Serum lipase
Triglycerides	
	HbA1c
Pregnancy test serum and urine[e]	
	Follicle-stimulating hormone[f]

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; CK-MB = creatine kinase-MB; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; RBC = red blood cells; WBC = white blood cells; VLDL = very low density lipoprotein cholesterol.

a All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.

b Urinary albumin and creatinine are measured; the ratio is calculated.

c Additional blood samples may be collected based on the investigator's judgment.

d CK-MB is to be assayed if the creatine kinase result is >1000 IU/L.

e Serum pregnancy test will be performed by central laboratory at Visit 1 for women of childbearing potential; a urine pregnancy test must be performed at Visit 3. Urine pregnancy tests may also be performed at the investigator's discretion during the study. A local laboratory may be used for urine pregnancy tests.

f Follicle-stimulating hormone test performed at Visit 1 for potential postmenopausal women age 45 years or above with an intact uterus, not on hormone therapy or oral contraceptives, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH≥40 mIU/mL and estradiol <30 pg/mL).

[g] This value will be calculated. If triglycerides >400 mg/dL, then direct LDL will be assayed.

Appendix 3. Study Governance Considerations

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 nature of the study, the potential risks and benefits of participating in the study, and that their participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the 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 study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, 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 protocol and related amendments and addenda, current Investigator Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

This study will be conducted in accordance with the protocol and with the:

- 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.

Appendix 3.1.5. Investigator Information

Physicians with a specialty in diabetes/endocrinology, cardiology, nephrology, internal medicine, family medicine, general medicine, or any other specialty physician who has experience treating Type 2 Diabetes with clinical research experience will participate as investigators in this clinical trial.

Appendix 3.1.6. 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 3.1.7. 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.

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

In addition, 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 ERBs with direct access to original source documents.

Appendix 3.2.1. Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture system (EDC) will be used in this study for the collection of eCRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the eCRF.

Additionally, clinical outcome assessment (COA) data (scales, self-reported diary data) will be collected by the subject/investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning

of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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 or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study H9X-MC-GBGO is described in the Clinical Research Agreement or Master Clinical Trial Agreement.

Appendix 4. Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 9.4.5.1 for guidance on appropriate test selection.

- For testing selected, analysis is required to be completed by the Lilly designated central laboratory except for those testings that are denoted as local below.
- Local testing may be performed in addition to central testing when required for immediate patient management.
- Results will be reported if a validated test or calculation is available.

Hematology

Hemoglobin

Hematocrit

Erythrocytes (RBCs - Red Blood Cells)

Leukocytes (WBCs - White Blood Cells)

Differential:

- Neutrophils, segmented
- Lymphocytes
- Monocytes
- Basophils
- Eosinophils

Platelets

Cell morphology (RBC and WBC)

Coagulation

Prothrombin Time, international normalized ratio (PT-INR)

Serology

Hepatitis A Virus (HAV) Testing:

- HAV Total Antibody
- HAV IgM Antibody

Hepatis B Virus (HBV) Testing:

- Hepatitis B surface antigen (HBsAg)
- Hepatitis B surface antibody (Anti-HBs)
- Hepatitis B core total antibody (Anti-HBc)

Clinical Chemistry

Total bilirubin

Direct bilirubin

Alkaline phosphatase (ALP)

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Gamma-glutamyl transferase (GGT)

Creatine kinase (CK)

Other Chemistry

Acetaminophen

Acetaminophen Protein Adducts [c]

Alkaline Phosphatase Isoenzymes [c]

Ceruloplasmin

Copper [c]

Ethyl Alcohol (EtOH)

Haptoglobin

Immunoglobulin IgA (Quantitative)

Immunoglobulin IgG (Quantitative)

Immunoglobulin IgM (Quantitative)

Phosphatidylethanol (PEth) [c]

Urine Chemistry

Drug Screen

Ethyl glucuronide (EtG) [c]

Other Serology

Hepatitis B core IgM antibody

Hepatitis B core IgG antibody

HBV DNA [d]

Hepatis C Virus (HCV) Testing:

HCV antibody

HCV RNA [d]

Hepatitis D Virus (HDV) Testing:

HDV antibody

Hepatitis E Virus (HEV) Testing:

HEV IgG antibody

HEV IgM antibody

HEV RNA [d]

Microbiology [c]

Culture:

Blood

Urine

Anti-nuclear antibody (ANA)

Anti-smooth muscle antibody (ASMA) [a]

Anti-actin antibody [c, b]

Epstein-Barr Virus (EBV) Testing:

EBV antibody

EBV DNA [d]

Cytomegalovirus (CMV) Testing:

CMV antibody

CMV DNA [d]

Herpes Simplex Virus (HSV) Testing:

HSV (Type 1 and 2) antibody

HSV (Type 1 and 2) DNA [c, d]

Liver Kidney Microsomal Type 1 (LKM-1) Antibody

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a Not required if anti-actin antibody is tested.

b Not required if anti-smooth muscle antibody (ASMA) is tested.

c Assayed ONLY by investigator-designated local laboratory if available; no central testing available.

d Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

Appendix 5. World Health Organization Classification of Diabetes and Diagnostic Criteria

Type 1 Diabetes: Type 1 diabetes 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: Type 2 diabetes, 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).

Appendix 6. Classification of Contraceptive Methods

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini pill
- NuvaRing
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle). Note: periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception
- Vasectomy – for men in clinical trials

Effective Methods of Contraception (must use combination of 2 methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

Appendix 7. Protocol Amendment H9X-MC-GBGO(a) Summary A Randomized, Double-Blind Trial Comparing the Effect of the Addition of Dulaglutide 1.5 mg versus the Addition of Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Patients with Type 2 Diabetes

Overview

Protocol H9X-MC-GBGO A Randomized, Double-Blind Trial Comparing the Effect of the Addition of Dulaglutide 1.5 mg versus the Addition of Placebo to Titrated Basal Insulin on Glycemic Control in Chinese Patients with Type 2 Diabetes has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table. Minor typographical corrections not affecting the protocol content are not summarized in this appendix.

Amendment Summary for Protocol H9X-MC-GBGO(a)

Section # and Name	Description of Change	Brief Rationale
Section 1. Synopsis	In the “Efficacy Analyses” part, the wording for analysis of body weight change was revised mainly by deleting "actual value/measurement” and “actual values”.	The deletion was due to that the actual value or measurement is not a secondary endpoint.
Section 2. Schedule of Activities	In Table GBGO.1., “Dispense study diary, instruct in use” was crossed at Visit 17 with a new footnote added mentioning “Safety data to be captured after discontinuation of study drug during safety follow-up period.”	This new footnote is to explain why study diary needs to be dispensed at Visit 17.
Section 2. Schedule of Activities	In Table GBGO.1., the superscript mentioning assessment of the patient’s compliance with insulin dose adjustment per TTT algorithm for “Laboratory tests” was deleted.	The superscript did not fit to “Laboratory tests”.
Section 2. Schedule of Activities Section 5.1. Overall Design Section 9.4.2. Vital Signs	The “heart rate” or “HR” was replaced by “pulse rate” or “PR”.	Per protocol, pulse rate instead of heart rate will be measured in the study.

Section 4. Objectives and Endpoints	For the fourth point in the exploratory efficacy part, "and without documented symptomatic hypoglycemia (BG ≤3.9 mmol/L) during the maintenance period (Weeks 12-28)" was deleted.	This semi-sentence was wrongly added here. Only the proportion of patients achieving HbA1c target of <7.0% and without weight gain (<0.1 kg) at 28 weeks will be investigated as planned.
Section 5.1. Overall Design	In the 3rd paragraph, "mean" was deleted from the "mean FBG ≥5.6 mmol/L" and wording was revised.	Since median FBG or mean FBG will be used for eligibility assessment, which depends on the number of FBG values collected prior to Visit 3 (Section 7.2.2.2.1), using "mean" is not accurate.
Section 5.1. Overall Design	In the 3rd paragraph, the wording was revised to redefine the stability and range of metformin and acarbose dose	The previous description did not specifically define dose stability for metformin and acarbose, and the dose range was not accurate.
Section 5.1. Overall Design	In the "Lead-in" part, "at the discretion of the investigator" was added to specify who determines the insulin dose adjustment regarding patient safety.	The previous expression did not clarify explicitly who should be the one that determines insulin dose adjustment.
Section 5.1. Overall Design	In the "Randomization" part, the wording for emphasizing that insulin dose assessment and adjustment should be done at least 3 days before Visit 3 was revised without changing the content	The previous expression is hard to be understood.
Section 5.1. Overall Design	In the "Stabilization Period" and "Titration Period" parts, the buffer time presented in the brackets for Visits 6, 8 and 10 were revised from "7 days" to "4 days".	The previous buffer time "7 days" was incorrect. As shown in Section 2. Schedule of Activities, the correct buffer time should be 4 days.
Section 5.1. Overall Design Section 7.2.2.2. Insulin Glargine	In the "Stabilization Period", "not later than 7 days after the first dosing of study drug" was deleted for describing decrease in insulin glargine dose for patients with baseline HbA1c ≤8.0%. Likewise, "(within 7 days)" was deleted in Section 7.2.2.2.	The deletions of "not later than 7 days" and "within 7 days" were suggested by the reviewer arguing that "it is difficult to see the rationale for the 7 day time window given, as the screening HbA1c can be used to adjust insulin dose and a second HbA1c measurement at randomization after only 2 weeks from the screening value does not really seem reasonable."
Section 5.1. Overall Design	In the title for the titration period, "Weeks 5 to 28" in the bracket was revised to "Weeks 4 to 28".	According to study period, Visit 6 will take place at Week 4. The previous number 5 was incorrect.

Section 5.1 Overall Design	For "Titration Period", the sentence "Any patient meeting criteria for severe, persistent hyperglycemia after 12 weeks of unrestricted insulin glargine dose adjustments will discontinue study drug and the study (see Section 7.7.5.3 for details)" was deleted.	The contenct was in conflict with that in Section 7.7.5.3.
Section 5.1. Overall Design	In the "Safety Follow-up (801) Visit" part, the safety follow-up visit for patients who complete the treatment period will take place around 4 weeks after last visit instead of the previously written "after their last dose".	The last injection of study drug will be at Week 27. According to study design, the 4-week interval should be the one between the last visit and safety follow-up visit.
Section 5.4. Scientific Rationale for Study Design Section 5.5. Justification for Dose	The TTT algorithm was adapted from Davies et al. (2005) instead of Riddle et al. (2003).	After evaluating comprehensive factors, such as the clinical practice in China, insulin treatment consensus, the probability of achieving primary endpoint/study results, the previous study experience, and whether the algorithm is validated, the TTT algorithm similar as the one used in I4L-GH-ABET study, which referred to AT. LANTUS study, will be applied in this protocol after internal alignment, with modification to have a minimal increase in insulin for FBG >5.6mmol/L.
Section 6.1. Inclusion Criteria	Criterion 4 was revised with redefining the dose stability and range of metformin and/or acarbose.	The previous wording of Criterion 4 was inaccurate.
Section 6.1. Inclusion Criteria	Criterion 11[a] was revised with switching the positions of urine pregnancy test and serum pregnancy test.	The previous Criterion 11[a] was inconsistent with Section 2 regarding the sequence of pregnancy tests.
Section 6.1. Inclusion Criteria	A new inclusion criterion was added as Criterion [40] to include the requirement for male contraception.	The criterion was to make the contraception inclusion criteria more complete.
Section 6.2. Exclusion Criteria	Criterion 15 was revised to exclude the patients with a history of severe hypoglycemia from the study.	This is a team decision. The revised criterion is in consistency with the one in GPHO protocol.

Section 6.2. Exclusion Criteria	Criterion 18 was revised to include patients with nonalcoholic fatty liver disease (NAFLD) into the study.	This is a team decision. Since in China many T2DM patients have NAFLD, the previous criterion will exclude many potentially eligible patients.
Section 6.2. Exclusion Criteria	For Criterion 27, the wording for remission from a clinically significant malignancy was revised.	The rewording according to internal alignment aimed to eliminate misunderstanding.
Section 7.1.1. Packaging and Labelling	"prefilled pens" was revised to "single-use pens".	The full name of "SUPs" should be single-use pens instead of prefilled pens.
Section 7.2. Method of Treatment Assignment Section 10.3.3.2. Secondary Analyses Section 10.3.4.3. Hypoglycemic Episodes Section 10.3.7.2. Subgroup Analyses	In terms of stratification by HbA1c at Visit 1 (screening), patients will be stratified to the groups with HbA1c <8.5% and ≥ 8.5% instead of with HbA1c ≤8.5% and >8.5%.	Stratification method by HbA1c was revised to be consistent with the one in GBGL, GBDK and GBCG protocols.
Section 7.2.2.2.1. Insulin Glargine Dose Titration Algorithm	For Table GBGO.4., "Median or Average BG before breakfast" will be used for titration of evening dose instead of only "Average BG". "at discretion of the investigator" was deleted. A note "Insulin glargine dose adjustment will be discussed with the patients and determined by the investigator before Week 8 as preparation and training for implementation of the patient self-titration according to the TTT algorithm after Week 8 (Section 5.1)" was added below the table.	Per protocol, median or average FBG will be used for insulin dose titration. Also, the decision of the titration after week 8 will be made and implemented by patients themselves. "at discretion of investigator" may cause misunderstanding that the insulin titration would still be decided by the investigator. A note added may better clarify who is the decision-maker for insulin dose titration at each stage.
Section 7.6. Treatment Compliance	The assessment dates for treatment compliance were revised. And the visits that require insulin dose assessment and adjustment were revised to "from randomization to Visit 17".	The dates were incorrect and inconsistent with those in Section 2.
Section 7.7. Concomitant Therapy	In table GBGO.5., "Y" was replaced with "N" for durgs with weight loss indication and systemic glucocorticoid therapy during safety follow-up period.	According to internal alignment, the two drug classes will be prohibited during safety follow-up period considering that these could affect the safety data of study drugs.

Section 7.7. Concomitant Therapy	In table GBGO.5., the footnote "c" for systemic glucocorticoid therapy was divided into 2 footnotes "c" and "d". A new one "d" with "within 4 weeks prior to Visit 1 or between Visits 1 and 3" was added for "Excluded" during screening/lead-in. In footnote "c", the explanation for "Chronic systemic glucocorticoid therapy" was deleted.	According to internal reviewers, the explanation for "Chronic systemic glucocorticoid therapy" was incorrect and unnecessary. The content of the previous footnote "c" does not fully fit for "systemic glucocorticoid therapy".
Section 7.7. Concomitant Therapy	In table GBGO.5., a new footnote "e" was added for "Insulins", explaining that the use of insulin glargine is allowed during screening/lead-in period. Also, the text "for acute therapy, rescue therapy and therapy during safety follow-up period, use of other basal insulins will not be allowed in both treatment groups" was moved from footnote "a" to "e".	Insulin glargine is one study drug. According to study design, insulin glargine is allowed during screening/lead-in period. And the text being moved from footnote "a" to "e" described the use of insulins instead of "acute therapy", which was not proper staying in "a".
Section 7.7. Concomitant Therapy	In table GBGO.5., for the previous footnote "e" (now "g"), "below" was replaced with "no more than" for describing the upper limit of the dose range.	This previous wording was inaccurate.
Section 7.7.1. Antihyperglycemia Medications	Anti-hyperglycemic medications except study drug, metformin and/or acarbose will be also allowed during safety follow-up period.	This revision is based on the study design.
Section 7.7.3. Systemic Glucocorticoids	The wording for the use of chronic systemic glucocorticoid therapy was revised, making the content consistent to the corresponding exclusion criterion.	According to study design, the chronic systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) is exclusionary if being in use or has been used during the 4-week period before screening or between Visits 1 and 3.
Section 7.7.5.1. Standards of Medical Care	In the second paragraph, the positions of signs and symptoms of hyperglycemia and hypoglycemia were switched with hypoglycemia being the first followed by hyperglycemia.	No changes to the content were made. The revision was only in the consideration of the consistency of the text structure.

Section 7.7.5.2. Management of Increased Hypoglycemia Risk	The wording about management of hypoglycemic event was revised to clarify that patients should first seek acute medical or emergency care if needed instead of calling the investigative site first.	The revision is to clarify the management of increased hypoglycemic events in consideration of patient safety.
Section 7.7.5.2. Management of Increased Hypoglycemia Risk	"3.0 mmol/L" was replaced with "<3.0 mmol/L" for definition of documented symptomatic hypoglycemia in the context.	The blood glucose should be in a range for defining documented symptomatic hypoglycemia.
Section 8.1.1. Permanent Discontinuation from Study Treatment	The item "If a patient requires a new intervention due to severe, persistent hyperglycemia" was deleted from the circumstances where patients will be discontinued from study treatment.	This circumstance does not belong to those where patients will be discontinued from study treatment according to study design, and this expression is in conflict with last sentence in Section 7.7.5.3.
Section 9.2.2.1 Hypoglycemia	Definitions and criteria for hypoglycemia were revised according to Lilly Diabetes Hypoglycemia Workgroup "White Paper on the Classification and Data Capture of Hypoglycemia Events" (version 5, April 22, 2020). Also, the paragraph about data recording in eCRF below the revised definitions and criteria for hypoglycemia was deleted.	The revision for the definitions and criteria for hypoglycemia was due to the template update. The paragraph was deleted since the content has been described in the beginning of this section.
Section 9.2.2.5. Cardiovascular Events	The "investigator reported terms" used for the analysis of CV events was replaced with "preferred terms". The wording was revised with the deletion of "data on any new CV event will be prospectively collected using a CV event eCRF". Instead, the text about recording of any clinically significant finding from vital signs or ECG into eCRF was added. Also, a new paragraph regarding monitoring and recording of deaths was added.	Since investigators often use different terms or different spellings for the same CV event, it makes sense to summarize AEs by preferred terms. The remaining revisions were made so as to keep consistency with Section 2. Schedule of Activities and the list of incidences of adverse event of special interest in Synopsis.
Section 9.4.1. Eletrocardiograms	In the third paragraph, a text "from the additional ECGs conducted at the discretion of the investigator" was added.	This addition was only to better clarify that the ECG from which clinical finding is identified is not the ECG at week 28.
Section 9.4.5.1.3. Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study	The language of additional hepatic data collection was revised according to "hepatic language non-oncology studies v1.3".	The hepatic language should be used.

Section 10.2. Populations for Analyses	In table GBGO.6., "at least 75% compliant with study drug for at least 75% of the visit" was deleted for the criteria of "Per-Protocol" population.	The reason is that the patients with at least 75% compliant with study drug for at least 75% of the visit are already included in the patients without protocol violation mentioned in the first point.
Section 10.3.1. General Statistical Considerations	The efficacy data from the patients with premature treatment discontinuation was added for being censored.	According to our statistician, this change aimed to clarify the statistical analysis in more detail.
Section 10.3.1. General Statistical Considerations Section 10.3.3.1. Primary Analyses Section 10.3.3.2. Secondary Analyses	Only MMRM will be used for analyzing primary and key secondary continueous efficacy measures. ANCOVA (with LOCF) was no longer used.	The ANCOVA (with LOCF) model could produce biased results.
Section 10.3.3.2. Secondary Analyses Section 10.3.4.3. Hypoglycemic Episodes	In the second paragraph, "screening HbA1c stratum" was changed to "baseline HbAc1 stratum" for models.	Models use baseline HbA1c (Visit 3) instead of screening HbA1c (Visit 1)
Section 10.3.3.3. Tertiary/Exploratory Analyses	Additional text about additional efficacy analysis without censoring the data after rescue therapy or premature treatment discontinuation was added.	This was revised based on the feedback form China's Center for Drug Evaluation on pre-investigational new drug application.
Section 10.3.4. Safety Analyses	"electrocardiogram" was added between "vital signs" and "laboratory analyses".	As mentioned in Section 10.3.4.6. Electrocardiogram, electrocardiogram will be included in safety analyses.
Section 10.3.4.3. Hypoglycemic Episodes	"≥ 3.0 mmol/L [54 mg/dL]" was added for defining glucose alert level together with "<3.9 mmol/L [70 mg/dL]".	The previous definition is inaccurate as defined in Section 9.2.2.1 Hypoglycemia
Section 11. References	References Ahmann A, et al. and Buse JB, et al. were deleted, the position of reference Rosenstock J, et al. was adjusted, and reference [ADA] was added.	References Ahmann A, et al. and Buse JB, et al. were repeatedly added. The reference Rosenstock J, et al. was wrongly positioned. The reference [ADA] was added due to hypoglycemia template update.

Appendix 1. Abbreviations and Definitions	The abbreviations "CEC", "DMC", "HR", "LOCF", "MAR", "MNAR", "PMM", "QTcF", "SDP", and "SmPC" were deleted. "ADA", "adjudication committee", "CK", "D.Bil", "EASD", "EQ-5D-5L", "FSH", "GAD", "ICA", "MDDAB", "MEN", "NAFLD", "NOAEL", "NPH", and "SUP" were added. "mellitus" was deleted for the abbreviation "T2D". The full name of "USPI" was revised to "United States prescribing information".	The deletions, additions, and revisions of these abbreviations were based on the document content.
Appendix 2. Clinical Laboratory Tests	"blood" was added into the footnote "c". And the superscript "c" was added at "Clinical Laboratory Tests" and removed from "Calcitonin" and "Pancreas (Exocrine)". In footnote "g", ">400 ng/mL" was changed to ">400 mg/dL".	This changes related to footnote and superscript "c" were to better comply with China's local requirements on blood sample collections. The unit change was to fix an error.
Appendix 4. Liver Safety: Suggested Actions and Follow-Up Assessment (Previously named as: Hepatic Monitoring Tests for Treatment Emergent Abnormality)	The new template was applied. And the superscript "c" was added for the tests "Acetaminophen Protein Adducts", "Alkaline Phosphatase Isoenzymes", "Copper", "Phosphatidylethanol (PEth)", "Ethyl glucuronide (EtG)", "Anti-actin antibody", and "HSV (Type 1 and 2) DNA". For the sentence at beginning mentioning the analysis of the selected testing is required to be completed by Lilly central laboratory, "microbiology" was replaced by "those tests that are denoted as local below".	The new version of the template was released by global for the hepatic monitoring. And these tests at which the superscript "c" was added were unavailable in the Lilly designated central laboratory after confirmation.
Appendix 6. Classification of Contraceptive Methods	The text mentioning that men should use contraceptive methods was deleted.	The deleted text is in conflict with the newly added Criterion [40] mentioning that no male contraception is required except in compliance with specific local government study requirements.

For the global revisions as shown below, their corresponding instances were not identified specifically with strikethrough/underscore in the following Revised Protocol Sections:

- According to Lilly Diabetes Hypoglycemia Workgroup "White Paper on the Classification and Data Capture of Hypoglycemia Events" (version 5, April 22, 2020), the blood glucose ≤3.9 mmol/L for the definition of level 1 hypoglycemia was revised to <3.9 mmol/L throughout the protocol.
- For statistical analyses, a Fisher's exact test rather than a Chi-square test is intended for binary outcomes. Therefore, the Chi-square test was either deleted or replaced with Fisher's exact test.
- Since the patients will stay in the study despite the occurrence of severe, persistent hyperglycemia, the incidence of initiation of rescure therapy instead of incidence of patients discontinuing the study due to severe, persistent hyperglycemia is one of the safety endpoints. Also, time to initiation of rescue therapy and the proportions of patients initiating rescue therapy due to severe, persistent hyperglycemia will be analyzed. The analyses for time to study discontinuation and proportions of patients discontinuing the study due to severe, persistent hyperglycemia are no longer applicable.

Revised Protocol Sections

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

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

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

1. Synopsis

Efficacy Analyses:

The primary e~~E~~valuation of ~~actual value/ measurement and~~ change from baseline for body weight will be performed using MMRM ~~and ANCOVA models~~ on the intention to treat (ITT) population. The analyses of other secondary efficacy measures that are continuous variables ~~(actual values and changes from baseline)~~ will be performed using MMRM on the ~~intention to treat (~~ITT~~)~~ population.

2. Schedule of Activities

Table GBGO.1. Schedule of Activities

	Screening/Lead In		Treatment Period																Safety Follow-Up
Visit	1	2	3[a]	4	5	6	7	8	9	10	11	12	13	14	15	16	17	ET[b]	801
Week of Treatment	-3	-2	0	1	2	4	5	6	7	8	10	12	15	18	21	24	28		32
Allowable Deviation (±Days)	±7	±3	0	±3	±3	±4	±2	±4	±2	±4	±2	±7	±2	±7	±2	±7	±7		±7
Fasting visit[c]			X									X					X	X	
Telephone visit							X		X		X		X		X				
Patient Education																			
Dispense study diary, instruct in use		X	X	X	X	X		X		X		X		X		X	X[m]	X	
Review and transfer to eCRF/return study diary			X	X	X	X		X		X		X		X		X	X	X	X
Remind patients about 7 point SMBG[n,m]		X								X						X			
Review/record 7-point SMBG values			X									X					X	X[o,n]	
Review fasting/4-point BG from SMBG[p]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Review study drug usage			X	X	X	X		X		X		X		X		X	X	X	
Review insulin dose and adjustment per TTT algorithm[q]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Dispense study drug and injection supplies			X			X				X				X					
Observe patient inject dulaglutide QW			X																
Patient returns study drug and injection supplies				X	X	X		X		X		X		X		X	X	X	
Assess dulaglutide compliance						X				X		X		X		X	X	X	
Assess compliance with weekly insulin dose adjustment per TTT algorithm				X	X	X		X[i,q]		X[i,q]		X[i,q]		X		X	X	X	
Laboratory tests[q]																			
[s]Serum pregnancy test[r]	X																		

	Screening/Lead In		Treatment Period																Safety Follow-Up
Visit	**1**	**2**	**3[a]**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**ET[b]**	**801**
Week of Treatment	**-3**	**-2**	**0**	**1**	**2**	**4**	**5**	**6**	**7**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**28**		**32**
Allowable Deviation (±Days)	**±7**	**±3**	**0**	**±3**	**±3**	**±4**	**±2**	**±4**	**±2**	**±4**	**±2**	**±7**	**±2**	**±7**	**±2**	**±7**	**±7**		**±7**
Fasting visit[c]			**X**									**X**					**X**	**X**	
Telephone visit							**X**		**X**		**X**		**X**		**X**				
Urine pregnancy test[d,e]			X														X	X	X
Follicle-stimulating hormone test[d,f]	X																		
Chemistry panel	X																X[g,h]	X[g,h]	
Serum creatinine, eGFR (CKD-EPI)[g,i]	X		X														X	X	

Abbreviations: 801 = safety follow-up visit; BG = blood glucose; BP = blood pressure; ~~eCRF = electronic case report form;~~ CV = cardiovascular; D = days; eCRF = electronic case report form; EQ-5D-5L = EuroQol 5-dimension questionnaire; ET = early termination; FSH = follicle-stimulating hormone; GAD = glutamic acid decarboxylase; HbA1c = ~~glycated~~ hemoglobin A1c; ~~HR = heart rate;~~ ICA = islet cell antibodies; IWRS = interactive web response system; IW-SP = Impact of Weight on Self-Perception Scale; ~~801 = safety follow-up visit;~~ MDDAB = Medication Delivery Device Assessment Battery; PR = pulse rate; ~~BG = blood glucose;~~ Rand = randomization; SMBG = Self-Monitored Plasma Glucose; SUP = Single-Use Pen; TTT = treat-to-target.

[m] Safety data to be captured after discontinuation of study drug during safety follow-up period.

[~~n~~] Patients will be asked to perform two 7-point SMBG profiles on two nonconsecutive days, in the 2-week period prior to Visit 3, as well as prior to Visit 12 and Visit 17. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime. If 7-point SMBG is not performed, then data from the most recent nonconsecutive 4-point SMBG (3 before each meal and one at bedtime) profiles can be used. If more than 2 SMBG profiles are available, the 2 most recent profiles on nonconsecutive days should be used. In the weeks that the 7-point profiles are performed, the 4-point SMBG profiles will not be needed.

[~~o~~] Review/record 7-point SMBG profile(s), only if applicable, based on previous study visit.

[~~p~~] Patients will be encouraged to collect a daily fasting BG and a weekly 4-point SMBG. Missing a fasting BG measurement will not be considered a protocol deviation.

[~~q~~] Insulin dose assessment and dose adjustment should be done at least 3 days prior to Visit 3 to ensure the collection of at least 3 days of FBG for patient eligibility assessment prior to randomization. The insulin glargine dose should be reduced by 20% at Visit 3 if baseline HbA1c ≤8.0%. Further dose adjustments are to start at Visit 6 per the TTT algorithm, and before that only in certain situations (for details see Section 5.1). The TTT algorithm should be used for dose adjustments until the last visit on randomized treatment (Visit 17 or ET Visit). After discontinuation of study drug, the investigator will decide on the most appropriate therapeutic regimen, and if applicable, the most appropriate insulin dose adjustment schedule. Refer to Protocol Section 7.2.2.2 for complete instructions on insulin dose adjustment.

[~~r~~] Assessment of the patient's compliance to the TTT algorithm will be collected in the eCRF at Visits 8, 10, and 12 for the period since the previous visit.

[~~s~~] A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only.

[~~t~~] A urine pregnancy test will be performed at Visit 3, with the result available prior to randomization and first injection of study drug, and at additional visits as shown in the schedule, for women of childbearing potential only. Additional pregnancy tests will be performed at the investigator's discretion or if required

per local regulations and/or institutional guidelines during the study.

[tu] Follicle-stimulating hormone test will be collected at Visit 1 for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL). After Visit 1, additional tests may be performed at the investigator's discretion during the study.

[uv] For those visits when fasting glucose is required, glucose will not be included in the chemistry panel.

[vw] Chronic Kidney Disease-Epidemiology (CKD-EPI) equation will be used to estimate the glomerular filtration rate.

4. Objectives and Endpoints

Objectives	Endpoints
Exploratory *Efficacy:* • To compare the addition of dulaglutide 1.5 mg QW with the addition of placebo QW to titrated basal insulin glargine for exploratory efficacy parameters after 28 weeks of treatment in patients with T2D.	• Frequency of insulin dose adjustments through 28 weeks; • Number of insulin dose assessments per TTT algorithm and compliance with the TTT algorithm at 6, 8, and 12 weeks; • Proportion of patients achieving HbA1c target of <7.0% and with no weight gain (<0.1 kg) at 28 weeks and without documented symptomatic hypoglycemia (BG<3.9 mmol/L) during the maintenance period (Weeks 12-28); • Proportion of patients achieving HbA1c target of <7.0% and without weight gain (<0.1 kg) at 28 weeks ~~and without documented symptomatic hypoglycemia (BG ≤ 3.9 mmol/L) during the maintenance period (Weeks 12-28)~~; • Proportion of patients achieving HbA1c target of <7.0% at 28 weeks and without documented symptomatic hypoglycemia (BG ≤~~≤~~ 3.9 mmol/L) during the maintenance period (Weeks 12-28);

5.1. Overall Design

Patients who meet all inclusion criteria and none of the exclusion criteria will enter a 2-week lead-in period. Only those patients who require further up-titration of the insulin glargine dose per TTT algorithm at the end of lead-in period (~~mean~~ FBG ≥5.6 mmol/L in the ~~from~~ prior week before Visit 3~~randomization ≥5.6 mmol/L~~) ~~(Visit 3 or randomization visit)~~ will then be randomized to 1 of the following treatment groups at Visit 3: (1) dulaglutide 1.5 mg QW as add-on to insulin glargine or (2) placebo QW as add-on to insulin glargine. Insulin glargine will be titrated using the treat-to-target (TTT) algorithm (Section 7.2.2.2.1). Metformin and/or acarbose dose must be~~ stable~~ kept unchanged for at least 3 months prior to Visit 1, and the dose should be within the inclusive range of half maximum to maximum approved daily dose per the locally-approved label during this period~~must meet requirements for more than or equal to half maximum daily dose;~~. P~~p~~atients will be required to continue pretrial metformin and/or acarbose during the lead-in and treatment periods. Patients will be treated for 28 weeks (a 4-week stabilization period followed by a 24-week titration period); after which patients will be required to complete a safety follow-up visit (801) approximately 4 weeks later.

Study Period I (Screening and Lead-In)

Lead-in (Visit 2 to Visit 3)

During the lead-in period, patients should continue their prestudy therapy and should not change the type of OAMs used or their doses in order to allow reliable assessment of HbA1c at baseline (Visit 3). If patients develop a condition that is a contraindication for the use of OAMs, they will be considered ineligible and must ~~be~~ discontinued from the trial before randomization. Insulin doses should be adjusted only for the safety of ~~the study participants~~patients (occurrence of hypoglycemia [fasting blood glucose (FBG) ≤~~<~~3.9 mmol/L] due to ~~inadequate~~ insulin dose or severe hyperglycemia, defined as mean daily BG from 4-point SMBG profile >15 mmol/L or mean weekly FBG >15 mmol/L). In these situations, the insulin dose will be adjusted ~~the patient will adjust the dose~~ per the TTT algorithm at the discretion of the investigator (see Section 7.2.2.2.1).

Study Period II (Treatment Period):

Randomization (Visit 3)

At Visit 3, patient should arrive to the clinic in the fasting state, ~~; the fasting state~~which should ~~have~~ lasted at least 8 hours, without having taken any doses of their study drug, OAMs and insulin glargine. Procedures at this visit will be performed as shown in the Schedule of Activities~~Study Schedule~~ (Section 2). The questionnaires (EQ-5D-5L and IW-SP) 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 preceding visit procedures.

Investigators will review the diary and assess patient eligibility (Section 6.1 and 6.2). Insulin dose should be kept unchanged for at least 3 days prior to Visit 3, so as to have at least 3 daily FBG values ready for eligibility assessment at Visit 3.~~Insulin dose assessment and insulin dose adjustment should be done at least 3 days prior to Visit 3 to ensure the collection of at least 3 days of FBG on the current insulin dose for eligibility assessment prior to randomization.~~ Patients who continue to be eligible will be randomized in a 1:1 ratio to one of the following treatment groups: (1) dulaglutide 1.5 mg QW as add-on to insulin glargine or (2) placebo QW as add-on to insulin glargine, with metformin and/or acarbose.

Stabilization Period (End of Visit 3 to Visit 6 [Weeks 0 to 4])

In addition, for patients with baseline HbA1c ≤8.0%, the insulin glargine dose will be decreased by 20% immediately after randomization~~, not later than 7 days after the first dosing of study drug~~, and will then remain unchanged during the stabilization period to decrease the risk of hypoglycemia.

The planned visits for this period, Visits 4, 5, and 6, will take place 1 week (±3 days), 2 weeks (±3 days), and 4 weeks (±~~7~~4 days) after randomization, respectively. Study procedures will be performed per the Schedule of Activities (Section 2).

Titration Period (End of Visit 6 to Visit 17 [Weeks ~~5~~4 to 28])

The planned office visits during this period (excluding the final visit), Visits 8 through 16, will take place at Week 6 (±~~7~~4 days), 8 (±4~~7~~ days), 12 (±7 days), 18 (±7 days), and 24 weeks (±7

days) after randomization. In addition to the office visits, 5 telephone visits will be scheduled ~~during this period~~ at Visit 7 (Week 5), Visit 9 (Week 7), Visit 11 (Week 10), Visit 13 (Week 15), and Visit 15 (Week 21) ~~will take place at Weeks 5, 7, 10, 15, and 21, respectively~~. At each of these visits, procedures will include assessments of SMBG, compliance with insulin titration algorithm, insulin dose, dulaglutide compliance (will be re-assessed at the office visit), hypoglycemic events, concomitant medications, and AEs. The data obtained at these telephone visits will be entered into the eCRFs at the next office visit.

Between Week 4 and Week 8, the insulin glargine dose adjustment will be discussed with the patients and determined by the investigator, and this procedure will be used as preparation and training for implementation of the patient self-titration according to the TTT algorithm (Table GBGO.4). After Week 8, the decision of the titration will be made and implemented by the patient in a weekly manner. Between Week 8 and Week 12, patients will be contacted by the study site personnel every 2 weeks (either telephone or office visit). Investigators or study site personnel will review the insulin dose adjustment made by the patient at each office visit or telephone visit. From Week 12 , patients will be contacted by the study site personnel every 3-4 weeks (either telephone or office visit), to enable the site to properly monitor patients' usage of the TTT algorithm. Investigators may perform additional telephone visits if necessary, or perform additional office visits if deemed necessary by the investigator. Also, more frequent insulin dose assessments may be requested by the investigator if clinically appropriate. ~~Any patient meeting criteria for severe, persistent hyperglycemia after 12 weeks of unrestricted insulin glargine dose adjustments will discontinue study drug and the study (see Section 7.7.5.3 for details).~~

The final office visit, Visit 17, will take place at Week 28 (±7 days). Study procedures at this visit are shown in the Schedule of Activities (Section 2). The EQ-5D-5L, IW-SP, and MDDAB modules 1, 2, 3b, and 4 questionnaires will 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 preceding visit procedures. A final physical examination will be performed, including weight and vital signs (sitting blood pressure [BP] and pulse~~heart~~ rate [P~~H~~R]) measurements and electrocardiogram (ECG) testing using the existing equipment at the site. Study drug will be discontinued and an appropriate diabetes treatment regimen will be prescribed per the investigator's judgment. A patient summary eCRF will be completed.

Study Period III (Safety Follow-Up Period):

Safety Follow-Up (801) Visit

All patients who complete the treatment period are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after last visit~~their last dose~~. Patients discontinuing the study early and performing an early termination (ET) visit will also be asked to perform the safety follow-up visit, so that the safety follow-up visit will be their final visit.

5.4. Scientific Rationale for Study Design

To ensure a valid comparison of the randomized study treatments, it is important that insulin glargine is titrated in an optimal way throughout the entire study. Patients will be required to use a TTT algorithm, which has been shown to be effective in enabling a high proportion of patients with T2D to achieve their therapeutic targets when treated with insulin glargine (Davies~~Riddle~~ et al. 200~~5~~3).

5.5. Justification for Dose

The TTT algorithm (Section 7.2.2.2.1), adapted from ~~Riddle~~Davies et al. (200~~3~~5), is a broadly accepted approach to insulin glargine dose adjustments and will be used in this study to target a FBG <5.6 mmol/L.

6.1. Inclusion Criteria

[4] doses of once daily insulin glargine and OAMs must be stable during the 3-month period prior to Visit 1. Insulin glargine dose is considered stable when all doses during this period are within the range defined by ±20% of the most commonly used insulin glargine dose during this same period. Doses of metformin and/or acarbose are considered stable when doses are unchanged during the same period, and the doses should be in the inclusive range of the half maximum to maximum approved daily dose per the locally-approved label~~are considered stable if all prescribed doses during this period are more than or equal to half maximum approved daily dose during the 3 months before Visit 1~~;

[11] Otherwise, women of child-bearing potential participating must agree to use one highly effective (less than 1% failure rate) method of contraception or use a combination of two effective methods of contraception until plasma concentration equals or is lower than the [*NOAEL* for embryo fetal effects].

[a] Women of child-bearing potential participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative ~~urine~~serum pregnancy test at the screening visit followed by a negative ~~serum~~urine pregnancy test within 24 hours prior to exposure.

[40] No male contraception required except in compliance with specific local government study requirements.

6.2. Exclusion Criteria

[15] have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1;

[18] have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease (NAFLD), or alanine aminotransferase (ALT) level >2.5 times the upper limit of the reference range, as determined by the central laboratory at study entry (Visit 1); patients with NAFLD are eligible for participation in this trial only if their ALT level is ≤2.5 times the upper limit of normal (ULN) for the reference range;

~~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 (patients with nonalcoholic fatty liver disease are eligible);~~

[27] have a history of active or untreated malignancy, or have been~~are~~ in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than~~during the~~ 5 years prior to Visit 1;

7.1.1. Packaging and Labelling

The sponsor will provide dulaglutide and placebo in single-use pens~~prefilled pens~~ (SUPs), which will be dispensed via an Interactive Web Response System (IWRS). Each SUP will be packaged in cartons to be dispensed. Each carton contains a 4-week supply, as each pen provides~~is~~ a weekly dose. Injections are to be administered as described in Section 7.2.2.

7.2. Method of Treatment Assignment

Patients will be randomized in a 1:1 ratio to (1) dulaglutide 1.5 mg QW as add-on to insulin glargineor (2) placebo QW as add-on to insulin glargine, with metformin and/or acarbose. Patients will also be stratified by HbA1c at Visit 1 (screening) (≤~~<~~8.5% *vs*. ≥~~>~~8.5%) and OAM usage (metformin alone, acarbose alone, metformin and acarbose) at Visit 3 (randomization) to achieve between-group comparability and to mitigate against the confounding ~~the~~ effects of the treatments with severity of disease or treatment with metformin and/or acarbose.

7.2.2.2. Insulin Glargine

For patients with baseline HbA1c ≤8.0%, the basal insulin dose will be decreased by 20% immediately ~~(within 7 days)~~ after randomization and will then remain unchanged during the stabilization period.

7.2.2.2.1. Insulin Glargine Dose Titration Algorithm

Table GBGO.4. Insulin Glargine Treatment-to-Target Algorithm

Median or Average BG Before Breakfast (for Titration of Evening Dose)	**Increase in Basal Dose (Units)**
<70 mg/dL (<3.9 mmol/L)	Decrease to previous lower dose*
70-<100 mg/dL (3.9-5.6 mmol/L)	No adjustment
100-<120 mg/dL (5.6-6.7 mmol/L)	+1 to~~-~~ +2 U[#] ~~(at discretion of the investigator)~~
120-<140 mg/dL (6.7-7.8 mmol/L)	+ 2 U
140-<180 mg/dL (7.8-10.0 mmol/L)	+ 4 U
≥180 mg/dL (>10.0 mmol/L)	+6 to~~-~~ +8 U[#] ~~(at discretion of the investigator)~~

* The patient will be administered with the previous lower dose if he/she has documented hypoglycemia or probable symptomatic hypoglycemia.

[#] Insulin glargine dose adjustment will be discussed with the patients and determined by the investigator before Week 8 as preparation and training for implementation of the patient self-titration according to the treatment-to-target algorithm after Week 8 (Section 5.1).

Abbreviations: BG = blood glucose; U = unit(s).

7.6. Treatment Compliance

- Treatment compliance for once weekly study drug is defined as taking at least 75% of the required injections of study drug,
    - Between Visit 3 (randomization) and Visit 6 (Week 4) ~~6~~, and
    - Since the previous visit, assessed at Visits 10 (Week 8), 12 (Week 12), 14 (Week 18), 16 (Week 24) and 17 (Week 28)

  Compliance is assessed by site personnel; this information will be entered in the eCRF.

Compliance with the TTT algorithm will be determined by the following:

- The study site will review and document patients' use of the insulin glargine TTT algorithm for appropriate number of assessments, appropriate assessment of the insulin dose, and subsequent dose adjustments at each visit from randomization to Visit 17~~the last study visit (801 or ET)~~. These data will be entered into the eCRF for the period prior to Visits 8 (Week 6), 10 (Week 8), and 12 (Week 12).

7.7. Concomitant Therapy

Table GBGO.5. Criteria for Use of Concomitant Medications that May Interfere with Efficacy and Safety Assessments

Drug Class	Use During Screening/Lead-In	Conditions for Use after Randomization		
		Acute therapy[a]	Rescue therapy	During Safety Follow-Up Period
Drugs with approved weight loss indication[b]	Excluded	N	N/A	N~~Y~~
Systemic glucocorticoid therapy[c]	Excluded[d] except for acute therapy[a]	Y	N/A	N~~Y~~
Antihyperglycemia medications				
Other GLP-1 RAs and related fixed-dose combinations	Excluded	N	N	N
DPP-4 inhibitors and related fixed-dose combinations	Excluded	N	N	N
Pramlintide	Excluded	N	N	N
SGLT2 inhibitors	Excluded	N	Y	Y
Insulins [e~~a~~]	Excluded	Y	Y	Y
Meglitinides	Excluded	N	Y	Y
Alpha-glucosidase inhibitors[f~~d~~]	Allowed	N/A	Y[g~~e~~]	Y
Sulphonylureas	Excluded	N	Y	Y
Thiazolidinediones	Excluded	N	Y	Y
Metformin[f~~d~~]	Allowed	N/A	Y[e]	Y

[a] Acute therapy = treatment for up to 14 days. ~~For acute therapy, rescue therapy and therapy during safety follow-up period, use of other basal insulins will not be allowed in both treatment groups.~~

[c] ~~Chronic systemic glucocorticoid therapy = treatment for up to 14 days. From 1 months prior to Visit 1 or between Visits 1 and 3; d~~Does not apply to topical, intraocular, intranasal, intra-articular, or inhaled preparations.

[d] Chronic systemic glucocorticoid therapy (>14 days) should be excluded within 4 weeks prior to Visit 1 or between Visits 1 and 3.

[e] Use of insulin glargline is allowed during screening/lead-in period. For acute therapy, rescue therapy and therapy during safety follow-up period, use of other basal insulins will not be allowed in both treatment groups.

[f~~d~~] Switching metformin or acarbose manufacturers is allowed as long as the dosage is the same. Changing to a metformin formulation with a different action profile (for example, from short-acting to long-acting metformin) is not permitted.

[g~~e~~] For rescue therapy, metformin or acarbose dose can be increased if the dose is ~~below~~ no more than maximum approved dose per country-specific label and is well tolerated.

7.7.1. Antihyperglycemia Medications

Anti-hyperglycemic medications, other than study drug, metformin and/or acarbose, are not allowed at any time during the study, except those ~~as allowed for~~ used as rescue therapy, and/or used after early study drug discontinuation or during safety follow-up period, or insulins for short-term ~~insulin~~ use. Rescue therapy with other glucose-lowering agents, including insulin, may be medically indicated in certain situations after randomization due to severe, persistent hyperglycemia or early discontinuation of study treatment. These situations are described in Section 7.7.5.3 and Section 8.1.1, respectively. If any such situation occurs, the patients may be treated with any locally-approved glucose-lowering agents. Other GLP-1 RAs, another basal insulin, or DPP-4 inhibitors, fixed-dose combination with component of GLP-1 receptor agonists or DPP-4 inhibitor, and pramlintide are prohibited medications and are not allowed as rescue therapies.

If any new anti-hyperglycemic medication is initiated after randomization at Visit 3 and prior to Visit 17 (end of Treatment Period), other than study drug, rescue therapy, ~~post~~ drugs used after early study drug discontinuation or during safety follow-up period, or insulins for short-term use ~~of insulin~~ for medical emergencies, the patient will be required to immediately discontinue the medication and the appropriate study deviation report will be generated. Any such violation of the protocol that lasts >14 consecutive days will exclude the patient from the Per-Protocol (PP) Population for analyses.

7.7.3. Systemic Glucocorticoids

Chronic systemic glucocorticoid therapy (>14 consecutive days; excluding topical, intraocular, intranasal, intra-articular, or inhaled preparations) is exclusionary if being in use or has been used ~~>14 consecutive days~~ during the 4-week period before study entry or between study entry and randomization at Visit 3. If glucocorticoid therapy is needed for more than 14 consecutive days during the treatment period, then patients will not be included in the PP analysis.

7.7.5.1. Standards of Medical Care

This section provides guidance on management of episodes of hypoglycemic events and events 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 (eg, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders) and hyperglycemia (eg, severe thirst, dry mouth, frequent micturition, or dry skin) ~~and hypoglycemia (eg, intense hunger, sweating, tremor, restlessness, irritability, depression, headaches, disturbed sleep, or transient neurological disorders)~~. Patients should be instructed to contact the investigative site in the event of severe hypoglycemia ~~severe, persistent hyperglycemia~~ or severe, persistent hyperglycemia ~~severe hypoglycemia~~ between study visits.

7.7.5.2. Management of Increased Hypoglycemia Risk

If a hypoglycemic event occurs, the patient should record in the study diary the BG level measured during the episode and prior to administration of treatment (if taken), as well as associated symptoms and treatment administered. Site personnel will enter this information into the hypoglycemia eCRF at each visit. ~~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.~~ Patients should be trained about signs and symptoms of hypoglycemia and how to manage hypoglycemia. Patients should first seek acute medical or emergency care if needed, and inform the investigative site as soon as possible after an event of severe hypoglycemia has occurred that requires assistance to administer corrective treatment.

In this study, increased risk of hypoglycemia is defined as having a single episode of severe hypoglycemia or having more than 1 episode of documented symptomatic hypoglycemia (≤3.0 mmol/L) within a 1-week period at any time during the Treatment Period.

8.1.1. Permanent Discontinuation from Study Treatment

- Any significant study drug-related hypersensitivity reaction;
- ~~If a patient requires a new intervention due to severe, persistent hyperglycemia;~~
- If a non-study GLP-1 receptor agonist is initiated, and the patient refuses to discontinue this medication;

9.2.2.1. Hypoglycemia

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the BG 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) in accordance with the ~~2017~~ 2020 ADA position statement on glycemic targets:

Level 1 hypoglycemia:

> **Glucose <70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L):** Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel particpants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L): This is also referred to as documented or blood glucose confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence of absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that **occurs at night** and presumably during sleep.

~~***Glucose Alert Value (Level 1):***~~

- ~~**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 BG level of *≤3.9 mmol/L.*~~
- ~~**Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG *≤3.9 mmol/L.*~~
- ~~**Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG *≤3.9 mmol/L.*~~

~~***Clinically Significant Hypoglycemia (Level 2):***~~

- ~~**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 BG level of *<3.0 mmol/L.*~~
- ~~**Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG *<3.0 mmol/L.*~~

- ~~**Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG *< 3.0 mmol/L.*~~

~~***Severe hypoglycemia (Level 3):***~~

- ~~**Severe hypoglycemia** is defined as an episode with severe cognitive impairment, 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. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.~~

~~***Other hypoglycemia categories:***~~

- ~~**Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.~~
- ~~**Relative hypoglycemia** is defined as any symptomatic event during which the person reports any of the typical symptoms of hypoglycemia and interprets those as indicative of hypoglycemia, but a measured BG concentration *>3.9 mmol/L* is collected.~~
- ~~**Probable symptomatic hypoglycemia** is defined as symptoms of hypoglycemia but BG measurement was not reported.~~

~~All reported cases of hypoglycemia will be reported on the hypoglycemia eCRF. If a hypoglycemic event meets the criteria of severe, it also needs to be recorded on the AE eCRF as serious and reported to Lilly as an SAE.~~

To avoid duplicate reporting, all consecutive BG values ~~<~~≤3.9 mmol/L occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013, ADA. 2020).

9.2.2.5. Cardiovascular Events

Vital signs (PR, SBP, DBP) will be monitored throughout the study, and 12-lead electrocardiograms (ECGs) will be monitored at screening and Visit 17 (Week 28). Any clinically relevant finding from vital signs and ECGs obtained before the first dosing of study drug that results in a diagnosis should be recorded in eCRF as a preexisting condition and medical history. Any clinically relevant finding from vital signs and ECGs that occurs after the first dosing of study drug and results in a diagnosis should be recorded as an AE in eCRF.

~~Information on CV risk factors will be collected on an eCRF at Visit 3 (baseline). In addition to monitoring of vital signs (PR, SBP, DBP) and 12-lead electrocardiograms (ECGs) throughout the study, data on any new CV event will be prospectively collected using a CV event eCRF.~~ CV events will be analyzed using preferred~~investigator reported~~ terms and abnormal ECG result.

Deaths will be monitored throughout the study. Relevant data from patients who experienced death will be entered into a specifically designed eCRF page by study site.

9.4.1. Electrocardiograms

After enrollment, if a clinically significant finding is identified from the additional ECGs conducted at the discretion of the investigator (including but not limited to changes in QT/QTc interval from baseline), the investigator will determine if the patient can continue on study drug.

9.4.2. Vital Signs Sitting BP and ~~heart rate (~~PH~~R)~~ will be measured using standardized equipment provided by the Sponsor according to the Schedule of Activities (Section 2). Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required (see Schedule of Activities Section 2). The participant should be allowed to sit quietly for 5 minutes before vital sign measurements. 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. At Visit 1 (screening), to determine which arm should be used to collect BP and PHR throughout the study. BP and PHR will be measured once in each arm and the arm that had the higher BP should be used to collect all 2 measurements of both BP and PHR at all study visits. For each parameter (~~H~~PR, SBP/diastolic blood pressure [DBP]), 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart. Each measurement of sitting ~~H~~PR and BP is to be recorded in the eCRF. Any AE related to changes in BP and ~~H~~PR should be reported.

9.4.5.1.3. Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study~~Hepatic Safety Data Collection~~

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants who meet 1 or more of the following 5 conditions:

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

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline
3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)

- In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic even

~~1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests if baseline ALT <1.5x ULN; In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests;~~

~~2. Elevated TBL to ≥ 2x ULN if baseline TBL <1.5x ULN (except for cases of known Gilbert's syndrome); In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline;~~

~~3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests if baseline ALP <1.5x ULN; In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests;~~

~~4. Hepatic event considered to be a SAE;~~

~~5. Discontinuation of study drug due to a hepatic event.~~

Note: the interval between the two consecutive blood tests should be at least 2 days.

10.2. Populations for Analyses <<GBDI protocol section 12.2.1.1>>

Table GBGO.7. Populations for Analyses

Population	Description
Per-Protocol (PP)	All patients in ITT and who also meet the following criteria: • Have no protocol deviations expected to impact the primary endpoint for HbA1c (see below); • Complete the treatment period (28 week [Visit 17]) for primary endpoint (that is, do not discontinue from the study drug early)~~;~~ • ~~At least 75% compliant with study drug for at least 75% of the visits~~.

10.3.1. General Statistical Considerations

Unless otherwise specified, listings will include all randomized patients. Both efficacy and safety analyses will be conducted using the intention to treat (ITT) population. Unless otherwise specified, e~~E~~fficacy data from patients who started rescue therapy or discontinued study treatment prematurely~~and remain in the study~~ will be censored from the point of initiating rescue treatment or premature discontinuation onwards. Selected analyses will also be conducted using the PP and Completers populations. The PP and Completers populations are subsets of the ITT population.

~~Two analysis models will be used for~~ T~~t~~he primary and key secondary continuous efficacy measures~~. The primary analysis~~ will be analyzed with mixed-model repeated measures (MMRM) ~~analysis~~ using restricted maximum likelihood (REML) (Section 10.3.3.1).

~~The secondary analysis for the primary and key secondary continuous endpoints will be analysis of covariance (ANCOVA) (Section 10.3.3.1 and 10.3.3.2). Missing endpoints will be imputed with the last (postbaseline) observation carried forward (LOCF).~~ The proportion of patients

achieving the target HbA1c of <7.0% will be analyzed using a longitudinal logistic regression with repeated measurements (Section 10.3.3.2).

10.3.3.1. Primary Analyses

The primary outcome is the difference in HbA1c change from baseline between treatment groups based on the ITT population at the planned end of the treatment period of 28 weeks. The ~~primary~~ analysis model will be a MMRM for HbA1c change from baseline to 28 weeks (Visit 17) in the ITT population with treatment, OAM use, visit and treatment-by-visit as fixed effects, baseline HbA1c as a covariate, and patient as a random effect.

The ~~primary~~ analysis model, MMRM, will be repeated using the PP and Completers populations. If the conclusion differs from that of the ITT population, the data and analyses will be further investigated.

~~The secondary analysis model will be an ANCOVA for HbA1c change from baseline to endpoint, with missing endpoints imputed with the LOCF using post-baseline data only.~~

10.3.3.2. Secondary Analyses

The key secondary continuous efficacy measures (change from baseline in body weight and FBG) will be analyzed using ~~both models, the~~ MMRM ~~and the ANCOVA with LOCF models~~. The MMRM model will include independent variables of treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), baseline~~screening~~ HbA1c stratum (≤~~<~~8.5% vs. ≥~~>~~8.5%), visit, and treatment-by-visit as fixed effects and baseline dependent variable as covariates. ~~The ANCOVA model will include independent variables of treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), screening HbA1c stratum (≤8.5% vs. >8.5%) as fixed effects and baseline dependent variable as covariates.~~

10.3.3.3. Tertiary/Exploratory Analyses

The other objectives include triple endpoint (HbA1c <7% and no weight gain [<0.1 kg] at 28 weeks, and no documented symptomatic hypoglycemia [BG ≤~~<~~3.9 mmol/L] during the maintenance period); double endpoint (HbA1c <7% at 28 weeks and no documented symptomatic hypoglycemia [BG ≤~~<~~3.9 mmol/L] during the maintenance period); Proportion of patients achieving HbA1c target <7.0% and without weight gain (<0.1 kg) at 28 weeks.

Furthermore, we will conduct some additional efficacy analysis without censoring the data after rescue therapy or premature treatment discontinuation (whichever occurs first). Missing endpoints will be imputed by jumping to the reference method. Measurements include actual HbA1c, body weight and FSG and frequency counts and percentage of patients achieving the HbA1c target of <7.0% and changes in these measures from baseline. We will analyze HbA1c, body weight and FSG by ANCOVA. Percentages of patients achieving the target of HbA1c <7.0% will be analyzed using longitudinal logistic regression with repeated measurements.

10.3.4. Safety Analyses

The safety analysis will include analysis of AEs, SAEs, hypoglycemic and hyperglycemic episodes, vital signs, electrocardiogram and laboratory analystes. Unless otherwise specified, the ITT population will be used for analyses of safety measures.

10.3.4.3. Hypoglycemic Episodes

Hypoglycemic episodes will be analyzed using 2 hypoglycemic thresholds: Level 1 (glucose alert level, <3.9 mmol/L [3.9 mmol/L70 mg/dL] and ≥ 3.0 mmol/L [54 mg/dL]) and Level 2 (clinically significant hypoglycemia level, <3.0 mmol/L [3.0 mmol/L 54 mg/dL]). Other categories, including the categories above defined with different glucose thresholds, may also be included in these analyses when deemed appropriate.

The incidence of hypoglycemic episodes will be summarized by frequencies and proportion for each treatment group, by visit as well as overall. Treatment differences in the incidence of hypoglycemic episodes will be assessed using Fisher's exact tests or Chi-square test. Treatment differences in rates of hypoglycemic episodes (episodes/patient/30 days; episodes/patient/year) will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution. The model will include treatment, OAM usage (metformin alone, acarbose alone, metformin and acarbose), baselinescreening HbA1c stratum (≤≤8.5% vs. ≥>8.5%), visit, treatment-by-visit interaction, and baseline hypoglycemia rate. The logarithm of days between visits will be included as an offset to account for possible unequal duration between visits and between patients.

10.3.7.2. Subgroup Analyses

- Baseline HbA1c (≤≤8.5%, >≥8.5%)

11. References

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Appendix 1. Abbreviations and Definitions

ADA	American Diabetes Association
adjudication committee	An external committee whose purpose is to evaluate study data and decide whether a study endpoint or other criterion has been met.
~~**CEC**~~	~~Clinical Endpoint Committee~~
CK	creatine kinase
D.Bil	direct bilirubin
~~**DMC**~~	~~Data Monitoring Committee~~
EASD	European Association for the Study of Diabetes
EQ-5D-5L	EuroQol 5-dimension questionnaire
~~**FDA**~~**FBG**	fasting blood glucose~~Food and Drug Administration~~
~~**FBG**~~ **FDA**	~~fasting blood glucose~~Food and Drug Administration
FSH	follicle-stimulating hormone
GAD	glutamic acid decarboxylase
~~**HR**~~	~~heart rate~~
ICA	islet cell antibodies

~~LOCF~~	~~last observation carried forward~~
~~MAR~~	~~missing at random~~
MDDAB	Medication Delivery Device Assessment Battery
MEN	multiple endocrine neoplasia
~~MNAR~~	~~missing not at random~~
NAFLD	nonalcoholic fatty liver disease
NOAEL	no-observed-adverse-effect level
NPH	neutral protamine Hagedorn
~~PMM~~	~~pattern-mixture model~~
~~QTcF~~	~~QT corrected for heart rate using Fridericia's formula~~
~~SDP~~SUP	single-~~dose~~ use pen
~~SmPC~~	~~Summary of Product Characteristics~~
T2D	type 2 diabetes ~~mellitus~~
USPI	United States Prescribing Information~~Package Insert~~

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests[a,c]

Calcitonin[e]

Pancreas (Exocrine)[e]

[c] Additional blood samples may be collected based on the investigator's judgment.

[g] This value will be calculated. If triglycerides >400 ~~ng/mL~~mg/dL, then direct LDL will be assayed.

Appendix 4. Liver Safety: Suggested Actions and Follow-Up Assessments~~Hepatic Monitoring Tests for Treatment-Emergent Abnormality~~

Hepatic Evaluation Testing – Refer to protocol Hepatic Safety Monitoring Section 9.4.5.1 for guidance on appropriate test selection.

- For testing selected, analysis is required to be completed by the Lilly designated central laboratory except for those testings that are denoted as local below.
- Local testing may be performed in addition to central testing when required for immediate patient management.
- Results will be reported if a validated test or calculation is available.

Hematology

Hemoglobin

Hematocrit

Erythrocytes (RBCs - Red Blood Cells)

Leukocytes (WBCs - White Blood Cells)

Differential:

Neutrophils, segmented

Lymphocytes

Monocytes

Basophils

Eosinophils

Platelets

Cell morphology (RBC and WBC)

Coagulation

Prothrombin Time, international normalized ratio (PT-INR)

Serology

Hepatitis A Virus (HAV) Testing:

HAV Total Antibody

HAV IgM Antibody

Hepatis B Virus (HBV) Testing:

Hepatitis B surface antigen (HBsAg)

Hepatitis B surface antibody (Anti-HBs)

Hepatitis B core total antibody (Anti-HBc)

Hepatitis B core IgM antibody

Clinical Chemistry

Total bilirubin

Direct bilirubin

Alkaline phosphatase (ALP)

Alanine aminotransferase (ALT)

Aspartate aminotransferase (AST)

Gamma-glutamyl transferase (GGT)

Creatine kinase (CK)

Other Chemistry

Acetaminophen

Acetaminophen Protein Adducts[c]

Alkaline Phosphatase Isoenzymes[c]

Ceruloplasmin

Copper[c]

Ethyl Alcohol (EtOH)

Haptoglobin

Immunoglobulin IgA (Quantitative)

Immunoglobulin IgG (Quantitative)

Immunoglobulin IgM (Quantitative)

Phosphatidylethanol (PEth) [c]

Urine Chemistry

Drug Screen

Ethyl glucuronide (EtG) [c]

Other Serology

Anti-nuclear antibody (ANA)

Hepatitis B core IgG antibody

HBV DNA [d]

Hepatis C Virus (HCV) Testing:

HCV antibody

HCV RNA [d]

Hepatitis D Virus (HDV) Testing:

HDV antibody

Hepatitis E Virus (HEV) Testing:

HEV IgG antibody

HEV IgM antibody

HEV RNA [d]

Microbiology [c]

Culture:

Blood

Urine

Anti-smooth muscle antibody (ASMA) [a]

Anti-actin antibody [c, b]

Epstein-Barr Virus (EBV) Testing:

EBV antibody

EBV DNA [d]

Cytomegalovirus (CMV) Testing:

CMV antibody

CMV DNA [d]

Herpes Simplex Virus (HSV) Testing:

HSV (Type 1 and 2) antibody

HSV (Type 1 and 2) DNA [c, d]

Liver Kidney Microsomal Type 1 (LKM-1) Antibody

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[a] Not required if anti-actin antibody is tested.

[b] Not required if anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed ONLY by investigator-designated local laboratory if available; no central testing available.

[d] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

Hepatic Monitoring Tests

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

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

[a] Assayed by Lilly-designated or local laboratory.

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

Appendix 6. Classification of Contraceptive Methods

Men, regardless of their fertility status, with non-pregnant women of child bearing potential partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus one additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or effective method of contraception, (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for at least 3 months after the last injection.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of estimated relevant potential exposure in women of childbearing potential.

Men who are in exclusively same sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

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