H9X-JE-GBGQ initial protocol

A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Two Doses of Dulaglutide in Combination with a Single Oral Antihyperglycemic Medication or as Monotherapy in Japanese Patients with Type 2 Diabetes Mellitus (AWARD-JPN: Assessment of Weekly Administration of LY2189265 in Diabetes – JAPAN)

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Title Page

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Protocol Number: H9X-JE-GBGQ

Amendment Number: This is the initial protocol.

Compound: Dulaglutide (LY2189265)

Study Phase: 3

Short Title: Efficacy and Safety of Two Doses of Dulaglutide (1.5 mg versus 0.75 mg) in Japanese Patients with Type 2 Diabetes (AWARD-JPN)

Acronym: AWARD-JPN

Sponsor Name: Eli Lilly Japan K.K.

Legal Registered Address: Eli Lilly Japan K.K., Kobe Hyogo Japan

Regulatory Agency Identifier Number(s): Not applicable

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Medical Monitor Name and Contact Information will be provided separately.

Approval Date: 15-Dec-2020 GMT

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Parallel Arm Study of the Efficacy and Safety of Two Doses of Dulaglutide in Combination with a Single Oral Antihyperglycemic Medication or as Monotherapy in Japanese Patients with Type 2 Diabetes Mellitus (AWARD-JPN: Assessment of Weekly AdministRation of LY2189265 in Diabetes – JAPAN)

Short Title: Efficacy and Safety of Two Doses of Dulaglutide (1.5 mg versus 0.75 mg) in Japanese Patients with Type 2 Diabetes (AWARD-JPN)

Rationale:

In Phase 3 confirmatory studies in Japanese patients with T2D (H9X-JE-GBDP and GBDY), once weekly (QW) dulaglutide 0.75 mg has shown non-inferiority to liraglutide 0.9 mg and superiority to insulin glargine in hemoglobin A1c (HbA1c) reduction (Araki et al. 2015; Miyagawa et al. 2015). Also, in a Phase 3 long-term safety study in combination with a single oral antihyperglycemic medication (OAM) (sulfonylurea, biguanides, α-glucosidase inhibitors, thiazolidinediones, or glinides) (H9X-JE-GBDQ) and in a Phase 4 study in combination with insulins (basal, mixed, or basal bolus) (H9X-JE-GBGF), it was shown that the anti-hyperglycemic effect of once-weekly dulaglutide 0.75 mg was sustained for the 52week treatment period (Emoto et al. 2015; Ishii et al. 2020).

However, dulaglutide 0.75 mg may not be sufficient in some participants for achieving the target HbA1c value. In Japanese Phase 3 and Phase 4 studies of dulaglutide 0.75 mg (monotherapy, combination with OAM, and combination with insulin), the percentage of participants achieving the target HbA1c value <7% was 47.4% to 83.1%, and the percentage of participants achieving the target HbA1c value ≤6.5% was 25% to 70.8%. That means there is some room to improve glycemic control with dulaglutide 0.75 mg and it is desired that the dose is increased to 1.5 mg, which is the most frequently prescribed dose worldwide.

The purpose of the proposed Phase 3 study (H9X-JE-GBGQ) is to assess the efficacy and safety of once-weekly (QW) dulaglutide 1.5 mg in comparison to dulaglutide 0.75 mg. The overall goal of this study is to gain regulatory approval for an additional dose of dulaglutide 1.5 mg in patients with T2D who require additional glucose control after treatment of dulaglutide 0.75 mg in Japan.

Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate that once-weekly dulaglutide 1.5 mg is superior to dulaglutide 0.75 mg for change from baseline in HbA1c at 26 weeks	• Change from baseline in HbA1c at 26 weeks
Secondary	
Efficacy • To compare dulaglutide 1.5 mg to 0.75 mg for efficacy parameters through 26 and 52 weeks	• Change from baseline in HbA1c • Proportion of participants achieving HbA1c target of ≤6.5% and <7.0% • Change from baseline in FSG • Change from baseline in 6-point SMBG • Change from baseline in body weight
Safety • To compare dulaglutide 1.5 mg to 0.75 mg for safety parameters through 26 and 52 weeks	• Incidence of TEAEs • Discontinuation of study intervention due to AEs • Incidence of hypoglycemic episodes • Change from baseline in vital signs (SBP, DBP, and pulse rate) • Change from baseline in laboratory tests[a]

Abbreviations: AEs = adverse events; DBP = diastolic blood pressure; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; SMBG = self-monitored blood glucose; TEAEs = treatment-emergent adverse events.

[a] Specified in Section 10.2 (Appendix 2).

Overall Design

Study H9X-JE-GBGQ is a Phase 3, multicenter, randomized, double-blind, parallel-group study in participants with T2D with inadequate glycemic control on a single OAM.

The OAMs include:

- sulfonylureas (SU)
- biguanides
- alpha-glucosidase inhibitors (a-GI)
- thiazolidinedione (TZD)
- glinides
- sodium-glucose cotransporter type 2 inhibitors (SGLT2i), and

- DPP-4 inhibitors (DPP-4i).

In each arm,

If taking	then participants are required
DPP-4i	to stop DPP-4i at randomization Note: In case of weekly DPP-4i, it must be stopped 1 week before randomization.
other OAMs	to continue the same dose of OAM during the study period exception: dose modifications are allowed in the event of hypoglycemia

Abbreviations: DPP-4i = DPP-4 inhibitors; OAM = oral antihyperglycemic medication.

Switching from DPP-4i is regarded as monotherapy of dulaglutide and taking other OAMs is regarded as combination therapy with OAM.

Disclosure Statement: This is a parallel-group treatment with 2 arms that is participant and investigator blinded.

Number of Participants:

Approximately 585 participants will be enrolled and randomized in order to obtain approximately 528 evaluable participants at 26 weeks (176 evaluable participants for dulaglutide 0.75 mg group and 352 evaluable participants for 1.5 mg group). For sample size determination see Section 9.2.

The number of enrolled participants will be 225 participants for DPP-4i, and 60 participants per OAM class for other OAMs (360 participants for other OAMs in total).

Intervention Groups and Duration:

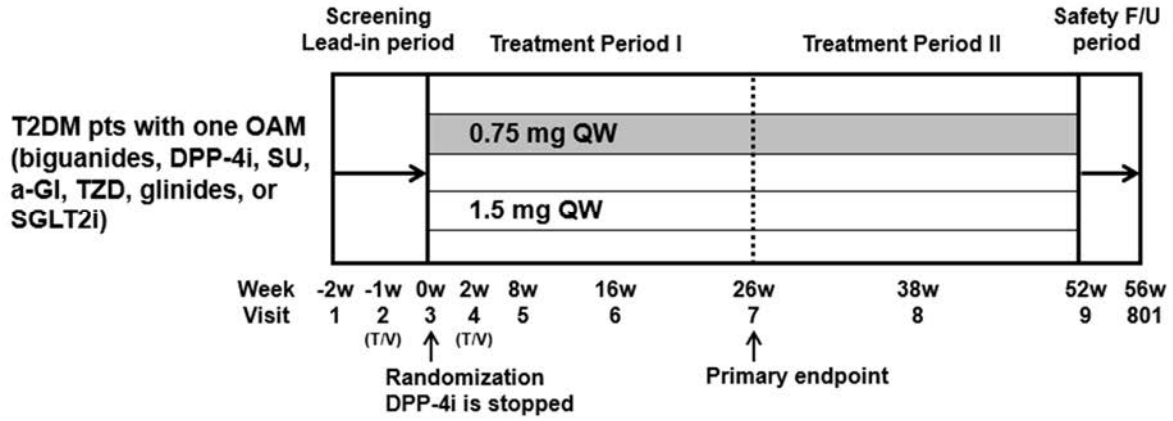
Participants will be randomized at Visit 3 in a 2:1 ratio to weekly subcutaneous injections of dulaglutide 1.5 mg or 0.75 mg.

The study will consist of 3 periods (See Section 1.2):

- an approximately 2-week screening/lead-in period
- a 52-week treatment period including Treatment Period I (26-week for the primary endpoint) and Treatment Period II (26-week), and
- a 4-week safety follow-up period.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: a-GI = alpha-glucosidase inhibitors; DPP-4i = dipeptidyl peptidase-4 inhibitor; F/U = follow up; OAM = oral antihyperglycemic medications; pts = patients; SGLT2i = sodium-glucose cotransporter type 2 inhibitors; SU = sulfonylureas; T2D = type 2 diabetes; T/V = telephone visit; TZD = thiazolidinedione; w = week; QW = once weekly.

Note: Visit 2 (Week -1) and Visit 4 (Week 2) will be conducted as a telephone visit.

1.3. Schedule of Activities (SoA)

Study Schedule Protocol H9X-JE-GBGQ

	Screening/ Lead-In		Treatment Period								Safety Follow-Up	Comments
			Treatment Period I					Treatment Period II				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ET**	**801**	
Week of Treatment	**-2**	**-1**	**0**	**2**	**8**	**16**	**26**	**38**	**52**	**ET**	**56**	
Allowable Deviation (Days)	**-7~+3**	**±3**		**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	The visit date is determined in relation to the date of the randomization visit (± the allowed visit window).
Fasting visit			**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	Participants 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 OAMs (if used). If the participant is not fasting, the participant should be called in for a new visit within the visit window.
Telephone visit		**X**		**X**								
Informed consent	**X**											
Inform eligibility to participants		**X**										
Randomization			**X**									Baseline assessments must be completed before processing in the IWRS.
Physical examination	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Medical history (general)	**X**											
Height	**X**											
Weight	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Vital signs (sitting SBP, DBP, and PR)	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart. (Section 8.2.2)
ECG	**X**		**X**				**X**		**X**	**X**	**X**	12-lead ECG (Section 8.2.3)
Adverse events	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Concomitant medications	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Hypoglycemic events			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Diabetes management education	**X**											All training should be repeated as needed to ensure participant compliance.
Dispense participant diary	**X**		**X**		**X**	**X**	**X**	**X**	**X**			
Review participant diary			**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	

	Screening/ Lead-In		Treatment Period								Safety Follow-Up	Comments
			Treatment Period I					Treatment Period II				
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ET**	**801**	
Week of Treatment	**-2**	**-1**	**0**	**2**	**8**	**16**	**26**	**38**	**52**	**ET**	**56**	
Allowable Deviation (Days)	**-7~+3**	**±3**		**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	The visit date is determined in relation to the date of the randomization visit (± the allowed visit window).
Dispense BG meter/supplies	**X**		**X**		**X**	**X**	**X**	**X**	**X**			During the study period, the participants are required to measure their pre-breakfast BG concentration at least once a week and record the BG concentration in their study diary.
BG meter, SMBG training	**X**											All training should be repeated as needed to ensure participant compliance.
6-point SMBG values			**X**				**X**					6-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day. These SMBG profiles will be collected by the participant twice (2 days) within 1 week prior to the assigned visits.
Dispense study intervention and/or injection supplies			**X**		**X**	**X**	**X**	**X**				
Injection training			**X**									All training should be repeated as needed to ensure participant compliance.
Observe participants inject study intervention			**X**									Participants should administer their first dose of study intervention at the end of this visit, after other study procedures and randomization.
Participants return study intervention and/or injection supplies					**X**	**X**	**X**	**X**	**X**	**X**		
Assess study intervention compliance					**X**	**X**	**X**	**X**	**X**	**X**		
Human chorionic gonadotropin (hCG)	**X**											Human chorionic gonadotropin (hCG) will be measured at Visit 1 for women of childbearing potential.
Follicle-stimulating hormone (FSH)	**X**											Follicle-stimulating hormone (FSH) will be measured at Visit 1 for potentially postmenopausal women.
Urine pregnancy test (local)			**X**		**X**	**X**	**X**	**X**	**X**	**X**		A local urine pregnancy test will be performed at Visit 3, with the result available prior to randomization and first injection of study intervention, and at additional visits as shown in the schedule, for women of childbearing potential only.
Hematology	**X**		**X**				**X**		**X**	**X**	**X**	
Clinical Chemistry	**X**		**X**				**X**		**X**	**X**	**X**	

	Screening/ Lead-In		Treatment Period								Safety Follow-Up	Comments
			Treatment Period I						Treatment Period II			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ET**	**801**	
Week of Treatment	**-2**	**-1**	**0**	**2**	**8**	**16**	**26**	**38**	**52**	**ET**	**56**	
Allowable Deviation (Days)	**-7~+3**	**±3**		**±3**	**±7**	**±7**	**±7**	**±7**	**±7**		**±7**	The visit date is determined in relation to the date of the randomization visit (± the allowed visit window).
Lipid panel	**X**		**X**				**X**		**X**	**X**	**X**	
Pancreatic amylase, lipase	**X**		**X**				**X**		**X**	**X**	**X**	
Calcitonin	**X**		**X**				**X**		**X**	**X**	**X**	
Urine chemistry	**X**		**X**				**X**		**X**	**X**	**X**	Urinary albumin and creatinine will be measured.
Urine albumin -to creatinine ratio (UACR)	**X**		**X**				**X**		**X**	**X**	**X**	
eGFR	**X**		**X**				**X**		**X**	**X**	**X**	eGFR: *Calculated by the Japanese Society of Nephrology equation*
Fasting serum glucose			**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
HbA1c	**X**		**X**		**X**	**X**	**X**	**X**	**X**	**X**	**X**	
Samples for storage			**X**				**X**		**X**	**X**		Plasma and serum stored samples. Additional samples may be collected at additional timepoints where required (in the event of severe hypersensitivity reactions such as anaphylaxis). See Section 8.3.3(f) and 8.9.

Abbreviations: BG = blood glucose; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ET = early termination; HbA1c = hemoglobin A1c; IWRS = interactive web-response system; OAM = oral antihyperglycemic medication; PR = pulse rate; SBP = systolic blood pressure; SMBG = self-monitored blood glucose.

2. Introduction

Dulaglutide (Trulicity®) is a once-weekly (QW) glucagon-like peptide-1 (GLP-1) receptor agonist (RA) that is approved for use as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes (T2D).

2.1. Study Rationale

In Phase 3 confirmatory studies in Japanese patients with T2D (H9X-JE-GBDP and GBDY), QW dulaglutide 0.75 mg has shown non-inferiority to liraglutide 0.9 mg and superiority to insulin glargine in hemoglobin A1c (HbA1c) reduction (Araki et al. 2015; Miyagawa et al. 2015). Also, in a Phase 3 long-term safety study in combination with a single oral antihyperglycemic medication (OAM) (sulfonylurea, biguanides, α-glucosidase inhibitors, thiazolidinediones, or glinides) (H9X-JE-GBDQ) and in a Phase 4 study in combination with insulins (basal, mixed, or basal bolus) (H9X-JE-GBGF), it was shown that the anti-hyperglycemic effect of QW dulaglutide 0.75 mg was sustained for the 52-week treatment period (Emoto et al. 2015; Ishii et al. 2020).

However, dulaglutide 0.75 mg may not be sufficient in some participants for achieving the target HbA1c value. In Japanese Phase 3 and Phase 4 studies of dulaglutide 0.75 mg (monotherapy, combination with OAM, and combination with insulin), the percentage of participants achieving the target HbA1c value <7% was 47.4% to 83.1%, and the percentage of participants achieving the target HbA1c value ≤6.5% was 25% to 70.8%. That means there is some room to improve glycemic control with dulaglutide 0.75 mg and it is desired that the dose is increased to 1.5 mg, which is the most frequently prescribed dose worldwide. Dulaglutide 1.5 mg has shown greater reduction of HbA1c compared to 0.75 mg (Wysham et al. 2014, Giorgino et al. 2015, Umpierrez et al. 2014, Ludvik et al. 2018, Nauck et al. 2014) in Study GBDA, GBDB, GBDC, GBCF, and GBGE, which compared the efficacy and safety of both doses as monotherapy or combination with OAM.

2.2. Background

The global approved doses of dulaglutide (0.75 mg and 1.5 mg) were selected in the global Phase 2/3 study H9X-MC-GBCF (Skrivanek et al. 2014). The purpose of the phase 2 part of Study GBCF was to identify an optimal dose using prespecified measures of efficacy (HbA1c and weight) and safety (diastolic blood pressure and heart rate). The results determined that dulaglutide 1.5 mg was the optimal dose, and dulaglutide 0.75 mg met the criteria for the second dose (Skrivanek et al. 2014). Efficacy and safety of both dulaglutide 0.75 mg and 1.5 mg were investigated in global Phase 3 studies H9X-MC-GBDA, GBDB, GBDC, GBDD, and GBCF (Wysham et al. 2014, Giorgino et al. 2015, Umpierrez et al. 2014, Blonde et al. 2015, and Nauck et al. 2014), and both doses were approved in the US, EU, and other regions worldwide based on these study results.

In Japan, in a Phase 1 study of dulaglutide in Japanese patients with T2D (H9X-JE-GBCL), pulse rate increase (>5 bpm) was observed in the dulaglutide 1.0 mg and 1.5 mg treatment groups. Although there was no clinically significant safety issue observed in the study other than pulse rate increase, it was decided to investigate the lower dose (less than 1.0 mg) in a Phase 2

study in Japanese patients with T2D (H9X-JE-GBCZ). In the GBCZ study, dulaglutide 0.25 mg, 0.5 mg, and 0.75 mg were investigated and the greatest efficacy was observed in the dulaglutide 0.75 mg treatment group (Terauchi et al. 2014). In Phase 3 studies in Japanese patients with T2D (H9X-JE-GBDP, GBDY, and GBDQ), clinical efficacy and safety of dulaglutide 0.75 mg was investigated and dulaglutide 0.75 mg was approved in 2015 in Japan based on results from those clinical studies.

Pulse rate elevations are now recognized to be a class effect common to all GLP-1 RAs (Lorenz et al. 2017). Despite increases in pulse rate, completed cardiovascular outcome studies for GLP-1 RAs have shown either neutral or favorable effects on the risk of major cardiovascular events compared to placebo in patients with T2D and high cardiovascular risk (Pfeffer et al. 2015; Marso et al. 2016a; Marso et al. 2016b; Holman et al. 2017). Also, in Study GBDJ (REWIND), dulaglutide 1.5 mg reduced a composite of cardiovascular outcome (MACE-3; death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) in T2D patients with high cardiovascular risk (Gerstein 2019).

The purpose of the proposed Phase 3 study (H9X-JE-GBGQ) is to assess the efficacy and safety of QW dulaglutide 1.5 mg in comparison to dulaglutide 0.75 mg. The overall goal of this study is to gain regulatory approval for an additional dose of dulaglutide 1.5 mg in patients with T2D who require additional glucose control after treatment of dulaglutide 0.75 mg in Japan.

2.3. Benefit /Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of dulaglutide may be found in the Investigator's Brochure (IB).

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To demonstrate that once-weekly dulaglutide 1.5 mg is superior to dulaglutide 0.75 mg for change from baseline in HbA1c at 26 weeks	• Change from baseline in HbA1c at 26 weeks
Secondary	
Efficacy • To compare dulaglutide 1.5 mg to 0.75 mg for efficacy parameters through 26 and 52 weeks	• Change from baseline in HbA1c • Proportion of participants achieving HbA1c target of ≤6.5% and <7.0% • Change from baseline in FSG • Change from baseline in 6-point SMBG • Change from baseline in body weight
Safety • To compare dulaglutide 1.5 mg to 0.75 mg for safety parameters through 26 and 52 weeks	• Incidence of TEAEs • Discontinuation of study intervention due to AEs • Incidence of hypoglycemic episodes • Change from baseline in vital signs (SBP, DBP, and pulse rate) • Change from baseline in laboratory tests[a]

Abbreviations: AEs = adverse events; DBP = diastolic blood pressure; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; SBP = systolic blood pressure; SMBG = self-monitored blood glucose; TEAEs = treatment-emergent adverse events.

[a] Specified in Section 10.2 (Appendix 2).

4. Study Design

4.1. Overall Design

Study H9X-JE-GBGQ is a Phase 3, multicenter, randomized, double-blind, parallel-group study in participants with T2D with inadequate glycemic control on a single OAM. The OAMs include:

- Sulfonylureas (SU)
- biguanides
- alpha-glucosidase inhibitors (a-GI)
- thiazolidinedione (TZD)
- glinides
- sodium-glucose cotransporter type 2 inhibitors (SGLT2i), and
- DPP-4 inhibitors (DPP-4i).

Participants will be randomized at Visit 3 in a 2:1 ratio to weekly subcutaneous injections of dulaglutide 1.5 mg or 0.75 mg.

In each arm,

If taking	**then participants are required**
DPP-4i	to stop DPP-4i at randomization Note: In case of weekly DPP-4i, it must be stopped 1 week before randomization.
other OAMs	to continue the same dose of OAM during the study period exception: dose modifications are allowed in the event of hypoglycemia

Abbreviations: DPP-4i = DPP-4 inhibitors; OAM = oral antihyperglycemic medication.

Switching from DPP-4i is regarded as monotherapy of dulaglutide and taking other OAMs is regarded as combination therapy with OAM.

The study will consist of 3 periods (See Section 1.2):

- an approximately 2-week screening/lead-in period
- a 52-week treatment period including Treatment Period I (26-week for the primary endpoint) and Treatment Period II (26-week), and
- a 4-week safety follow-up period.

Screening (Visit 1)

At Visit 1, the investigator or site staff will initiate the assessment of participant eligibility for the study. The participant will sign the informed consent form (ICF) and receive a participant

identification number before any study procedures are performed. Procedures at Visit 1 will be performed as shown in the schedule of activities (SoA) (Section 1.3).

The participant and their caregiver(s) will be provided;

- diabetes management education
- glucometer and training on how to perform self-monitored blood glucose (SMBG)
- visit-specific diaries and training on how to record blood glucose (BG) values, OAM, hypoglycemic events, other concomitant medications, and adverse events (AEs).

During the screening/lead-in period, participants are required to continue their pre-study OAM therapy and should not change the type of OAMs used or their doses in order to allow reliable assessment of HbA1c at Visit 3.

Visit 2 (telephone visit)

At Visit 2, the investigator or site staff will inform participants of the screening results and instruct participants to perform the 6-point SMBG twice (2 days) before Visit 3.

In case of weekly DPP-4i, it must be stopped 1 week before randomization.

Visit 3

At Visit 3, participants should arrive at the study site in an at least 8-hour fasting state. In the fasted status, intake of water is allowed.

After confirming participant eligibility, participants will be randomized in a 2:1 ratio to weekly injections of dulaglutide 1.5 mg or 0.75 mg at Visit 3.

Randomization will be stratified by pre-study OAM class and HbA1c at Visit 1.

Stratification factors	**Groups**
pre-study OAM class	SU biguanides TZD a-GI glinides SGLT2i DPP-4i
HbA1c at Visit 1	low (<8.5% for DPP-4i class and <9.0% for other OAM classes) high (≥8.5% for DPP-4i class and ≥9.0% for other OAM classes)

Abbreviations: a-GI = alpha-glucosidase inhibitors; DPP-4i = DPP-4 inhibitor; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medications; SGLT2i = sodium-glucose, cotransporter type 2 inhibitors; SU = sulfonylureas; TZD = thiazolidinedione.

Participants will be instructed on how to use the Single-use pen and will inject their first dose of study intervention under the supervision of study personnel while in the clinic for Visit 3, after

randomization and other study procedures . The date and time of the first dosing of study intervention should be recorded on the eCRF.

Participants are required to continue using their concomitant OAMs, except for DPP-4i, throughout the treatment period. If a participant uses daily DPP-4i, it is required that the participants stop using daily DPP-4i at randomization.

Following randomization, participants will participate in a 52-week treatment period.

Treatment Period (Visit 3 to Visit 9)

Procedures during the treatment period will be performed as shown in the SoA (Section 1.3).

From Visit 3 through Visit 9 (except Visit 4), participants should arrive at the study site in an at least 8-hour fasting state. In the fasted state, intake of water is allowed.

Throughout the treatment period, participants will collect all of the following data in the participant diary:

- SMBG,
- dosing dates and time,
- hypoglycemic events,
- AEs, and
- concomitant medications.

The study site personnel will review the data at the next office visit.

At each office visit,

- study diaries will be collected,
- new study diaries will be dispensed (and instructions will be reviewed),
- used and unused study intervention and injection supplies will be returned, and
- new supplies will be dispensed as needed.

At Week 52 or the early termination (ET) visit, all used and unused study intervention will be returned.

Discontinuation or dose changes of concomitant OAMs are not permitted, except in certain situations (Section 6.5). Participants 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 intervention (Section 6.5).

Safety Follow-Up Period

Procedures during the safety follow-up period will be performed as shown in the SoA (Section 1.3).

All participants who complete the treatment period (both I and II) are required to complete Visit 801, a safety follow-up visit approximately 4 weeks after the last visit of the treatment period. During the safety follow-up period, participants will not receive study intervention.

The safety follow-up period will also be applied to participants who discontinue from the study. In this case, the Safety Follow-Up visit (Visit 801) will occur approximately 4 weeks after the ET visit.

Participants are required to return any remaining study diaries to the study site at the end of this period.

Early Termination Visit

Every attempt will be made to keep participants in the study irrespective of their adherence to treatment with study intervention.

At any time after Visit 3 (randomization), a participant who is to discontinue from the study before Visit 9 will have an ET visit conducted. At this visit, procedures will occur as shown in the SoA (Section 1.3). Participants should be instructed to return any remaining used or unused study intervention supplies and diaries to the study site at this visit. Participants will be asked to perform the Safety Follow-Up visit (Visit 801) approximately 4 weeks after the ET visit, so that the Safety Follow-Up visit (Visit 801) will be their final visit. If the participant is not able to perform the Safety Follow-Up visit (Visit 801), the ET visit will be the final study visit. A participant summary electronic case report form (eCRF) will be completed.

4.2. Scientific Rationale for Study Design

This study is designed to compare efficacy and safety of dulaglutide 1.5 mg QW versus dulaglutide 0.75 mg in patients with T2D who are inadequately controlled on single OAM. Scientific rationale of study design elements is shown in the table.

Study Design Element	Scientific Rationale
Double-blind	The double-blind design was chosen to prevent bias in research results.
Parallel-group comparison	The parallel-group design for comparison of interventions was chosen to evaluate 52-week long-term safety as 1 of the secondary objectives. The parallel-group design is generally applied in Phase 3 studies.
Study duration	The planned treatment duration of 52 weeks is adopted to assess long-term efficacy and safety, which is required by the Guideline for Clinical Evaluation of Oral Hypoglycemic Agents issued in 2010.
Primary endpoint	The primary efficacy assessment of 26 weeks is adopted in this study. This duration is common to evaluate the stable effect of antidiabetics.

Study Design Element	Scientific Rationale
	HbA1c, used as the primary endpoint parameter, is regarded as reliable and accurate with respect to efficacy assessment in individuals and populations with T2D.
Concomitant medications	Concomitant use of DPP-4i is not allowed in this study because both GLP-1 receptor agonists and DPP-4i decrease blood glucose via GLP-1 receptors. Concomitant OAM other than DPP-4i is required to continue at the same dose during the study period; however, OAM dose modifications are allowed in the event of hypoglycemia. Restrictions of concomitant medication other than OAM are described in Section 6.5.
HbA1c at Visit 1	Enrollment criteria of HbA1c is 8-10% for other OAM classes, except DPP-4i for which it is 7.5-9.5% for DPP-4i. These criteria were set to secure enrollment of participants who are not well controlled by single OAM, and approximately 0.5% worsening in HbA1c after stopping DPP-4i is expected.

Abbreviations: a-GI = alpha-glucosidase inhibitors; DPP-4i = DPP-4 inhibitor; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medications; SGLT2i = sodium-glucose, cotransporter type 2 inhibitors; SU = sulfonylureas; T2D = type 2 diabetes; TZD = thiazolidinedione

4.3. Justification for Dose

Dulaglutide 0.75 mg is the currently approved dose in Japan. Clinical efficacy and safety of dulaglutide 0.75 mg in Japanese participants has been investigated in Phase 3 studies (H9X-JE-GBDP and GBDY). The results of these studies demonstrated that dulaglutide 0.75 mg is superior to insulin glargine, and non-inferior to liraglutide 0.9 mg in HbA1c reduction.

Dulaglutide 1.5 mg is 1 of the approved doses for the treatment of patients with T2D across countries, except Japan. Both 0.75 mg and 1.5 mg were approved based on the clinical results obtained from Global Phase 3 studies (H9X-MC- GBDA, GBDB, GBDC, GBDD, and GBCF). Dulaglutide 1.5 mg was also investigated in a cardiovascular (CV) outcome study (H9X-MC-GBDJ). This study showed that dulaglutide 1.5 mg reduced a composite of CV outcome (MACE-3; death from CV causes, nonfatal myocardial infarction, or nonfatal stroke) in T2D patients with high CV risk.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all required phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5. Study Population

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

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Race and Age

1. Japanese participants aged ≥20 years at the time of signing the informed consent.

Type of Participant and Disease Characteristics

2. Patients with T2D for ≥6 months according to the World Health Organization (WHO) classification.
3. Treated with stable doses of a single OAM (biguanides, DPP-4i, SU, a-GI, TZD, glinides, or SGLT2i) for at least 8 weeks prior to Visit 1; the dose must be more than or equal to minimum maintenance dose as shown in Section 10.7, Appendix 7. Participants taking DPP-4i must agree to stop taking it at randomization. In case of weekly DPP-4i, it must be stopped 1 week before randomization.
4. Have the following HbA1c result at Visit 1, as assessed by the central laboratory:
   - Participants taking DPP-4i: ≥7.5% and ≤9.5%,
   - Participants taking another OAM: ≥8.0% and ≤10.0%

Weight

5. Stable body weight for at least 8 weeks prior to Visit 1 (not changed by more than 5% in the past 8 weeks);
6. Have a body mass index (BMI) of ≥18.5 kg/m^2 and <35 kg/m^2 at Visit 1;

Sex

7. Males or nonpregnant females (women of childbearing potential participating must agree to remain on contraception during study period);

Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Female participants:

- Women not of childbearing potential (WNOCBP) may participate in this study and include those who are infertile due to surgical sterilization, congenital anomaly or postmenopausal (see Section 10.4, Appendix 4 for definition details).
- Women of childbearing potential (WOCBP) may participate in this study.
  - WOCBP participating must agree to remain completely abstinent (if this is their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) without sexual relationships with

males, use 2 effective methods of contraception, 1 of which must at least be highly effective (see Section 10.4, Appendix 4) from screening until 4 weeks after the last dose of randomized therapy.
    - WOCBP must test negative for pregnancy as indicated by negative serum pregnancy test at screening (Visit 1) followed by a negative urine pregnancy test prior to the first exposure (Visit 3; Section 1.3, SoA).

- Woman must not be breastfeeding

b. Male participants:
No male contraception is required except in compliance with specific local government study requirements.

Please refer to Section 10.4, Appendix 4 for definitions and additional guidance related to contraception.

Informed Consent

8. Capable of giving signed informed consent as described in Section 10.1, Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other

9. In the investigator's opinion, are well-motivated, capable, and willing to self-inject treatment, perform finger stick BG monitoring, and maintain a study diary.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

10. Have type 1 diabetes (T1D);
11. Have a history of ≥1 episode of ketoacidosis or hyperosmolar state/coma;
12. Have had ≥1 episode of severe hypoglycemia and/or ≥1 episode of hypoglycemia unawareness within the last 6 months;
13. Have had any of the following CV conditions within 8 weeks prior to Visit 1: acute myocardial infarction (MI), New York Heart Association Class III or Class IV heart failure, or cerebrovascular accident (stroke);
14. Have a known clinically significant gastric emptying abnormality (e.g., severe diabetic gastroparesis or gastric outlet obstruction) or have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (e.g., sleeve gastrectomy) or chronically take drugs that directly reduce gastrointestinal motility;

15. 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; participants with NAFLD are eligible for participation in this study;
16. Have had chronic or acute pancreatitis any time prior to study entry;
17. Have lipase and/or pancreatic amylase >3 times the upper limit of the reference range as determined by the central laboratory;
18. Have an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2 (<45 mL/min/1.73 m^2 for participants who take biguanides and SGLT2i), as calculated by the central laboratory at Visit 1 using the Japanese Society of Nephrology equation;
19. Have any self or family history of type 2A or type 2B multiple endocrine neoplasia (MEN 2A or 2B) in the absence of known C-cell hyperplasia (this exclusion includes participants with a family history of MEN 2A or 2B, whose family history for the syndrome is rearranged during transfect [RET]-negative; the only exception for this exclusion will be for a participant whose family members with MEN 2A or 2B have a known RET mutation and the potential participant for the study is negative for the RET mutation);
20. Have any self or family history of medullary C-cell hyperplasia, focal hyperplasia, or carcinoma (including sporadic, familial, or part of MEN 2A or 2B syndrome);
21. Have serum calcitonin ≥20 pg/mL, as determined by the central laboratory at study entry;
22. Have evidence of significant, active autoimmune abnormality (e.g., lupus, rheumatoid arthritis) that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 12 months;
23. Have evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxicosis, adrenal crises), in the opinion of the investigator.
24. Have active or untreated malignancy, or have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years;
25. Have any hematologic condition that may interfere with HbA1c measurement (e.g., hemolytic anemias, sickle-cell disease);
26. Known proliferative retinopathy or maculopathy requiring acute treatment according to the opinion of the investigator;
27. Have a history of transplanted organ (corneal transplants [keratoplasty] are allowed);

Prior/Concomitant Therapy

28. Have history of use of any injectable therapy for T2D treatment (GLP-1 receptor agonists and insulin, and so on) or oral semaglutide within 3 months prior to Visit 1, except for short-term (14 consecutive days) use of insulin for acute conditions;
29. Have been treated with any other excluded medication (Sanorex® [mazindol] and chronic systemic glucocorticoid therapy) within 8 weeks prior to Visit 1; excluded glucocorticoids must not have been used for >14 days within 8 weeks prior to Visit 1;

Prior/Concurrent Clinical Study Experience

30. Are currently enrolled in any other clinical study involving a study intervention or any other type of medical research judged not to be scientifically or medically compatible with this study;
31. Have participated, within the last 30 days, in a clinical study involving a study intervention. If the previous study intervention has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed;
32. Have previously completed or withdrawn from this study or any other study investigating dulaglutide;

Other Exclusions

33. 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;
34. Are Lilly employees;
35. Have any other conditions (including known drug or alcohol abuse or psychiatric disorder) or circumstances (including known or anticipated plans for relocation or extended travel) that may preclude the participant from following the protocol and completing the study.

5.3. Lifestyle Considerations

Per Section 1.3, qualified medical staff will provide diabetes management counseling. The counseling includes

- instructions on
  - diet, and
  - exercise,

and

- education about
  - the signs and symptoms, and
  - treatment of hypoglycemia.

Participants 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.

Study participants should be instructed not to donate blood or blood products during the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Participants who do not qualify based upon Visit 1 laboratory measurements will have an opportunity to have 1 additional screening visit with repeat screening laboratory tests with allowable deviation (days) described in SoA (Section 1.3).

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Participants will be randomized in a 2:1 ratio to receive dulaglutide 1.5 mg and 0.75 mg, respectively, each administered weekly as a subcutaneous injection in participants with T2D who are already taking a stable dose of OAM. Participants will receive the study intervention for 52 weeks.

See the minimum maintenance dose of OAMs in Section 10.7, Appendix 7.

ARM Name	0.75 mg Dulaglutide	1.5 mg Dulaglutide
Intervention Name	Dulaglutide	Dulaglutide
Type	Drug	Drug
Dose Formulation	Single-use pen	Single-use pen
Dosage Level(s)	0.75 mg once weekly	1.5 mg once weekly
Route of Administration	Subcutaneous injection	Subcutaneous injection
Use	Comparator	Experimental
Sourcing	Provided centrally by the Sponsor via interactive web-response system (IWRS)	Provided centrally by the Sponsor via IWRS
Packaging and Labeling	Study intervention will be provided in autoinjectors (single-use pens) packaged in cartons to be dispensed. Clinical study materials will be labeled according to country regulatory requirements.	Study intervention will be provided in autoinjectors (single-use pens) packaged in cartons to be dispensed. Clinical study materials will be labeled according to country regulatory requirements.

[a] Information provided in this table (dose formulation, sourcing) may change throughout the study.

6.1.1. Medical Devices

The study intervention provided for use in the study is the dulaglutide Single-use pen.

- 1.5 mg Dulaglutide (3 mg/mL) in a 0.5 mL Single-use pen
- 0.75 mg Dulaglutide (1.5 mg/mL) in a 0.5 mL Single-use pen

The prefilled pen is intended for self-administration as well as administration via another person depending on the injection site chosen. The prefilled pen being used in this study is the same prefilled pen used in the marketed product platform device. The combination products provided for use in the study are dulaglutide autoinjector. Any medical device-related AEs, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 10.6).

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
3. The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the IP Operation/Handling Procedure.

6.3. Measures to Minimize Bias: Randomization and Blinding

To preserve the blinding of the study, the Lilly study team will be blinded to double-blind treatment assignments until after the primary endpoint database lock. A limited number of study team members will have access to the unblinded treatment assignments and unblinded data at the time of the primary endpoint database lock. The primary endpoint database lock is planned to occur after all participants have completed visits up to Visit 7 (Week 26) or discontinued the study prior to Visit 7 (Week 26). Investigators, site staff, clinical monitors, participants, and study team members who interact directly with site personnel after primary endpoint database lock will remain blinded to the treatment assignments until the final database lock.

All participants will be centrally assigned to randomized study intervention using an IWRS. Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's intervention assignment is unblinded, the sponsor

must be notified immediately after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a sponsor clinical research physician (CRP) or clinical research scientist (CRS) for the participant to continue in the study.

6.4. Study Intervention Compliance

When participants or caregivers administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by reconciling the number of Single-use pens dispensed with the number returned and confirming the record of administration in the participant's diary. This information will be documented in the source documents and eCRF. A participant is considered compliant if he/she receives 75% of the required injections.

6.5. Concomitant Therapy

In this study, participants taking DPP-4i are required to stop DPP-4i treatment at randomization. In case of weekly DPP-4i, it must be stopped 1 week before randomization. Participants taking other OAMs are required to continue the same dose of OAM during the study period; however, OAM dose modifications are allowed in the event of hypoglycemia.

Participants 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 intervention (Section 5.2).

Prohibited medications include

- Any other antihyperglycemic medications, except for study-specified permitted concomitant OAMs
- Any medications that promote weight loss (e.g., Sanorex® [mazindol])
- Any chronic (>2 weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations)

Short-term insulin use is allowed for certain clinical situations (e.g., elective surgery, during hospitalization, hyperosmolar states). Rescue therapy with insulins will be also allowed in certain situations after randomization due to severe, persistent hyperglycemia (see Section 6.5.1). If insulin is prescribed as a rescue therapy, it must be differentiated from short-term use of insulin therapy for medical emergencies when reported in the eCRF. After early discontinuation of study intervention, any antihyperglycemic medications, except for GLP-1 receptor agonists may be allowed.

Investigative site staff will inform participants 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 participant will inform the investigator or a designated site staff member as soon as possible.

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

Any medication or vaccine (including over-the-counter [OTC] or prescription medicines, vitamins, and/or herbal supplements) or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency for concomitant therapy of special interest

The CRP or CRS should be contacted if there are any questions regarding concomitant or prior therapy.

6.5.1. Management of Participants with Severe, Persistent Hyperglycemia

Add-on glycemic rescue therapy with insulin will be allowed for participants who meet any of the following prespecified criteria for severe, persistent hyperglycemia. In this case, the investigator determines if a new intervention is warranted, after noncompliance with the assigned therapeutic regimen is ruled out as the reason for hyperglycemia. Participants should continue administering assigned study intervention. Glycemic rescue therapy by adding other OAM and increasing dose of study-specified concomitant OAM will not be allowed.

The criteria are as follows:

a) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period any time during the first 8 weeks post-randomization;
   OR
b) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >240 mg/dL (>13.3 mmol/L) over at least a consecutive 2-week period at any time 9 to 26 weeks post-randomization;
   OR
c) Blood glucose concentration measured by weekly 1-point SMBG before breakfast >200 mg/dL (>11.1 mmol/L) over a consecutive 2-week period at any time 27 to 52 weeks post-randomization.

6.6. Dose Modification

No adjustments in study intervention doses will be allowed.

6.7. Intervention after the End of the Study

Study intervention will not be made available after conclusion of the study to participants. There is no compassionate use program in this study.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, the participant will remain in the study to be evaluated for all planned efficacy and safety measurements. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Possible reasons leading to permanent discontinuation of study intervention include:

Participant Decision

The participant requests to discontinue study intervention.

Discontinuation due to a hepatic event or liver test abnormality.

Participants who are discontinued from study intervention due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the eCRF (Section 10.5, Appendix 5). Discontinuation of the study intervention for abnormal liver tests **should be** considered by the investigator when a participant meets 1 of the following conditions after consultation with the Lilly's CRP or CRS:

- ALT or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
- ALT or AST >5X ULN for more than 2 weeks
- ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or international normalized ratio (INR) >1.5
- 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%)

Additional circumstances in which participants will be discontinued from the study intervention include:

A participant will be discontinued from study intervention due to any of the following:

- If a participant is inadvertently enrolled and it is determined that continued study intervention would not be medically appropriate (See Section 7.2.1)
- If a participant misses 3 continuous injections
- Acute or chronic pancreatitis

- If a participant 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 participant is diagnosed with C-cell hyperplasia or medullary thyroid carcinoma (MTC) after randomization
- Any other treatment-emergent AE (TEAE), SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- Any significant study intervention-related hypersensitivity reaction;
- If any other antihyperglycemic medications except for study-specified concomitant OAMs and insulin is initiated, and the participant refuses to discontinue these medications
- If female participant becomes pregnant (Section 7.2)
- If a participant is diagnosed with T1D
- If an investigator, site personnel performing assessments, or participant is unblinded
- if the participant or the participant's designee, for example, legal guardian, requests that the participant be withdrawn from study intervention
- If the investigator or sponsor decides that the participant should be withdrawn from study intervention; if the investigator decides to permanently discontinue study intervention because of an SAE or a clinically significant laboratory value, Lilly or its designee should be alerted immediately.

Participants who discontinue the study intervention permanently will receive another glucose-lowering intervention (Section 6.5) and will continue participating in the study according to the protocol to collect all planned efficacy and safety measurements.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1. Temporary Discontinuation

In certain situations, after randomization, the investigator may need to temporarily discontinue (interrupt) study intervention (for example, due to an AE or a clinically significant laboratory value). If study intervention interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 10.3 of this protocol. Every effort should be made by the investigator to maintain participants on study intervention and to restart study intervention after any temporary interruption, as soon as it is safe to do so.

Investigators should inform the Sponsor that study intervention has been temporarily interrupted. The data related to temporary interruption of study intervention will be documented in source documents and entered in the eCRF.

7.2. Participant Discontinuation/Withdrawal from the Study

Every attempt should be made to keep participants in the study irrespective of their adherence to treatment with study intervention in order to minimize the amount of missing data and to enable assessment of study objectives as planned by the study protocol.

A participant may withdraw from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if 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
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, an early termination visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued both from the study intervention and from the study at that time.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study intervention unless there are extenuating circumstances that make it medically necessary for the participant to continue on study intervention. If the investigator and the sponsor CRP or CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP or CRS to allow the inadvertently enrolled participant to continue in the study with or without treatment with study intervention. Safety follow-up should be performed as outlined in Section 1.3 (SoA), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

A participant 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 or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3.)
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

The primary efficacy measure will be evaluated at 26 weeks:

- Change from baseline in HbA1c.

8.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be evaluated through 26 and 52 weeks:

- Change from baseline in HbA1c.
- Proportion of participants achieving HbA1c target of ≤6.5% and <7.0%;
- Change from baseline in FSG ;
- Change from baseline in 6-point SMBG;
- Change from baseline in body weight;

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded, per Section 1.3.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, thyroid exam, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3).

- The participant should sit quietly for 5 minutes before vital sign measurements are taken. For each parameter, 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart. Blood pressure (BP) can be measured by either an automated or semi-automated blood pressure machine, but the same machine must be used during study period.
- Vital sign measurements should be taken before obtaining an electrocardiogram (ECG) tracing and before collection of blood samples for laboratory testing, at visits where required.

8.2.3. Electrocardiograms

- 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT interval (QTc).
- Electrocardiograms will initially 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 participant is still present, for immediate participant management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of the study intervention should be reported to Lilly or its designee as an AE via the eCRF.
- All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG vendor, except for the screening ECG, which will be performed locally. The central ECG vendor will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist at the central ECG vendor for further evaluation of machine-read measurements or to meet regulatory requirements. The machine-read ECG intervals and heart rate may be used for data analysis and report-writing purposes, unless a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

8.2.4. Clinical Safety Laboratory Assessments

- See Section 10.2, Appendix 2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator, or CRP or CRS.
    - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
    - All protocol-required laboratory assessments, as defined in Section 10.2 Appendix 2, must be conducted in accordance with the SoA and standard collection requirements.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then report the information as an AE.

8.2.5. Hepatic Monitoring

Participants who have abnormal liver tests during the study

Close hepatic monitoring

Laboratory tests (Section 10.5, Appendix 5), including ALT, AST, ALP, total bilirubin, direct bilirubin, γ-glutamyltranspeptidase (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 1 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
Total bilirubin <1.5x ULN	Total bilirubin ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
Total bilirubin ≥1.5x ULN	Total bilirubin ≥2x baseline (except for participants with Gilbert's syndrome)

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 CRP or CRS. 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 lab results stabilize. Monitoring of ALT, AST, ALP, and total bilirubin should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

A comprehensive evaluation (Section 10.5, Appendix 5) should be performed to search for possible causes of liver injury if 1 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
Total bilirubin <1.5x ULN	Total bilirubin ≥2x ULN (except for participants 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
Total bilirubin ≥1.5x ULN	Total bilirubin ≥1.5x baseline (except for participants with Gilbert's syndrome)

* 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 participant's history and initial results, further testing should be considered in consultation with the Lilly's CRP or CRS, 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 blood 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.

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

Additional hepatic safety data collection in hepatic safety eCRF 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 total bilirubin to ≥ 2x ULN (if baseline total bilirubin <1.5x ULN) (except for cases of known Gilbert's syndrome)

- In participants with baseline total bilirubin ≥1.5x ULN, the threshold should be Total bilirubin ≥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 intervention due to a hepatic event

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

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Section 10.3, Appendix 3:

- AEs
- SAEs
- Product complaints (PCs)

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	signing of the informed consent form (ICF)	the follow-up visit	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	signing of the ICF	start of intervention	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE and SAE updates – after start of study intervention	start of intervention	participation in study has ended	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	4 weeks after the last dose of study intervention	Within 24 hours of learning of the pregnancy	SAE eCRF[a]	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Product Complaints					
Product Complaints (PC) associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form[b]	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form[b]	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)[c]	Participation in study has ended	N/A	Promptly	Product Complaint form	

[a] Pregnancy itself is not considered to be an AE or SAE. 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.

[b] AEs and SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.

[c] The PC which the investigator becomes aware of after the study has ended.

8.3.2. Pregnancy

Pregnancy (maternal or paternal exposure to study intervention) does not meet the definition of an adverse event. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Appendix 10.3 to collect data on the outcome for both mother and fetus.

8.3.3. Adverse Events of Special Interest

Adverse events of special interest (AESIs) for this program include:

a. Hypoglycemia
b. Severe, persistent hyperglycemia

c. Pancreatitis
d. C-cell hyperplasia and C-cell neoplasms
e. Cardiovascular events
f. Hypersensitivity reactions

If a, b, c, d, e, or f are reported, sites will be prompted to collect additional details/data on the specific eCRFs.

Hypoglycemia

Participants will collect information on episodes of hypoglycemia starting from Visit 3 (Week 0) until the last study visit (ET visit or Visit 801). Participants 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 SoA (Section 1.3). 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 participants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia

Glucose <54 mg/dL (3.0 mmol/L): Level 2 hypoglycemia 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 or 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 eCRF 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 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 participant should receive additional education, if deemed appropriate. It is important that each case of suspected or confirmed hypoglycemia be properly categorized with respect to severity.

Severe Persistent Hyperglycemia

Severe, persistent hyperglycemia will be collected as an AE during the study to assess the risk of extreme imbalance in glycemic control, as defined in Section 6.5.1. Details of antihyperglycemic medication initiated as rescue therapy for severe, persistent hyperglycemia per these criteria will be collected on the antihyperglycemic concomitant therapy eCRF.

Pancreatitis

Diagnosis of acute pancreatitis

Acute pancreatitis is defined as an AE of interest in all studies with dulaglutide, including this study.

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; Koizumi 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, pancreatic, or both) and/or lipase ≥3 x ULN;
- characteristic findings of acute pancreatitis on computed tomography (CT), scan or magnetic resonance imaging (MRI)

If acute pancreatitis is suspected, the investigator should

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Each case 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 intervention.

Discontinuation for acute pancreatitis

If acute pancreatitis is diagnosed, the participant must discontinue use of the study intervention.

Case adjudication and data entry

An independent clinical endpoint committee (CEC) will adjudicate all suspected cases of acute pancreatitis. 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 participants 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.

Asymptomatic elevation of serum amylase and/or lipase

Each participant will have measurements of pancreatic amylase and lipase (assessed at the central laboratory) as shown on the SoA (Section 1.3), 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 participants (Nauck et al. 2016; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or p-amylase ≥3X ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

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 5.2). Participants 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 study will include reporting of thyroid TEAEs and measurements of calcitonin according to the SoA (Section 1.3). 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.

Participants who develop serum calcitonin increases ≥50% of the screening value AND an absolute value ≥20 pg/mL and <35 pg/mL at Visit 7 (Week 26) will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the participant 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.

Participants with an increase in serum calcitonin ≥50% of screening value AND an absolute value ≥35 pg/mL at Visit 7 (Week 26) will be recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

For participants 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.

Cardiovascular Events

Vital signs (PR, systolic blood pressure [SBP], diastolic blood pressure [DBP]) will be monitored throughout the study, and 12-lead ECGs will be monitored per the SoA (Section 1.3). Any clinically relevant finding from vital signs and ECGs obtained before the first dosing of study intervention that results in a diagnosis should be recorded in the 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 intervention and results in a diagnosis should be recorded as an AE in eCRF. Cardiovascular events will be analyzed using preferred terms and abnormal ECG result.

Hypersensitivity Reactions

All 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 hypersensitivity reaction eCRF for any AEs or SAEs deemed related to study intervention by the investigator. In the event of severe hypersensitivity reactions (i.e., generalized urticaria or anaphylaxis), serum and plasma samples should also be collected as close as possible to the occurrence of the event. Samples for follow-up assessment may also be collected within 4 weeks of the recovery from the event. Study intervention should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study intervention (Section 7.1.1). Study intervention may be restarted when/if it is safe to do so, in the opinion of the investigator. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

If study intervention is permanently discontinued, the participant will receive another glucose-lowering treatment, judged by the investigator to be appropriate based on the participant's clinical status, and will continue in the study to collect all planned efficacy and safety measurements.

Injection site reactions will be collected on an eCRF separate from the hypersensitivity reaction eCRF.

8.4. Treatment of Overdose

For this study, if the duration of injections between 2 doses are within 72 hours of each other it will be considered an overdose.

In the event of an overdose, the investigator should:

1. Contact the clinical research associate (CRA) immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the CRP or CRS based on the clinical evaluation of the participant.

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

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable.

8.8. Biomarkers

Not applicable.

8.9. Immunogenicity Assessments

There are no planned assessments for anti-dulaglutide antibodies for this study. However, plasma and serum samples may be used to evaluate antibody production to dulaglutide and dulaglutide drug concentrations, in the event of hypersensitivity reactions.

Samples may be stored for a maximum of 7 years (or according to local regulations) following the last participant's last visit for the study at a facility selected by the sponsor to enable further analysis of immune responses to dulaglutide.

8.10. Health Economics OR Medical Resource Utilization and Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

The alternative hypothesis for the primary objective is:

Dulaglutide 1.5 mg is superior to dulaglutide 0.75 mg, relative to the mean change in HbA1c from baseline at Week 26.

9.2. Sample Size Determination

Approximately 732 participants will be screened to achieve 585 participants randomly assigned in a 2:1 ratio to dulaglutide 1.5 mg group and dulaglutide 0.75 mg group (390 and 195 participants, respectively). Assuming a drop-out rate of 10%, 528 participants will be evaluable for an estimated total of 352 evaluable participants in the dulaglutide 1.5 mg group and 176 evaluable participants in the dulaglutide 0.75 mg group.

This sample size provides at least 90% power for demonstrating superiority of dulaglutide 1.5 mg to dulaglutide 0.75 mg in the HbA1c change from baseline at Week 26. This assumes a true treatment difference of -0.3% with a common standard deviation (SD) of 1.0% for the change in HbA1c from baseline.

For participants taking DPP-4i prior to randomization, target numbers of participants randomized for 1.5 mg and 0.75 mg are 150 and 75 (total 225 participants).

For participants taking other OAMs, target numbers of participants randomized for 1.5 mg and 0.75 mg are 240 (40 per OAM class) and 120 (20 per OAM class). In total, 360 participants (60 per OAM class) will be randomized for other OAMs.

9.3. Populations for Analyses

The following analysis populations are defined in Table 1.

Table 1. Populations for Analyses

Population	Description
Entered	All participants who sign the ICF.
Randomized	All participants who are randomized to a treatment arm.
Nonrandomized	All participants entered, but not randomized to a treatment arm.
Intention-to-treat (ITT) set	All randomly assigned participants who are exposed to at least 1 dose of study intervention for an assigned treatment arm. Participants will be included in the treatment group they were randomized to.
Efficacy analysis set for Period I (EAS1)	Data obtained during Treatment Period I (26-week) from the ITT set, excluding data after initiating rescue antihyperglycemic medication or discontinuing study intervention (last dose date + 7 days). In the event of a treatment error, participants will be

	analyzed according to the treatment they were randomly assigned to receive.
Safety analysis set for Period I (SS1)	Data obtained during Treatment Period I from the ITT set, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.
Efficacy analysis set for Period I and II (EAS2)	Data obtained during Treatment Period I and II (52-week) from the ITT set, excluding data after initiating rescue antihyperglycemic medication or discontinuing study intervention (last dose date + 7 days). In the event of a treatment error, participants will be analyzed according to the treatment they were randomly assigned to receive.
Safety analysis set for Period I and II (SS2)	Data obtained during both Treatment Period I, II and safety F/U period from the ITT set, regardless of adherence to study intervention or initiation of rescue antihyperglycemic medication.

9.4. Statistical Analyses

9.4.1. General Considerations

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all confidence intervals (CIs) will be given at a 2-sided 95% level.

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 SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

The primary efficacy assessment, guided by efficacy "estimand", will be conducted using the EAS1/EAS2 to compare dulaglutide 1.5 mg with dulaglutide 0.75 mg. The "efficacy" estimand measures the benefit of treatment when taken as directed.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of dulaglutide 1.5 mg with dulaglutide 0.75 mg, irrespective of adherence to study intervention or initiation of antihyperglycemic rescue therapy. Thus, the safety analyses will be conducted using the SS1 or SS2. Selected safety analysis (for example, hypoglycemia) may be conducted excluding data after initiation of another antihyperglycemic therapy.

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment arms relative to continuous measurements assessed over time will be a mixed-model for repeated measures (MMRM), with terms of treatment, visit and treatment by visit interaction, pre-study

OAM class (see stratification factors in Section 4.1), and baseline measurement as a covariate. An unstructured covariance matrix will model the relationship of within participant errors.

The Kaplan-Meier method will be used for estimation of cumulative event free survival rates over time, and Cox proportional hazards regression analysis will be used to compare hazard rates among treatments.

Summary statistics for categorical measures, including categorized continuous measures, will include sample size, frequency, and percentages. Fisher's exact test will be used to examine the treatment difference in categorical outcomes. Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. Summary statistics for discrete count measures will include sample size, mean, SD, median, minimum, and maximum. The negative binomial regression model will be used for the treatment comparison of discrete count measures.

The statistical analysis plan (SAP) will be finalized prior to the first unblinding (for the 26 weeks primary outcome database lock) and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and secondary endpoints.

9.4.2. Treatment Arm Comparability

9.4.2.1. Participant Disposition

Frequency counts and percentages of all participants screened, randomized, and receiving at least 1 dose of study intervention (dulaglutide 1.5 mg or 0.75 mg), will be presented by treatment arm. Of the participants in the ITT population, frequency, counts and percentages of participants completing the study, prematurely discontinuing the study, including the reason for premature discontinuation, will be presented by treatment arm. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study by treatment arm will be provided.

9.4.2.2. Participant Characteristics

Demographics, medical history, and concomitant illness will be summarized by treatment arm using the ITT population.

9.4.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by anatomical therapeutic chemical classification and treatment arm using the ITT population. In particular, the incidence of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint. Dose modifications of oral antihyperglycemic medications will also be compared between treatment arms.

9.4.2.4. Treatment Compliance

Of the participants in the ITT population, frequency counts and percentages of participants prematurely discontinuing study interventions, including the reason for premature discontinuation, will be presented by treatment arm. A Kaplan-Meier analysis of time from randomization to premature study intervention discontinuation by treatment arm will be provided.

Treatment compliance is defined as taking at least 75% of required injections of study intervention. Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment arm using the ITT population.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

The primary efficacy analysis will be conducted using EAS1. The primary analysis model for HbA1c measurements over time will be an MMRM using restricted maximum likelihood. The response variable of MMRM will be change in HbA1c from baseline values obtained at each scheduled postbaseline visit up to 26 weeks. The independent variable of MMRM will be treatment, pre-study OAM class, visit, and treatment-by-visit as fixed effects, and baseline value as a covariate. An unstructured covariance structure will be used to model the within-participant errors.

9.4.3.2. Secondary Analyses

For HbA1c change from baseline to 52 weeks, the same MMRM model as the primary analysis will be used with EAS2.

Analyses of other continuous secondary efficacy measures will be performed using MMRM with the addition of HbA1c stratum (low and high) in the primary analysis model using EAS1 or EAS2. For percentages of participants achieving target HbA1c ≤6.5% and <7.0%, this endpoint will be analyzed using a longitudinal logistic regression with repeated measurements.

9.4.4. Safety Analyses

All safety analyses will be conducted using both the SS1 and SS2 to assess the safety parameters through 26 and 52 weeks, unless otherwise stated.

Study Intervention Exposure

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

Adverse Events

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

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

Summaries (if appropriate) of AESI defined in Section 8.3.3 will be generated.

Hypoglycemic Episodes

Section 8.3.3 contains definitions of categories of hypoglycemia. A listing of individual hypoglycemic episodes by participant will be presented. Summaries will include both incidence and rates of hypoglycemia for the ITT population excluding data after initiation of another antihyperglycemic therapy.

The incidence of hypoglycemic episodes will be summarized by 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 will be analyzed using a generalized linear mixed-effects model assuming negative binomial distribution if data warrant; otherwise, the Wilcoxon rank-sum test will be used. The model will include treatment, pre-study OAM class, baseline HbA1c stratum (low and high), 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 participants.

Severe, Persistent Hyperglycemia

Listings and summaries (if appropriate) will be provided for participants with at least 1 event of severe, persistent hyperglycemia.

Vital Signs

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

Descriptive statistics for the actual measurements and changes from baseline for SBP, DBP and PR will be presented by treatment and visit. The change from baseline to endpoint will be analyzed using MMRM with the addition of HbA1c stratum (low, high) in the model.

Laboratory Analyses

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

For continuous laboratory analytes, the change from baseline to endpoint will be analyzed using MMRM with the addition of HbA1c stratum (low, high) in the model. For qualitative laboratory analytes, counts and percentages of participants with normal and abnormal values will be analyzed using Fisher's exact test.

9.4.5. Other Analyses

Subgroup analyses by pre-study OAM class will be performed for:

- Change in HbA1c from baseline
- Change in body weight from baseline
- AEs/SAEs
- Hypoglycemic events

For change in HbA1c and body weight from baseline, subgroup analyses by age group, gender, duration of diabetes group, baseline HbA1c group and baseline body weight group will be performed. Additional details will be provided in the SAP.

9.5. Interim Analyses

Analyses of safety and efficacy in Treatment Period I, including the primary analysis, will be conducted using EAS1 and SS1 after all participants have completed Week 26 visit or prematurely discontinued from the study prior to Week 26 visit, thus after the primary outcome database lock. The analyses for Treatment Period I is not considered as interim analyses.

Only the sponsor's unblinded study team members are authorized to access and evaluate unblinded efficacy and safety data from Treatment Period I. The investigators and sponsor's blinded team members will remain blinded until the final database lock of the study.

No adjustment for type I error is needed since this is the primary analysis for the study.

Details of the methods of maintaining the blind and unblinding process are specified in the separate blinding and unblinding plan document.

9.6. Data Monitoring Committee

Not applicable.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
    - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
    - Applicable ICH Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), International Council for Harmonization (ICH) guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement (CTA).

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health

Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.
- The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Committees Structure

Prospective adjudication of pancreatic AEs will be performed for this study.

10.1.5. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the study, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or

annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF. This might include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits (QTLs) will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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 (participant-focused outcome instrument) (e.g. hypoglycemia event-related information) will be collected by the participant via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the eCRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and assures appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.10. Investigator Information

Physicians with a specialty in diabetology will participate as investigators in this clinical study.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the central laboratory unless designated as local in the SOA and in the table below.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the eCRF.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy Testing will be performed as detailed in the SoA (Section 1.3).

Investigators must document their review of the laboratory safety results.

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

Clinical Laboratory Tests

Hematology:
- Hemoglobin
- Hematocrit
- Erythrocyte count (RBC)
- Mean cell volume (MCV)
- Mean cell hemoglobin concentration (MCHC)
- Leukocytes (white blood cells [WBC])
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets

Urine Chemistry:
- Albumin
- Creatinine

Pregnancy Testing (serum, female only):

To confirm menopause
- Follicle-stimulating hormone (FSH)

To confirm pregnancy
- Human chorionic gonadotropin

Pregnancy Test (urine, female only) (local)

Hemoglobin A1c

Fasting serum glucose

Calcitonin

Clinical Chemistry:
- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total bilirubin
- Direct bilirubin
- Alkaline phosphatase (ALP)
- Alanine aminotransferase (ALT)
- Aspartate aminotransferase (AST)
- Gamma-glutamyl transferase (GGT)
- Blood urea nitrogen (BUN)
- Creatinine
- Creatine kinase (CK)[a]
- Uric acid
- Calcium
- Albumin

Lipid Panel:
- Total Cholesterol
- High-density lipoprotein cholesterol (HDL-C)
- Low-density lipoprotein cholesterol (LDL-C)[c]
- Triglycerides

Pancreas (exocrine):
- Lipase
- Pancreatic Amylase

Calculations:
- Albumin/creatinine ratio (urine)
- eGFR[b]

Storage samples:
- Serum
- Plasma

[a] Creatine kinase (CK) MB (CK-MB) is to be assayed if CK result >1000 IU/L.

[b] eGFR will be calculated by the Japanese Society of Nephrology equation.
$eGFR = 194 \times Cr^{-1.094} \times Age^{-0.287}$
(male x1, female x0.739)

[c] Calculated using the Friedewald equation. Reflex to direct LDL assay if triglyceride value >400mg/dL.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization (ISO) 14155.
- Both the investigator and the sponsor will comply with all local medical device reporting requirements.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 for the list of sponsor medical devices.

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdose should be reported regardless of sequelae. • “Lack of efficacy” or “failure of expected pharmacological action” per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition. • Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate eCRF page and product complaint information is reported on the Product Complaint Form.

  Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Sponsor or designee in lieu of completion of the eCRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
• The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The investigator will also consult the IB in his/her assessment. • For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee. • The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment. • The causality assessment is 1 of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Sponsor or designee with a copy of any post-mortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool.

- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor by telephone.
- Contacts for SAE reporting can be found in site training materials.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in site training materials.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.
- An investigator who receives an investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Contraception Guidance:

Word/Phrase	Definition
Women of child bearing potential	Females are considered a woman of child bearing potential (WOCBP) if • they have had at least 1 cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. Following menarche, a woman is considered fertile until becoming post-menopausal, unless permanently sterile. If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.
Women not of childbearing potential	Females are considered women not of childbearing potential (WNOCBP) if • they are premenarchal • they have a congenital anomaly such as Mullerian agenesis • they are infertile due to surgical sterilization, or • they are post-menopausal. Examples of surgical sterilization include: documented hysterectomy, documented bilateral oophorectomy, documented bilateral salpingectomy, or tubal ligation. For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry. Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview
Post-menopausal state	The post-menopausal state should be defined as: 1. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause such as anorexia nervosa, AND With a follicle-stimulating hormone >40 mIU/mL; or 3. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

	* Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.
Reproductive Toxicology Studies	Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Must…	**Must not…**

agree to either remain abstinent, or	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or

stay in a same sex relationship without sexual relationships with males	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or in a same sex relationship, as part of their preferred and usual lifestyle

Topic	**Condition**
Pregnancy testing	Negative serum result at screening followed by a negative urine result within 24 hours prior to treatment exposure (refer to Section 1.3, SoA).
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective (less than 1% failure rate)

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.
Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal, • post coital douche • lactational amenorrhea

Males may participate in this trial.

No male contraception is required except in compliance with specific local government study requirements.

Collection of Pregnancy Information

Female Participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 10.3. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study intervention and the study. If the participant is discontinued from the study intervention, follow the standard discontinuation process and continue directly to the study follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive dulaglutide.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.

10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic Evaluation Testing

See protocol Section 8.2.5 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for those denoted as local below.

Local testing may be performed in addition to central testing when necessary for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs – red blood cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs – white blood cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts [a]
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
	Copper
Coagulation	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (Peth)
Hepatitis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HbsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)

Hematology	**Clinical Chemistry**
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [b]
HBV deoxyribonucleic acid (DNA) [c]	Anti-actin antibody [d]
Hepatitis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV ribonucleic acid (RNA) [c]	EBV DNA [c]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA [c]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [c]	HSV (Type 1 and 2) DNA [c]
Microbiology [e]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

[a] Assayed by central laboratory if available. If not available at the central lab, local lab testing only is allowed
[b] Not required if anti-actin antibody is tested.
[c] Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
[d] Not required if anti-smooth muscle antibody (ASMA) is tested.
[e] Assayed ONLY by investigator-designated local laboratory no central testing available.

10.6. Appendix 6: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Section 10.3, Appendix 3 for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.7. Appendix 7: Minimum Maintenance Dose of Oral Antihyperglycemic Medications

Class	Generic Name	Minimum Maintenance Dose (mg per day)
dipeptidyl peptidase-4 (DPP-4) inhibitor	sitagliptin	50
	vildagliptin	100
	alogliptin	25
	linagliptin	5
	teneligliptin	20
	anagliptin	200
	saxagliptin	5
	trelagliptin	100 (mg per week)
	omarigliptin	25 (mg per week)
sulfonylureas	glibenclamide	1.25
	gliclazide	40
	glimepiride	0.5
biguanides	buformin	100
	metformin	750
alpha-glucosidase inhibitors	acarbose	300
	voglibose	0.6
	miglitol	150
thiazolidinedione	pioglitazone	15
glinides	nateglinide	270
	mitiglinide	30
	repaglinide	1.5
sodium-glucose cotransporter type 2 (SGLT-2) inhibitors	ipragliflozin	50
	dapagliflozin	5
	luseogliflozin	2.5
	tofogliflozin	20
	canagliflozin	100
	empagliflozin	10

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10.8. Appendix 8: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval but need to be reported as soon as possible. All approvals must be retained in the study records

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with Good Clinical Practice, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed Consent

Additional consent from the participant will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits,"
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct During Exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

1. Remote visits

In source documents and the eCRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of adverse events (AEs), serious adverse events (SAEs), and product complaints remain unchanged. Furthermore, every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, AEs, hypoglycemic events, treatment adherence and concomitant medications.

Mobile healthcare:

Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, collection of blood samples, physical assessments and collection of health information.

Other alternative locations: Other procedures that may be done at an alternate location in exceptional circumstances, are laboratory draws.

2. Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, HbA1c testing must be conducted centrally at Visit1 (Screening visit), Visit 3 (0 weeks), and Visit 7 (26 weeks) . The local laboratory must be qualified in accordance with applicable local regulations.

3. Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf,
- arranging delivery of study supplies

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.

- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

4. Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the screening visit are valid for a maximum of 28 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If paused for 28 days or less from screening to randomization visit: the participant will proceed to the next study visit per the usual SoA.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the eCRF.

Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.

- If paused for more than 28 days from screening to randomization visit: The participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen fail in the eCRF. This screen fail is allowed in addition to the main protocol screen fail. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

5. Adjustments to Visit Windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

Visit Allowance in Exceptional Circumstances

	Screening and Lead-In		Treatment Period								Safety Follow-Up
			Treatment Period I					Treatment Period II			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**ET**	**801**
Week of Treatment	**-2**	**-1**	**0**	**2**	**8**	**16**	**26**	**38**	**52**	**ET**	**4 weeks after Visit 9**
Allowable Deviation (Days)	**-14 ~ +3**	**±3**		**±7**	**±14**	**±14**	**±28**	**±28**	**±28**		**-7 ~ +28**

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visits types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.9. Appendix 9: Abbreviations

Term	Definition
AE	adverse event
AESIs	AEs of special interest
a-GI	alpha-glucosidase inhibitors
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BG	blood glucose
blinding/masking	A double-blind study is 1 in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the participants are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CEC	clinical endpoint committee
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CMV	cytomegalovirus
COA	clinical outcome assessment
Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRA	clinical research associate
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.
CRS	clinical research scientist
CT	computed tomography
CTA	clinical trial agreement
CV	cardiovascular

DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
Device Deficiencies	Equivalent to product complaint
DPP-4i	dipeptidyl peptidase-4 inhibitor
EAS1	efficacy analysis set for Period I
EAS2	efficacy analysis set for Period I and II
EBV	Epstein-Barr virus
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture system
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HDV	Hepatitis D virus
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator’s Brochure
ICF	informed consent form
INR	International normalized ratio
ICH	International Council for Harmonization
IEC	Independent Ethics Committees

Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	International normalized ratio
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.
IRB	Institutional Review Boards
ISO	International Organization for Standardization
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web-response system
MedDRA	Medical Dictionary for Regulatory Activities
MEN	multiple endocrine neoplasia
MI	myocardial infarction
mITT	modified Intent-to-Treat
MMRM	mixed-model for repeated measures
MRCP	magnetic resonance cholangiopancreatography
MRI	magnetic resonance imaging
MTC	Medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
NIMP	Non-investigational Medicinal Product
OAM	oral antihyperglycemic medications
OTC	over the counter

participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
QT	QT interval
QTc	corrected QT interval
QTL	quality tolerance limit
QW	once weekly
RA	receptor agonist
RET	rearranged during transfect
RNA	ribonucleic acid
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
SERMs	selective estrogen receptor modulators
SGLT2i	sodium-glucose cotransporter type 2 inhibitors
SMBG	self-monitored blood glucose
SoA	schedule of activities
SOC	system organ class
SS1	Safety analysis set for Period I
SS2	Safety analysis set for Period I and II
SU	sulfonylureas
T1D	Type 1 diabetes
T2D	Type 2 diabetes

TBL	total bilirubin level
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.
TZD	thiazolidinedione
ULN	upper limit of normal
WHO	World Health Organization
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

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