

Clinical Study Protocol Amendment Version (a) I8F-JE-GPGO

A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus (SURPASS J-mono)

NCT03861052

Approval Date: 17-Jan-2019

**Protocol I8F-JE-GPGO(a)**  
**A Phase 3 Study of Tirzepatide Monotherapy Compared to**  
**Dulaglutide 0.75 mg in Patients with Type 2 Diabetes**  
**Mellitus (SURPASS J-mono)**

**Confidential Information**

The information contained in this document is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of tirzepatide (LY3298176), unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

**Note to Regulatory Authorities:** This document may contain protected personal data and/or commercially confidential information exempt from public disclosure. Eli Lilly and Company requests consultation regarding release/redaction prior to any public release. In the United States, this document is subject to Freedom of Information Act (FOIA) Exemption 4 and may not be reproduced or otherwise disseminated without the written approval of Eli Lilly and Company or its subsidiaries.

Tirzepatide (LY3298176)

Eli Lilly Japan K.K  
Kobe, Hyogo Japan

Protocol Electronically Signed and Approved by Lilly: 18 Dec 2018  
Amendment (a) Electronically Signed and Approved by Lilly  
on approval date provided below.

Approval Date: 17-Jan-2019 GMT

## Table of Contents

Section	Page
Protocol I8F-JE-GPGO(a) A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus (SURPASS J-mono).....	1
Table of Contents.....	2
1. Synopsis .....	9
2. Schedule of Activities .....	13
3. Introduction .....	17
3.1. Study Rationale.....	17
3.2. Background.....	17
3.3. Benefit/Risk Assessment .....	18
4. Objectives and Endpoints.....	20
5. Study Design.....	22
5.1. Overall Design .....	22
5.2. Number of Participants.....	24
5.3. End of Study Definition .....	25
5.4. Scientific Rationale for Study Design.....	25
5.5. Justification for Dose .....	25
6. Study Population.....	27
6.1. Inclusion Criteria.....	27
6.2. Exclusion Criteria .....	28
6.3. Lifestyle Restrictions.....	31
6.4. Screen Failures.....	31
7. Treatments .....	32
7.1. Treatments Administered .....	32
7.1.1. Packaging and Labeling .....	32
7.1.2. Medical Devices.....	32
7.2. Method of Treatment Assignment .....	33
7.2.1. Selection and Timing of Doses.....	33
7.3. Blinding .....	33
7.4. Dosage Modification .....	34
7.5. Preparation/Handling/Storage/Accountability.....	34
7.6. Treatment Compliance .....	34
7.7. Concomitant Therapy .....	35
7.7.1. Management of Patients with Gastrointestinal Symptoms.....	35

7.8. Treatment after the End of the Study .....	36
7.8.1. Treatment after Study Completion.....	36
7.8.2. Special Treatment Considerations .....	36
8. Discontinuation Criteria .....	37
8.1. Discontinuation from Study Treatment .....	37
8.1.1. Permanent Discontinuation from Study Treatment .....	37
8.1.2. Temporary Interruption of Study Treatment .....	38
8.1.3. Discontinuation of Inadvertently Enrolled Patients.....	38
8.2. Discontinuation from the Study.....	38
8.3. Lost to Follow-Up.....	39
9. Study Assessments and Procedures .....	40
9.1. Efficacy Assessments.....	40
9.1.1. Primary Efficacy Assessments .....	40
9.1.2. Secondary Efficacy Assessments.....	40
9.1.2.1. 7-Point Self-Monitored Blood Glucose Profiles .....	40
9.1.3. Appropriateness of Assessments .....	40
9.2. Adverse Events .....	41
9.2.1. Serious Adverse Events.....	41
9.2.1.1. Suspected Unexpected Serious Adverse Reactions.....	42
9.2.2. Adverse Events of Special Interest .....	43
9.2.2.1. Hypoglycemia .....	43
9.2.2.2. Severe, Persistent Hyperglycemia.....	44
9.2.2.3. Pancreatitis.....	45
9.2.2.4. Thyroid Malignancies and C-Cell Hyperplasia.....	46
9.2.2.5. Major Adverse Cardiovascular Events .....	46
9.2.2.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders .....	46
9.2.2.7. Hypersensitivity Events .....	46
9.2.2.7.1. Injection Site Reactions .....	47
9.2.2.7.2. Anti-Drug Antibodies .....	47
9.2.2.8. Diabetic Retinopathy Complications.....	47
9.2.2.9. Hepatobiliary Disorders.....	47
9.2.2.10. Severe Gastrointestinal Adverse Events .....	47
9.2.2.11. Acute Renal Events .....	47
9.2.2.12. Amputation/Peripheral Revascularization .....	47
9.2.2.13. Major Depressive Disorder/Suicidal Ideation.....	48
9.2.2.14. Individual Clinical Events Adjudication.....	48
9.2.3. Complaint Handling .....	48

9.3. Treatment of Overdose.....	48
9.4. Safety.....	48
9.4.1. Electrocardiograms .....	48
9.4.2. Vital Signs .....	49
9.4.3. Laboratory Tests .....	49
9.4.4. Immunogenicity Assessments .....	49
9.4.5. Safety Monitoring .....	50
9.4.5.1. Hepatic Safety Monitoring.....	50
9.5. Pharmacokinetics .....	51
9.6. Pharmacodynamics .....	51
9.7. Pharmacogenomics .....	51
9.7.1. Whole Blood Samples for Pharmacogenetic Research.....	51
9.8. Biomarkers.....	52
9.9. Health Economics .....	52
9.9.1. European Quality of Life (EQ-5D-5L).....	52
9.9.2. Diabetes Treatment Satisfaction Questionnaire (DTSQ).....	53
10. Statistical Considerations .....	54
10.1. Sample Size Determination .....	54
10.2. Populations for Analyses.....	54
10.3. Statistical Analyses .....	55
10.3.1. General Statistical Considerations .....	55
10.3.2. Treatment Group Comparability.....	56
10.3.2.1. Patient Disposition.....	56
10.3.2.2. Patient Characteristics .....	56
10.3.2.3. Concomitant Therapy .....	56
10.3.2.4. Treatment Compliance.....	56
10.3.3. Efficacy Analyses .....	56
10.3.3.1. Primary Analyses .....	56
10.3.3.2. Secondary Analyses.....	57
10.3.3.3. Tertiary/Exploratory Analyses .....	57
10.3.4. Safety Analyses.....	57
10.3.4.1. Hypoglycemic Events.....	58
10.3.4.2. Gastrointestinal Events .....	58
10.3.4.3. Adjudicated Cardiovascular Events .....	58
10.3.4.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms.....	58
10.3.5. Evaluation of Immunogenicity .....	59
10.3.6. Other Analyses.....	59

10.3.6.1. Health Economics.....	59
10.3.6.2. Subgroup Analyses.....	59
10.3.7. Interim Analyses .....	59
11. References .....	60
12. Appendices .....	62

**List of Tables**

<b>Table</b>		<b>Page</b>
Table GPGO.1. Schedule of Activities .....		14
Table GPGO.2. Objectives and Endpoints.....		20
Table GPGO.3. Treatment Regimens .....		32

**List of Figures**

<b>Figure</b>	<b>Page</b>
Figure GPGO.1. Illustration of study design for Clinical Protocol I8F-JE-GPGO.....	24

**List of Appendices**

<b>Appendix</b>		<b>Page</b>
Appendix 1.	Abbreviations and Definitions.....	63
Appendix 2.	Clinical Laboratory Tests.....	68
Appendix 3.	Study Governance Considerations.....	70
Appendix 4.	Hepatic Monitoring Tests for Treatment-Emergent Abnormality.....	74
Appendix 5.	World Health Organization Classification of Diabetes and Diagnostic Criteria .....	75
Appendix 6.	Classification of Contraceptive Methods.....	76
Appendix 7.	Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period.....	77
Appendix 8.	Protocol Amendment I8F-JE-GPGO(a) Summary A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus (SURPASS J-mono) .....	78

## 1. Synopsis

### Title of Study:

A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus (SURPASS J-mono).

### Rationale:

Tirzepatide is a once-weekly (QW) dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon like peptide-1 (GLP-1) receptor agonist. Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. The structure of tirzepatide is based on the GIP sequence and includes a C20 fatty di-acid moiety **CCI** [REDACTED]. Tirzepatide is administered by subcutaneous (SC) administration.

Study I8F-JE-GPGO (GPGO) is a multicenter, randomized, double-blind, parallel, active-controlled, 52-week Phase 3 study designed to assess the efficacy and safety of SC administered QW tirzepatide (5, 10, and 15 mg), compared to dulaglutide 0.75 mg in patients with type 2 diabetes mellitus (T2DM) who have discontinued oral antihyperglycemic medication (OAM) monotherapy or are OAM-naïve. The primary endpoint will be to demonstrate that QW tirzepatide 5 mg, and/or 10 mg, and/or 15 mg are superior to dulaglutide 0.75 mg in glycated hemoglobin (HbA1c) change from baseline to 52 weeks, based on Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2012).

### Objectives/Endpoints:

Objectives	Endpoints
<b>Primary</b> <ul style="list-style-type: none"> <li>To demonstrate that once-weekly tirzepatide 5 mg, and/or 10 mg, and/or 15 mg are superior to dulaglutide 0.75 mg in HbA1c change from baseline to 52 weeks in patients with T2DM who have discontinued OAM monotherapy or are OAM-naïve</li> </ul>	<ul style="list-style-type: none"> <li>Mean change in HbA1c from baseline at Week 52</li> </ul>
<b>Secondary</b> <b>Efficacy</b> <ul style="list-style-type: none"> <li>To compare the efficacy of once-weekly tirzepatide versus dulaglutide 0.75 mg at 52 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Mean change in HbA1c</li> <li>Proportion of patients who achieve HbA1c &lt;7%, ≤6.5%, and &lt;5.7%</li> <li>Mean change in FSG</li> <li>Mean change in daily average 7-point SMBG profiles</li> <li>Mean change in body weight</li> <li>Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline</li> <li>Mean change in fasting insulin</li> <li>Mean change in fasting C-peptide</li> <li>Mean change in HOMA-2</li> </ul>

Objectives	Endpoints
<b>Safety</b> <ul style="list-style-type: none"> <li>To compare the safety of once-weekly tirzepatide versus dulaglutide 0.75 mg at 52 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of TEAEs</li> <li>Early discontinuations of investigational product due to AEs</li> <li>Adjudicated all deaths and nonfatal major CV events</li> <li>Adjudicated pancreatic AEs</li> <li>Serum calcitonin</li> <li>Incidence of allergic and hypersensitivity reactions</li> <li>Incidence of injection site reactions</li> <li>Incidence of treatment-emergent ADAs to tirzepatide</li> <li>The change in systolic and diastolic blood pressure, and heart rate from baseline</li> <li>Occurrence of hypoglycemic episodes</li> <li>Time to initiation of rescue therapy for severe persistent hyperglycemia</li> </ul>

Abbreviations: ADAs = anti-drug antibodies; AE = adverse event; CV = cardiovascular; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medication; SAE = serious adverse event; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

### Summary of Study Design:

Study GPGO is a multicenter, randomized, double-blind, parallel, active-controlled, 52-week Phase 3 study which will assess the safety and efficacy of tirzepatide (5, 10, and 15 mg) compared to dulaglutide 0.75 mg in approximately 636 randomized patients with T2DM who have discontinued OAM monotherapy or are OAM-naïve.

### Treatment Arms and Duration:

Study GPGO will consist of 3 periods: a 4-week (OAM-naïve) or 10-week (at least 8-week OAM washout) screening/lead-in period, followed by a 52-week treatment period, and a 4-week safety follow-up period. Patients will be randomized in a 1:1:1:1 ratio (tirzepatide [5, 10, 15 mg], and dulaglutide 0.75 mg).

Patients will be stratified based on baseline HbA1c ( $\leq 8.5\%$  or  $>8.5\%$ ), baseline body mass index (BMI) ( $<25$  or  $\geq 25 \text{ kg/m}^2$ ), and washout of antidiabetic medication (yes or no).

### Number of Patients:

A total of approximately 636 patients (159 patients per treatment group) will be randomized.

**Statistical Analysis:****Sample size**

The trial is powered to assess superiority of tirzepatide doses (5 mg, and/or 10 mg, and/or 15 mg), versus dulaglutide 0.75 mg, relative to mean change from baseline in HbA1c at 52 weeks, under the following assumptions: use of 2-sample t-test to compare treatment means utilizing HbA1c data collected before initiation of any rescue medication and premature treatment discontinuation; up to 15% subjects initiating any rescue medication or premature treatment discontinuation; at least 0.5%, 0.5%, and 0.4% superior mean reduction in HbA1c from baseline at 52 weeks for tirzepatide 15, 10, and 5 mg, respectively, compared to dulaglutide 0.75 mg; and a common standard deviation (SD) of 1.0%. On the basis of these assumptions, randomizing 636 subjects using a 1:1:1:1 randomization ratio to tirzepatide 5 mg (159 patients), tirzepatide 10 mg (159 patients), tirzepatide 15 mg (159 patients), and dulaglutide 0.75 mg (159 patients) is required to ensure at least 90% power to establish superiority of tirzepatide 10-mg and/or 15-mg doses, compared to dulaglutide 0.75 mg at a 2-sided significance level of 0.025, followed by superiority of tirzepatide 5 mg, compared to dulaglutide 0.75 mg only if superiority of tirzepatide 10 mg or 15 mg is declared. Tirzepatide 5 mg will be tested at a 2-sided significance level of 0.05 if superiorities of both 10 mg and 15 mg are declared. Tirzepatide 5 mg will be tested at a 2-sided significance level of 0.025 if superiority of either 10 mg or 15 mg is declared. This parallel gatekeeping procedure controls family-wise Type 1 error rate at a 2-sided 0.05 level (Dmitrienko et al. 2003).

**Efficacy Analyses**

Efficacy and safety will be assessed using the modified intention-to-treat (mITT) population, which consists of all randomly assigned participants who are exposed to at least 1 dose of investigational product. The primary efficacy of tirzepatide versus dulaglutide 0.75 at 52 weeks will be guided by the “efficacy” estimand. The “efficacy” estimand represents efficacy prior to discontinuation of investigational product without confounding effects of rescue therapy for persistent severe hyperglycemia.

The primary efficacy assessment, guided by the “efficacy” estimand, will use the Efficacy Analysis Set (EAS), which consists of data obtained before the initiation of any rescue therapy and before premature treatment discontinuation. The analysis model for change from baseline in HbA1c assessed over time up to the 52-week visit, will be a mixed-model for repeated measures (MMRM), with terms: treatment, visit, and treatment-by-visit interaction, stratification factors: baseline BMI group (<25 or  $\geq 25$  kg/m<sup>2</sup>) and washout of antidiabetic medication (yes or no) as fixed effects, baseline HbA1c as a covariate. An unstructured covariance structure will model relationship of within-patient errors.

A robustness of the primary efficacy assessment, guided by the “treatment-regimen” estimand, will be conducted. This assessment will analyze change from baseline in HbA1c to 52-week visit using an analysis of covariance (ANCOVA) with terms, treatment, baseline BMI group (<25 or  $\geq 25$  kg/m<sup>2</sup>), washout of antidiabetic medication (yes or no), and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using the Full Analysis Set (FAS) at the

52-week visit, which consists of all available change from baseline in HbA1c data at the 52-week visit, irrespective of whether they were obtained while the participants had discontinued the investigational product or whether the participant had been given rescue medication.

Additionally, data for subjects with missing values will be imputed based on observed data in the same treatment arm from subjects who had their efficacy measure at the Week 52 visit assessed after early discontinuation of investigational product and/or initiation of rescue medication (retrieved drop outs). Analysis will be conducted with multiple imputations and statistical inference over multiple imputations will be guided by the method proposed by (Rubin 1987). No multiplicity adjustments will be made for conducting 2 efficacy assessments for different estimands.

### **Safety Analysis**

Safety assessments will be based on all available data, irrespective of whether they were obtained while the participants had discontinued the investigational product or whether the participant had been given rescue medication. Summary statistics will be provided for incidence of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), study discontinuation due to adverse events (AEs), investigational product discontinuation due to AEs and deaths from first dose to end of safety follow-up. Counts and proportions of subjects experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups. For continuous laboratory analytes, summary statistics will be provided by visit, with statistical comparisons among treatment at each visit conducted using a MMRM analysis. Selected safety analysis (eg, hypoglycemia) will be conducted after excluding data while on rescue therapy or data after starting another antihyperglycemic medication, which is allowed after the permanent discontinuation of investigational product. Additional details, including analysis of AEs of special interest, will be provided in the statistical analysis plan (SAP).

## 2. Schedule of Activities

Table GPGO.1. Schedule of Activities

	Screening	Lead-in	Treatment												Follow-up
	1 <sup>a</sup>	2	3	4	5	6	7	8	9	10	11	12	13	ET <sup>b</sup>	801 <sup>c</sup>
<b>Study Visit</b>	<b>1<sup>a</sup></b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>ET<sup>b</sup></b>	<b>801<sup>c</sup></b>
<b>Week of Treatment</b>	<b>-4 or -10</b>	<b>-2</b>	<b>0</b>	<b>4</b>	<b>8</b>	<b>12</b>	<b>16</b>	<b>20</b>	<b>24</b>	<b>32</b>	<b>40</b>	<b>48</b>	<b>52</b>	<b>—</b>	<b>56</b>
<b>Visit Window (days)</b>	<b>±7</b>	<b>±7</b>	<b>—</b>	<b>±7</b>	<b>—</b>	<b>±7</b>									
<b>Fasting Visit<sup>d</sup></b>	X		X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Clinical Assessments</b>															
Informed consent	X														
Medical history	X														
Demographics	X														
Previous diabetes therapy	X														
Physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dilated Fundoscopic Examination <sup>e</sup>		X													
Height	X														
Weight	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference			X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (2 sitting BP and HR) <sup>f</sup>	X		X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG <sup>g</sup>	X			X								X		X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hypoglycemic events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Laboratory Tests</b>															
Pregnancy test (serum) <sup>h</sup>		X													
Pregnancy test (urine) <sup>i</sup>			X			X			X		X		X	X	
Follicle-stimulatinghormone test, estradiol <sup>j</sup>	X														
HbA1c	X	X	X	X		X			X		X		X	X	
Fasting Serum Glucose			X	X		X			X		X		X	X	
Insulin			X		X			X		X		X		X	X
C-peptide			X		X			X		X		X		X	X
Hematology	X		X		X			X		X		X		X	X
Chemistry panel	X		X		X			X		X		X		X	X
Lipid panel			X		X			X		X		X		X	X
Urinary albumin/creatinine ratio	X										X		X	X	X
eGFR (CKD-EPI)	X		X									X		X	X
Lipase, pancreatic amylase	X		X		X			X		X		X		X	X
Calcitonin	X				X			X		X		X		X	X
Review screening lab test results			X												

## Schedule of Activities

	Screening	Lead-in	Treatment												Follow-up
			3	4	5	6	7	8	9	10	11	12	13	ET <sup>b</sup>	
<b>Study Visit</b>	<b>1<sup>a</sup></b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>	<b>6</b>	<b>7</b>	<b>8</b>	<b>9</b>	<b>10</b>	<b>11</b>	<b>12</b>	<b>13</b>	<b>ET<sup>b</sup></b>	<b>801<sup>c</sup></b>
<b>Week of Treatment</b>	<b>-4 or -10</b>	<b>-2</b>	<b>0</b>	<b>4</b>	<b>8</b>	<b>12</b>	<b>16</b>	<b>20</b>	<b>24</b>	<b>32</b>	<b>40</b>	<b>48</b>	<b>52</b>	<b>—</b>	<b>56</b>
<b>Visit Window (days)</b>	<b>±7</b>	<b>±7</b>	<b>—</b>	<b>±7</b>	<b>—</b>	<b>±7</b>									
<b>Fasting Visit<sup>d</sup></b>	X		X	X	X	X	X	X	X	X	X	X	X	X	X
<b>Laboratory Tests</b>															
Pharmacogenetics sample <sup>k</sup>			X												
Immunogenicity (ADAs) <sup>l</sup>			X	X		X			X		X		X	X	X
PK sample for immunogenicity <sup>m</sup>			X	X		X			X		X		X	X	X
Nonpharmacogenetic samples for storage			X		X			X		X		X	X	X	X
<b>Patient Education and Supplies</b>															
Dispensing of SMBG meter/supplies		X	X	X	X	X	X	X	X	X	X	X			
SMBG meter training		X													
Weekly fasting SMBG measurement <sup>n</sup>			X	X	X	X	X	X	X	X	X	X	X	X	X
7-point SMBG measurement <sup>o</sup>				X											X
Dispensing of study diary and instruct in use		X	X	X	X	X	X	X	X	X	X	X	X	X	
Study diary review			X	X	X	X	X	X	X	X	X	X	X	X	X
Subcutaneous injection training/ injection site inspection/ review of technique		X													
Dispensing of investigational product and injection supplies			X	X	X	X	X	X	X	X	X	X	X		
Return of used investigational product containers, unused study medication and study diary				X	X	X	X	X	X	X	X	X	X	X	X
Assessment of investigational product compliance				X	X	X	X	X	X	X	X	X	X	X	X
<b>Patient-Reported Outcomes</b>															
EQ-5D-5L			X									X		X	X
DTSQs			X												
DTSQc												X		X	X

**Schedule of Activities**

Abbreviations: ADAs = antidrug antibodies; BP = blood pressure; CKD-EPI = Chronic Kidney Disease-Epidemiology; DTSQc = Diabetes Treatment

Satisfaction Questionnaire (change); DTSQs = Diabetes Treatment Satisfaction Questionnaire (status); ECG = electrocardiogram; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EQ-5D-5L = European Quality of Life – dimensions; ET = early termination; FBG = fasting blood glucose; FSH = follicle stimulating hormone; HbA1c = glycated hemoglobin; HR = heart rate; OAM = oral antihyperglycemic medication; PK = pharmacokinetics; SMBG = self-monitored blood glucose.

- a Visit 1 should be 4 weeks (OAM-naïve) or 10 weeks (at least 8-week OAM washout and extra 2 weeks before Visit 3) prior to Visit 3. For OAM washout, patients must complete the 8-week washout period prior to Visit 2.
- b ET visit is conducted within 14 days after the decision of study discontinuation.
- c Visit 801 should be 4 weeks after Visit 13 or 4 weeks after early termination.
- d Patients should be reminded to report to the site in a fasting condition, after a period of approximately 8 hours without eating, drinking (except water), or any significant physical activity and before taking investigational product.
- e Dilated fundoscopic examination will be performed by an eye-care professional (ophthalmologist or optometrist) for all patients between Visit 2 and Visit 3 to exclude patients with proliferative diabetic retinopathy and/or diabetic maculopathy or nonproliferative diabetic retinopathy that requires acute treatment. The results from this examination will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy. Follow up dilated fundoscopic examination should be performed when clinically indicated, and, the results recorded on the retinopathy eCRF (See exclusion criterion #11 Section 6.2).
- f Vital sign measurements should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, at visits where required. 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. BP must be taken with an automated blood pressure machine.
- g A single 12-lead ECG will be recorded, after the patient has been lying supine for 5 minutes. A local ECG will be performed at screening. The ECGs during the treatment period will be electronically transmitted via modem to the centralized ECG vendor designated by Lilly.
- h Serum pregnancy test to be performed by the central laboratory at Visit 1 for women of childbearing potential only.
- i Urine pregnancy tests can be performed as required at local laboratories. A urine pregnancy test must be performed at Visit 3 with the result available prior to randomization and first injection of investigational product (s) for women of childbearing potential only. Additional pregnancy tests will be performed at Visits 6, 9, 11, 13, and ET. Pregnancy tests may also be performed at the investigator's discretion during the study.
- j FSH test performed at Visit 1 for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state ( $FSH \geq 40$  mIU/mL and estradiol  $<30$  pg/mL).
- k The blood sample should be collected at Visit 3 before any investigational product has been given to the patient.
- l In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADAs, PK, and exploratory immune safety sample.
- m PK samples for immunogenicity must be taken prior to drug administration.
- n The patients are required to measure their fasting (pre-breakfast) blood glucose (FBG) concentration at least once a week at approximately the same time of day before OAMs have been taken. By the investigator's decision, the frequency of measurement of FBG could be increased.
- o 7-point SMBG profiles (glucose measurements before breakfast, lunch, dinner, and bedtime and 2-hours after breakfast, lunch, and dinner) should be performed on 2 days within the 2 weeks prior to Visit 3 (0 weeks), and Visit 13 (52 weeks).

### 3. Introduction

#### 3.1. Study Rationale

Tirzepatide is a once-weekly (QW) dual glucose-dependent insulinotropic polypeptide (GIP)/glucagon like peptide-1 (GLP-1) receptor agonist. Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the GIP and GLP-1 receptors. The structure of tirzepatide is based on the GIP sequence and includes a C20 fatty di-acid moiety CCI [REDACTED]. Tirzepatide is administered by subcutaneous (SC) administration. Study I8F-JE-GPGO (GPGO) is a Phase 3 study designed to assess the safety and efficacy of SC administered QW tirzepatide (5, 10, and 15 mg), compared to dulaglutide 0.75 mg in patients with type 2 diabetes mellitus (T2DM) who have discontinued oral antihyperglycemic medication (OAM) monotherapy or are OAM-naïve. The primary endpoint will be to demonstrate that QW tirzepatide 5 mg, and/or 10 mg, and/or 15 mg are superior to dulaglutide 0.75 mg as measured by the change from baseline in glycated hemoglobin (HbA1c) after 52 weeks of treatment, based on Guideline for Clinical Evaluation of Oral Hypoglycemic Agents (Pharmaceutical and Food Safety Bureau/Evaluation and Licensing Division Notification No. 0709-1. 2012).

The data from this trial, together with the data from other Phase 3 trials, are expected to provide robust benefit/risk profiles of individual doses of tirzepatide, as required by regulatory agencies for regulatory submission and marketing approval.

#### 3.2. Background

Tirzepatide is currently being investigated for its potential use in the treatment of hyperglycemia in T2DM. In normal physiology, the incretins GIP and GLP-1 are secreted from enteroendocrine cells in the gut following a meal, and these incretins enhance the physiological response to food, including sensation of satiety, insulin secretion, and nutrient disposal (Baggio and Drucker 2007). Patients with T2DM have impaired incretin responses (Baggio and Drucker 2007). Incretin-based treatments that are currently available fall within 2 classes: GLP-1 receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (Neumiller 2015). Most GLP-1 receptor agonists have a beneficial effect on glucose metabolism through the enhancement of glucose-dependent insulin secretion, reduction of inappropriately elevated glucagon levels, and a delay in gastric emptying. Dipeptidyl peptidase-4 inhibitors indirectly exert an incretin effect by preventing the proteolytic breakdown and inactivation of endogenous agonists of gastric inhibitory polypeptide receptor (GIPR) and the GLP-1 receptor. Each class has its therapeutic limitations. For example, dosing of GLP-1 receptor agonists may be limited by gastrointestinal (GI) adverse effects and DPP-4 inhibitors are limited in efficacy by the fact that they inhibit degradation of endogenous incretins, but even when protected from degradation the endogenous incretins do not reach plasma levels similar to what is attained with exogenous incretin analog treatment. As a dual receptor agonist, tirzepatide binds both GIP and GLP-1 receptors and combines the signaling of each receptor for improved glycemic control. By virtue of being a GIP/GLP dual receptor agonist, tirzepatide has the potential of reaching higher efficacy in target tissues such as the insulin-producing pancreatic  $\beta$ -cells that express both the GIPR and GLP-1 receptors before reaching its therapeutic limitation. Tirzepatide may furthermore attain

additional efficacy by recruiting metabolically active tissues not targeted by classical GLP-1 analogs (for example, adipose tissue as indicated by the observation of increased energy utilization [Baggio and Drucker 2007]).

Three tirzepatide clinical trials have completed dosing and analysis: a Phase 1 study, Study I8F-MC-GPGA (GPGA), and 2 Phase 2 studies, Study I8F-MC-GPGB (GPGB) and I8F-MC-GPGF (GPGF). One Phase 1 study, Study I8F-JE-GPGC (GPGC) is ongoing in Japan.

The safety and tolerability and pharmacokinetic (PK)/pharmacodynamic (PD) profiles of tirzepatide at doses and escalation regimens administered in Study GPGA supported further development of tirzepatide for QW dosing in patients with T2DM.

Phase 2 studies have evaluated the efficacy, tolerability, and safety of tirzepatide in patients with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy.

Study GPGB, a 26-week Phase 2 study compared the efficacy, tolerability, and safety of 4 doses (1, 5, 10, and 15 mg [titrated]), of QW tirzepatide, compared with QW dulaglutide 1.5 mg and QW placebo in 318 patients with T2DM, with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy. Tirzepatide 5 mg, 10 mg, and 15 mg significantly lowered HbA1c and body weight in a dose-dependent manner in comparison to placebo. In addition, reductions in HbA1c for the tirzepatide 5-, 10-, and 15-mg doses were greater than with dulaglutide 1.5 mg QW. Similar to adverse events (AEs) observed with the GLP-1 receptor agonist class and the Phase 1 Study GPGA, most of the tirzepatide AEs were GI-related, consisting mainly of nausea, vomiting, and diarrhea, which were mild-to-moderate in intensity and dose-dependent. Serious AEs (SAEs) were balanced across the treatment groups and none of the groups in the study reported severe hypoglycemia (Frias et al. 2018).

Study GPGF, a 3-month, Phase 2 study, was designed to examine the efficacy, and tolerability of 3 different titration schemes (longer time intervals between dose escalations and different dose escalations), to reach the highest tirzepatide planned doses of 12 mg and 15 mg, compared with placebo in patients with T2DM who have inadequate glycemic control with diet and exercise alone or with a stable dose of metformin monotherapy. Study GPGF was designed to support the evaluation of optimized dosing regimen(s) in Phase 3.

In addition, the safety, tolerability, and PK/PD of tirzepatide are being evaluated in the ongoing Study GPGC; a Phase 1, 8-week multiple ascending dose (MAD) study in Japanese patients with T2DM. This study involves a comparison of 3 once-weekly SC dose levels of tirzepatide (2.5-mg to 10-mg titration regimen for Cohort 1; 5-mg to 15-mg titration regimen for Cohort 2; and 5-mg fixed dose for Cohort 3), or placebo. The interim safety and tolerability data of Study GPGC supports the use of doses up to 15 mg of tirzepatide in Japanese patients.

### **3.3. Benefit/Risk Assessment**

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

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

## 4. Objectives and Endpoints

Table GPGO.2 shows the objectives and endpoints of the study.

**Table GPGO.2. Objectives and Endpoints**

Objectives	Endpoints
<b>Primary</b> <ul style="list-style-type: none"> <li>To demonstrate that once-weekly tirzepatide 5 mg, and/or 10 mg, and/or 15 mg are superior to dulaglutide 0.75 mg in HbA1c change from baseline to 52 weeks in patients with T2DM who have discontinued OAM monotherapy or are OAM-naïve</li> </ul>	<ul style="list-style-type: none"> <li>Mean change in HbA1c from baseline at Week 52</li> </ul>
<b>Secondary</b> <p><b>Efficacy</b></p> <ul style="list-style-type: none"> <li>To compare the efficacy of once-weekly tirzepatide versus dulaglutide 0.75 mg at 52 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Mean change in HbA1c</li> <li>Proportion of patients who achieve HbA1c &lt;7%, ≤6.5%, and &lt;5.7%</li> <li>Mean change in FSG</li> <li>Mean change in daily average 7-point SMBG profiles</li> <li>Mean change in body weight</li> <li>Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline</li> <li>Mean change in fasting insulin</li> <li>Mean change in fasting C-peptide</li> <li>Mean change in HOMA-2</li> </ul>
<p><b>Safety</b></p> <ul style="list-style-type: none"> <li>To compare the safety of once-weekly tirzepatide versus dulaglutide 0.75 mg at 52 weeks</li> </ul>	<ul style="list-style-type: none"> <li>Incidence of TEAEs</li> <li>Early discontinuations of investigational product due to AEs</li> <li>Adjudicated all deaths and nonfatal major CV events</li> <li>Adjudicated pancreatic AEs</li> <li>Serum calcitonin</li> <li>Incidence of allergic and hypersensitivity reactions</li> <li>Incidence of injection site reactions</li> <li>Incidence of treatment-emergent ADAs to tirzepatide</li> <li>The change in systolic and diastolic blood pressure, and heart rate from baseline</li> <li>Occurrence of hypoglycemic episodes</li> <li>Time to initiation of rescue therapy for severe persistent hyperglycemia</li> </ul>

Abbreviations: ADAs = anti-drug antibodies; AE = adverse event; CV = cardiovascular; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; OAM = oral antihyperglycemic medication; SAE = serious adverse event; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

## 5. Study Design

### 5.1. Overall Design

Study GPGO is a multicenter, randomized, double-blind, parallel, active-controlled, 52-week Phase 3 study which will assess the safety and efficacy of tirzepatide (5, 10, and 15 mg), compared to dulaglutide 0.75 mg in approximately 636 randomized patients with T2DM who have discontinued OAM monotherapy or are OAM-naïve.

Study GPGO will consist of 3 periods:

- a 4-week (OAM-naïve) or 10-week (at least 8-week OAM washout) screening/lead-in period
- a 52-week treatment period
- a 4-week safety follow-up period

Patients will be randomized in a 1:1:1:1 ratio (tirzepatide 5, 10, 15 mg, and dulaglutide 0.75 mg).

Patients will be stratified based on baseline HbA1c ( $\leq 8.5\%$  and  $>8.5\%$ ), baseline BMI ( $<25$  or  $\geq 25$  kg/m<sup>2</sup>), and washout of antidiabetic medication (yes or no) (see [Figure GPGO.1](#)).

Screening procedures and patient training (disease monitoring and management procedures, study diaries, and study procedures) will be performed at Visits 1 and 2 (screening and lead-in periods). The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility at Visit 2.

A patient who has been taking OAM monotherapy must complete the 8-week washout period prior to Visit 2.

At Visit 2, the screening laboratory results will be reviewed. For those patients meeting all other eligibility requirements, a dilated fundoscopic examination performed by an ophthalmologist or optometrist, must be completed between Visit 2 and Visit 3 to ensure patients with proliferative diabetic retinopathy, diabetic maculopathy, or nonproliferative diabetic retinopathy that requires acute treatment, are identified and excluded.

At Visit 3, patients will perform all required baseline study procedures (including the collection of all baseline laboratory measures and electrocardiograms [ECGs]) and confirm all eligibility criteria prior to randomization and prior to taking the first dose of investigational product.

Following randomization, the patient will inject the first dose of investigational product at the study site, according to the dose escalation regimen. The date and time of the first dose of investigational product should be recorded on the electronic case report form (eCRF). Beginning at randomization, all patients will receive investigational product according to the randomized treatment arm for the duration of the 52-week treatment period. A safety follow-up visit will occur approximately 4 weeks following the last dose of the investigational product.

The starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW for the duration of the study in the tirzepatide 5-mg arm. For the 10-mg arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg

every 4 weeks (2.5 to 5 to 7.5 to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5 to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study. Patients will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments (Section 7.7).

Investigative site staff will inform patients that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study. This may not be possible when initiated for treatment of medical emergencies, in which case the patient will inform the investigator or a designated site staff member as soon as possible. Any additional medication initiated during the course of the study (including over-the-counter [OTC] drugs) must be documented, and the name of the drug(s) and the date(s) of administration must be recorded in the patient's diary and on the "Concomitant Medications" section of the eCRF.

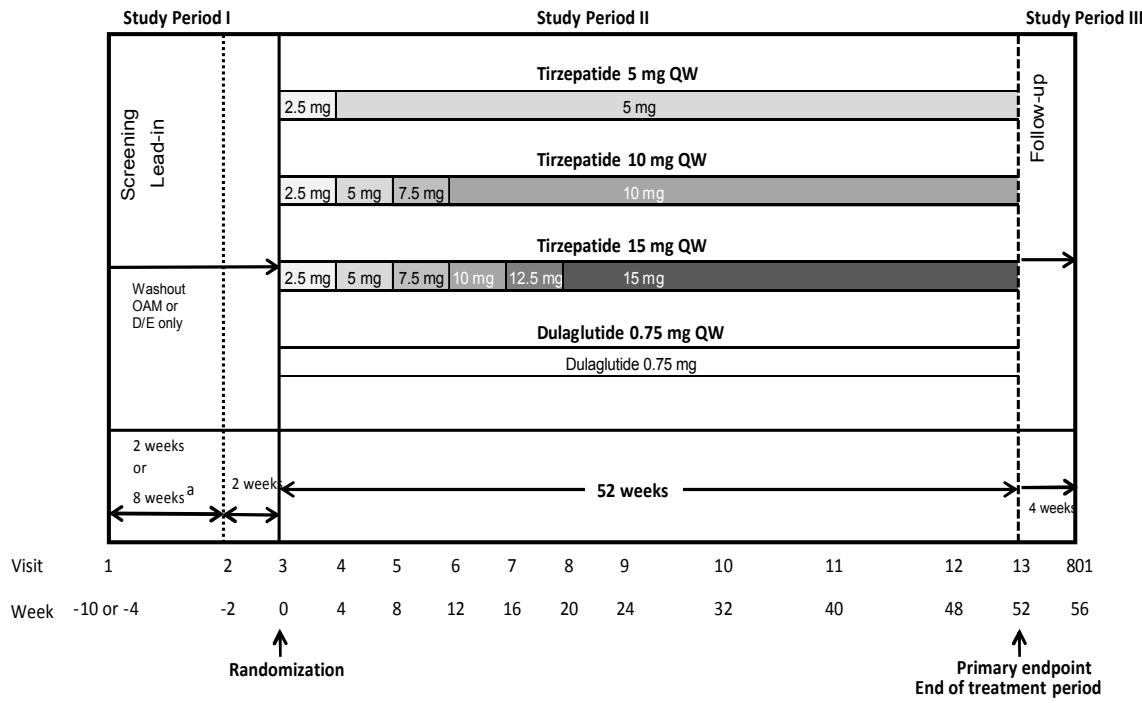
Antihyperglycemic medications other than investigational products are not allowed at any time during the study, except as allowed for rescue therapy, after early investigational product discontinuation. An additional therapeutic intervention should be considered in patients who develop severe, persistent hyperglycemia after randomization at the discretion of investigator in accordance with American Diabetes Association/European Association for the Study of Diabetes guidance. Rescue therapy with antihyperglycemic medications, including insulins, will be allowed in certain situations after randomization due to severe, persistent hyperglycemia. In this case, GLP-1 receptor agonists and DPP-4 inhibitors are not allowed as rescue therapies.

After early discontinuation of study treatment, any antihyperglycemic medications, except for GLP-1 receptor agonists may be allowed. Short-term insulin use for up to 14 days is allowed for certain clinical situations (eg, elective surgery, during hospitalization, hyperosmolar states). 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.

All nonstudy medications will be recorded on source documents at all visits.

Study governance considerations are described in detail in [Appendix 3](#).

[Figure GPGO.1](#) illustrates the study design.



Abbreviation: D/E = diet and exercise therapy; OAM = oral antihyperglycemic medication; QW = once weekly.

a At least 8-weeks or more OAM monotherapy washout must be completed prior to V2.

Note: All doses will be administered QW subcutaneously using single-use pens.

**Figure GPGO.1. Illustration of study design for Clinical Protocol I8F-JE-GPGO.**

## 5.2. Number of Participants

The trial is powered to assess superiority of tirzepatide doses versus dulaglutide 0.75 mg relative to mean change from baseline in HbA1c at 52 weeks under the following assumptions: use of 2-sample t-test to compare treatment means utilizing HbA1c data collected before initiation of any rescue medication and premature treatment discontinuation; up to 15% subjects initiating any rescue medication or premature treatment discontinuation; at least 0.5%, 0.5% and 0.4% superior mean reduction in HbA1c from baseline at 52 weeks for tirzepatide 15, 10, and 5 mg, respectively, compared to dulaglutide 0.75 mg; and a common standard deviation (SD) of 1.0%. On the basis of these assumptions, randomizing 636 subjects using a 1:1:1:1 randomization ratio to tirzepatide 5 mg (159 patients), tirzepatide 10 mg (159 patients), tirzepatide 15 mg (159 patients) and dulaglutide 0.75 mg (159 patients) is required to ensure at least 90% power to establish superiority of tirzepatide 10 mg and/or 15 mg doses compared to dulaglutide 0.75 mg at a 2-sided significance level of 0.025, followed by superiority of tirzepatide 5 mg, compared to dulaglutide 0.75 mg, only if superiority of tirzepatide 10 mg or 15 mg is declared. Tirzepatide 5 mg will be tested at a 2-sided significance level of 0.05 if superiorities of both 10 mg and 15 mg are declared. Tirzepatide 5 mg will be tested at a 2-sided significance level of 0.025 if

superiority of either 10 mg or 15 mg is declared. This parallel gatekeeping procedure controls family-wise Type 1 error rate at a 2-sided 0.05 level (Dmitrienko et al. 2003).

### 5.3. End of Study Definition

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

### 5.4. Scientific Rationale for Study Design

The primary objective of this trial is to compare the effect of tirzepatide and dulaglutide on overall glycemic control over a 52-week treatment period, as measured by change in HbA1c from baseline, in patients with T2DM who have discontinued OAM monotherapy or are OAM-naïve. Tirzepatide will be investigated in this population to better understand its effect on glycemic control in patients who remain hyperglycemic despite OAM monotherapy or diet/exercise only. Dulaglutide was selected as an incretin-mimetic comparator because it has a similar mechanism of action and it is a marketed compound in Japan for monotherapy of T2DM, to determine the comparative benefits and risks of QW tirzepatide. The doses of tirzepatide (5, 10, and 15 mg) have been chosen for this study, based on safety and efficacy data from Phase 1 and 2 studies. The dose of dulaglutide (0.75 mg) was selected, based upon the approved label in Japan.

The trial design and visit schedule is expected to allow patients to stabilize on their glycemic status and to minimize the potential confounding effect of previous OAM therapy during the lead-in period, assuring that the treatment groups are balanced at randomization. The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the trial outcome. The frequency of clinic visits postrandomization is intended to encourage patients and investigators interaction for frequent assessment of study treatments.

The efficacy measure, HbA1c, was chosen for the primary objective because it is an accepted surrogate endpoint for a clinically relevant outcome. Other measures of blood glucose (BG) control (eg, daily profiles, variability of BG) will also be assessed.

### 5.5. Justification for Dose

Tirzepatide doses of 5 mg, 10 mg, and 15 mg administered SC QW will be evaluated in this study.

These doses and associated escalation schemes were selected based on assessment of safety, efficacy (glycemic and weight loss benefit), and GI tolerability data followed by exposure response modeling of data in T2DM patients in Phase 1 and 2 studies. Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks would permit adequate time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

The maximum proposed dose of 15 mg maintains an exposure multiple of 1.6 to 2.4 to the no-observed-adverse-effect level doses in 6-month monkey and rat toxicology studies.

The selected dose and escalation scheme would enable further evaluation of benefit/risk considerations for 5-, 10-, and 15-mg doses of tirzepatide.

Based on interim data in Study GPGC, there were no clinically meaningful differences in the PK, PD, and safety profile between Japanese patients and non-Japanese patients. Hence, the doses and associated escalation schemes chosen for this Phase 3 study GPGO are the same as that chosen for global studies.

## 6. Study Population

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

### 6.1. Inclusion Criteria

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

#### Type of Patient and Disease Characteristics

- [1] Have been diagnosed with T2DM based on the World Health Organization classification at least 8 weeks prior to the screening visit (Visit 1).

#### Patient Characteristics

- [2] Are OAM-naïve (diet and exercise only) or are taking OAM monotherapy except for thiazolidinedione (TZD) and are willing to discontinue this medication. Patients taking OAM monotherapy must complete an 8-week washout period prior to Visit 2.
- [3] Have HbA1c meeting the following criteria, as determined by the central laboratory at Visit 1 and Visit 2:
  - [3a] for patients who are OAM-naïve at Visit 1,  $\geq 7.0\%$  to  $\leq 10.0\%$  at both Visit 1 and Visit 2.
  - [3b] for patients who have been taking OAM monotherapy at Visit 1,  $\geq 6.5\%$  to  $\leq 9.0\%$  at Visit 1, and  $\geq 7.0\%$  to  $\leq 10.0\%$  at Visit 2.
- [4] Are of stable weight ( $\pm 5\%$ ) during the 3 months preceding Visit 1; and agree to not initiate an intensive diet and/or exercise program during the study with the intent of reducing body weight other than the lifestyle and dietary measures for diabetes treatment.
- [5] Have body mass index (BMI) of  $\geq 23 \text{ kg/m}^2$  at Visit 1.
- [6] 20 years or older at the time of signing informed consent:
  - [6a] Male patients (see [Appendix 6](#) for more details):  
Male patients should be willing to use reliable contraceptive methods throughout the study and for at least 3 months after last injection.
  - [6b] Female patients:  
Female patients not of childbearing potential due to surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) congenital anomaly (ie, Müllerian agenesis) or menopause.

Women with an intact uterus are deemed postmenopausal if they are 45 years old, and

- have not taken hormones or oral contraceptives within the last year and had cessation of menses for at least 1 year.

OR

- have had at least 6 months of amenorrhea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH  $\geq 40$  mIU/mL and estradiol  $< 30$  pg/mL).

Female patients of child-bearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:

- test negative for pregnancy at Visit 1 based on a serum pregnancy test.

AND

- if sexually active, agree to use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the trial and for 30 days, thereafter.
- not be breastfeeding.

[7] In the investigator's opinion, are well-motivated, capable, and willing to:

- a) perform 7-point self-monitored blood glucose (SMBG) testing.
- b) learn how to self-inject treatment (tirzepatide or dulaglutide), as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the investigational product; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the investigational product).
- c) are willing and able to inject investigational products QW.
- d) maintain a study diary, as required, for this protocol.
- e) Have a sufficient understanding of the primary language of the country such that they will be able to complete the patient questionnaires.

[8] Have given written informed consent to participate in this study in accordance with local regulations and the Ethical Review Board (ERB) governing the study site.

## 6.2. Exclusion Criteria

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

### Medical Conditions

[9] Have type 1 diabetes mellitus (T1DM).

[10] Had chronic or acute pancreatitis any time prior to study entry (Visit 1).

[11] Have a history of:

- proliferative diabetic retinopathy.

or

- diabetic maculopathy.

or

- nonproliferative diabetic retinopathy that requires acute treatment.

(A dilated fundoscopic examination, performed by an ophthalmologist or optometrist between Visit 2 and Visit 3, is required to confirm eligibility.)

[12] Have a history of severe hypoglycemia and/or hypoglycemia unawareness within the 6 months prior to Visit 1.

[13] Have had 1 or more episodes of ketoacidosis or hyperosmolar state/coma requiring hospitalization within the 6 months prior to Visit 1.

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

[15] Have any of the following cardiovascular (CV) conditions within 2 months prior to Visit 1: acute myocardial infarction, cerebrovascular accident (stroke), or hospitalization due to heart failure.

[16] Have a history of New York Heart Association Functional Classification IV congestive heart failure.

[17] 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  $>3.0$  times the upper limit of the reference range, as determined by the central laboratory at study entry; patients with NAFLD are eligible to participate only if their ALT level is  $\leq 3.0$  times the upper limit of normal (ULN) for the reference range

[18] Have an estimated glomerular filtration rate (eGFR)  $<30$  mL/min/1.73 m<sup>2</sup> (or lower than the country-specific threshold for discontinuing metformin therapy per local label), calculated by Chronic Kidney Disease-Epidemiology (CKD-EPI), as determined by central laboratory at Visit 1.

[19] Have evidence of a significant, uncontrolled endocrine abnormality (eg, thyrotoxicosis or adrenal crises), in the opinion of the investigator.

[20] Have family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 (MEN-2).

[21] Have a serum calcitonin level of  $\geq 35$  ng/L at Visit 1.

- [22] Have evidence of a significant, active autoimmune abnormality (eg, lupus or 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 had a transplanted organ (corneal transplants [keratoplasty] allowed) or are awaiting an organ transplant.
- [24] Have a history of an active or untreated malignancy, or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, *in situ* carcinomas of the cervix, or *in situ* prostate cancer) for less than 5 years.
- [25] Have a history of any other condition (such as known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, may preclude the patient from following and completing the protocol.
- [26] Have any hematological condition that may interfere with HbA1c measurement (eg, hemolytic anemias, sickle-cell disease).

#### **Prior/Concomitant Therapy**

- [27] Have history of use of any injectable therapy for T2DM treatment (pramlintide, GLP-1 receptor agonists, and insulin) except for the use of insulin for treatment of gestational diabetes, or short term use ( $\leq 14$  days) for acute conditions, such as acute illness, hospitalization or elective surgery.
- [28] Are receiving chronic ( $>2$  weeks or 14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations) or have received such therapy within 1 month prior to Visit 1 and/or between study entry (Visits 1) and randomization (Visit 3).
- [29] Have been treated with drugs that promote weight loss (eg, Sanorex<sup>®</sup> [mazindol]) within 3 months prior to Visit 1 and/or between study entry (Visit 1) and randomization (Visit 3).

#### **Prior/Concurrent Clinical Trial Experience**

- [30] Are currently enrolled in, or discontinued within the last 30 days from, a clinical trial involving any other clinical study involving an investigational product or investigational drug or device or off-label use of a drug or device (other than the investigational product/device used in this study), or are currently enrolled in any other clinical study involving an investigational product 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 trial involving an investigational product. If the previous investigational product has a long half-life, 30 days or 5 half-lives (whichever is longer) should have passed.
- [32] Have previously completed or withdrawn from this study or any other study investigating tirzepatide.

### 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.

### 6.3. Lifestyle Restrictions

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

Patients should continue their usual exercise habits and generally follow a healthy meal plan (with consistent meal size and time of day) throughout the course of the study. Dietary counseling may be reviewed throughout the study, as needed. Per inclusion criterion [4] (Section 6.1), patients should not initiate during the study an organized diet and/or exercise weight reduction program other than the lifestyle and dietary measures for diabetes treatment.

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

### 6.4. Screen Failures

Subjects 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.

## 7. Treatments

### 7.1. Treatments Administered

In this study, patients will receive treatment with 1 of the 3 doses of tirzepatide (5 mg, 10 mg, and 15 mg) or with dulaglutide 0.75 mg, each administered QW as SC injection(s) in patients with T2DM. Patients will receive 1 administration of double-blinded investigational product at a time throughout the study.

Table GPGO.3 shows the randomized treatments for the entire treatment period.

**Table GPGO.3. Treatment Regimens**

Name of Drug	Dosage	Frequency	Drug Formulation	Route of Administration
<b>Investigational Compound</b>				
Tirzepatide	5 mg <sup>a</sup>	QW	Single-use pen	SC
	10 mg <sup>a</sup>	QW	Single-use pen	SC
	15 mg <sup>a</sup>	QW	Single-use pen	SC
<b>Comparator</b>				
Dulaglutide	0.75 mg	QW	Single-use pen	SC

Abbreviations: QW = once weekly; SC = subcutaneous.

a The starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, followed by an increase to 5 mg QW, for the duration of the study in the tirzepatide 5-mg arm. For the 10-mg arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For the 15-mg arm, the starting dose of tirzepatide will be 2.5 mg QW for 4 weeks, then the dose will be increased by 2.5 mg every 4 weeks (2.5 to 5 to 7.5 to 10 to 12.5 to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

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

- explaining the correct use of the investigational product to the patient
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection, as well as records of interruptions in investigational product administration
- instructing patient to discard all used single-use pens for tirzepatide in a closeable, puncture-resistant container and to dispose according to local regulations

#### 7.1.1. Packaging and Labeling

Clinical trial materials will be labeled according to the country's regulatory requirements. Tirzepatide 5 mg, 10 mg, 15 mg, and dulaglutide 0.75 mg will be supplied by Lilly in single-use pens.

#### 7.1.2. Medical Devices

The manufactured medical devices provided for use in the study are the tirzepatide and dulaglutide single-use pens.

## 7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to 1 of the double-blinded treatment arms at Visit 3. Assignment to treatment arms will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Patients will be randomized in a 1:1:1:1 ratio to receive 5 mg tirzepatide, 10 mg tirzepatide, 15 mg tirzepatide, or 0.75 mg dulaglutide. The randomization will be stratified by baseline HbA1c ( $\leq 8.5\%$  or  $> 8.5\%$ ), baseline BMI ( $< 25$  or  $\geq 25 \text{ kg/m}^2$ ), and washout of antidiabetic medication (yes or no).

### 7.2.1. Selection and Timing of Doses

Assignment to 1 of the 3 tirzepatide doses or dulaglutide 0.75-mg dose will occur at randomization. There are no restrictions on the time of day each weekly dose is given, but it is advisable to administer SC injections on the same day and same time each week. The actual date and time of all dose administrations will be recorded in the subject's eCRF. If a dose of investigational product, including tirzepatide 5 mg, 10 mg, 15 mg or dulaglutide 0.75 mg, is missed, the patient should take it as soon as possible, unless it is within 72 hours of the next dose, in which case that dose should be skipped and the next dose taken at the appropriate time.

## 7.3. Blinding

This is a double-blind study.

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

Emergency codes, generated by a computer drug-labeling system, will be available to the investigator. These codes, which reveal the patient's treatment group when opened, may be opened during the study ONLY if the patient's well-being requires knowledge of the patient's treatment assignment.

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

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

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

Upon completion of the study, all codes must be returned to Lilly or its designee.

#### **7.4. Dosage Modification**

No adjustment in investigational product doses (tirzepatide 5mg, 10 mg, 15 mg, or dulaglutide 0.75 mg) will be allowed.

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

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

- Confirming that appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.
- Ensuring that only participants enrolled in the study may receive study treatment and only authorized site staff may supply or administer study treatment. All study treatments 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 site staff.
- Ensuring that the investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

The study site must store the investigational product in a locked and secure environment. Please refer to the investigational product label for specific storage conditions. Patients will receive insulated bags with cooling gel packs for use in transporting the investigational product from the site to home.

Temperature logs must be maintained to verify correct storage conditions at the investigator site and throughout the study. Patients should be instructed to store the investigational product in their refrigerator, but are not required to maintain temperature logs.

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

#### **7.6. Treatment Compliance**

Investigational product compliance will be determined by the following:

- Investigational product administration data will be recorded by the patient and reviewed by the investigator at each study visit.
- The patients will be instructed to return any unused investigational product and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

In the 3 tirzepatide treatment arms, as well as the dulaglutide arm, treatment compliance overall is defined as taking at least 75% of the total required doses of investigational product. Similarly,

a patient will be considered significantly noncompliant if he/she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication.

In addition to the assessment of a patient's compliance with the investigational product administration, other aspects of compliance with the study treatments will be assessed at each visit, based on the patient's adherence to the visit schedule, completion of study diaries, the results of home BG monitoring, and any other parameters the investigator considers necessary.

Initially, patients considered to be poorly compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

## 7.7. Concomitant Therapy

Patients will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments. Prohibited medications include following;

- Any antihyperglycemic medications, except for concomitant OAMs
- Any medications that promote weight loss (eg, 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 (eg, elective surgery, during hospitalization, hyperosmolar states). Rescue therapy with antihyperglycemic medications, including insulins, may be medically indicated in certain situations after randomization, due to severe, persistent hyperglycemia (see [Appendix 7](#)). In this case, GLP-1receptor agonists and DPP-4 inhibitors are not allowed as rescue therapies. After early discontinuation of study treatment, any antihyperglycemic medications, except for GLP-1receptor agonists may be allowed. 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.

Investigative site staff will inform patients that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the study. This may not be possible when initiated for treatment of medical emergencies, in which case the patient will inform the investigator or a designated site staff member as soon as possible. Any additional medication initiated during the course of the study (including OTC drugs) must be documented, and the name of the drug and the date(s) of administration must be recorded in the patient's diary and on the "Concomitant Medications" section of the eCRF.

All nonstudy medications will be recorded on the eCRF at all visits.

Nonstudy medications taken by patients who are screened, but not randomized, will not be reported to Lilly, unless an SAE occurs.

### 7.7.1. Management of Patients with Gastrointestinal Symptoms

In the Phase 2 program, the most commonly reported treatment-emergent adverse events (TEAEs) for patients receiving tirzepatide were nausea, vomiting, and diarrhea. The tirzepatide

dose escalation scheme has been designed to improve GI tolerability. The escalation period is considered to be 24 weeks, which allows 20 weeks to escalate to 15 mg and an additional 4 weeks to reach steady state. During the dose escalation period, every effort should be made by the investigator to be able to escalate and maintain patients on the corresponding investigational product dosage.

To mitigate GI symptoms and manage patients with intolerable GI AEs, the investigator should:

- Advise patients to eat smaller meals, (eg, splitting 3 daily meals into 4 or more smaller meals), and to stop eating when they feel full.
- Prescribe symptomatic medication (eg, antiemetic or antidiarrheal medication) per local country availability and individual patient needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
- Temporarily interrupt tirzepatide or dulaglutide (eg, omit 1 dose). The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF.
- After the interruption, restart investigational product with the patient taking medication to alleviate his/her GI symptoms (Section 8.1.2).
- If intolerable GI symptoms or events persist despite the above measures, the investigator may decide to discontinue investigational products. De-escalation of investigational products will not be allowed. Patients who stop the investigational product permanently will receive another glucose-lowering intervention and will continue participating in the study, according to the protocol, to collect all planned efficacy and safety measurements. The new glucose-lowering intervention will be recorded on the eCRF specified for collecting antihyperglycemic medications.

In the event that intolerable persistent GI symptoms occur after the escalation period (after Week 24), the investigator should take the above measures to keep the patient on study treatment before stopping the investigational product permanently and initiate another glucose-lowering intervention.

## 7.8. Treatment after the End of the Study

### 7.8.1. Treatment after Study Completion

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

### 7.8.2. Special Treatment Considerations

An additional therapeutic intervention should be considered for patients with persistent hyperglycemia, as described in [Appendix 7](#).

## 8. Discontinuation Criteria

### 8.1. Discontinuation from Study Treatment

#### 8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of investigational product:

- **Patient Decision**
  - the patient requests to discontinue investigational product.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via the eCRF.

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

  - alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >8X upper limit of normal (ULN)
  - ALT or AST >5X ULN for more than 2 weeks
  - ALT or AST >3X ULN and total bilirubin level (TBL) >2X ULN or 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%)
- In addition, patients will be discontinued from the investigational product in the following circumstances:
  - If a patient is inadvertently enrolled and it is determined that continued treatment with investigational product would not be medically appropriate (see Section 8.1.3)
  - Acute or chronic pancreatitis
  - If a patient is diagnosed with medullary thyroid carcinoma (MTC) after randomization
  - If a patient is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
  - Any significant investigational product-related hypersensitivity reaction

- Any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent investigational product discontinuation is the appropriate measure to be taken
- If female patient becomes pregnant
- If a patient is diagnosed with T1DM
- The patient misses  $\geq 3$  consecutive weekly injections of the investigational product

Patients who stop the investigational product permanently may receive another antihyperglycemic medication except for GLP-1 receptor agonists, and will continue participating in the trial, according to the protocol, to collect all planned efficacy and safety measurements.

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

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

In certain situations, after randomization, the investigator may need to temporarily interrupt investigational product. Every effort should be made by the investigator to maintain patients on investigational product and to restart investigational product after any temporary interruption, as soon as it is safe to do so.

- If the number of consecutive doses missed is  $\leq 2$ , the treatment can be restarted at the dose defined in the protocol, if the drug was well-tolerated prior to discontinuation.

If investigational product interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 9.2 of this protocol. The data related to temporary interruption of study treatment will be entered on the eCRF.

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

If the Sponsor or investigator identify a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment, unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the Sponsor CRP/CRS agree it is medically appropriate to continue, the investigator must obtain documented approval from the Sponsor CRP/CRS to allow the inadvertently enrolled patient to continue in the study with or without treatment with investigational product. Safety follow up is as outlined in Section 2 (Schedule of Activities), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

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

In order to minimize the amount of missing data and to enable assessment of study objectives, as planned in the study protocol, every attempt will be made to keep patients in the study, irrespective of the following:

- adherence to investigational product
- adherence to visit schedule

- missing assessments
- investigational product discontinuation due to AE (Section 8.1.1)
- development of comorbidities
- development of clinical outcomes

The circumstances listed above are not valid reasons for discontinuation from the study.

Patients will be discontinued in the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- if a female patient becomes pregnant
- if a patient is diagnosed with T1DM
- investigator decision
  - the investigator decides that the patient should be discontinued from the study
- patient decision
  - the patient requests to be withdrawn from the study

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

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

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

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

### **8.3. Lost to Follow-Up**

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Every attempt will be made to minimize the number of patients considered lost to follow-up at the end of the study. Patients will be informed about the importance of completing the study and providing updated contact information to the study site, when necessary.

## 9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, with the study procedures and their timing (including tolerance limits for timing).

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

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

### 9.1. Efficacy Assessments

#### 9.1.1. Primary Efficacy Assessments

The primary efficacy measurement in this study is mean change in HbA1c from baseline at Week 52, as determined by the central laboratory.

#### 9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be evaluated at Week 52:

- Mean change in HbA1c
- Proportion of patients who achieve HbA1c <7%, ≤6.5%, and <5.7%
- Mean change in fasting serum glucose (FSG)
- Mean change in daily average 7-point SMBG profiles
- Mean change in body weight
- Proportion of patients who achieve weight loss of ≥5%, ≥10%, and ≥15% from baseline
- Mean change in fasting insulin
- Mean change in fasting C-peptide
- Mean change in Updated Homeostasis Model Assessment (HOMA-2)

##### 9.1.2.1. 7-Point Self-Monitored Blood Glucose Profiles

Patients will be asked to perform a 7-point SMBG profile on 2 days during the 2 weeks before Visits 3, and 13 (refer to the Schedule of Activities in Section 2). Patients will test and record SMBG concentrations in their study diaries before each meal (breakfast, lunch, and dinner), approximately 2 hours after the start of each meal, and at bedtime. The 7-point SMBG profiles will be entered into eCRF and analyzed.

#### 9.1.3. Appropriateness of Assessments

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

## 9.2. Adverse Events

Investigators are responsible for monitoring the safety of patients who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the patient.

The investigator is responsible for the appropriate medical care of patients during the study.

Investigators must document their review of each laboratory safety report.

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

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

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

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

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

The investigator answers yes/no when making this assessment.

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

If a patient's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying, if possible, the circumstances leading to discontinuations of treatment.

### 9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization

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

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the Sponsor begins after the patient has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the Sponsor as per SAE reporting requirements and timelines (see Section 9.2) if it is considered reasonably possibly related to study procedure.

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

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

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

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

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

## 9.2.2. Adverse Events of Special Interest

### 9.2.2.1. Hypoglycemia

Patients will collect information in the study diary on episodes of hypoglycemia starting from Visit 1 until the last study visit. For that purpose, patients will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia in the study according to the Schedule of Activities (Section 2).

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the blood glucose [BG] values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2017 American Diabetes Association position statement on glycemic targets (American Diabetes Association 2017):

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

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a BG level of  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG  $\leq 70$  mg/dL ( $\leq 3.9$  mmol/L).

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

- **Documented symptomatic hypoglycemia** is defined as any time a patient feels that he/she is experiencing symptoms and/or signs associated with hypoglycemia, and has a BG level of  $< 54$  mg/dL ( $< 3.0$  mmol/L).
- **Documented asymptomatic hypoglycemia** is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG  $< 54$  mg/dL ( $< 3.0$  mmol/L).
- **Documented unspecified hypoglycemia** is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG  $< 54$  mg/dL ( $< 3.0$  mmol/L).

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

- **Severe hypoglycemia** is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

***Nocturnal hypoglycemia:***

- **Nocturnal hypoglycemia** is defined as any hypoglycemic event that occurs between bedtime and waking.

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

To avoid duplicate reporting, all consecutive BG values  $\leq 70$  mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

**9.2.2.2. Severe, Persistent Hyperglycemia**

Add-on glycemic rescue therapy will be allowed for patients 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. Patients should continue administering assigned investigational products . 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 postrandomization  
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 9-16 weeks postrandomization  
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 beyond the first 16 weeks postrandomization  
OR
- d) HbA1c  $\geq 8.5\%$  (69 mmol/mol) at 24 weeks, with inadequate response to the existing regimen, defined as improvement in HbA1c over the last 3 months (Week 12 to Week 24) that is  $<0.3\%$ .

Investigators should first confirm that the patient is fully compliant with the assigned therapeutic regimen and that he/she does not have an acute condition that is raising his/her BG. For patients who meet criteria for severe persistent hyperglycemia, the investigator will decide, in consultation with the patient, on an appropriate antihyperglycemic medication (rescue therapy). Investigators should follow national standards of care for diabetes management in respective participating countries or the American Diabetes Association/ European Association for the Study of Diabetes guidance (Inzucchi et al. 2015). Antihyperglycemic medications, including insulin, will be allowed as the rescue intervention. In this case, GLP-1 receptor agonists and

DPP-4 inhibitors are not allowed as rescue therapies. Patients who receive a new intervention should also continue administering investigational products for the remaining period in the trial.

### 9.2.2.3. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with tirzepatide, including this trial. Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately one-half of the cases [Banks and Freeman 2006; Koizumi et al. 2006]; the pain is often associated with nausea and vomiting)
- serum amylase (total and/or pancreatic) and/or lipase  $\geq 3 \times$ ULN
- characteristic findings of acute pancreatitis on computed tomography (CT) scan or magnetic resonance imaging (MRI).

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed). Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with tirzepatide, but will continue in the study on another antihyperglycemic medication. The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

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

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

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee (CEC). In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible

pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page by study site. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

#### **9.2.2.4. Thyroid Malignancies and C-Cell Hyperplasia**

Individuals with personal or family history of MTC and/or MEN-2 will be excluded from the study. The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy, including MTC, papillary carcinoma, and measurements of calcitonin. This data will be captured in specific eCRFs. The purpose of calcitonin measurements is to assess the potential of tirzepatide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Tirzepatide should be discontinued (after first confirming the value) if postrandomization calcitonin value is  $\geq 35$  ng/mL and has increased at least 50% over baseline. A consultation with a thyroid specialist (if not available, an endocrinologist) should be obtained. If the increased calcitonin value ( $\geq 35$  ng/mL and increases by  $\geq 50\%$ , compared with baseline) is observed in a patient who has administered a medication that is known to increase serum calcitonin, this medication should be stopped and calcitonin levels should be measured after an appropriate washout period. If the confirmed calcitonin value is  $< 35$  ng/mL, tirzepatide should be restarted when it is safe to do so.

#### **9.2.2.5. Major Adverse Cardiovascular Events**

Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians, external to Lilly, with cardiology expertise. The nonfatal CV AEs to be adjudicated include: myocardial infarction (MI); hospitalization for unstable angina; hospitalization for heart failure; coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack. Relevant data from patients who experienced death or nonfatal CV AEs will be entered into a specifically designed eCRF page by study site.

#### **9.2.2.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders**

Treatment-emergent cardiac conduction disorders will be further evaluated. Patients who develop any event from this group of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine the exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions, as described in Section 9.2.1, must be reported as SAEs.

#### **9.2.2.7. Hypersensitivity Events**

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs or, if any serious criterion is met, as SAEs. Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to investigational product(s), via an eCRF created for this purpose. Additional samples should also be collected, as outlined in Section 9.4.4. Investigational product should be temporarily

interrupted in any individual suspected of having a severe or serious allergic reaction to investigational product. Investigational product may be restarted when/if it is safe to do so, in the opinion of the investigator. If investigational product is permanently discontinued, the patient will receive another glucose-lowering treatment, judged by the investigator to be appropriate, based on the patient's clinical status, and will continue in the trial to collect all planned efficacy and safety measurements.

#### **9.2.2.7.1. *Injection Site Reactions***

Injection site reactions will be collected on the eCRF, separate from the hypersensitivity reaction eCRF. At the time of AE occurrence, samples will be collected for measurement of tirzepatide anti-drug antibodies (ADAs) and tirzepatide concentration.

#### **9.2.2.7.2. *Anti-Drug Antibodies***

The occurrence of ADA formation will be assessed, as outlined in Section [9.4.4](#).

#### **9.2.2.8. *Diabetic Retinopathy Complications***

Dilated retinal fundoscopic examination will be performed by an eye-care professional (ophthalmologist or optometrist) for all patients between Visit 2 and Visit 3 to exclude patients with proliferative retinopathy and/or maculopathy. The results from this examination will be recorded on a specific retinopathy eCRF as a baseline measure of retinopathy.

A follow-up, dilated fundoscopic examination should be performed when clinically indicated by any AE suspected of worsening retinopathy, and the findings should be recorded on the retinopathy eCRF.

#### **9.2.2.9. *Hepatobiliary Disorders***

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated, as outlined in Section [9.4.5.1](#) and [Appendix 4](#).

#### **9.2.2.10. *Severe Gastrointestinal Adverse Events***

Tirzepatide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs, as well as antiemetic/antidiarrheal use, will be collected in the eCRF. For detailed information concerning the management of GI AEs, please refer to Section [7.7.1](#).

#### **9.2.2.11. *Acute Renal Events***

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. Gastrointestinal AEs have been reported with tirzepatide, including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 receptor agonists (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Patients should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

#### **9.2.2.12. *Amputation/Peripheral Revascularization***

All cases of amputation and peripheral revascularization should be reported as an AE.

### **9.2.2.13. Major Depressive Disorder/Suicidal Ideation**

The prevalence of depressive symptoms and disorders is increased in patients with T1DM or T2DM (American Diabetes Association 2017). Any AE of major depressive disorder or suicidal ideation should be reported.

### **9.2.2.14. Individual Clinical Events Adjudication**

- All AEs of acute or chronic pancreatitis, as well as cases of pancreatic hyperenzymemia only, that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be adjudicated by an independent committee of expert physicians.
- Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians, external to Lilly, with cardiology expertise. The nonfatal CV AEs to be adjudicated include: MI; hospitalization for unstable angina; hospitalization for heart failure; coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention); and cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

### **9.2.3. Complaint Handling**

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

Patients will be instructed to contact the investigator as soon as possible if they have complaints or problems with the investigational product or drug delivery system, so that the situation can be assessed.

## **9.3. Treatment of Overdose**

Investigational product overdose (more than the specified number of injections) will be reported as an AE. In the event of overdose, refer to the IB for tirzepatide and to the package insert for dulaglutide.

## **9.4. Safety**

### **9.4.1. Electrocardiograms**

For each patient, ECGs should be collected, according to the Schedule of Activities (Section 2). Electrocardiograms should be recorded according to the study-specific recommendations included in the Manual of Operations for the study.

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 patient is still present, for immediate subject management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE via the eCRF.

All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory except for the screening ECG which will be performed by a local laboratory. The central ECG laboratory will perform a basic quality control check (eg, 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 laboratory 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).

#### **9.4.2. Vital Signs**

For each patient, vital signs measurements (systolic blood pressure, diastolic blood pressure, and heart rate), height, weight, and waist circumference, should be conducted according to the Schedule of Activities (Section 2) and following the study-specific recommendations included in the Manual of Operations for the study.

Any clinically significant findings from vital signs measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via the eCRF.

#### **9.4.3. Laboratory Tests**

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

With the exception of laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

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

#### **9.4.4. Immunogenicity Assessments**

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against tirzepatide as specified in the Schedule of Activities (Section 2).

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antibody production against tirzepatide. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity sample. All samples for immunogenicity should be taken predose, when applicable and possible. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples will be collected (including ADAs, PK, and, exploratory immune safety sample), as close to the onset of the event as possible, at the resolution of the event, and 30 days following the event. Instructions for the collection and handling of blood samples will be provided by the Sponsor.

The actual date and time (24-hour clock time) of each sampling will be recorded. Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of the tirzepatide at a laboratory approved by the Sponsor. Samples collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post-end of treatment).

Treatment-emergent ADAs are defined in Section 10.3.5.

Samples with tirzepatide ADAs detected will be titered and evaluated for their ability to neutralize the activity of assigned treatment (tirzepatide-neutralizing antibodies). Samples with tirzepatide ADAs detected will also be tested for cross-reactive binding to native GIP and GLP-1, and, if such is detected, then, for neutralizing antibodies against native GIP and GLP-1, respectively.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period, if local regulations and ERBs allow, at a facility selected by the Sponsor. The duration allows the Sponsor to respond to future regulatory requests related to tirzepatide. Any samples remaining after 15 years will be destroyed. Immunogenicity information that would unblind the study will not be reported to investigative sites or blinded personnel (until the study has been unblinded).

#### **9.4.5. Safety Monitoring**

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

##### **9.4.5.1. Hepatic Safety Monitoring**

If a study patient experiences elevated ALT  $\geq 3X$  ULN, ALP  $\geq 2X$  ULN, or elevated TBL  $\geq 2X$  ULN, liver testing ([Appendix 4](#)) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

##### **Hepatic Safety Data Collection**

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

- elevation of serum ALT to  $\geq 5X$  ULN on 2 or more consecutive blood tests
- elevated serum TBL to  $\geq 2X$  ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to  $\geq 2X$  ULN on 2 or more consecutive blood tests
- patient discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be a SAE

## 9.5. Pharmacokinetics

A PK sample will be collected at the same time points as the immunogenicity sample per the Study Schedule of Activities (Section 2). All samples for PK assessment should be taken predose. PK samples will be collected from patients allocated to the dulaglutide arm, but the samples will not be assayed for dulaglutide concentration.

The date and time of SC injection must be recorded on the eCRF from the study diaries.

The date and time at which each sample was drawn must be recorded on the laboratory requisition form.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry (LC/MS) method.

Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year following last patient visit for the study.

Drug concentration information that would unblind the study will not be reported to investigative sites or blinded personnel (until the study has been unblinded).

## 9.6. Pharmacodynamics

Pharmacodynamics will not be evaluated in this study.

## 9.7. Pharmacogenomics

### 9.7.1. Whole Blood Samples for Pharmacogenetic Research

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

Samples will not be used to conduct unspecified disease or population genetic research, either now or in the future. Samples will be used to investigate variable response to tirzepatide and to investigate genetic variants thought to play a role in T2DM. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

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

Molecular technologies are expected to improve during the 15-year storage period and, therefore, cannot be specifically named. However, existing approaches include whole genome or exome sequencing, genome wide association studies, and candidate gene studies. Regardless of

technology utilized, genotyping data generated will be used only for the specific research scope described in this section.

## 9.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, mechanism of action, variability of patient response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including deoxyribonucleic acid (DNA), ribonucleic acid (RNA), proteins, lipids, and other cellular elements.

Serum and plasma samples for nonpharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2), where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to tirzepatide, pathways associated with T2DM, mechanism of action of tirzepatide, and/or research method or in validating diagnostic tools or assay(s) related to T2DM.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last patient visit for the study, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of tirzepatide or after tirzepatide becomes commercially available. Any samples remaining after 15 years will be destroyed.

## 9.9. Health Economics

The following questionnaires will be completed by the patients at specific clinic visits, according to the Schedule of Events (Section 2). At these visits, the questionnaires should be completed before the patient has discussed his/her medical condition or progress in the study with the investigator and/or site staff, and before any other study procedures if the patient is not adversely affected by his/her fasting condition.

### 9.9.1. European Quality of Life (EQ-5D-5L)

Generic health-related quality of life (HR-QoL) will be assessed using the European Quality of Life – 5 Dimensions – 5 Level (EQ-5D-5L) (EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of healthcare, as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3125 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the

levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale (VAS) records the respondent's self-rated health status on a vertical graduated (0 to 100) VAS. In conjunction with the health state data, it provides a composite picture of the respondent's health status.

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

### ***9.9.2. Diabetes Treatment Satisfaction Questionnaire (DTSQ)***

The status (s) and change (c) versions of the Diabetes Treatment Satisfaction Questionnaire (DTSQ) will be used during the study to assess the patients' satisfaction with their diabetes treatment and the perceived frequency of hyperglycemia and hypoglycemia. The questionnaire contains 8 items (Bradley 1994). Each item is rated on a 7-point Likert scale. Six items (1, and 4 through 8) are summed to produce a measure of treatment satisfaction ranging from 0 "very dissatisfied" to 6 "very satisfied." The remaining 2 items (2 and 3) are treated individually. Item 2 measures the perceived frequency of hyperglycemia on a scale ranging from 0 "none of the time" to 6 "most of the time," and Item 3 measures the perceived frequency of hypoglycemia on the same scale. The change version has the same 8 items as the status version with a small alteration of the wording of Item 7. The DTSQc response options differ from those of the DTSQs to produce measures of relative change rather than absolute satisfaction.

## 10. Statistical Considerations

### 10.1. Sample Size Determination

The trial is powered to assess superiority of tirzepatide doses (5 mg, and/or 10 mg, and/or 15 mg), versus dulaglutide 0.75 mg, relative to mean change from baseline in HbA1c at 52 weeks, under the following assumptions: use of 2 sample t-test to compare treatment means utilizing HbA1c data collected before initiation of any rescue medication and premature treatment discontinuation; up to 15% subjects initiating any rescue medication or premature treatment discontinuation; at least 0.5%, 0.5%, and 0.4% superior mean reduction in HbA1c from baseline at 52 weeks for tirzepatide 15, 10, and 5 mg, respectively, compared to dulaglutide 0.75 mg; and a common standard deviation (SD) of 1.0%. On the basis of these assumptions, randomizing 636 subjects using a 1:1:1:1 randomization ratio to tirzepatide 5 mg (159 patients), tirzepatide 10 mg (159 patients), tirzepatide 15 mg (159 patients), and dulaglutide 0.75 mg (159 patients) is required to ensure at least 90% power to establish superiority of tirzepatide 10-mg and/or 15-mg doses, compared to dulaglutide 0.75 mg at a 2-sided significance level of 0.025, followed by superiority of tirzepatide 5 mg, compared to dulaglutide 0.75 mg only if superiority of tirzepatide 10 mg or 15 mg is declared. Tirzepatide 5 mg will be tested at a 2-sided significance level of 0.05 if superiorities of both 10 mg and 15 mg are declared. Tirzepatide 5 mg will be tested at a 2-sided significance level of 0.025 if superiority of either 10 mg or 15 mg is declared. This parallel gatekeeping procedure controls family-wise Type 1 error rate at a 2-sided 0.05 level (Dmitrienko et al. 2003).

### 10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Analysis Set	Description
Screened patients	All participants who sign informed consent
Randomized patients	All patients who are randomly assigned a treatment arm
Modified intention-to-treat (mITT) set	All randomly assigned participants who are exposed to at least 1 dose of investigational product.
Efficacy analysis set (EAS)	Data obtained during Study Period II from mITT, excluding data after initiating rescue antihyperglycemic medication or stopping investigational product (last dose date + 7 days). In the event of a treatment error, participants will be analyzed according to the treatment they were randomized.
Full analysis set (FAS)	Data obtained during Study Period II from mITT, regardless of adherence to investigational product or initiation of rescue antihyperglycemic medication.
Safety analysis set (SAS)	Data obtained during both Study Period II and III from mITT, regardless of adherence to investigational product or initiation of rescue antihyperglycemic medication.

## 10.3. Statistical Analyses

### 10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory data analyses may be conducted, as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) will be calculated at 95%, 2-sided. In statistical summaries and analyses, patients will be analyzed as randomized.

Efficacy and safety will be assessed using the modified intention-to-treat (mITT) population, which consists of all randomly assigned participants who are exposed to at least 1 dose of investigational product. The primary efficacy of tirzepatide versus dulaglutide 0.75 at 52 weeks will be guided by the “efficacy” estimand using the efficacy analysis set (EAS). The “efficacy” estimand represents efficacy prior to discontinuation of investigational product without confounding effects of rescue therapy for persistent severe hyperglycemia.

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model for comparisons among treatment arms relative to continuous measurements assessed over time will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction as stratification factors; baseline HbA1c ( $\leq 8.5\%$  or  $> 8.5\%$ ), baseline BMI group ( $< 25$  or  $\geq 25$  kg/m<sup>2</sup>), and washout of antidiabetic medication (yes or no) as fixed effects; and baseline measurement as a covariate. An unstructured covariance structure will model the relationship of within-patient 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.

A multiplicity adjustment will be applied to control the overall type I error rate of primary efficacy endpoint assessments controlling at a 2-sided 0.05 level.

Other statistical methods may be used, as appropriate, and details will be documented in the SAP.

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

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

Frequency counts and percentages of all patients screened, randomized, and receiving at least 1 dose of investigational product will be presented by treatment groups. A listing of randomized patients not receiving investigational product will be provided. Of the patients in the mITT set, frequency counts and percentages of patients completing the study, prematurely discontinuing the study, including reason for premature discontinuation, will be presented by treatment groups. A Kaplan-Meier analysis of time from randomization to premature discontinuation from study, by treatment group, will be provided. Patients with important protocol deviations will be listed.

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

Demographic, medical history, and preexisting conditions will be descriptively summarized, by treatment groups, using the mITT set.

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

Concomitant medications, including previous therapy for diabetes, will be summarized by Anatomical Therapeutic Chemical classification and treatment arm, using the mITT set. In particular, the time to initiation of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint.

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

Treatment compliance, overall, is defined as taking at least 75% of the total required injections of investigational product. Frequency counts and percentages of patients compliant to investigational product will be summarized by treatment arms and visits, using the mITT set.

### **10.3.3. Efficacy Analyses**

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

The primary efficacy measure is HbA1c change from baseline at 52 weeks, and the primary comparison is to compare tirzepatide doses versus dulaglutide 0.75 mg. Superiority of each tirzepatide dose will be demonstrated if the upper limit of the 97.5% or 95% CI for the difference between tirzepatide dose and dulaglutide 0.75 mg is below 0.

The statistical analyses for the primary efficacy measure of HbA1c change from baseline at 52 weeks will examine the following 3 hypotheses:

- $H_1$ : the 15-mg dose of tirzepatide is superior to dulaglutide 0.75 mg
- $H_2$ : the 10-mg dose of tirzepatide is superior to dulaglutide 0.75 mg
- $H_3$ : the 5-mg dose of tirzepatide is superior to dulaglutide 0.75 mg

$H_1$  and  $H_2$  will be tested at a 2-sided significance level of 0.025, followed by testing  $H_3$  only if  $H_1$  and/or  $H_2$  are declared.  $H_3$  will be tested at a 2-sided significance level of 0.05 if  $H_1$  and  $H_2$  are declared.  $H_3$  will be tested at a 2-sided significance level of 0.025 if either  $H_1$  or  $H_2$  is declared. This parallel gatekeeping procedure controls family-wise Type 1 error rate at a 2-sided 0.05 level (Dmitrienko et al. 2003).

The primary efficacy assessment, guided by the “efficacy” estimand, will use the EAS, which consists of data obtained before the initiation of any rescue therapy and before premature treatment discontinuation. The analysis model for change from baseline in HbA1c assessed over time up to the 52-week visit will be an MMRM, with terms: treatment, visit, and treatment-by-visit interaction as stratification factors; baseline BMI group (<25 or  $\geq$ 25 kg/m<sup>2</sup>) and washout of antidiabetic medication (yes or no) as fixed effects; and baseline HbA1c as a covariate. An unstructured covariance structure will model the relationship of within-patient errors.

A robustness of the primary efficacy assessment, guided by the “treatment-regimen” estimand, will be conducted. This assessment will analyze change from baseline in HbA1c to the 52-week visit using an analysis of covariance (ANCOVA) with terms, treatment, baseline BMI group (<25 or  $\geq$ 25 kg/m<sup>2</sup>), washout of antidiabetic medication (yes or no), and baseline HbA1c as a covariate. The ANCOVA analysis will be conducted using the Full Analysis Set (FAS) at the 52-week visit, which consists of all available changes from baseline in HbA1c data at the 52-week visit, irrespective of whether they were obtained while the participants had discontinued the investigational product or whether the participant had been given rescue medication. Additionally, data for subjects with missing values will be imputed, based on observed data in the same treatment arm from subjects who had their efficacy measure at the Week 52 visit assessed after early discontinuation of investigational product and/or initiation of rescue medication (retrieved dropouts). Analysis will be conducted with multiple imputations and statistical inference over multiple imputations will be guided by the method proposed by (Rubin 1987). No multiplicity adjustments will be made for conducting 2 efficacy assessments for different estimands.

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

Analysis of change from baseline in body weight at the 52-week visit will be conducted in a manner similar to the primary efficacy analyses with change in weight from baseline as the response variable and baseline body weight as a covariate.

Comparisons among treatments relative to the proportion of patients achieving HbA1c target value of <7.0% (53 mmol/mol),  $\leq$ 6.5%, and <5.7% at the 52-week visit will be conducted using a logistic regression analysis with terms: treatment, baseline BMI group (<25 or  $\geq$ 25 kg/m<sup>2</sup>), washout of antidiabetic medication (yes or no), and baseline HbA1c as a covariate. In the analysis of patients achieving HbA1c target value relative to the “efficacy” estimand, subjects with missing values at the 52-week visit will be excluded.

#### **10.3.3.3. Tertiary/Exploratory Analyses**

All exploratory efficacy analyses will be guided by the “efficacy” estimand and will be conducted using the EAS. Details will be provided in the SAP.

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

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of tirzepatide doses with dulaglutide 0.75 mg, irrespective of adherence to investigational product or initiation of rescue therapy. Thus, the safety analysis will be conducted using the

Safety Analysis Set (SAS). A selected safety analysis will be conducted after excluding data on rescue therapy.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized MedDRA Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, investigational product discontinuation due to AEs, and deaths. Counts and proportions of subjects experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

A selected safety analysis (eg, hypoglycemia) will be conducted after excluding data while on rescue therapy or data after starting another antihyperglycemic medication, which is allowed after the permanent discontinuation of investigational product. Additional details, including analysis of AEs of special interest, will be provided in the SAP.

#### **10.3.4.1. Hypoglycemic Events**

Incidence of documented symptomatic hypoglycemia events and severe hypoglycemia in each category (either total or nocturnal) will be compared between tirzepatide doses and dulaglutide 0.75 mg, using negative binomial regression analysis. Summaries and analysis will be repeated, excluding data following initiation of rescue antihyperglycemic medication.

#### **10.3.4.2. Gastrointestinal Events**

Summaries and analyses for incidence and severity of nausea, vomiting, and diarrhea will be provided by each treatment.

#### **10.3.4.3. Adjudicated Cardiovascular Events**

Listing of deaths, myocardial infarctions, strokes, and hospitalization for unstable angina confirmed by an independent CEC will be provided. The dates of randomization, event, first dose, and last dose of investigational product, and time from randomization to event will be listed.

#### **10.3.4.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms**

Values and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. The analysis model to make comparisons among treatment arms, relative to continuous change from baseline values assessed over time, will be an MMRM, with terms: treatment, baseline HbA1c ( $\leq 8.5\%$  or  $> 8.5\%$ ), baseline BMI group ( $< 25$  or  $\geq 25$  kg/m<sup>2</sup>), washout of antidiabetic medication (yes or no); baseline measurement will be used as a covariate. An unstructured covariance structure will model relationship of within-patient errors.

The percentages of patients with treatment-emergent abnormal, high, or low laboratory measures at any time will be summarized and compared between treatment groups by using Fisher's exact test. A treatment-emergent abnormal value is defined as a change from normal value at baseline to an abnormal value at any time during the follow-up. A treatment-emergent high result is defined as a change from a value less than or equal to the high limit at baseline to a value greater

than the high limit at any time during Periods II and III. A treatment-emergent low result is defined as a change from a value greater than or equal to the low limit at baseline to a value less than the low limit at any time during Periods II and III. High limit and low limit will be provided in the SAP.

### ***10.3.5. Evaluation of Immunogenicity***

The frequency and percentage of patients with preexisting ADAs, with treatment-emergent ADAs, and with treatment-emergent neutralizing antibodies to tirzepatide will be tabulated by tirzepatide dose. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline (treatment-induced ADAs) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADAs). For the treatment-emergent ADA patients, the distribution of maximum titers will be described by tirzepatide dose. The frequency of neutralizing antibodies to tirzepatide and/or cross-reactive and neutralizing antibodies to endogenous counterparts will be tabulated in treatment-emergent ADA-positive patients.

The relationship between the presence of antibodies and tirzepatide PK and PD response including safety and efficacy to tirzepatide may be assessed.

### ***10.3.6. Other Analyses***

#### ***10.3.6.1. Health Economics***

Analyses of actual and change from baseline in patient-reported outcome (PRO) scores will be conducted using linear models with baseline PRO scores, treatment, and other factors that may be considered relevant. These variables will be specified in the SAP.

#### ***10.3.6.2. Subgroup Analyses***

Subgroup analyses of mean change in HbA1c, mean change in body weight, AEs, and hypoglycemic events will be provided by age, gender, baseline BMI group ( $<25$  or  $\geq 25$  kg/m<sup>2</sup>), duration of diabetes, and baseline HbA1c ( $\leq 8.5\%$ ,  $>8.5\%$ ). Additional details will be provided in the SAP.

### ***10.3.7. Interim Analyses***

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

## 11. References

Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998;15(7):539-553.

American Diabetes Association. Glycemic Targets. Sec 6. In Standards of Medical Care in Diabetes—2017. *Diabetes Care*. 2017;40(Suppl 1):S48-S56. Available at: [http://care.diabetesjournals.org/content/40/Supplement\\_1/S48](http://care.diabetesjournals.org/content/40/Supplement_1/S48). Accessed September 26, 2018.

Aroda VR, Ratner R. The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes : a review. *Diabetes Metab Res Rev*. 2011;27(6):528-542.

Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterology*. 2007;132(6):2131-2157.

Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400.

Bradley C. The diabetes treatment satisfaction questionnaire: DTSQ. In: Bradley C, editor. *Handbook of Psychology and Diabetes: a guide to psychological measurement in diabetes research and practice*. Chur, Switzerland: Harwood Academic Publishers; 1994.

Danne T, Philotheou A, Goldman D, Guo X, Ping L, Cali A, Johnston P. A randomized trial comparing the rate of hypoglycemia--assessed using continuous glucose monitoring--in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatr Diabetes*. 2013;14(8):593-601.

Dmitrienko A, Offen WW, Westfall PH. Gatekeeping strategies for clinical trials that do not require all primary effects to be significant. *Stat Med*. 2003;22(15):2387-2400.

EuroQoL Group. EQ-5D-5L User guide: basic information on how to use the EQ-5D-5L instrument. Version 2.1. 2015. Available at: [https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L\\_UserGuide\\_2015.pdf](https://euroqol.org/wp-content/uploads/2016/09/EQ-5D-5L_UserGuide_2015.pdf). Accessed October 17, 2018.

Frias JP, Nauck MA, Van J, Kutner ME, Cui X, Benson C, Urva S, Gimeno RE, Milicevic Z, Robins D, Haupt A. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. *Lancet*. 2018;392(10160):2180-2193.

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care*. 2015;38(1):140-149.

Koizumi M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, Sekimoto M, Hirota M, Kimura Y, Takeda K, Isaji S, Otsuki M, Matsuno S; JPN. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32.

Nauck MA, Frossard JL, Barkin JS, Anglin G, Hensley IE, Harper KD, Milicevic Z. Assessment of pancreas safety in the development program of once-weekly GLP-1 receptor agonist dulaglutide. *Diabetes Care*. 2017;40(5):647-654.

Neumiller JJ. Incretin-based therapies. *Med Clin North Am*. 2015;99(1):107-129.

Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons Inc.; 1987.

Steinberg WM, Buse JB, Ghorbani ML, Ørsted DD, Nauck MA; LEADER Steering Committee; LEADER Trial Investigators. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER Randomized Trial. *Diabetes Care*. 2017a;40(7):966-972.

Steinberg WM, Rosenstock J, Wadden TA, Donsmark M, Jensen CB, DeVries JH. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the SCALE clinical development program. *Diabetes Care*. 2017b;40(7):839-848.

Weinberg ME, Bacchetti P, Rushakoff RJ. Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *J Diabetes Sci Technol*. 2010;4(3):577-582.

## 12. Appendices

---

## Appendix 1. Abbreviations and Definitions

---

<b>Term</b>	<b>Definition</b>
<b>ADA</b>	anti-drug antibodies
<b>AE</b>	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
<b>ALP</b>	alkaline phosphatase
<b>ALT</b>	alanine aminotransferase
<b>ANCOVA</b>	analysis of covariance
<b>AST</b>	aspartate aminotransferase
<b>BG</b>	blood glucose
<b>BMI</b>	body mass index
<b>CEC</b>	Clinical Events Classification
<b>CI</b>	confidence interval
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>CKD-EPI</b>	Chronic Kidney Disease-Epidemiology
<b>COA</b>	clinical outcome assessment
<b>complaint</b>	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
<b>compliance</b>	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
<b>CRF</b>	case report form
<b>CRP</b>	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
<b>CRS</b>	clinical research scientist
<b>CSR</b>	clinical study report

Term	Definition
<b>CT</b>	computed tomography
<b>CV</b>	cardiovascular
<b>DNA</b>	deoxyribonucleic acid
<b>DPP-4</b>	dipeptidyl-peptidase-4
<b>DTSQc</b>	Diabetes Treatment Satisfaction Questionnaire (change)
<b>DTSQs</b>	Diabetes Treatment Satisfaction Questionnaire (status)
<b>EAS</b>	efficacy analysis set
<b>ECG</b>	electrocardiogram
<b>eCRF</b>	electronic case report form
<b>EDC</b>	electronic data capture system
<b>eGFR</b>	estimated glomerular filtration rate
<b>enroll</b>	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
<b>enter</b>	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
<b>EQ-5D-5L</b>	European Quality of Life – 5 Dimension -5 Level Questionnaire
<b>ERB</b>	ethical review board
<b>ET</b>	early termination
<b>FAS</b>	full analysis set
<b>FBG</b>	fasting blood glucose
<b>FSG</b>	fasting serum glucose
<b>FSH</b>	follicle-stimulating hormone
<b>GCP</b>	good clinical practice
<b>GI</b>	gastrointestinal
<b>GIP</b>	glucose-dependent insulinotropic polypeptide
<b>GIPR</b>	gastric inhibitory polypeptide receptor
<b>GLP-1</b>	glucagon like peptide-1

Term	Definition
<b>HbA1c</b>	glycated hemoglobin
<b>HOMA-2</b>	Updated Homeostasis Model Assessment
<b>HR-QoL</b>	health-related quality of life
<b>IB</b>	Investigator's Brochure
<b>ICF</b>	informed consent form
<b>ICH</b>	International Conference on Harmonisation
<b>Informed consent</b>	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
<b>INR</b>	International Normalized Ratio
<b>interim analysis</b>	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
<b>investigational product</b>	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
<b>IRB</b>	Institutional Review Board
<b>ITT</b>	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
<b>IWRS</b>	interactive web-response system
<b>LC/MS</b>	liquid chromatography/mass spectrometry
<b>MAD</b>	multiple ascending dose
<b>MedDRA</b>	Medical Dictionary for Regulatory Activities
<b>MEN-2</b>	multiple endocrine neoplasia syndrome type 2
<b>MI</b>	myocardial infarction
<b>MITT</b>	modified intention-to-treat
<b>MMRM</b>	mixed-model repeated measures

Term	Definition
<b>MRI</b>	magnetic resonance imaging
<b>MTC</b>	medullary thyroid carcinoma
<b>NAFLD</b>	nonalcoholic fatty liver disease
<b>OAM</b>	oral antihyperglycemic medication
<b>OTC</b>	over the counter
<b>PD</b>	pharmacokinetics
<b>PK</b>	pharmacokinetics
<b>PRO</b>	patient-reported outcomes
<b>QW</b>	once weekly administration
<b>RNA</b>	ribonucleic acid
<b>SAE</b>	serious adverse event
<b>SAP</b>	statistical analysis plan
<b>SAS</b>	safety analysis set
<b>SC</b>	subcutaneous
<b>SD</b>	standard deviation
<b>screen</b>	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
<b>SGLT-2i</b>	sodium-glucose cotransporter type 2 inhibitor
<b>SMBG</b>	self-monitored blood glucose
<b>SUSAR</b>	suspected unexpected serious adverse reaction
<b>T1DM</b>	type 1 diabetes mellitus
<b>T2DM</b>	type 2 diabetes mellitus
<b>TBL</b>	total bilirubin
<b>TE</b>	treatment-emergent
<b>TEAE</b>	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.

---

<b>Term</b>	<b>Definition</b>
<b>TZD</b>	thiazolidinedione
<b>ULN</b>	upper limit of normal

---

---

## Appendix 2. Clinical Laboratory Tests

---

**Clinical Laboratory Tests**

<b>Hematology<sup>a</sup></b>	<b>Clinical Chemistry<sup>a</sup></b>
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Chloride
Mean cell volume (MCV)	Bicarbonate
Mean cell hemoglobin concentration (MCHC)	Total bilirubin
Leukocytes (WBC)	Direct bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Alanine aminotransferase (ALT/SGPT)
Monocytes	Aspartate aminotransferase (AST/SGOT)
Eosinophils	Gamma-glutamyl transferase (GGT)
Basophils	Blood urea nitrogen (BUN)
Platelets	Creatinine
	Creatine kinase (creatinine phosphokinase) <sup>d</sup>
<b>Urinalysis<sup>a,b</sup></b>	
Albumin	Uric acid
Creatinine	Calcium
	Albumin
<b>Nonpharmacogenetic Stored Samples<sup>a</sup></b>	<b>Lipid Panel (fasting)<sup>a</sup></b>
Serum	Total cholesterol
EDTA plasma	High-density lipoprotein-cholesterol (HDL-C)
P800 plasma	Low-density lipoprotein-cholesterol (LDL-C) <sup>e</sup>
	Very low-density lipoprotein-cholesterol (VLDL-C)
	Triglycerides
	<b>Pharmacogenetics Sample<sup>a</sup></b>
	<b>Pregnancy test (females only)<sup>a,f</sup></b>
	Follicle-stimulating hormone (FSH) <sup>g</sup>
	Estradiol <sup>g</sup>
<b>Immunogenicity<sup>j</sup></b>	<b>HbA1c<sup>a</sup></b>
Anti-tirzepatide antibody	
<b>Hepatitis Testing<sup>a,c</sup></b>	<b>Glucose, fasting<sup>a,h</sup></b>
<b>Endocrine<sup>a</sup></b>	<b>Pancreas (exocrine)<sup>a</sup></b>
Calcitonin	Pancreatic amylase
	Lipase
<b>Pharmacokinetics</b>	<b>C-peptide<sup>a</sup></b>
Tirzepatide plasma levels	Insulin, fasting <sup>h</sup>
	<b>eGFR (calculated by CKD-EPI equation)<sup>i</sup></b>

---

Abbreviations: CKD-EPI = Chronic Kidney Disease-Epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; FSH = follicle stimulating hormone; HbA1c = hemoglobin A1c; RBC = red blood cell; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; WBC = white blood cell.

- a All tests will be performed or sample stored by the Lilly-designated central laboratory.
- b Urinary albumin and creatinine are measured at a central laboratory and the ratio is calculated.
- c As needed per hepatic monitoring criteria (refer to [Appendix 4](#)).
- d Creatine kinase MB (CK-MB) is to be assayed if creatine kinase result >1000 IU/L.
- e Low-density lipoprotein is calculated using the Friedwald equation.
- f A serum pregnancy test will be performed at Visit 1 for women of childbearing potential only and will be analyzed at a central laboratory. Pregnancy tests may be repeated at any time during the study and analyzed locally at the investigator's discretion. Urine pregnancy test will be performed by a local laboratory.
- g FSH test performed at Visit 1 for postmenopausal women at least 45 years of age with an intact uterus, not on hormone therapy, and who have had spontaneous amenorrhea for more than 6 months and less than 12 months and estradiol levels consistent with a postmenopausal state (FSH  $\geq$ 40 mIU/mL and estradiol <30 pg/mL).
- h Fasting serum glucose and insulin values will be used to calculate beta-cell function and insulin sensitivity using the updated Homeostasis Model Assessment (HOMA2). Fasting serum glucose samples must be obtained after 8 hours or more without eating, drinking (other than water) or performing any significant physical activity.
- i Estimated glomerular filtration rate will be calculated by the central laboratory at required visits and included in lab result reports.
- j Assayed by a Lilly-designated laboratory.

---

## **Appendix 3. Study Governance Considerations**

---

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

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

The investigator is responsible for:

- ensuring that the patient/patient's legal representative understands the nature of the study, the potential risks and benefits of participating in the study, and that his/her participation is voluntary.
- ensuring that informed consent is given by each patient or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the patient/ patient's legal representative may have throughout the study and sharing in a timely manner any new information that may be relevant to the patients/ patient's legal representative's willingness to continue his/her participation in the study.
- ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

#### ***Appendix 3.1.2. Recruitment***

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

#### ***Appendix 3.1.3. Ethical Review***

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

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

- the protocol and related amendments and addenda, current Investigator's Brochure (IB) and updates during the course of the study
- informed consent form
- other relevant documents (eg, curricula vitae, advertisements)

#### ***Appendix 3.1.4. Regulatory Considerations***

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

- consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable ICH GCP Guidelines
- applicable laws and regulations

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

#### ***Appendix 3.1.5. Investigator Information***

Physicians with a specialty in diabetes/endocrinology, cardiology, nephrology, internal medicine, family medicine, general medicine, or any other specialty physician who has experience treating type 2 diabetes mellitus (T2DM) and clinical research experience in T2DM will participate as investigators in this clinical trial.

#### ***Appendix 3.1.6. Protocol Signatures***

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

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

#### ***Appendix 3.1.7. Final Report Signature***

The clinical study report (CSR) coordinating investigator will sign the final CSR for this study, indicating to the best of his/her knowledge, the report accurately describes the conduct and results of the study.

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

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

## Appendix 3.2. Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms (CRFs), and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate CRF data and use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

In addition, Lilly or its representatives will periodically check a sample of the patient data recorded against source documents at the study site. The study may be audited by Lilly or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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

### Appendix 3.2.1. Data Capture System

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

An electronic data capture system (EDC) will be used in this study for the collection of the 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 electronic CRF (eCRF).

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

Data collected via the Sponsor-provided data capture system(s) will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

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

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

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

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

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

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

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

#### ***Appendix 3.4. Publication Policy***

The publication policy for Study I8F-JE-GPGO is described in the Letter of Agreement.

---

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

---

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

### Hepatic Monitoring Tests

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

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

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

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

Prothrombin Time  
Prothrombin Time, INR

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

Hepatitis A antibody, total  
Hepatitis A antibody, IgM  
Hepatitis B surface antigen  
Hepatitis B surface antibody  
Hepatitis B Core antibody  
Hepatitis C antibody  
Hepatitis E antibody, IgG<sup>c</sup>  
Hepatitis E antibody, IgM<sup>c</sup>

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

Total bilirubin  
Direct bilirubin  
Alkaline phosphatase  
ALT  
AST  
GGT  
CPK

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

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

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

---

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

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

<sup>b</sup> Reflex/Confirmation tests may be performed depending on regulatory requirements and/or testing availability.

<sup>c</sup> Hepatitis E Virus testing in endemic areas only.

---

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

---

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

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

---

## Appendix 6. Classification of Contraceptive Methods

---

### Highly Effective Methods of Contraception:

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

### Effective Methods of Contraception:

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

Men, regardless of their fertility status, with non-pregnant women of child bearing potential partners must agree to use 2 forms of effective contraception, where at least 1 form is highly effective for the duration of the study and for at least 3 months after the last injection.

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

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

---

## **Appendix 7. Management of Patients with Severe, Persistent Hyperglycemia during the Treatment Period**

---

Below are criteria for deciding when and how to intervene with patients who do not reach glycemic targets. An additional therapeutic intervention should be considered in patients who develop severe, persistent hyperglycemia after randomization at the discretion of the investigator in accordance with American Diabetes Association/European Association for the Study of Diabetes guidance (Inzucchi et al. 2015). Rescue treatment with antihyperglycemic medications, including insulins, will be allowed. In this case, GLP-1RA and DPP-4 inhibitors are not allowed as rescue therapies. Rescue medication will be prescribed as add-on to randomized treatment, and patients will continue to follow the protocol-specified visit schedule.

Add-on glycemic rescue therapy will be allowed for patients based on the following criteria:

- 1) The patient is fully compliant with the assigned therapeutic regimen

AND

- 2) Has no acute condition that raises blood glucose

AND

- a) Blood glucose concentration measured by weekly 1-point SMBG before breakfast profile  $>270$  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 9-16 weeks postrandomization

OR

- c) Blood glucose concentration measured by weekly 1-point SMBG before breakfast  $>200$  mg/dL ( $>11.1$  mmol/L) over at least a consecutive 2-week period at any time beyond the first 16 weeks postrandomization

OR

- d) HbA1c  $\geq 8.5\%$  (69 mmol/mol) at 24 weeks, with inadequate response to the existing regimen defined as improvement in HbA1c over the last 3 months (Week 12 to Week 24) that is  $<0.3\%$ .

---

**Appendix 8. Protocol Amendment I8F-JE-GPGO(a)  
Summary A Phase 3 Study of Tirzepatide Monotherapy  
Compared to Dulaglutide 0.75 mg in Patients with Type 2  
Diabetes Mellitus (SURPASS J-mono)**

---

## Overview

Protocol I8F-JE-GPGO A Phase 3 Study of Tirzepatide Monotherapy Compared to Dulaglutide 0.75 mg in Patients with Type 2 Diabetes Mellitus (SURPASS J-mono) has been amended. The new protocol is indicated by amendment (a) and will be used to conduct the study in place of any preceding version of the protocol.

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

- Changes to the table of Objectives/Endpoints in section 1 and section 4 to delete some of abbreviations
- A change to section 3.2 to clarify the description of Phase 2 studies
- A change to section 7.2.1 to correct the timing of administration of investigational product when missed
- A change to section 7.6 to align with study procedure
- Changes to section 7.7 to add prohibited comcomitant therapy
- Changes to section 9.2 to align with study procedure
- A change to section 9.2.2.2 for consistency with Appendix 7
- A change to section 9.2.3 to align with study procedure
- A change to section 9.9.1 to correct the number of health states used in EQ-5D-5L
- Changes to section 10.3.3.1 to correct explanation of statistical testing procedure
- Change to Appendix 6 for consistency with inclusion criterion [6b]

## Revised Protocol Sections

<b>Note:</b>	Deletions have been identified by <del>strike-throughs</del> .
	Additions have been identified by the use of <u>underline</u> .

### 1. Synopsis

#### Objectives/Endpoints:

Abbreviations: ADAs = anti-drug antibodies; AE = adverse event; ~~AUC = area under the concentration versus time curve; Cmax = maximum plasma concentration; CGM = continuous glucose monitoring; CV = cardiovascular; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; MTC = Medullary Thyroid Carcinoma; OAM = oral antihyperglycemic medication; SAE = serious adverse event; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.~~

### 3.2. Background

.....  
Serious AEs (SAEs) were balanced across the treatment groups, and none of the groups in ~~the either~~ study reported severe hypoglycemia (Frias et al. 2018).  
.....

### 4. Objectives and Endpoints

Abbreviations: ADAs = anti-drug antibodies; AE = adverse event; ~~AUC = area under the concentration versus time curve; Cmax = maximum plasma concentration; CGM = continuous glucose monitoring; CV = cardiovascular; FSG = fasting serum glucose; HbA1c = hemoglobin A1c; MTC = Medullary Thyroid Carcinoma; OAM = oral antihyperglycemic medication; SAE = serious adverse event; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.~~

#### 7.2.1. Selection and Timing of Doses

.....  
If a dose of investigational product, including tirzepatide 5 mg, 10 mg, 15 mg or dulaglutide 0.75 mg, is missed, the patient should take it as soon as possible, unless it is within 72 48 hours of the next dose, in which case that dose should be skipped and the next dose taken at the appropriate time.

#### 7.6. Treatment Compliance

.....  
In addition to the assessment of a patient's compliance with the investigational product administration, other aspects of compliance with the study treatments will be assessed at each visit, based on the patient's adherence to the visit schedule, ~~compliance with the concomitant antihyperglycemic medication regimen~~, completion of study diaries, the results of home BG monitoring, and any other parameters the investigator considers necessary.

## 7.7. Concomitant Therapy

Prohibited medications include following:

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

## 9.2. Adverse Event

Investigators should record their assessment of the potential relatedness of each AE to study procedure, ~~and investigational product, and study device(s),~~ via eCRF.

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

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

### 9.2.2.2. Severe, Persistent Hyperglycemia

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 9-16 ~~8 to 16~~ weeks post-randomization;

## 9.2.3. Complaint Handling

Patients will be instructed to contact the investigator as soon as possible if they have complaints or problems with the investigational product or drug delivery system, so that the situation can be assessed.

### 9.9.1. European Quality of Life – 5 Dimension – 5 Level (EQ-5D-5L)

The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, unable to perform/extreme problems), for a total of 3125 3254 possible health states.

.....

### 10.3.3.1 Primary Analyses

The primary efficacy measure is HbA1c change from baseline at 52 weeks, and the primary comparison is to compare tirzepatide doses versus dulaglutide 0.75 mg. Superiority of each tirzepatide dose will be demonstrated if the upper limit of the 97.5% or 95% CI for the difference between tirzepatide dose and dulaglutide 0.75 mg is below 0.

The statistical analyses for the primary efficacy measure of HbA1c change from baseline at 52 weeks will examine the following 3 hypotheses:

- $H_1$ : the 15-mg dose of tirzepatide is superior to dulaglutide 0.75 mg
- $H_2$ : the 10-mg dose of tirzepatide is superior to dulaglutide 0.75 mg
- $H_3$ : the 5-mg dose of tirzepatide is superior to dulaglutide 0.75 mg

$H_1$  and  $H_2$  will be tested at a 2-sided significance level of 0.025, followed by testing  $H_3$  only if  $H_1$  and/or  $H_2$  are declared.  $H_3$  will be tested at a 2-sided significance level of 0.05 if  $H_1$  and  $H_2$  are declared.  $H_3$  will be tested at a 2-sided significance level of 0.025 if either  $H_1$  or  $H_2$  is declared. This parallel gatekeeping procedure controls family-wise Type 1 error rate at a 2-sided 0.05 level (Dmitrienko et al. 2003).

## Appendix 6. Classification of Contraceptive Methods

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

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

Men, regardless of their fertility status, with non-pregnant women of child bearing potential partners must agree to use 2 forms of effective contraception, where at least 1 form is highly effective either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (<1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or effective method of contraception (such as diaphragms with spermicide or cervical sponge) for the duration of the study and for at least 3 months after the last injection.

Leo Document ID = 9caf24ab-57dc-45da-8ad8-8ae004094393

Approver: PPD

Approval Date & Time: 17-Jan-2019 01:05:51 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 17-Jan-2019 03:32:25 GMT

Signature meaning: Approved