Protocol I8F-MC-GPHT(b)

A Multiple Dose Titration Study in Chinese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Tirzepatide

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Tirzepatide (LY3298176)

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1. Protocol Synopsis

Title of Study:
A Multiple Dose Titration Study in Chinese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Tirzepatide.

Rationale:
Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptors being developed as a weekly treatment for type 2 diabetes mellitus (T2DM). This study of tirzepatide, I8F-MC-GPHT (GPHT), will investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of tirzepatide administered once weekly for 16 or 24 weeks as subcutaneous (SC) injections to Chinese patients with T2DM.

Objective(s)/Endpoints:

Objectives	Endpoints
Primary To investigate the safety and tolerability of tirzepatide after multiple SC doses administered to Chinese patients with T2DM	Incidence of TEAEs
Secondary To characterize the PK of tirzepatide after multiple SC doses in Chinese patients with T2DM	AUC and C_{max} of tirzepatide

Abbreviations: AUC = area under the concentration-time curve; C_{max} = maximum observed drug concentration; PK = pharmacokinetics; SC = subcutaneous; 7p-SMPG = 7-point self-monitored plasma glucose; T2DM = type 2 diabetes mellitus.

Summary of Study Design:

Study GPHT is a Phase 1, randomized, placebo-controlled, multiple dose titration study in Chinese patients with T2DM.

Treatment Arms and Planned Duration for an Individual patient:
This study consists of 2 cohorts. Approximately 12 Chinese patients with T2DM will be randomized within a cohort to receive tirzepatide or placebo. For Cohort 1, 16 weekly SC doses of tirzepatide or placebo will be administered in a ratio of 10 tirzepatide:2 placebo. For Cohort 2, 24 weekly SC doses of tirzepatide or placebo will be administered in a ratio of 10 tirzepatide:2 placebo.

Patients in Cohort 1 will receive either tirzepatide with titration regimen starting from 2.5 mg for Days 1, 8, 15, and 22 (Weeks 0 to 3), 5 mg for Days 29, 36, 43, and 50 (Weeks 4 to 7), 7.5 mg for Days 57, 64, 71, and 78 (Weeks 8 to 11), and 10 mg for Days 85, 92, 99, and 106 (Weeks 12 to 15), or corresponding volume-matched placebo.

Patients in Cohort 2 will receive either tirzepatide with titration regimen starting from 2.5 mg for Days 1, 8, 15, and 22 (Weeks 0 to 3), 5 mg for Days 29, 36, 43, and 50 (Weeks 4 to 7), 7.5 mg for Days 57, 64, 71, and 78 (Weeks 8 to

11), 10 mg for Days 85, 92, 99, and 106 (Weeks 12 to 15), 12.5 mg for Days 113, 120, 127, and 134 (Weeks 16 to 19), and 15 mg for Days 141, 148, 155, and 162 (Weeks 20 to 23), or corresponding volume-matched placebo.

Number of Patients:
Approximately 24 Chinese patients with T2DM may be enrolled to ensure approximately 16 patients complete the study, in compliance with the defined dosing regimen.

Statistical Analysis:

Pharmacokinetics, PD, and efficacy analyses will be conducted on data from all patients who receive at least 1 dose of the IP and have evaluable PK, PD, and efficacy data. Safety analyses will be conducted for all enrolled patients, whether or not they completed all protocol requirements.

Safety: All IP and protocol procedure-related adverse events will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. Safety parameters that will be assessed include safety laboratory parameters, vital signs, electrocardiogram parameters, injection-site reactions, and hypoglycemia.

Efficacy: The efficacy of tirzepatide to reduce glucose and weight will be assessed. All parameters will be listed and summarized using standard descriptive statistics.

Pharmacodynamics: Lipids and subjective appetite sensation (VAS) will be listed and summarized using descriptive methodology.

Pharmacokinetics: The primary parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration-time curve (AUC), and time to C_{max} (T_{max}) of tirzepatide. Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported. Pharmacokinetic parameters will be summarized using descriptive statistics. The mean concentration-time profiles in linear and semilog scale for each tirzepatide-treated group will be presented.

Immunogenicity: The frequency and percentage of subjects/patients with preexisting antidrug antibodies (ADAs) and with treatment-emergent (TE) ADA to tirzepatide will be tabulated. The frequency of neutralizing antibodies to tirzepatide and/or cross-reactive to endogenous counterparts may also be tabulated in TE ADA patients.

The relationship between the presence of antibodies, antibody titres, and clinical parameters (for example, AEs) may be assessed. Likewise, the relationship between antibody titers, PK parameters, and PD response to tirzepatide may be assessed.

2. Schedule of Activities

Study Schedule Protocol I8F-MC-GPHT Cohort 1 Except for Treatment Period

Procedure	**Screening**	**Lead-in**	**Treatment Period**	**Follow-Up**		
Days	**Day -28 ~ -17**	**Day -14 ±1**		**Day 120 ±2**	**Day 141 ±2**	**ED2[a]**
Outpatient Visit	**1**	**2**		**13**	**14**	
Fasting Visit [b]	X				X	X
Informed Consent	X					
Outpatient Visit	X	X		X	X	X
Dispense Study Diary & Training		X				
BG Meters/Test Stripes Dispense & Training		X				
Study Drug Injection Training		X				
Medical History	X					
Pre-existing Disease and AEs	X	X		X	X	X
Hypoglycemic Events	X	X		X	X	X
Concomitant Treatment	X	X		X	X	X
Height, Race	X					
Body Weight [c]	X				X	X
Body Temperature	X				X	X

Procedure	Screening	Lead-in	Treatment Period	Follow-Up		
Days	**Day -28 ~ -17**	**Day -14 ±1**		**Day 120 ±2**	**Day 141 ±2**	**ED2[a]**
Outpatient Visit	**1**	**2**		**13**	**14**	
Fasting Visit [b]	X				X	X
Vital Signs (BP/PR)	X				X	X
Physical Examinations [d]	X				X	X
12-lead ECG	X				X	X
Chest X-Ray [e]	X					
Clinical Safety Lab (Hematology, Chemistry, Urinalysis) [f]	X				X	X
Clinical Safety Lab (Pancreatic Enzyme) [f]	X				X	X
Serology (HBV/HCV/HIV) [f]	X					
Urine Drug and Alcohol Screen [f, g]	X					
Pregnancy Test, FSH [f, h]	X					
Calcitonin	X					
Hemoglobin A1c	X					
7-Point SMPG		X [i]				

Procedure	**Screening**	**Lead-in**	**Treatment Period**	**Follow-Up**		
Days	**Day -28 ~ -17**	**Day -14 ±1**		**Day 120 ±2**	**Day 141 ±2**	**ED2[a]**
Outpatient Visit	**1**	**2**		**13**	**14**	
Fasting Visit [b]	X				X	X
PK Sampling [j]				X	X	X
Immunogenicity					X	X

Study Schedule Protocol I8F-MC-GPHT Cohort 1 for Treatment Period

Treatment Period	**2.5 mg**							**5 mg**							**7.5 mg**		**10 mg**									
Week	**0**					**1**	**2**	**4**	**6**		**7**				**8**	**10**	**12**	**13**	**14**	**15**					**16**	
Day	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ±1**	**29 ±1**	**43 ±1**	**49**	**50**	**51**	**52**	**53**	**57 ±1**	**71 ±1**	**85 ±1**	**92 ±1**	**99 ±1**	**105**	**106**	**107**	**108**	**109**	**113**	**ED 1[a]**
Visit	**V3**	**V3a**	**V3b**	**V3c**	**V3d**	**V4**	**TV**	**V5**	**TV**	**V6**	**V6a**	**V6b**	**V6c**	**V6d**	**V7**	**TV**	**V8**	**V9**	**V10**	**V11**	**V11a**	**V11b**	**V11c**	**V11d**	**V12**	
Fasting Visit [b]		X				X		X			X				X		X				X				X	X
Admission to CRU	X									X										X						
Inpatient stay at CRU [k]	X	X	X	X	X					X	X	X	X	X						X	X	X	X	X		
Discharge from CRU					X									X										X		
Outpatient Visit						X		X							X		X	X	X						X	
Randomization		X																								
Dose Administration [l]		X				X	X	X	X		X				X	X	X	X	X		X					
Pre-existing Disease and AEs	X	X	X	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	X	X	X
Concomitant Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Temperature	X	Pre																								X

Treatment Period	**2.5 mg**							**5 mg**							**7.5 mg**		**10 mg**								
Week	**0**					**1**	**2**	**4**	**6**		**7**				**8**	**10**	**12**	**13**	**14**	**15**					**16**	
Day	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ±1**	**29 ±1**	**43 ±1**	**49**	**50**	**51**	**52**	**53**	**57 ±1**	**71 ±1**	**85 ±1**	**92 ±1**	**99 ±1**	**105**	**106**	**107**	**108**	**109**	**113**	**ED 1[a]**
Visit	**V3**	**V3a**	**V3b**	**V3c**	**V3d**	**V4**	**TV**	**V5**	**TV**	**V6**	**V6a**	**V6b**	**V6c**	**V6d**	**V7**	**TV**	**V8**	**V9**	**V10**	**V11**	**V11a**	**V11b**	**V11c**	**V11d**	**V12**	
Fasting Visit [b]		X				X		X			X				X		X				X				X	X
Vital Signs (BP/PR)	X	Pre, 2h, 4h, 8h	24 h	48 h	72 h	Pre		Pre			Pre				Pre		Pre				Pre				X	X
Physical Examinations [d]																										X
12-lead ECG	X	Pre	24 h	48 h	72 h	Pre		Pre			Pre				Pre		Pre				Pre	24h	48 h	72h	X	X
Clinical Safety Lab (Hematology, Chemistry, Urinalysis) [f]	X		24 h	48 h	72 h	Pre		Pre							Pre		Pre				Pre				X	X
Clinical Safety Lab (Pancreatic Enzyme) [f]	X	Pre						Pre							Pre		Pre				Pre				X	X
Calcitonin		Pre																							X	X
Hemoglobin A1c		Pre						Pre							Pre		Pre								X	X
7-Point SMPG	X						X		X							X			X						X	
FBG		Pre				Pre		Pre							Pre		Pre								X	
Lipid Panel		Pre				Pre		Pre							Pre		Pre								X	

Treatment Period	**2.5 mg**							**5 mg**							**7.5 mg**		**10 mg**									
Week	**0**					**1**	**2**	**4**	**6**		**7**				**8**	**10**	**12**	**13**	**14**	**15**					**16**	
Day	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ±1**	**29 ±1**	**43 ±1**	**49**	**50**	**51**	**52**	**53**	**57 ±1**	**71 ±1**	**85 ±1**	**92 ±1**	**99 ±1**	**105**	**106**	**107**	**108**	**109**	**113**	**ED 1[a]**
Visit	**V3**	**V3a**	**V3b**	**V3c**	**V3d**	**V4**	**TV**	**V5**	**TV**	**V6**	**V6a**	**V6b**	**V6c**	**V6d**	**V7**	**TV**	**V8**	**V9**	**V10**	**V11**	**V11a**	**V11b**	**V11c**	**V11d**	**V12**	
Fasting Visit [b]		X				X		X			X				X		X				X				X	X
Body Weight [c]		Pre				Pre		Pre							Pre		Pre				Pre,				X	
Meal Intake and Appetite [m]	L/D		L/D									L/D										L/D				
PK Sampling [j]		Pre D, 8h	24 h	48 h	72 h	168h		Pre D			Pre D, 8h	24 h	48 h	72 h	Pre D		Pre D	Pre D	Pre D		Pre D, 8h	24h	48 h	72h	168h	X
Immunogenicity		Pre						Pre							Pre		Pre								X	X
Pharmacogenetic Samples		Pre																								

Study Schedule Protocol I8F-MC-GPHT Cohort 2 except for Treatment Period

Procedure	**Screening**	**Lead-in**	**Treatment Period**	**Follow-Up**		
Days	**Day -28 ~ -17**	**Day -14 ±1**		**Day 176 ±2**	**Day 197 ±2**	**ED2[a]**
Outpatient Visit	**1**	**2**		**15**	**16**	
Fasting Visit [b]	X				X	X
Informed Consent	X					
Lead-in		X				
Outpatient Visit	X	X		X	X	X
Dispense Study Diary & Training		X				
BG Meters/Test Stripes Dispense & Training		X				
Study Drug Injection Training		X				
Medical History	X					
Pre-existing Disease and AEs	X	X		X	X	X
Hypoglycemic Events	X	X		X	X	X
Concomitant Treatment	X	X		X	X	X
Height, Race	X					

Procedure	Screening	Lead-in	Treatment Period	Follow-Up		
Days	**Day -28 ~ -17**	**Day -14 ±1**		**Day 176 ±2**	**Day 197 ±2**	**ED2[a]**
Outpatient Visit	**1**	**2**		**15**	**16**	
Fasting Visit [b]	X				X	X
Body Weight [c]	X				X	X
Body Temperature	X				X	X
Vital Signs (BP/PR)	X				X	X
Physical Examinations [d]	X				X	X
12-lead ECG	X				X	X
Chest X-Ray [e]	X					
Clinical Safety Lab (Hematology, Chemistry, Urinalysis) [f]	X				X	X
Clinical Safety Lab (Pancreatic Enzyme) [f]	X				X	X
Serology (HBV/HCV/HIV) [f]	X					
Urine Drug and Alcohol Screen [f, g]	X					
Pregnant Test, FSH [f, h]	X					
Calcitonin	X					

Procedure	**Screening**	**Lead-in**	**Treatment Period**	**Follow-Up**		
Days	**Day -28 ~ -17**	**Day -14 ±1**		**Day 176 ±2**	**Day 197 ±2**	**ED2[a]**
Outpatient Visit	**1**	**2**		**15**	**16**	
Fasting Visit [b]	X				X	X
Hemoglobin A1c	X					
7-Point SMPG		X [i]				
PK Sampling [j]				X	X	X
Immunogenicity					X	X

Study Schedule Protocol I8F-MC-GPHT Cohort 2 for Treatment Period

Treatment Period	**2.5 mg**							**5 mg**							**7.5 mg**		**10 mg**		**12.5 mg**		**15 mg**									
Week	**0**					**1**	**2**	**4**	**6**		**7**				**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**		**23**				**24**	
Day	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**49**	**50**	**51**	**52**	**53**	**57**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113± 1**	**127± 1**	**141± 1**	**148± 1**	**155± 1**	**161± 1**	**162**	**163**	**164**	**165**	**169**	**ED 1[a]**
Visit	**V3**	**V3a**	**V3b**	**V3c**	**V3d**	**V4**	**TV**	**V5**	**TV**	**V6**	**V6a**	**V6b**	**V6c**	**V6d**	**V7**	**TV**	**V8**	**TV**	**V9**	**TV**	**V10**	**V11**	**V12**	**V13**	**V13a**	**V13b**	**V13c**	**V13d**	**V14**	
Fasting Visit [b]		X				X		X			X				X		X		X		X				X					
Admission to CRU	X									X														X						
Inpatient stay at CRU [k]	X	X	X	X	X					X	X	X	X	X										X	X	X	X	X		
Discharge from CRU					X									X														X		
Outpatient Visit						X		X							X		X		X		X	X	X						X	X
Randomization		X																												
Dose Administration [l]		X				X	X	X	X		X				X	X	X	X	X	X	X	X	X		X					
Pre-existing Disease and AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Treatment Period	**2.5 mg**							**5 mg**							**7.5 mg**		**10 mg**		**12.5 mg**		**15 mg**								
Week	**0**					**1**	**2**	**4**	**6**		**7**				**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**		**23**				**24**	
Day	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**49**	**50**	**51**	**52**	**53**	**57**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113± 1**	**127± 1**	**141± 1**	**148± 1**	**155± 1**	**161± 1**	**162**	**163**	**164**	**165**	**169**	**ED 1[a]**
Visit	**V3**	**V 3a**	**V 3b**	**V 3c**	**V 3d**	**V4**	**TV**	**V5**	**TV**	**V6**	**V 6a**	**V 6b**	**V 6c**	**V 6d**	**V7**	**TV**	**V8**	**TV**	**V9**	**TV**	**V10**	**V11**	**V12**	**V13**	**V 13a**	**V 13b**	**V 13c**	**V 13d**	**V14**	
Fasting Visit [b]		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	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Treatment	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Body Temperature	X	Pre																												X
Vital Signs (BP/PR)	X	Pre, 2h, 4h, 8h	24h	48h	72h	Pre		Pre			Pre				Pre		Pre		Pre		Pre				Pre				X	X
Physical Examinations [d]																														X
12-lead ECG	X	Pre	24h	48h	72h	Pre		Pre			Pre				Pre		Pre		Pre		Pre				Pre	24h	48h	72h	X	X

Treatment Period	**2.5 mg**							**5 mg**							**7.5 mg**		**10 mg**		**12.5 mg**		**15 mg**									
Week	**0**					**1**	**2**	**4**	**6**		**7**				**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**		**23**				**24**	
Day	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**49**	**50**	**51**	**52**	**53**	**57**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113± 1**	**127± 1**	**141± 1**	**148± 1**	**155± 1**	**161± 1**	**162**	**163**	**164**	**165**	**169**	**ED 1[a]**
Visit	**V3**	**V 3a**	**V 3b**	**V 3c**	**V 3d**	**V4**	**TV**	**V5**	**TV**	**V6**	**V 6a**	**V 6b**	**V 6c**	**V 6d**	**V7**	**TV**	**V8**	**TV**	**V9**	**TV**	**V10**	**V11**	**V12**	**V13**	**V 13a**	**V 13b**	**V 13c**	**V 13d**	**V14**	
Fasting Visit [b]		X				X		X			X				X		X		X		X				X					
Clinical Safety Lab (Hematology, Chemistry, Urinalysis) [f]	X		24 h	48 h	72 h	Pre		Pre							Pre		Pre		Pre		Pre								X	X
Clinical Safety Lab (Pancreatic Enzyme) [f]	X	Pre						Pre							Pre		Pre		Pre		Pre								X	X
Calcitonin		Pre																											X	X
Hemoglobin A1c		Pre						Pre							Pre		Pre		Pre		Pre								X	X
7-Point SMPG	X						X		X							X		X		X			X						X	

Treatment Period	**2.5 mg**							**5 mg**							**7.5 mg**		**10 mg**		**12.5 mg**		**15 mg**									
Week	**0**					**1**	**2**	**4**	**6**		**7**				**8**	**10**	**12**	**14**	**16**	**18**	**20**	**21**	**22**		**23**				**24**	
Day	**-1**	**1**	**2**	**3**	**4**	**8**	**15 ± 1**	**29 ± 1**	**43 ± 1**	**49**	**50**	**51**	**52**	**53**	**57**	**71 ± 1**	**85 ± 1**	**99 ± 1**	**113± 1**	**127± 1**	**141± 1**	**148± 1**	**155± 1**	**161± 1**	**162**	**163**	**164**	**165**	**169**	**ED 1[a]**
Visit	**V3**	**V 3a**	**V 3b**	**V 3c**	**V 3d**	**V 4**	**TV**	**V 5**	**TV**	**V 6**	**V 6a**	**V 6b**	**V 6c**	**V 6d**	**V 7**	**TV**	**V 8**	**TV**	**V9**	**TV**	**V10**	**V11**	**V12**	**V13**	**V 13a**	**V 13b**	**V 13c**	**V 13d**	**V 14**	
Fasting Visit [b]		X				X		X			X				X		X		X		X				X					
FBG		Pre				Pre		Pre							Pre		Pre		Pre		Pre								X	
Lipid Panel		Pre				Pre		Pre							Pre		Pre		Pre		Pre								X	
Body Weight [c]		Pre				Pre		Pre							Pre		Pre		Pre		Pre								X	
Meal Intake and Appetite [m]	L/D		L/D									L/D														L/D				
PK Sampling [j]		PreD, 8h	24h	48h	72h	168h		PreD			PreD, 8h	24h	48h	72h	168h		PreD		PreD		PreD	PreD	PreD		PreD, 8h	24h	48h	72h	168h	X
Immunogenicity		Pre						Pre							Pre		Pre												X	X
Pharmacogenetic Samples		Pre																												

Abbreviations: AE= adverse event; BG=blood glucose; BP=blood pressure; CRU = clinical research unit; ECG=electrocardiogram; ED=early discontinuation; FBG=fasting blood glucose; FSH = follicle-stimulating hormone; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; IP=investigational product; lab = laboratory; L/D = lunch and dinner; PK = pharmacokinetics; PR=pulse rate; Pre = predose; PreD = predose for PK sampling; SC = subcutaneous; SMPG=self-monitored plasma glucose; TV=telephone visit; V = visit.

a A patient who discontinues from Cohort 1 between Day 1 and Day 113, inclusive, will complete ED1 procedures as soon as possible. The patient will be asked to complete ED2 procedures after a washout period of at least 28 days from the last IP administration. The patient who discontinues from Cohort 1 after the completion of Day 113 will complete ED2 procedures after a washout period of at least 28 days from the last IP administration. A patient who discontinues from Cohort 2 between Day 1 and Day 169, inclusive, will complete ED1 procedures as soon as possible. The patient will be asked to complete ED2 procedures after a washout period of at least 28 days from the last IP administration. The patient who discontinues from Cohort 2 after the completion of Day 169 will complete ED2 procedures after a washout period of at least 28 days from the last IP administration.

b Patients will be required to fast overnight for at least 8 hours before taking the first SC dose of tirzepatide (or placebo) and before each blood sample draw on fasting visit.

c Weight will be measured in a consistent way per Section 9.1, always predose.

d Full physical examination / medical assessment at screening. Symptom-directed physical examination/medical assessment at all other time points, and as deemed necessary by the investigator.

e Patients who have completed chest x-ray within the past 12 months and whose x-ray and/or report are available for review are exempt from the chest x-ray examination. The required chest x-ray is a single posterior anterior (PA) x-ray. If evidence of an abnormality, a lateral chest x-ray will be performed.

f These tests will be performed at the local laboratory.

g Additional urine drug screen or breath ethanol tests may be performed at the investigator's discretion.

h Females only. Blood pregnancy test will be done on screening; urine test at other times as indicated, or when performed at the investigator's discretion.

i Patients will conduct the 7-point SMPG every 3 days since Day -13 during lead-in period and will record readings in patient diary.

j A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon by both the investigator and sponsor.

k Patients may be required to remain at the CRU longer than the planned discharge day at the investigator's discretion to assure patients' safety or to provide additional safety monitoring.

l If a dose of tirzepatide 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 should be taken at the appropriate time. In Cohort 1, apart from time points indicated in SOA, tirzepatide should also be administered in Weeks 3, 5, 9, and 11. In Cohort 2, apart from time points indicated in SOA, tirzepatide should also be administered in Weeks 3, 5, 9, 11, 13, 15, 17, and 19.

m Meal intake and subjective rating of appetite sensation will be evaluated before and 4 to 5 hours after standardized lunch and dinner meals on Days –1 and 2 Day 51 (for both cohorts), and Day 107 for Cohort 1 and Day 163 for Cohort 2. The standardized lunch and dinner meals will be provided at least 4 hours after the previous meal. The subjective rating of appetite sensations is measured using a 100-mm visual analogue scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption before and 4 to 5 hours after the standardized lunch and dinner meals. Refer to Section 9.6.2 for details.

3. Introduction

3.1. Study Rationale

Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors being developed for the treatment of type 2 diabetes mellitus (T2DM). This study of tirzepatide, I8F-MC-GPHT (GPHT), will investigate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and efficacy of tirzepatide administered once weekly (QW) for either 16 weeks or 24 weeks as subcutaneous (SC) injections to Chinese patients with T2DM.

3.2. Background

Tirzepatide, a peptide with a modified GIP sequence, is a dual receptor agonist that binds both GIP and GLP-1 receptors. Following a meal, enteroendocrine cells in the gut secrete the incretins GIP and GLP-1. These incretins enhance the sensation of satiety, insulin secretion, and nutrient disposal (Baggio and Drucker 2007). Patients with T2DM have impaired incretin responses (Baggio and Drucker 2007). Currently available incretin-based treatments fall within 2 classes: GLP-1 receptor agonists (GLP-1 RAs) and dipeptidyl peptidase-4 (DPP-IV) inhibitors (Neumiller 2015).

Tirzepatide, a GIPR and GLP1R coagonist, is a chemically synthesized peptide consisting of a linear peptide component of 39 amino acid residues conjugated to a C20 fatty acid moiety. As a dual agonist, tirzepatide binds both GIP and GLP-1 receptors and combines the signalling of each receptor for improved glycaemic control. By virtue of being a dual incretin mimetic, tirzepatide has the potential of reaching higher efficacy in target tissues, such as the insulin-producing pancreatic ß-cells that express both GIPR and GLP-1R before reaching its therapeutic limitation. Furthermore, tirzepatide may attain additional efficacy by recruiting metabolically active tissues not targeted by selective GLP-1R analogues (for example, adipose tissue as indicated by the observation of increased energy utilization) (Baggio and Drucker 2007).

The clinical data to date have characterized the PK, PD, as well as preliminary efficacy and safety results of tirzepatide. Three tirzepatide clinical trials have completed dosing and analyses: (1) Phase 1 Study I8F-MC-GPGA, a single-ascending dose/multiple-ascending dose study in healthy subjects and multidose study in patients with T2DM, (2) Phase 2 Study I8F-MC-GPGB (GPGB), a placebo- and active-controlled dose-ranging study in T2DM, and (3) Phase 2 Study I8F-MC-GPGF (GPGF), a placebo-controlled efficacy and titration study in patients with T2DM.

The Phase 1 Study GPGA was a combination of single ascending dose (SAD) and multiple ascending dose (MAD) study in healthy subjects and a multiple dose study in patients with T2DM. Study GPGA investigated the safety, tolerability, pharmacokinetics (PK), and

pharmacodynamics (PD) of tirzepatide administered as SC injections. A total of 142 subjects (89 healthy subjects and 53 patients with T2DM) received at least 1 dose of treatment. Doses of tirzepatide ranged from 0.25 mg to 8 mg in the SAD (with maximum tolerated dose achieved at 5 mg); multiple doses from 0.5 mg to 4.5 mg QW; and titrated doses up to 10 mg QW for 4 weeks in healthy subjects; and multiples doses at 0.5 mg and 5 mg QW and titrated to 15 mg QW for 4 weeks in T2DM patients.

Doses higher than 5 mg were better tolerated when attained via escalation. Maximum tolerated dose of tirzepatide in healthy subjects following single-dose administration was 5 mg. A dose of 15 mg tirzepatide was administered in patients with T2DM by accelerated dose escalation over 4 weeks (5/5/10/15 mg) and while considered to be safe, was associated with high incidence of gastrointestinal (GI) events. Gastrointestinal adverse events (AEs) (nausea, vomiting, diarrhea, decreased appetite, abdominal distension) were the most frequently reported events by both healthy subjects and patients with T2DM and were dose related. Most AEs were mild in severity, few were moderate, and none were reported as severe. There were no apparent trends in chemistry, hematology, or urinalyses. A few subjects experienced elevations in lipase and/or amylase levels, but these episodes were not associated with drug-related risk of pancreatitis.

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, and 10 mg [titrated]; 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 5mg, 10mg, and 15-mg significantly lowered glycated hemoglobin (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 gastrointestinal (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 either study reported severe hypoglycemia (Frias et al. 2018). Study GPGF, a 3-month Phase 2 study, was designed to examine the efficacy, safety, and tolerability of QW tirzepatide administered in 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 and was designed to support evaluation of optimized dosing regimen(s) in Phase 3.

As it was recognised that the titration scheme employed in Study GPGB was unlikely to be optimal for reduction of GI-related AEs expected with tirzepatide, Study GPGF was designed to

explore alternative titration schemes (longer time intervals between dose escalations and different dose escalations) to support evaluation of optimised dosing regimen(s) in Phase 3. Study GPGF demonstrated that a longer time between dose increases and/or smaller dose escalations are better tolerated than rapid or large step-size dose escalations, as indicated by lower frequency of GI tolerability AEs and fewer patients discontinuing treatment compared to the data observed in Study GPGB.

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 safety and tolerability data of Study GPGC supports the use of doses up to 15 mg of tirzepatide in Japanese patients.

Tirzepatide PK was studied across a range of doses administered as single doses or multiple doses via a once-weekly dosing regimen. Based on the cumulative data to date, tirzepatide PK appeared linear and dose proportional during the dose range studied. Peak concentrations were observed at 1 to 2 days postdose, and the half-life was approximately 5 days.

In summary, the data from Study GPGB and Study GPGF support continued development of tirzepatide as a treatment for T2DM. Lilly proposes to conduct five Phase 3 randomised, controlled glycaemic-control trials. The doses selected for this study are 2.5, 5, 7.5, 10, 12.5, and 15 mg, which will be administered in a dose-escalation scheme that uses 2.5-mg dose increments and 4-week intervals.

3.3. Benefit/Risk Assessment

To minimize the risk of hyperglycemia due to the washout of prestudy oral antidiabetic medication, patients will monitor their fasting glucose levels using self-monitored plasma glucose (SMPG). Episodes of hyperglycemia will be reported and managed by the investigator or designated physician (Section 9.4.4.4.1).

Because tirzepatide is a long-acting, GIP and GLP-1 receptor dual agonist, the potential risks associated with tirzepatide may be similar to the risks associated with other long-acting GLP-1 receptor agonists. The known risks associated with increased GLP-1 receptor activity include but are not limited to GI-related adverse reactions (particularly nausea, vomiting, and diarrhea), pancreatitis, cardiovascular risk (increased heart rate), hypoglycemia, systemic allergic reaction, injection-site reactions, antibody formation, and medullary thyroid carcinoma (MTC). In previous tirzepatide Phase 1 and Phase 2 studies, the observed AEs were consistent with that of other GLP-1 agonists.

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

More information about the known risks for the QW GLP-1 receptor agonists can be found in the Bydureon® ([exenatide extended-release] for injectable suspension) package insert (Astra Zeneca 2018, China).

4. Objectives and Endpoints

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

Table GPHT.1. Objectives and Endpoints

Primary Objectives	**Endpoints**
To investigate the safety and tolerability of tirzepatide after multiple SC doses administered to Chinese patients with T2DM	Incidence of TEAEs
Secondary Objectives	**Endpoints**
To characterize the PK of tirzepatide after multiple SC doses in Chinese patients with T2DM	AUC and C_{max} of tirzepatide
Exploratory Objectives	**Endpoints**
To investigate the efficacy of tirzepatide after multiple SC doses administered to Chinese patients with T2DM	Hemoglobin A1c, body weight, fasting plasma glucose levels, 7p-SMPG
To investigate the exploratory PD effects of tirzepatide after multiple SC doses administered to Chinese patients with T2DM	Lipids, subjective appetite sensation (VAS)
To evaluate the formation of ADAs to tirzepatide after multiple SC doses administered to Chinese patients with T2DM	Presence of ADAs to tirzepatide

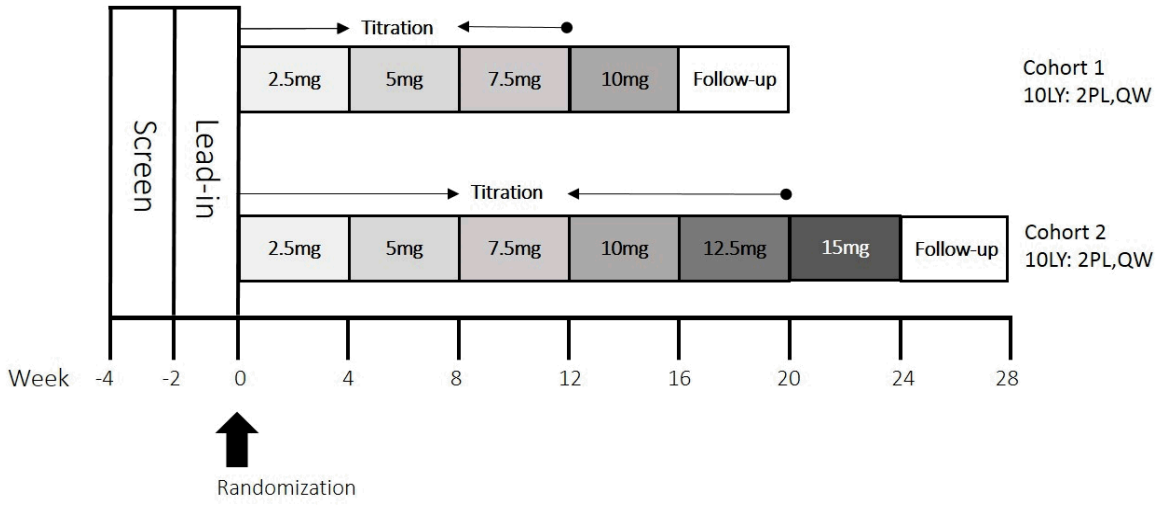
Abbreviations: ADA = antidrug antibody; AUC = area under the concentration-time curve; C_{max} = maximum observed drug concentration; PD = pharmacodynamic; PK = pharmacokinetics; SC = subcutaneous; 7p-SMPG = 7-point self-monitored plasma glucose; T2DM = type 2 diabetes mellitus; VAS = visual analogue scale.

5. Study Design

5.1. Overall Design

Study GPHT is a Phase 1, patient- and investigator-blind, placebo-controlled, randomized, multiple dose titration study in Chinese patients with T2DM.

Study governance considerations are described in detail in Appendix 3. Figure GPHT 5.1 illustrates the study design.



Abbreviations: LY = tirzepatide; PL = placebo; QW = once weekly.

Figure GPHT 5.1. Illustration of study design for Protocol I8F-MC-GPHT.

Patients will be administered either 16 or 24 weekly SC doses of tirzepatide or placebo. Section 2 outlines study procedures and timing for pre-study, treatment, and follow-up phases.

Screening (Visit 1)

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. Before performing any study procedures, the patient will sign the informed consent form (ICF). Procedures at this visit will be performed as shown in the Schedule of Activities, Section 2. Patients who meet all applicable inclusion criteria and none of the applicable exclusion criteria (Section 6) at Visit 1 will continue on their prestudy therapy between Visits 1 and 2.

Lead-in (Visit 2 to Visit 3)

At Visit 2, patients and their caregiver(s), if applicable, will receive a glucometer, study diaries, and training on how to perform self-monitoring of plasma glucose and record blood glucose

values, hypoglycemic events, medications, and AEs. Patients will also be trained on disease management and study procedures; this training can be repeated at subsequent visits as deemed appropriate.

Patients will conduct the 7-point SMPG approximately every 3 days since Day -13 during the lead-in period and will record readings in patient diary. Prior oral antidiabetic medication (OAM) should be discontinued during the lead-in period.

Treatment Period

Patients will be admitted to the clinical research unit (CRU) on Day -1. If the investigator decides not to administer the first dose to a patient on a particular day based on the results of medical assessments, vital signs, or electrocardiograms (ECGs), the patient's visit may be rescheduled, and any procedures performed up to that point may be repeated.

Cohort 1

Patients in Cohort 1 will receive either tirzepatide with titration regimen starting from 2.5 mg for Weeks 0 through 3 followed by 5 mg for Weeks 4 through 7, 7.5 mg for Weeks 8 through 11, and 10 mg for Weeks 12 through 15, or corresponding volume-matched placebo. During CRU visits 3a, 4, 5, 6a, 7, 8, 9, 10 and 11a, site staff will administer SC doses of tirzepatide or placebo. Patients may either self-administer or visit the CRU to have staff administer SC doses of tirzepatide or placebo at the beginning of Weeks 2, 3, 5, 6, 9, 10, and 11.

Cohort 2

Patients in Cohort 2 will receive either tirzepatide with titration regimen starting from 2.5 mg for Weeks 0 through 3 followed by 5 mg for Weeks 4 through 7, 7.5 mg for Weeks 8 through 11, 10 mg for Weeks 12 through 15, 12.5 mg for Weeks 16 through 19, and 15 mg for Weeks 20 through 23, or corresponding volume-matched placebo. During CRU visits 3a, 4, 5, 6a, 7, 8, 9, 10, 11, 12 and 13a, site staff will administer SC doses of tirzepatide or placebo. Patients may either self-administer or visit the CRU to have staff administer SC doses of tirzepatide or placebo at the beginning of Weeks 2, 3, 5, 6, 9, 10, 11, 13, 14, 15, 17, 18, and 19.

Pharmacokinetic sampling and safety assessments, including AEs, concomitant medications, medical assessments, clinical laboratory tests, vital signs, and ECGs, will be performed according to the Schedule of Activities (Section 2).

The investigator or qualified designee will review all available inpatient safety data before discharging patients from the CRU on the morning of each planned discharge day, provided they are deemed medically fit by the investigator. Patients may be required to remain at the CRU longer than the planned discharge day at the investigator's discretion to assure patients' safety or

to provide additional safety monitoring. Patients will be discharged after the review of all final safety assessments from the last follow-up visit is completed by the investigator.

Follow-Up Period

Visits for safety follow-up and PK sampling will occur on 2 separate visits. These visits will be approximately 7 and 28 days after the last dose of investigational product (IP).

5.2. Number of Participants

Approximately 24 Chinese patients with T2DM may be enrolled so that approximately 16 complete the study, in compliance with the defined dosing regimen. For purposes of this study, a patient completes the study when all scheduled procedures shown in the Schedule of Activities (Section 2) have been finished.

5.3. End of Study Definition

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

5.4. Scientific Rationale for Study Design

The patient- and investigator-blinded, randomized, placebo-controlled design minimizes the bias on safety and tolerability assessments and allows for a strong comparison between tirzepatide and placebo.

The selection of patients with T2DM is appropriate and in keeping with standard regional practices for clinical pharmacology studies. The inclusion and exclusion criteria are chosen to select patients free from other significant illnesses or conditions that could affect their safety or interfere with the study objectives.

The proposed PK sampling scheme enables understanding of the PK at the starting dose and at interim time points prior to achieving the final doses of 10 or 15 mg in the respective cohorts. Based upon the available clinical PK data for tirzepatide, the follow-up period of this study is considered adequate to achieve the study objectives.

5.5. Justification for Dose

In this study, 10 mg and 15 mg doses were selected to evaluate safety, tolerability, PK, PD, and efficacy of tirzepatide in Chinese patients with T2DM. Also, these selected doses will support dose selection in future clinical trials in patients with T2DM in China. These doses and associated titration schemes were selected based on low ethnic sensitivity of GLP-1 RA class for T2DM treatment and assessment of safety, efficacy (glycemic and weight loss benefit), and GI

tolerability data followed by exposure response modeling of data in patients with T2DM in Phase 1 and 2 studies. Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation in 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 anticipated dose-limiting safety and tolerability of tirzepatide are GI-related AEs, such as nausea and vomiting (Section 3.2), which have been consistently demonstrated with the GLP-1 drug class. The selected dose and titration scheme would enable further evaluation of benefit/risk considerations for 10 mg and 15 mg doses of tirzepatide.

6. Study Population

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

A chest x-ray will be completed at screening unless one has been obtained within the past 12 months, and the x-ray and/or report are available for review. For this study, the required chest x-ray is a single posterior anterior (PA) x-ray. Only if the PA x-ray shows evidence of an abnormality, a lateral chest x-ray will be performed.

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

Screening may occur up to Day -28 to Day -17 prior to enrollment. Patients who are not enrolled within 12 days of screening may be subjected to an additional medical assessment and/or clinical measurements to confirm their eligibility.

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

6.1. Inclusion Criteria

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

[1] Chinese males or females with T2DM between the ages of 20 and 70 years, inclusive, at screening. Native Chinese is defined as a patient who has all 4 biological grandparents and both biological parents to be of Chinese origin

[1a] male patients:

agree to use an effective method of contraception (barrier contraceptives such as latex condoms) for the duration of the study and or at least 3 months after the last dose of IP

[1b] female patients:

women not of childbearing potential because of surgical sterilization (hysterectomy or bilateral oophorectomy or tubal ligation) or menopause; women with an intact uterus are deemed postmenopausal if they are aged 45 years or older, and

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

OR

- who had at least 6 months of amerorrhoea with follicle-stimulating hormone (FSH) and estradiol levels consistent with a postmenopausal state (FSH ≥40 mIU/mL and estradiol <30 pg/mL)

OR

women patients of childbearing 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

[2] have T2DM controlled with diet and exercise alone or are stable on a single OAM, metformin, acarbose, or sulphonylureas only (other types of OAM [DPP-IV inhibitors, sodium-glucose cotransporter-2 inhibitors, and thiazolidinediones] are not allowed in this study), for at least 3 months

[3] have a HbA1c ≥7.0% and ≤10.5% for patients treated with diet and exercise only, and for the patients treated with antidiabetic medications, HbA1c ≥6.5% and ≤10.0%, at screening visit

[4] have a body mass of ≥23 kg/m^2, inclusive

[5] have clinical laboratory test results within normal reference range for the population or study site, or results with acceptable deviations that are judged to be not clinically significant by the investigator; abnormalities of blood glucose, serum lipids, urinary glucose, and urinary protein consistent with T2DM are acceptable

[6] have venous access sufficient to allow for blood sampling as per the protocol

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

[8] are able and willing to give signed informed consent

6.2. Exclusion Criteria

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

6.2.1. Medical Conditions

[9] have type 1 diabetes mellitus

[10] have a history of proliferative diabetic retinopathy, diabetic maculopathy or nonproliferative diabetic retinopathy that requires acute treatment

[11] have a history of ketoacidosis or hyperosmolar state/coma requiring hospitalization within the 6 months prior to Visit 1

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

[13] have known hemoglobinopathy (alpha-thalassemia), hemolytic anemia, sickle cell anemia, a hemoglobin value <11.0 g/dL (males) or <10.0 g/dL (females), or any other condition known to interfere with HbA1c methodology

[14] have a history of heart block or PR interval >220 msec or any abnormality in the 12-lead ECG at screening that, in the opinion of the investigator, increases the risks associated with participating in the study

[15] have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis) or GI disorder (for example, relevant esophageal reflux or gall bladder disease) or a GI disease that impacts gastric emptying (for example, gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogues or DPP-IV inhibitors; patients with dyslipidemia and patients who have had cholecystolithiasis (removal of gall stones) and/or cholecystectomy (removal of gall bladder) in the past, with no further sequelae, may be included in the study at the discretion of the investigator

[16] have a personal or family history of MTC or have multiple endocrine neoplasia syndrome type 2 (MEN-2)

[17] have a serum calcitonin level of ≥35 ng/L (pg/mL), as determined by central laboratory at Visit 1

[18] have any skin conditions (including, but not limited to, tattoos or scars) that may interfere with the interpretation of assessment or administration of IP

[19] have known allergies to tirzepatide, GLP-1 analogues, or related compounds or any components of the formulation

[20] have a history of atopy or clinically significant multiple or severe drug allergies, intolerance to topical corticosteroids, or severe postdose hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

[21] have serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) >2× the upper limit of normal (ULN) or total bilirubin level (TBL) >1.5× ULN (with the exception of Gilbert's syndrome)

[22] have an eGFR <45 mL/min/1.73 m^2 at screening, calculated by Chronic Kidney Disease-Epidemiology (CKD-EPI), as determined at Visit 1

[23] have evidence of significant active neuropsychiatric disorders

[24] show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies and/or HIV antigen at screening

[25] show evidence of hepatitis B or positive hepatitis B surface antigen at screening

[26] show evidence of hepatitis C or positive hepatitis C antibody at screening

[27] have a history of malignancy within 5 years before screening

[28] have a significant history of or current cardiovascular (for example, myocardial infarction, congestive heart failure, cerebrovascular accident, venous thromboembolism), respiratory, hepatic, renal, GI, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk while taking the IP; or of interfering with the interpretation of data

6.2.2. Prior/Concomitant Therapy

[29] have used or intend to use over-the-counter or prescription medication (herbal supplements, systemic glucocorticoids, immunomodulatory drugs, drugs with propensity for dermal reactions, drugs with known liver toxicity, etc.) within 7 days prior to dosing and during the study without agreement by the sponsor; for inclusion, stable doses of antihypertensive agents, aspirin, and lipid-lowering agents are allowed; occasional paracetamol/acetaminophen up to a 2-g dose in a 24-hour period may be allowed for inclusion at the discretion of the investigator (refer to Section 7.7)

[30] have a history of insulin therapy except for the use of insulin for treatment of gestational diabetes or acute, temporary use of insulin (≤14 days), for example, for acute illness, hospitalization, elective surgery

[31] have received chronic (lasting >14 consecutive days) systemic glucocorticoid therapy (excluding topical, intra-articular, and inhaled preparations) in the past year or have received any glucocorticoid therapy within 30 days before screening

[32] have used any traditional Chinese treatments within 30 days prior to study enrollment or intend to use any traditional Chinese treatment during the study

6.2.3. Prior/Concurrent Clinical Trial Experience

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

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

[35] have previously completed or withdrawn from this study or any other study investigating tirzepatide, and have previously received the IP

6.2.4. Other Exclusions

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

[37] are Lilly employees

[38] are women who are lactating

[39] have donated blood of more than 400 mL within the previous 12 weeks (males) or in the past 16 weeks (females), any blood donation (including apheresis) within the past 4 weeks, or total volume of blood donation in the past year is 1200 mL (males) or 800 mL (females) or more at screening

[40] have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) (1 unit = 12 oz or 360 mL of beer, 5 oz or 150 mL of wine, 1.5 oz or 45 mL of distilled spirits) or are unwilling to stop alcohol consumption during the 24 hours before and 72 hours post dose administration, and 24 hours before each admission to CRU and each outpatient visit, and throughout the duration of each CRU visit

[41] currently smoke in excess of 10 cigarettes/day or use tobacco or nicotine substitutes (within the past 6 months of screening), or subjects unwilling to refrain from smoking or are unable to abide by CRU restrictions

[42] regularly use known drugs of abuse or show positive findings on drug screening

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

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Patients will be required to fast overnight for at least 8 hours on fasting visit as described in the Schedule of Activities (Section 2). During fasting, water may be consumed freely. Standard meals will be provided after approximately 15 minutes from IP administration in the CRU. Standardized lunch and dinner meals will be provided in the CRU to assess meal intake and subjective rating of appetite sensation (Section 9.6.2).

When not residing in the CRU, patients should maintain their routine prestudy dietary patterns as much as possible.

6.3.2. Caffeine, Alcohol, and Tobacco

Caffeine: During the stay at CRU, patients should refrain from caffeinated foods and beverages such as cola, chocolate drinks, tea, and coffee. Patients will be allowed to maintain their regular caffeine consumption outside the CRU throughout the study period.

Alcohol: No alcohol will be allowed 24 hours before each admission to CRU and each outpatient visit, throughout the duration of each CRU visit, and 72 hours following IP administration. Between CRU visits, daily alcohol consumption should not exceed 3 units for males and 2 units for females (a unit is defined in Exclusion Criterion [40], Section 6.2)

Tobacco: No nicotine use will be permitted while at the CRU. When not at the CRU, patients may smoke no more than 10 cigarettes or consume the equivalent amount of nicotine per day.

6.3.3. Activity

Patients will be advised to maintain their regular levels of physical activity/exercise during the study. When certain study procedures are in progress at the site, patients may be required to remain supine, recumbent, or sitting.

6.4. Screen Failures

Individuals who do not meet this study's participation criteria may be re-screened once. The interval between re-screenings should be at least 2 weeks. If re-screened, the individual must sign a new ICF and will be assigned a new identification number. Repeating laboratory or clinical tests is not considered a re-screen.

7. Treatment

7.1. Treatment Administered

This study involves a comparison of QW SC dose levels of tirzepatide (2.5 mg to 10 mg titration regimen for Cohort 1 and 2.5 mg to 15 mg titration regimen for Cohort 2) with corresponding volume-matched placebo. Table GPHT.2 shows the treatment regimens.

For Cohort 1, 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 mg to 5 mg to 7.5 mg to 10 mg) until the 10-mg dose is reached and maintained for the duration of the study. For Cohort 2, 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 mg to 5 mg to 7.5 mg to 10 mg to 12.5 mg to 15 mg) until the 15-mg dose is reached and maintained for the duration of the study.

Table GPHT.2. Tirzepatide Treatment Regimens

Cohort	Treatment Period Interval					
	Weeks 0 to 3	Weeks 4 to 7	Weeks 8 to 11	Weeks 12 to 15	Weeks 16 to 19	Weeks 20 to 23
1	2.5 mg	5 mg	7.5 mg	10 mg		
2	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg

Note: All doses will be administered once weekly using a single-dose pen.

All injections will be administered into the SC tissue of the abdominal wall. Injection sites will be alternated weekly between 4 sites on the abdominal wall (that is, right and left upper quadrants and right and left lower quadrants). During CRU visits as shown in the Schedule of Activities, Section 2, site staff will administer SC doses of tirzepatide or placebo. For dosing at non-CRU visits, patients may either self-administer or visit the CRU to have staff administer SC doses of tirzepatide or placebo.

The investigator or designee is responsible for

- explaining the correct use of the IP to the site personnel and the patient
- verifying that instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- instructing patients to discard all used single-dose pens (SDPs) for tirzepatide in a closeable, puncture-resistant container and dispose according to local regulations

7.1.1. Packaging and Labeling

The sponsor will provide tirzepatide in SDP. These will be dispensed via an interactive web-response system (IWRS). SDP will be packaged in cartons to be dispensed. Each SDP contains a specific dose and is administered as a single injection. The SDP will be packaged for each dose strength: 2.5mg, 5mg, 7.5mg, 10mg, 12.5mg, 15mg and placebo to match. The IP will be labeled according to the country's regulatory requirements.

7.1.2. Medical Devices

The products provided for use in the study are tirzepatide investigational SDP.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to receive either tirzepatide or placebo in a 5:1 ratio at Visit 3a. Assignment to treatment groups will be determined by a computer-generated random sequence using an IWRS.

7.2.1. Selection and Timing of Doses

There are no restrictions on the time of day each weekly dose of tirzepatide is given, but it is advisable to administer the SC injections on the same day and same time each week. The actual date and time of dose administrations will be recorded by investigator at dosing visit on site or by the patient on self-administration day.

If a dose of tirzepatide 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 should be taken at the appropriate time. Missed doses may not result in patient discontinuation from the study. For more information on missed doses, please refer to Section 7.6.

7.3. Blinding

The dosing regimen is patient- and investigator-blind. Investigators, site staff, clinical monitors, and patients will remain blinded to the treatment assignments until the study is complete. Blinding will be maintained throughout the study as described in the separate Blinding Plan.

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

If a patient's study treatment assignment is unblinded, the patient must discontinue from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist or clinical research physician (CRP) for the study participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study patient's emergency code.

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's safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator must promptly document the decision and rationale and notify Lilly as soon as possible.

For the blinded items in the clinical laboratory tests, please refer to Appendix 2.

7.4. Dose Modification

Dose adjustments are not permitted in this study.

7.5. Preparation/Handling/Storage/Accountability

The investigator or designee must confirm the maintenance of appropriate temperature conditions (2°C to 8°C), as communicated by the sponsor, during transit for all IPs received. The investigator or designee should report and resolve any discrepancies before use of the IP.

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

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

Patients will receive insulated bags with cooling gel packs for use in transporting the IP carton from the site to home.

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

7.6. Treatment Compliance

Study drug compliance will be determined by the following:

- study drug administration data will be recorded by the investigator or patient (self-administration), and reviewed by the investigator at each study visit and

- the patients will be instructed to return any unused study drug and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

Patients who are significantly noncompliant will be permanently discontinued from study medication. A patient will be considered significantly noncompliant if he /she misses 4 or more doses of study medication. Similarly, a patient will be considered significantly noncompliant if they are 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 IP 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 medication, completion of study diaries, the results of home blood glucose 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

Treatment with drugs that are excluded under the entry criteria (Section 6) is not permitted. These medications include traditional Chinese medicines, herbal supplements, systemic glucocorticoids, immunomodulatory drugs, drugs with propensity for dermal reactions, drugs with known liver toxicity, etc.

Patients on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. These medications (refer to Section 6) include antihypertensive agents, aspirin, and lipid-lowering agents.

Apart from those listed earlier, patients should avoid concomitant medication; however, at their discretion, the investigator may administer acetaminophen (1 g, maximum 2 g/day) for treatment of headache, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the patient may be at the discretion of the investigator after consultation with a Lilly clinical pharmacologist, CRP, or clinical research scientist (CRS).

Study site personnel will record any concomitant medications used during the course of the study in the electronic case report form (eCRF).

7.7.1. Management of Patients with Gastrointestinal Symptoms

Patients will be guided on dietary behaviors that may help mitigate symptoms of nausea and vomiting, for example, eating smaller meals, splitting 3 daily meals into 4 or smaller ones, and stopping eating when they feel full. For patients experiencing intolerable persistent GI symptoms, the investigator may consider prescribing symptomatic medication (for example, antiemetic medication).

7.8. Treatment after the End of the Study

Not applicable for this study.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

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

- ALT or AST >8X ULN
- ALT or AST >5X ULN sustained for more than 2 weeks or
- ALT or AST >3X ULN and TBL >2X ULN or international normalized ratio >1.5 or
- 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, a patient will be discontinued from using the IP in case of abnormal pancreatic tests when he or she meets the following condition:

- lipase and/or amylase are confirmed to be ≥3× ULN. Please refer to the algorithm for the monitoring of pancreatic events in Appendix 5.

8.1.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical pharmacologist/CRP and the investigator to determine if the patient may continue in the study. If both agree, it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical pharmacologist/CRP to allow the inadvertently enrolled patient to continue in the study with or without continued treatment with IP.

8.2. Discontinuation from the Study

Patients will be discontinued under the following circumstances:

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

8.3. Patients/Subjects Lost to Follow-up

The investigator will consider a patient lost to follow-up if they repeatedly miss scheduled visits and cannot be contacted by the study site. Site personnel are expected to make diligent attempts to contact patient who miss scheduled visits or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

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

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

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

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

9.1. Efficacy Assessments

The following efficacy measures will be collected at the times shown in the Schedule of Activities.

- Change in HbA1c from baseline to prespecified time points.
- Change in weight from baseline to prespecified time points. Site personnel will measure weight in a consistent manner using a calibrated scale according to the Schedule of Activities (Section 2). Patients will be weighted in light clothing at approximately the same time in the morning before dosing and after an overnight fast and evacuation of the bowels and the bladder, if possible. During the treatment period, weight will be measured twice on each scheduled occasion, with the patient stepping off the scale between measurements. The personnel will record both weight measurements in the source document and the eCRF. Whenever possible, patients will use the same scale for all weight measurements throughout the study.
- Fasting serum glucose level measured in the central laboratory (actual values and change from baseline to predefined time points).
- 7-point SMPG profile (actual values and change from baseline to pre-specified time points). Patients will be asked to perform 7-point SMPG profiles over a 24-hour period, on nonconsecutive days, according to the Schedule of Activities. The 7-point profile consists of pre-meal and 2-hour postprandial SMPG measurements for the morning, midday, and evening meals in 1 day, and at bedtime. Pre-meal measurements should be taken before the patient begins eating the meal. Patients should record their glucose measurements in their patient diaries, which are considered source documents and are to

be returned to the investigator at each study visit. Values from the 7-point SMPG profile will be transferred from the diary and recorded on the eCRF.

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 will record all relevant AE/SAE information in the CRF.

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

Investigators must document their review of each laboratory safety report.

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

After the ICF is signed, study site personnel will record, via 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. Additionally, site personnel will record any change in the condition(s) and the occurrence and nature of any AEs.

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

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

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

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

9.2.1. Serious Adverse Events

An SAE is any AE from this study that results in 1 of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above.

Study site personnel must alert the Lilly CRP/CP, or its designee, of any SAE as soon as practically possible.

Additionally, study site personnel must alert Lilly Global Patient Safety, or its designee, of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed up with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information.

Although all AEs are recorded in the eCRF after signing informed consent, SAE reporting to the sponsor begins after the patient has signed informed consent and has received IP. However, if an SAE occurs after signing informed consent, but prior to receiving IP, AND is considered Reasonably Possibly Related to a study procedure then it MUST be reported.

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator reports as related to IP or procedure. Lilly has procedures that will be followed for the recording and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

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

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

9.3. Treatment of Overdose

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

Refer to the IB for tirzepatide.

9.4. Safety

9.4.1. Laboratory Tests

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

9.4.2. Vital Signs

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

Blood pressure and pulse rate should be measured after approximately 5 minutes in the supine position.

If orthostatic measurements are required, patients should be supine for approximately 5 minutes and stand for at least 2 minutes. If the patient feels unable to stand, personnel will record only the supine vital signs.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If warranted, site personnel may measure additional vital signs during each study period.

Body temperature will be measured as specified in the Schedule of Activities and as clinically indicated (Section 2).

9.4.3. Electrocardiograms

For each patient, 12-lead digital ECGs should be collected according to the Schedule of Activities (Section 2).

Site personnel should report any clinically significant findings from ECGs that result in a diagnosis and occur after the patient receives the first dose of the IP to Lilly, or its designee, as an AE via eCRF.

For each patient, personnel will collect a single 12-lead digital ECG at screening and follow-up or early termination visit according to the Schedule of Activities (Section 2). Electrocardiograms may be obtained at additional times, when deemed clinically necessary. The investigational site should store all ECGs recorded.

Electrocardiograms must be recorded before collecting any blood samples for safety or PK tests. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

At the site, a qualified physician (the investigator or qualified designee) will interpret ECGs as soon as possible. Ideally, ECG interpretation will occur while the patient is still present to determine whether the patient meets entry criteria at the relevant visit(s) and for immediate patient management, should any clinically relevant findings be identified.

If a clinically significant quantitative or qualitative change from baseline is identified (including, but not limited to, changes in QT interval/QT interval corrected for heart rate using Fridericia's formula from baseline) after enrollment, the investigator will assess the patient for symptoms (for example, palpitations, near syncope, syncope) to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document their review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point. Any new clinically relevant finding should be reported as an AE.

9.4.4. Safety Monitoring

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

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

- trends in safety data
- laboratory analytes
- AEs including GI events, hypoglycemia, injection-site reactions, hypersensitivity reactions, and pancreatitis

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

9.4.4.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (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, the investigator should initiate clinical and laboratory monitoring based on consultation with the Lilly clinical pharmacologist, CRP, or CRS. Monitoring should continue until levels normalize and/or are returning to approximate baseline levels.

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

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

9.4.4.2. Pancreatic Safety

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 half 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 ≥3X 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 [p-amylase] and lipase) should be obtained via the local laboratory. Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with investigational product, but will continue in the study on another glucose-lowering regimen (details on rescue intervention will be provided). The most appropriate diabetes therapeutic regimen will be decided by the investigator, based on the patient's clinical status. A review of the patient's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

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

Each patient will have measurements of p-amylase and lipase (assessed at the local 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, b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or p-amylase ≥3X ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the 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. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from patients with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page by study site or Lilly staff. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

9.4.4.3. Hypersensitivity Reactions

The investigator will report all hypersensitivity reactions either as AEs or, if any serious criterion is met, as SAEs. In the event of suspected drug hypersensitivity reactions (immediate or nonimmediate) in subjects who experience moderate to severe injection reactions as assessed by the investigator, unscheduled blood samples will be collected for PK and ADA analyses at the following time points:

- as close as possible to the onset of the event
- at the resolution of the event
- 30 (±3) days following the event.

Additionally, unscheduled serum samples for immune safety laboratory testing (including, but not limited to β tryptase, total immunoglobulin E, complement and cytokine panel testing) should also be collected at approximately 60 to 120 minutes and 4 to 6 weeks after the onset of the event in these subjects. 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.

9.4.4.3.1. Injection-site Reactions

Injection-site assessments for local tolerability will be conducted, when reported as

- an AE from a subject, or
- a clinical observation from an investigator.

Reported injection-site reactions will be characterized within the following categories:

- edema
- erythema
- induration
- itching
- pain

All injection-site reactions reported as AEs will be closely monitored until resolution. The report of a clinically significant AE of injection-site reaction may prompt notification of the sponsor, clinical photography, and referral for dermatologic evaluation and consideration of a skin biopsy and laboratory evaluations (ALT, AST, complete blood count with absolute count for eosinophils, and additional immunogenicity testing). Investigational site staff will be provided with separate instructions/training on how to evaluate injection-site reactions and their severity in a consistent manner. Photographs of injection-site reactions may be taken in a standardized manner for record-keeping purposes; however, the photographs will not be used to evaluate the severity of injection-site reaction.

9.4.4.4. Glucose Monitoring

Site personnel will instruct patients on how to use the glucose meter provided by the site and conduct SMPG tests. In addition to the plasma glucose (PG) monitoring, patients will be educated on the symptoms of hypoglycemia and hyperglycemia. Throughout their participation in the study, patients will monitor PG levels. The site will provide patients with diaries and instructions on how to record PG results whenever the patient experiences symptoms of hypoglycemia, while not in the CRU. The investigator or designee will review PG results clinically indicative of hypoglycemia or hyperglycemia.

Additionally, site personnel will require patients who were taking OAM at screening to monitor their PG in the morning before breakfast during the lead-in period.

9.4.4.4.1. Hyperglycemia and Hypoglycemia Reporting

Episodes of hyperglycemia (fasting plasma/serum glucose >270 mg/dL [15 mmol/L]) or hypoglycemia (plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]) will be reported by the investigator or designated physician who will be responsible for advising the patient on what further actions to take. At their discretion, the investigator may request additional monitoring.

If the fasting plasma/serum glucose during the dosing period exceeds the acceptable level, defined as hyperglycemia on 3 or more separate days during any 2-week period between screening and the end of the dosing period, the patient will be evaluated further at the study site.

If fasting plasma/serum glucose continues to exceed the acceptable level, the investigator will discontinue the IP and initiate treatment with an appropriate antidiabetic agent. The patient will continue to be followed up in the study (for safety, PK, and immunogenicity assessment) for at least 28 days after their last dose. If hyperglycemia occurs during the follow-up period, the patient will remain in the study until completion of the planned follow-up.

Site personnel will record hypoglycemia episodes on specific eCRF pages. The investigator will treat hypoglycemia appropriately and may perform additional monitoring of plasma/serum glucose levels. The following categories of the 2017 American Diabetes Association position statement on glycemic targets (America Diabetes Association 2017) on the basis of recommendations of the International Hypoglycaemia Study Group (International Hypoglycaemia Study Group 2017) should be applied for reporting in the eCRF and evaluation of hypoglycemic events.

The main categories of hypoglycemia are outlined as follows:

Documented Glucose Alert Level (Level 1): plasma/serum glucose ≤70 mg/dL (3.9 mmol/L)

- **Documented symptomatic hypoglycemia:** with typical symptoms of hypoglycemia.
- **Documented asymptomatic hypoglycemia:** without typical symptoms of hypoglycemia.
- **Documented unspecified hypoglycemia:** with no information about symptoms of hypoglycemia available. (This has been called unclassifiable hypoglycemia.)

Documented Clinically Significant Hypoglycemia (Level 2): with similar criterion as above except for the threshold plasma/serum glucose <54 mg/dL (3.0 mmol/L)

- **Level 2 documented symptomatic hypoglycemia**
- **Level 2 documented asymptomatic hypoglycemia**
- **Level 2 documented unspecified hypoglycemia**

Severe Hypoglycemia (Level 3)

- **Severe hypoglycemia (in adults):** Patients had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person required to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma/serum glucose measurements may not be available during such events, but neurological recovery attributable to the restoration of plasma/serum glucose concentration to normal is considered sufficient evidence that the event was induced by a low plasma/serum concentration (plasma/serum glucose ≤70 mg/dL [3.9 mmol/L]).
- **Severe hypoglycemia requiring medical attention:** Severe hypoglycemic events when patients require therapy by health care providers (Emergency Medical Technicians, emergency room personnel, etc.) are of particular interest to payers. Therefore, some

clinical trials may collect data on this subset of severe hypoglycemia episodes, especially if economic outcomes analyses may be based on trial results.

Other Hypoglycemia

- **Nocturnal hypoglycemia:** Any documented hypoglycemic event (including severe hypoglycemia) that occurs at night and presumably during sleep. At Lilly, this is captured as hypoglycemia that occurs between bedtime and waking. This definition is more useful than the commonly used ~midnight to ~6 AM definition, which does not take patients' individual sleep times into consideration and is consistent with the American Diabetes Association recommendations for reporting events that occur during sleep (American Diabetes Association 2005). It is also important to collect the actual time a hypoglycemic event occurred to allow further characterization of hypoglycemia timing (for example, to allow analysis of frequency of events occurring during a 24-hr time period). Nocturnal hypoglycemia may occur at severity Levels 1, 2, or 3.

- **Relative hypoglycemia (also referred to as pseudohypoglycemia [Seaquist et al. 2013]):** An event during which typical symptoms of hypoglycemia occur, that does not require the assistance of another person, and is accompanied by plasma/serum glucose >70 mg/dL (3.9 mmol/L). The plasma/serum glucose value for patients with chronically poor glycemic control can decrease so rapidly that patients may report symptoms of hypoglycemia before their plasma/serum glucose concentration falls below 70 mg/dL (3.9 mmol/L). Events with plasma/serum glucose ≤7 mg/dL should not be categorized as relative hypoglycemia. Evaluation and statistical analysis of this category is optional. However, if a patient reports a relative hypoglycemic event where assistance from another person was received or the patient experienced significant symptoms, the study team should clarify the circumstances to ensure the event is not a severe hypoglycemia event and report it appropriately.

- **Probable symptomatic hypoglycemia:** Symptoms of hypoglycemia were present, but a plasma/serum glucose measurement was not reported.

- **Overall (or total) hypoglycemia:** This optional category combines most cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia). It does not include relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, that event should only be counted once in the category of overall (or total) hypoglycemia.

If a hypoglycemic event meets the criteria of severe, it needs to be recorded as serious in the eCRF (that is, recorded as an SAE). In the case of a hypoglycemic event (other than severe), the actual glucose value, if measured, should be recorded in the eCRF, with any treatments

administered, and not be recorded as an AE. Cases of hypoglycemia may be treated with foods rich in carbohydrates such as fruit, juice, skimmed milk, or energy bars. All episodes of hypoglycemia that are determined by the investigator to constitute severe hypoglycemia according to the definition above should be reported as SAEs.

9.4.4.5. Nausea and Vomiting

Nausea and vomiting events are considered AEs of interest and will be recorded as AEs in the eCRF. For event assessment of severity, duration, and investigator's opinion of relatedness to IP and protocol procedure will be captured.

9.4.4.6. 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 and 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 post randomization calcitonin value is ≥35 ng/L (pg/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 (≥35 pg/mL and increases by ≥50% compared to 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 wash out period. If the confirmed calcitonin value is <35 pg/mL, tirzepatide should be restarted when it is safe to do so.

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3 mL each will be collected to determine the plasma concentrations of tirzepatide. A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between both the investigator and sponsor. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour time period) of each sampling will be recorded.

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

9.5.1. Bioanalysis

A laboratory approved by the sponsor will analyze samples. A facility designated by the sponsor will store samples.

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method. Analyses of samples collected from patient who received placebo are not planned.

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

9.6. Pharmacodynamics

Assessment of tirzepatide pharmacology may include lipid profile (total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol, triglycerides), meal intake and appetite, and immunogenicity assessments. Additional exploratory PD analysis may be analyzed as deemed appropriate.

Blood samples will be obtained for the measurement of PD. The scheduled times for the collection of these samples are as listed in the Schedule of Activities (Section 2). The timing of PD samples is intended to assess pharmacologic effects of tirzepatide. The sampling times may be modified at the discretion of the sponsor, but the total number of the samples or total blood volume will not increase.

The sample(s) will be stored for up to a maximum of 1 year after the last patient visit for the study at a facility selected by the sponsor. The chemistry panel will be destroyed in 60 days and 7-point samples will not be stored.

9.6.1. Lipids

Lipid profile (total cholesterol, high-density lipoprotein, very low-density lipoprotein, and triglycerides), as indicated in the Schedule of Activities (Section 2), will be assayed using validated analytical methods. Instructions for the collection and handling of blood samples for these analyses will be provided by the sponsor.

9.6.2. Meal Intake and Appetite

To explore the effects of tirzepatide on meal intake and appetite sensation, patients will be provided standardized lunch and dinner meals with an approximate total energy and macronutrient contents of 700 kCal and 20% protein, 25% fat, and 55% carbohydrate according to the Schedule of Activities (Section 2). The meal intake will be recorded in the source

document. The subjective rating of appetite sensations is measured using a 100-mm visual analogue scale (VAS) for parameters of hunger, fullness, satiety, and prospective food consumption before and 4 to 5 hours after the standardized lunch and dinner meals. The standardized lunch and dinner meals will be provided at least 4 hours after the previous meal. The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000). The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "extremely" and "not at all." Patients are required to rate their subjective sensations on four 100-mm scales combined with the questions: "How hungry do you feel right now?", "How satisfied do you feel right now?", "How full do you feel right now?", and "How much food do you think you could eat right now?" A staff member will use a caliper to measure the distance from 0 to the mark that the patient placed on the VAS and record the measurement in the source document. Overall appetite score is calculated as the average of the 4 individual scores—satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4 (van Can et al. 2014). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

9.6.3. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples will be collected to determine antidrug antibody (ADA) production against the tirzepatide. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time point to determine the plasma concentrations of tirzepatide. All samples for immunogenicity should be taken predose when applicable and possible. All patients will have an ADA sample measured at early discontinuation or at the follow-up visit (Day 141 for Cohort 1 and Day 197 for Cohort 2) approximately 5 weeks after the last dose of tirzepatide. Follow-up visit will assess immunogenicity at washout of tirzepatide (5 half-lives at the end of treatment).

In the event of a drug hypersensitivity reaction, see Section 9.4.4.3 for instructions of collection and handling of blood samples.

Immunogenicity will be assessed using a validated assay designed to detect and titer ADA in the presence of tirzepatide at a laboratory approved by the sponsor. Samples with detected ADA will be tested for cross-reactive binding to native GIP and GLP-1. Antibodies may be further evaluated for their ability to neutralize the activity of tirzepatide. In vivo laboratory indicators for glycemic control (fasting blood glucose and HbA1c), effect on weight loss, and PK will be utilized to detect potential neutralizing effect of ADA against tirzepatide.

Treatment-emergent (TE) ADAs are defined in Section 10.3.5.

Antidrug antibody samples will be stored as per local regulation/EC requirements. Samples will be immediately destroyed once tirzepatide is launched or there is no further request on testing the samples from China authority.

9.7. Genetics

A 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 exposure or 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 investigative site personnel.

Samples will be retained for a maximum of 15 years after the last patient visit, or for a shorter period if local regulations and/or ERBs impose shorter time limits, for the study at a facility selected by Lilly. 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 is 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, multiplex assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

9.8. Biomarkers

This section is not applicable for this study.

9.9. Health Economics

This section is not applicable for this study.

10. Statistical Considerations and Data Analysis

10.1. Sample Size Determination

The sample size for the study was chosen to provide sufficient data to evaluate the primary objective of this study and is not intended to achieve any priori statistical requirements.

Approximately 24 Chinese patients with T2DM may be enrolled so that approximately 16 patients complete the study with compliant defined dosing regimen. Patients will be administered either 16 (Cohort 1) or 24 (Cohort 2) weekly SC doses of tirzepatide or placebo in a ratio of 10 tirzepatide:2 placebo for both cohorts.

Replacement of discontinued patients is not planned because the sample size is determined considering the expected drop-out rate.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

All patients who discontinue from the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given.

10.2.2. Study Participant Characteristics

The patient's age, sex, weight, height, or other demographic characteristics will be recorded and may be used in the PK, PD, efficacy, and safety analyses as quantitative or classification variables.

10.3. Statistical Analyses

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

Pharmacokinetics, PD, and efficacy analyses will be conducted on data from all patients who receive at least 1 dose of the IP and have evaluable PK, PD, and efficacy data.

Patients who received placebo within each cohort of the study will be pooled for PD, efficacy, and safety analyses.

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

Additional exploratory analyses of the data will be conducted as deemed appropriate. Statistical analyses will be fully detailed in the statistical analysis plan.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

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

The incidence of symptoms for each treatment will be presented by severity and by association with IP as perceived by the investigator. Symptoms reported to occur before the first IP dosing will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

The number of IP-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety laboratory parameters, vital signs, ECG parameters, injection-site reactions, and hypoglycemia. The parameters will be listed and summarized using standard descriptive statistics. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Efficacy Analyses

The efficacy of tirzepatide to reduce glucose and weight will be assessed. Efficacy measures that will be assessed include HbA1c, body weight, fasting PG, and 7p-SMPG. All parameters will be listed and summarized using standard descriptive statistics. Further analysis may be performed.

The individual observed and mean time profile of the postdose efficacy parameters will be plotted by treatment group.

10.3.3. Pharmacokinetic Analyses

10.3.3.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for tirzepatide will be calculated using standard noncompartmental methods of analysis.

The primary parameters for analysis will be maximum drug concentration (C_{max}), area under the concentration-time curve (AUC), and time to C_{max} (T_{max}) of tirzepatide. Other

noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported. Model-based analysis may be performed combined with data from other studies.

10.3.3.2. Pharmacokinetic Statistical Inference

Pharmacokinetic parameters will be summarized using descriptive statistics by dosing regimen. The mean concentration-time profiles in linear and semilog scales for each tirzepatide-treated group will be presented.

10.3.4. Evaluation of Pharmacodynamics

Pharmacodynamic parameters that will be assessed include lipids and subjective appetite sensation (VAS). The parameters will be listed and summarized using standard descriptive statistics.

10.3.5. Evaluation of Immunogenicity

The frequency and percentage of subjects/patients with preexisting ADA and with TE ADA to tirzepatide will be tabulated. Treatment-emergent ADA 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 ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). For the TE ADA patients, the distribution of maximum titers will be described. The frequency of neutralizing antibodies to tirzepatide and/or cross-reactive to endogenous counterparts may be tabulated in TE ADA patients.

The relationship between the presence of antibodies, antibody titers, and clinical parameters (for example, AEs) may be assessed. Likewise, the relationship between antibody titers, PK parameters, and PD response to tirzepatide may be assessed.

10.3.6. Interim Analyses

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

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	antidrug antibody
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
blinding	A procedure in which 1 or more parties to the study are kept unaware of the treatment assignment(s). Unless otherwise specified, blinding will remain in effect until final database lock. A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
Cmax	Maximum observed drug concentration
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all the study-related requirements, good clinical practice (GCP) requirements, and the applicable regulatory requirements.
confirmation	A process used to confirm that laboratory test results meet the quality requirements defined by the laboratory generating the data and that Lilly is confident that results are accurate. Confirmation will either occur immediately after initial testing or will require that samples be held to be re-tested at some defined time point, depending on the steps required to obtain confirmed results.

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician, or other medical officer.
CRS	clinical research scientist
CRU	clinical research unit
CT	computed tomography
DPP	dipeptidyl peptidase
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the study are those who have been assigned to a treatment.
enter	Patients entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FSH	follicle-stimulating hormone
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus

IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
informed consent	A process by which a patient voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the patient's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
investigational product (IP)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical study, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
investigator	A person responsible for the conduct of the clinical study at a study site. If a study is conducted by a team of individuals at a study site, the investigator is the responsible leader of the team and may be called the principal investigator.
IWRS	interactive web-response system
legal representative	An individual or judicial or other body authorized under applicable law to consent, on behalf of a prospective patient, to the patient's participation in the clinical study.
MAD	multiple-ascending dose
MEN-2	multiple endocrine neoplasia syndrome type 2
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
OAM	oral antidiabetic medication
PA	posterior anterior
PG	plasma glucose
PK/PD	pharmacokinetic(s)/pharmacodynamic(s)

QW	once weekly
RA	receptor agonist
randomize	the process of assigning subjects/patients to an experimental group on a random basis
SAE	serious adverse event
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SDP	single-dose pen
SMPG	self-monitored plasma glucose
SUSAR	suspected unexpected serious adverse reaction
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE	treatment emergent
Tmax	time to maximum drug concentration
ULN	upper limit of normal
VAS	visual analogue scale

Appendix 2. Clinical Laboratory Tests

Safety Laboratory Tests

Hematology[a]
- Hematocrit
- Hemoglobin
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin
- Mean cell hemoglobin concentration
- Leucocytes (WBC)
- Platelets

Differential WBC absolute counts of:
- Neutrophils
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils

Urinalysis[a]
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Bilirubin
- Urobilinogen
- Blood
- Leucocytes
- Microscopy[c]

Lipid Panel[d,e]
- HDL-C
- LDL-C (calculated)
- Total cholesterol
- Triglycerides

Serology[a,b]
- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody and/or HIV antigen

Clinical Chemistry (Fasting)[a]
- Sodium
- Potassium
- Chloride
- Creatinine
- Calcium
- Phosphorus
- Glucose
- Blood urea nitrogen
- Uric acid
- Total protein
- Albumin
- Total bilirubin
- Alkaline phosphatase (ALP)
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Lipase
- Amylase
- eGFR[b]

Other Tests
- Pregnancy test (urine, serum)[a,c]
- Follicle-stimulating hormone[a,b,c]
- Fasting blood glucose[d]
- Urine drug and alcohol screen[a]
- Hemoglobin A1c[d]
- Pharmacogenetic sample (storage)[b,d,e,]
- Calcitonin[f]
- Tirzepatide plasma levels[d,e,f]
- Immunogenicity[e,f]

Abbreviations: eGFR = estimated glomerular filtration ratio; HDL-C = high-density lipoprotein cholesterol; HIV = human immunodeficiency virus; LDL-C = low-density lipoprotein cholesterol; RBC = red blood cell; WBC = white blood cell.

a Performed at local laboratories.
b Performed at screening only.
c If clinically indicated, per investigator's discretion.
d Performed at a central laboratory.
e These results will not be reported to study sites.
f Assayed at Lilly-designated laboratory.

Appendix 3. Study Governance, Regulatory, and Ethical Considerations

Informed Consent

The investigator is responsible for

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

Recruitment

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

Ethical Review

The investigator must give assurance that the 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 study site(s). Lilly or its representatives must approve the ICF before it is used at the study 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 current IB and updates during the course of the study
- ICF
- relevant curricula vitae

Regulatory Considerations

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

1) consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki and Council for International Organisations of Medical Sciences International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulation

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

Protocol Signatures

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

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

Final Report Signature

The investigator with the most enrolled patients will serve as the final report coordinating investigator. If this investigator is unable to fulfill this function, another investigator will be chosen by Lilly to serve as the final report coordinating investigator.

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

Data Quality Assurance

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

- provide instructional material to the study sites, as appropriate.
- provide training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the case report forms, and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.

- review and evaluate CRF data and/or use standard computer edits to detect errors in data collection.
- conduct a quality review of the database.

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

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

Data Collection Tools/Source Data

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

Data Protection

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

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

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 4. Hepatic Monitoring Tests for Treatment-Emergent Abnormality

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with patients in consultation with Lilly clinical pharmacologist, CRP, or CRS.

Hepatic Monitoring Tests

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

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 5. Blood Sampling Summary

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

Protocol I8F-MC-GPHT Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples		Total Volume (mL)	
		Cohort 1	Cohort 2	Cohort 1	Cohort 2
Screening serology and serum pregnancy tests[a]	9[b]	1	1	9	9
Clinical safety laboratory tests[a]	10[b]	12	13	120	130
Lipid panel	2.5	6	8	15	20
Pancreatic enzyme	3	9	10	27	30
Calcitonin	2.5	3	3	7.5	7.5
Tirzepatide pharmacokinetics	3	24	26	72	78
Potential additional tirzepatide pharmacokinetic samples	3	3	3	9	9
Fasting blood glucose	4.5	6	8	27	36
HbA1c	2	6	8	12	16
Immunogenicity	10	6	6	60	60
Pharmacogenetics	10	1	1	10	10
Total				369[c]	406[c]

Abbreviation: HbA1c = hemoglobin A1c.

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

[b] Because screening and safety (chemistry and hematology) tests are performed at local laboratories at each site, this volume is an estimate and will vary depending on the local laboratory's testing requirements.

[c] The maximum blood volume will increase if follow-up visits for antidrug antibody testing are needed.

Appendix 6. Protocol Amendment I8F-MC-GPHT(b) Summary - A Multiple Dose Titration Study in Chinese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Tirzepatide

Overview

Protocol I8F-MC-GPHT, A Multiple Dose Titration Study in Chinese Patients with Type 2 Diabetes Mellitus to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics, and Efficacy of Tirzepatide, has been amended. The new protocol is indicated by Amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

This amendment is not considered a substantial protocol amendment.

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

- Single-site has been removed from the study design because more than one site may be used for screening and enrollment in this study.
- The appendix referenced in Section 9.4.4.1 Hepatic Safety has been corrected to Appendix 4.

Revised Protocol Sections

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

1. Protocol Synopsis

Summary of Study Design:

Study GPHT is a Phase 1, ~~single-site,~~ randomized, placebo-controlled, multiple dose titration study in Chinese patients with T2DM.

5.1 Overall Design

Study GPHT is a Phase 1, ~~single-site,~~ patient- and investigator-blind, placebo-controlled, randomized, multiple dose titration study in Chinese patients with T2DM.

9.4.4.1. Hepatic Safety

If a study patient experiences elevated ALT ≥3X ULN, ALP ≥2X ULN, or elevated TBL ≥2X ULN, liver tests (Appendix ~~5~~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.

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