H9X-MC-GBGM Protocol

Relative Bioavailability of an Investigational Single Dose of Dulaglutide after Subcutaneous Administration by a Single Dose Pen Compared to a Prefilled Syringe in Healthy Subjects

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Dulaglutide (LY2189265)

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Clinical Pharmacology Protocol Electronically Signed and Approved by Lilly on date provided below.

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1. Protocol Synopsis

Title of Study:
Relative Bioavailability of an Investigational Single Dose of Dulaglutide after Subcutaneous Administration by a Single Dose Pen Compared to a Prefilled Syringe in Healthy Subjects

Rationale: The current commercially used single dose pen (SDP) at the same injection volume (0.5 mL) and a new higher dulaglutide concentration formulation will be used for dose delivery in future Phase 3 studies evaluating investigational dulaglutide doses that are higher than the currently approved 0.75- and 1.5-mg doses.

Study GBGM will evaluate the relative bioavailability of a 4.5-mg dulaglutide dose administered subcutaneously (SC) as a single SDP injection of the higher dulaglutide concentration (test) compared to the same dose administered as three 1.5-mg prefilled syringe (PFS) injections of the current commercial formulation (reference).

Objectives/Endpoints:

Objectives	Endpoints
Primary To evaluate the relative bioavailability of a single dose of dulaglutide administered SC to healthy subjects as a single injection by SDP (test) compared to 3 injections by PFS (reference).	Pharmacokinetic parameters including area under the concentration versus time curve (AUC) and maximum observed drug concentration (C_{max}) for dulaglutide administered by a SDP compared to PFS.
Secondary To assess the tolerability of a single dose of dulaglutide administered SC to healthy subjects as a single injection by SDP compared to 3 injections by PFS.	Incidence of treatment-emergent adverse events (AEs).

Summary of Study Design:
Study H9X-MC-GBGM is a Phase 1, single-center, open-label, randomized, 2-period, crossover study in healthy subjects to evaluate the relative bioavailability of 4.5 mg dulaglutide administered SC as a single injection by SDP (test) compared to 3 injections by PFS (reference).

Treatment Arms and Planned Duration for an Individual Subject:
Subjects will undergo a screening examination within 27 days prior to enrollment. For Periods 1 and 2, on the morning of Day 1 of each period, subjects will receive a single SC dose of dulaglutide administered according to their assigned treatment sequence following an overnight fast of approximately 8 hours. At a minimum, subjects will remain at the clinical research unit (CRU) until collection of the 168-hour (Day 8) pharmacokinetic (PK) sample. There will be a washout period of at least 28 days between doses in Periods 1 and 2. Each subject will be required to return to the CRU for a follow-up visit 28±3 days after the last dulaglutide dose. The total duration for each subject (from screening through the follow-up visit) is approximately 84 days.

Number of Subjects:
Approximately 24 subjects will be enrolled in order that at least 18 subjects complete the study.

Statistical Analysis:

Pharmacokinetic: The primary PK parameters to be estimated for dulaglutide will be C_{max} and AUC from time zero to infinity (AUC[0-∞]). Other noncompartmental parameters, such as AUC from time zero to 168 hours (AUC[0-168h]), AUC from time zero to 336 hours (AUC[0-336h]), time to C_{max} (t_{max}), apparent terminal elimination half-life, apparent total body clearance of drug, apparent volume of distribution, and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), may be reported.

The PK parameter estimates will be evaluated to determine the relative bioavailability of dulaglutide administered SC by SDP (test) compared to dulaglutide administered by PFS (reference). The PK parameters will be summarized using descriptive statistics by treatment. Log-transformed C_{max} and AUC(0-∞) (primary parameters) and AUC(0-168h) and AUC(0-336h) (secondary parameters) will be evaluated in a linear mixed-effects analysis of variance model with fixed effects for treatment (SDP or PFS), period, and sequence and a random effect for subject within sequence. The ratios of least squares geometric means of SDP compared to PFS, as well as the corresponding 90% confidence intervals (CIs), will be estimated and reported. The t_{max} will be analyzed nonparametrically using the Wilcoxon ranked sum test. Estimates of the median difference and the corresponding 90% CIs will be calculated. Additional analysis may be conducted if deemed appropriate.

Safety: All investigational product and protocol procedure 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 investigational product as perceived by the investigator. Symptoms reported to occur prior to enrollment 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 regulatory dictionary. The number of investigational product-related serious AEs will be reported. Safety parameters that will be assessed include safety clinical laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. The change from baseline (Day 1 predose of each period) in vital signs will be analyzed and summarized. The change from baseline (Day -1 of each period) in amylase and lipase will also be summarized. Electrocardiograms and physical examinations will be performed for safety monitoring purposes and will not be presented. Additional analysis will be performed if warranted upon review of the data.

2. Schedule of Activities

Study Schedule Protocol H9X-MC-GBGM

Procedure	Screening	Periods 1 and 2										ET/Follow-up	Comments
	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 15	28 ±3 days after last dulaglutide dose	
Informed Consent	X												
Subject Admission to CRU		X											
Subject Discharge from CRU										X			
Outpatient Visit	X										X	X	
Investigational Product Administration			X										There is a minimum of 28 days washout period between doses for Period 1 and Period 2.
Medical History	X												
Height	X												
Weight	X	X									X	X	
Vital Signs (supine) (hours)	X	X	Predose	24	48							X	Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator.
Clinical Laboratory Tests	X	X									X	X	See Appendix 2, Clinical Laboratory Tests, for details.
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	
Injection Site Reaction Assessment (hours)			Predose, 0, 6, 12	24		X				X	X	X	0-hour assessment should be performed within 5 minutes after subcutaneous injection. Additional assessments may be performed if deemed necessary by the investigator.
PK Samples (hours)			Predose	24	48	72	96	120	144	168	336	X	Sampling times are relative to the time of study treatment administration (0 hour). Sampling times are given as targets to be achieved within reasonable limits. If a subject withdraws from the study prior to completion of scheduled PK sampling for a given period, every effort will be taken to draw an unscheduled blood sample for PK assessment. This will not be required if a sample has already been taken within the previous 24 hours. For ET, a PK sample can be taken at any time during the visit timed close to the immunogenicity sample.

	Screening	Periods 1 and 2										ET/Follow-up	Comments
Procedure	Days -28 to -2	Day -1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 15	28 ±3 days after last dulaglutide dose	
Pregnancy Test	X	X										X	Females only. Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed for women of childbearing potential at Day -1 for each period and at ET/Follow-up.
Physical Exam	X	X										X	After screening, medical assessment only performed to include medical review and targeted examination, as appropriate.
12-lead ECG	X											X	Single 12-lead ECG will be collected. ECGs must be recorded before collecting any blood samples. Subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection.
Genetic Sample			X										Single sample for pharmacogenetic analysis taken prior to dosing on Day 1 in Period 1 only.
Immunogenicity Samples			Predose									X	All samples for immunogenicity should be taken predose, when applicable and possible.

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ET = early termination; PK = pharmacokinetic(s).

Note: If multiple procedures take place at the same time point, the following order of the procedures should be used: ECG, vital signs, and venipuncture.

3. Introduction

3.1. Study Rationale

Presently there is an ongoing Phase 2 study (Protocol H9X-MC-GBGJ / Double-Blind, Placebo-Controlled, 18-Week Trial of Investigational Dulaglutide Doses versus Placebo in Patients with Type 2 Diabetes on Metformin Monotherapy) designed to provide initial safety and efficacy data for 2 investigational dulaglutide doses (3.0 mg and 4.5 mg) that are higher than the currently approved 0.75- and 1.5-mg doses; these higher doses could provide data that show improved clinical benefits, including greater reduction in hemoglobin A1c (HbA1c) and greater body weight reduction, with an acceptable safety profile. Prefilled syringes (PFSs) are being used to administer dulaglutide doses in this Phase 2 study.

To confirm applicability of the GBGJ safety and efficacy data to future Phase 3 studies where a single dose pen (SDP) and new formulation (Table GBGM.2) will be used, Study GBGM will evaluate the relative bioavailability of a 4.5-mg dulaglutide dose administered subcutaneously (SC) as a single SDP injection of the new higher dulaglutide concentration (test) compared to the same dose administered as three 1.5-mg PFS injections of the current commercial formulation (reference). Details regarding the new formulation are presented in Module 3 of the CTA.

3.2. Background

Dulaglutide exhibits glucagon-like peptide-1 (GLP-1) mediated effects, including glucose-dependent potentiation of insulin secretion, inhibition of glucagon secretion, delay of gastric emptying, and weight loss. Preclinical and clinical experience to date support the use of dulaglutide as a once-weekly injection to improve glycemic control in patients with type 2 diabetes (T2D).

Dulaglutide received regulatory approval for the treatment of T2D in the United States on 18 September 2014, and in the European Union on 21 November 2014 for use as 0.75- and 1.5-mg doses administered by SDP or PFS (Trulicity® United States Prescribing Information [USPI] 2017; Trulicity® Summary of Product Characteristics [SmPC] 2016).

3.3. Benefit/Risk Assessment

The proposed dose of dulaglutide to be used in this study is 4.5 mg.

Dulaglutide is currently approved for use as 0.75- and 1.5-mg doses. A higher dulaglutide dose of 4.5 mg in healthy subjects was chosen for this study (GBGM) based on simulations which included data collected in Studies GBCD and GBCF (Barrington et al. 2011, Skrivanek et al. 2014).

Study GBCD was a multiple ascending dose study where dulaglutide doses up to 8 mg were administered weekly for 5 weeks to patients with T2D. GLP-1-related gastrointestinal effects (nausea, vomiting, and diarrhea) were of mild to moderate in intensity over the dose range of 1 to 8 mg; therefore, the 8-mg dose was considered to be a tolerable dose. Robust glucodynamic activity consistent with sustained GLP-1 pharmacology was observed over the dose range 0.3 to 8 mg dulaglutide. Reductions in fasting and postprandial glucose, and glucose-dependent insulin

secretion were demonstrated after 5 weeks of once-weekly SC dulaglutide administration. Study GBCF was a Phase 2/3 study in patients with T2D in which dulaglutide doses up to 3 mg were administered weekly, with a limited number of patients at the highest dose of 3 mg. The benefit/risk profile favored the 1.5-mg dulaglutide dose for further development based on a predefined clinical utility index.

The results of simulations including data from Studies GBCD and GBCF suggest the 4.5-mg dose may provide a clinically relevant improvement in Hb1Ac and body weight reduction in comparison to the 1.5-mg dose after 26 weeks.

Nonclinical studies and clinical studies in healthy subjects and in patients with T2D support that dulaglutide may be safely administered to humans with careful monitoring for potential adverse effects. Dulaglutide-related changes in both rat and monkey chronic repeat-dose toxicity studies (6 months duration in rats; 9 months duration in monkeys) were generally consistent with, or secondary to, GLP-1 pharmacology. The primary effects of dulaglutide administration to rats and monkeys were dose dependent decreases in food consumption with secondary decreases in body weight gain. None of these effects were adverse to the health of the animals. No dose-limiting target organ toxicity occurred in either species. The no-observed-adverse-effect levels (NOAELs) for target organ toxicity in chronic repeat-dose toxicity studies of dulaglutide in rats (6 months) and monkeys (9 months) were 16.3 mg/kg and 8.15 mg/kg, respectively. Relative to the maximum human dose in Study GBGJ (4.5 mg/week), the predicted area under the concentration versus time curve (AUC) exposure multiples at the NOAELs in rats and monkeys are 55- and 162-fold, respectively. Similar to other GLP-1R agonists, fetal skeletal effects were observed in the embryo-fetal development studies of dulaglutide in pregnant rats and rabbits. The fetal skeletal effects occurred at 15- and 4-fold the 4.5-mg/week dulaglutide dose in pregnant rats and rabbits, respectively, based on AUC.

There is no anticipated therapeutic benefit for the subjects in this study.

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

In addition, detailed information about the known and expected benefits and risks of dulaglutide may be found in the Trulicity USPI (2017) and SmPC (2016).

4. Objectives and Endpoints

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

Table GBGM.1. Objectives and Endpoints

Objectives	Endpoints
Primary To evaluate the relative bioavailability of a single dose of dulaglutide administered subcutaneously (SC) to healthy subjects as a single injection by single dose pen (SDP; test) compared to 3 injections by prefilled syringe (PFS; reference).	Pharmacokinetic parameters AUC and maximum observed drug concentration (C_{max}) for dulaglutide administered by a SDP compared to PFS.
Secondary To assess the tolerability of a single dose of dulaglutide administered SC to healthy subjects as a single injection by SDP compared to 3 injections by PFS.	Incidence of treatment-emergent adverse events.

5. Study Design

5.1. Overall Design

Study GBGM is a Phase 1, single-center, open-label, randomized, 2-period, crossover study in healthy subjects to evaluate the relative bioavailability of 4.5 mg of a new formulation (Table GBGM.2) of dulaglutide administered SC as a single injection by SDP (test) compared to 3 injections by PFS (reference). Treatment sequences and randomization are described in Section 7.2.

Each subject will provide informed consent for study participation and will undergo a screening examination within 27 days prior to enrollment.

In each treatment period, subjects will be admitted to the clinical research unit (CRU) on Day -1. On the morning of Day 1, following an overnight fast of approximately 8 hours, subjects will receive a single SC dose of dulaglutide administered according to their assigned treatment sequence. Blood samples will be collected predose and up to 336 hours postdose to measure dulaglutide concentrations. At a minimum, subjects will remain at the CRU until collection of the 168-hour (Day 8) pharmacokinetic (PK) sample in each period.

There will be a washout period of at least 28 days between doses in Periods 1 and 2. Each subject will be required to return to the CRU for a follow-up visit 28 ±3 days after the last dulaglutide dose. The total duration for each subject (from screening through the follow-up visit) is approximately 84 days.

Safety and tolerability will be assessed throughout the study by means of vital sign measurement, physical examination, clinical laboratory tests, electrocardiograms (ECGs), and AE recording.

Study governance considerations are described in detail in Appendix 3.

5.2. Number of Participants

Approximately 24 subjects may be enrolled so that at least 18 evaluable subjects complete the study. For purposes of this study, a subject 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) for the last subject.

5.4. Scientific Rationale for Study Design

Conducting this study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications in patients.

An open-label design is required, as subjects and staff administering the injections will be able to distinguish between the SDP and PFS, including number of injections. In order to minimize any potential period-effect, a randomized, 2-sequence, crossover design has been selected. Based on the apparent terminal elimination half-life ($t_{1/2}$) of dulaglutide of approximately 5 days

(Trulicity® USPI 2017), a washout period of at least 28 days between doses is considered sufficient not to impact the PK outcome of the second period.

Pharmacokinetic sampling up to 336 hours is sufficient to generate an evaluable PK profile for dulaglutide. A single dose of dulaglutide will be administered in each period, as this is considered sufficient to evaluate the relative bioavailability of dulaglutide administered via the 2 devices (SDP versus PFS).

5.5. Justification for Dose

The dose selected for this study (4.5 mg) is the highest dose for the Phase 2 study (GBGJ). Based on PK/pharmacodynamic model projections, doses higher than the currently approved 0.75- and 1.5-mg doses that are included in Study GBGJ were identified based on their potential to yield greater HbA1c reductions and weight loss, with an acceptable safety and tolerability profile. Based on predicted plasma exposures in patients with T2D receiving the highest investigational dulaglutide dose of 4.5 mg, the margins of safety (i.e., plasma exposure multiples at the NOAEL) in chronic toxicology studies in monkeys and rats were 162-fold and 55-fold, respectively. Additional details are provided in Section 3.3.

Dulaglutide is approved for SC administration by SDP or PFS (Trulicity® USPI 2017; previously demonstrated to be bioequivalent). Therefore, this study will compare the PK of 2 formulations of dulaglutide administered by these 2 devices. Safety and efficacy data using the commercial formulation and device will also be obtained in the planned Phase 3 trial (Study GBGL).

6. Study Population

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

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 27 days prior to enrollment. Subjects who are not enrolled within 27 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, are not permitted.

6.1. Inclusion Criteria

Subjects are eligible for inclusion in the study only if they meet all of the following criteria at screening and/or enrollment:

[1] are overtly healthy males or females, as determined by medical history and physical examination

[1a] male subjects:

i. Men with partners of childbearing potential, for the duration of the study and for 120 days after the last dose of study drug, will either remain abstinent (if this is their preferred and usual lifestyle) or use at least 1 highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or an effective method of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges). The subject may choose to use a barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.)

ii. Men should refrain from sperm donation for the duration of the study and for 120 days after the last dose of study drug

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

[1b] female subjects:

i. Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males

ii. Otherwise, women of childbearing potential participating must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of 2 effective methods of contraception for the entirety of the study

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

   b. Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double barrier method is not considered acceptable due to the high failure rate when these methods are combined

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

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

   b. post-menopausal – defined as

      i. A woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had either

         1. cessation of menses for at least 1 year, or

         2. at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone >40 mIU/mL; or

ii. A woman 55 years or older not on hormone therapy, who has had at least 6 months of spontaneous amenorrhea; or

iii. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy

[2] are at least 18 years old

[3] have a body mass index (BMI) $\geq$23 kg/m^2

[4] have clinical laboratory test results within normal reference range for the population or investigative site, or results with acceptable deviations that are judged to be not clinically significant by the investigator

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

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

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

6.2. Exclusion Criteria

Subjects will be excluded from study enrollment if they meet any of the following criteria at screening and/or enrollment:

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

[9] are Lilly employees or are employees of a third-party involved in the study who require exclusion of their employees

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

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

[12] have previously completed or withdrawn from this study or any other study investigating dulaglutide within 3 months prior to screening

[13] have known allergies to GLP-1-related compounds including dulaglutide, any components of the formulation, or history of significant atopy

[14] have an abnormality in the 12-lead ECG that, in the opinion of the investigator, increases the risks associated with participating in the study

[15] have an abnormal blood pressure and/or pulse rate as determined by the investigator

[16] have a history or presence of cardiovascular, respiratory, hepatic, renal, endocrine, hematological, or neurological disorders capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data

[17] have a history or presence of pancreatitis (history of chronic pancreatitis or idiopathic acute pancreatitis) or gastrointestinal disorder (e.g., relevant esophageal reflux or gall bladder disease) or any gastrointestinal disease which impacts gastric emptying (e.g., gastric bypass surgery, pyloric stenosis, with the exception of appendectomy) or could be aggravated by GLP-1 analogs. Subjects with dyslipidemia and subjects who 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 screening physician

[18] have family history of medullary thyroid cancer (MTC) or a genetic condition that predisposes to MTC

[19] have known or ongoing psychiatric disorders considered clinically significant in the opinion of the investigator

[20] regularly use known drugs of abuse and/or show positive findings on drug screening

[21] show evidence of human immunodeficiency virus (HIV) infection and/or positive HIV antibodies

[22] show evidence of hepatitis C and/or positive hepatitis C antibody

[23] show evidence of hepatitis B and/or positive hepatitis B surface antigen

[24] are women who are pregnant or lactating

[25] have donated blood of more than 500 mL within 4 weeks prior to screening

[26] have used or intend to use over-the-counter medication other than acetaminophen within 7 days prior to dosing or prescription medication (with the exception of vitamin/mineral supplements and/or hormone replacement therapy [HRT]) within 14 days prior to dosing

[27] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) or 14 units per week (males over 65 and females), are unwilling to stop alcohol consumption from at least 48 hours prior to Check-in (Day -1) until discharge from the CRU in each period, or are unwilling to limit intake to a maximum of 2 units per day on all other days from screening through follow-up

(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)

[28] smoke more than 10 cigarettes (or equivalent in nicotine) per day, and are unwilling to refrain from smoking on the day of dulaglutide administration or are unable to abide by CRU restrictions

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

6.2.1. Rationale for Exclusion of Certain Study Candidates

Criteria [8] and [9] prevent conflict of interest in study participants. Criteria [10] through [29] exclude medical conditions, medication intolerance, concomitant medication use, and other items that may confound the assessment of study endpoints.

6.3. Lifestyle and/or Dietary Requirements

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

6.3.1. Meals and Dietary Restrictions

Prior to dulaglutide dosing (Day 1 of Periods 1 and 2), subjects will be fasted for approximately 8 hours and a standard breakfast will be provided approximately 15 minutes after dosing.

6.3.2. Caffeine, Alcohol, and Tobacco

No alcohol will be allowed from at least 48 hours prior to admission (Day -1) until discharge, and alcohol intake will be limited to a maximum of 2 units/day on all other days from screening through the follow-up visit (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).

Subjects will be questioned about their smoking habits at screening. Smoking will not be permitted on dosing days and subjects will abide by CRU restrictions.

6.3.3. Activity

Subjects should not undertake unaccustomed vigorous or prolonged exercise from screening through the post study follow-up visit.

6.4. Screen Failures

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

7. Treatment

7.1. Treatment Administered

On Day 1 of each period, subjects will receive a single dose of 4.5 mg dulaglutide administered SC as a single SDP injection or as 3 injections by PFS according to the randomization schedule. There will be a minimum 28-day washout period between doses. Table GBGM.2 shows the treatment regimens.

Doses will be administered into the SC tissue of the abdominal wall. A separate Instructions for Use document will be provided by Lilly. Where possible, the same member of staff should administer the injections to all subjects. Prior to dulaglutide dosing, subjects will be fasted for approximately 8 hours and a standard breakfast will be provided approximately 15 minutes after dosing.

Table GBGM.2. Treatments Administered

Treatment Name	LY2189265	LY2189265
Formulation and Presentation	Solution in a prefilled syringe	Solution in a single dose pen[a]
Dose	3 x 1.5 mg (4.5 mg total dose)	1 x 4.5 mg (4.5 mg total dose)
Concentration	3.0 mg/mL	9.0 mg/mL
Volume per Injection	0.5 mL	0.5 mL
Number of Injections	3	1
Dosing Instructions	SC injection in abdomen	SC injection in abdomen

Abbreviations: SC = subcutaneous.

[a] Increased polysorbate 80 content to accommodate higher dulaglutide content.

The investigator or designee is responsible for:

- explaining the correct use of the investigational product(s) to the site personnel
- verifying that instructions are followed properly
- maintaining accurate records of investigational product dispensing and collection
- returning all unused medication to Lilly or its designee at the end of the study

Note: In some cases, sites may destroy the material if, during the investigative site selection, the evaluator has verified and documented that the site has appropriate facilities and written procedures to dispose of clinical materials.

7.1.1. Packaging and Labeling

Dulaglutide will be supplied by Lilly as a 3.0-mg/mL solution in PFS (Trulicity® USPI 2017) and as a 9.0-mg/mL solution in SDP. Both the PFS and the SDP should be stored refrigerated (2°C to 8°C) and allowed to warm to room temperature for at least 30 minutes (up to 24 hours) prior to use.

The investigational product will be labeled according to the country's regulatory requirements.

7.1.2. Drug Delivery Devices

The manufactured medical devices provided for use in the study include a PFS containing 1.5 mg dulaglutide (0.5 mL at 3.0 mg/mL) and a SDP containing 4.5 mg dulaglutide (0.5 mL at 9.0 mg/mL).

The medical devices will be labeled according to the country's regulatory requirements.

7.2. Method of Treatment Assignment

Eligible subjects will be randomized to 1 of the 2 treatment sequences (Table GBGM.3). Randomization tables will be prepared by the statistician or designee for the study and provided to the site pharmacists involved in dose preparation. The allocation and dispensing of the investigational product will be fully documented and verified by a second person. Detailed records of the amounts of the investigational product received, dispensed, and remaining at the end of the study will be maintained by the site pharmacist.

Approximately the same number of subjects will be randomized to each treatment sequence.

Table GBGM.3. Treatment Sequences

Treatment Sequence	Period 1	Period 2
1	Prefilled Syringe	Single Dose Pen
2	Single Dose Pen	Prefilled Syringe

7.2.1. Selection and Timing of Doses

The doses will be administered according to the randomization schedule at approximately the same times on each day. The actual time of all dose administrations will be recorded in the subject's electronic case report form (eCRF).

Prior to dulaglutide dosing, subjects will be fasted for approximately 8 hours and a standard breakfast will be provided approximately 15 minutes after dosing.

7.3. Blinding

This is an open-label study due to the objective nature of the PK data and the different appearance, shape, size, and functionality of the devices.

7.4. Dose Modification

Dose adjustments are not allowed in this study.

7.4.1. Special Treatment Considerations

If a device malfunctions before the needle is inserted (i.e., unable to activate the device, unable to unlock and/or unable to pull the needle shield), a replacement will be given. If the device malfunctions during the injection process (e.g., needle did not retract), the device will not be replaced, and all planned assessments will continue. The investigator or designee will fill out a

complaint form, collect the associated device, submit the complaint form, and return the suspect device to Lilly.

7.5. Preparation/Handling/Storage/Accountability

Both the PFS and the SDP should be stored refrigerated (2°C to 8°C) and allowed to warm to room temperature for at least 30 minutes (up to 24 hours) prior to use.

The investigator or designee must confirm appropriate temperature conditions have been maintained, as communicated by sponsor, during transit for all investigational product received and any discrepancies are reported and resolved before use of the study treatment.

Only participants enrolled in the study may receive investigational product or study materials, and only authorized site staff may supply or administer investigational product. All investigational products 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 study treatment accountability, reconciliation, and record maintenance (such as receipt, reconciliation, and final disposition records).

At the end of the study, and with agreement from Lilly, both used and unused PFSs and SDPs, with the exception of a product complaint, may be destroyed by a qualified vendor.

7.6. Treatment Compliance

The investigational product will be administered at the clinical site, and documentation of treatment administration will occur at the site.

7.7. Concomitant Therapy

With the exception of vitamin/mineral supplements and/or HRT, prescription medications are not to be taken from 14 days prior to drug administration and throughout the study.
Over-the-counter medications other than acetaminophen are not to be taken from 7 days prior to drug administration and throughout the study. The use of topical medication may be permitted if no evidence of chronic dosing with the risk of systemic absorption exists.

In general, concomitant medication should be avoided; however, acetaminophen (1 g, maximum 4 g per 24 hours) may be administered at the discretion of the investigator for treatment of headaches, etc. If the need for concomitant medication (other than acetaminophen) arises, inclusion or continuation of the subject may be at the discretion of the investigator after consultation with a Lilly Clinical Pharmacologist (CP) or Clinical Research Physician (CRP). Any medication used during the course of the study must be documented.

7.8. Treatment after the End of the Study

Not applicable for this study.

8. Discontinuation Criteria

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

8.1. Discontinuation from Study Treatment

If the subject has an elevated amylase and/or lipase value, or is suspected of having pancreatitis, please refer to the pancreatic safety monitoring algorithm (Appendix 6).

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

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5× upper limit of normal (ULN)
- ALT or AST >3× ULN sustained for more than 2 weeks, or
- ALT or AST >3× ULN and total bilirubin level (TBL) >2× ULN or international normalized ratio >1.5, or
- ALT or AST >3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- Alkaline phosphatase (ALP) >3× ULN
- ALP >2.5× ULN and TBL >2× ULN
- ALP >2.5× ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

8.1.1. Discontinuation of Inadvertently Enrolled Subjects

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

8.2. Discontinuation from the Study

Subjects will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice

- Investigator Decision
    - the investigator decides that the subject should be discontinued from the study
- Subject Decision
    - the subject, or legal representative, requests to be withdrawn from the study

8.3. Subjects Lost to Follow-up

A subject will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel are expected to make diligent attempts to contact subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities, detailing the study procedures and their timing.

Appendix 2 lists the clinical 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. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

9.1. Efficacy Assessments

This section is not applicable for this study.

9.2. Adverse Events

Investigators are responsible for monitoring the safety of subjects 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 subject.

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

Investigators must document their review of each laboratory safety report.

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

After the informed consent form is signed, study site personnel will record, via eCRF, the occurrence and nature of each subject'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, study device, 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 investigational product, 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 subject's investigational product 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 one of the following:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (i.e., 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 subject or may require intervention to prevent one of the other outcomes listed in the definition above
- when a condition related to the SDP or PFS necessitates medical or surgical intervention to preclude either permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned

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 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 subject has signed informed consent and has received investigational product. However, if an SAE occurs after signing informed consent, but prior to receiving investigational product, 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 subject summary eCRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and the investigator 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 investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

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

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

9.3. Treatment of Overdose

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

Refer to the IB and Trulicity® USPI (2017).

9.4. Safety

9.4.1. Laboratory Tests

For each subject, clinical laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2) and as clinically indicated. Clinical laboratory assessments will include amylase and lipase.

9.4.1.1. Amylase and Lipase Tests

Serum amylase and lipase measurements will be collected as part of the clinical laboratory testing as well as at time points specified in the Schedule of Activities (Section 2). Where indicated in the Schedule of Activities, amylase and lipase results must be reviewed by the study physician prior to dulaglutide dosing on subsequent days. Additional measurements may be performed at the investigator's discretion. Further diagnostic assessments will be recommended whenever lipase and/or amylase is/are confirmed to be ≥3× ULN at any visit post randomization, even if the subject is asymptomatic (as per the algorithm for the monitoring of pancreatic events in Appendix 6, and if pancreatitis is confirmed, the case will be further defined during an adjudication process).

9.4.2. Vital Signs

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

Blood pressure and pulse rate should be measured after at least 5 minutes supine.

Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. If orthostatic measurements are required, subjects should be supine for at least 5 minutes and stand for at least 2 minutes. If the subject feels unable to stand, supine vital signs only will be recorded. Additional vital signs may be measured during each study period if warranted.

9.4.3. Electrocardiograms

For each subject, a single 12-lead digital ECG will be collected according to the Schedule of Activities (Section 2). Electrocardiograms must be recorded before collecting any blood samples. Subjects must be supine for at least 5 minutes before ECG collection and remain supine but awake during ECG collection. Electrocardiograms may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the subject is still present, to determine whether the subject meets entry criteria at the relevant visit(s) and for immediate subject management, should any clinically relevant findings be identified.

If a clinically significant finding is identified (including, but not limited to, changes in QT interval or corrected QT interval from baseline) after enrollment, the investigator will determine if the subject can continue in the study. The investigator, or qualified designee, is responsible for determining if any change in subject management is needed, and must document his/her review of the ECG printed at the time of collection. Any new clinically relevant finding should be reported as an AE.

9.4.4. Physical Examination

Physical examinations and routine medical assessments will be conducted as specified in the Schedule of Activities (Section 2) and as clinically indicated.

9.4.5. Body Weight

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

9.4.6. Injection Site Reactions

Local tolerability at the injection site will be evaluated for erythema, induration, pain, pruritus, rash, and edema as indicated in Section 2 and reported in the eCRF. If one or more symptom(s) of an injection site reaction (ISR) is reported during the assessment, a single AE for ISR will be recorded on the AE page of the eCRF.

9.4.7. Safety Monitoring

The Lilly CP 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 CP or CRP will periodically review the following data:

- trends in safety data
- laboratory analytes including lipase and amylase
- AEs including monitoring of ISRs

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

9.4.7.1. Hepatic Safety

If a study subject experiences elevated ALT ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 4) should be repeated within 3 to 5 days including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatinine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator based on consultation with the Lilly CP or CRP. 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 ≥5× ULN on 2 or more consecutive blood tests
- elevated serum TBL to ≥2× ULN (except for cases of known Gilbert's syndrome)
- elevation of serum ALP to ≥2× ULN on 2 or more consecutive blood tests
- subject discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

9.5. Pharmacokinetics

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 4 mL each will be collected to determine the plasma concentrations of dulaglutide. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and 24-hour clock time of each dose and PK sampling will be recorded.

9.5.1. Bioanalysis

Samples will be analyzed at a laboratory approved by the sponsor and stored at a facility designated by the sponsor.

Concentrations of dulaglutide will be assayed using a validated radioimmunoassay method.

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

9.6. Pharmacodynamics

9.6.1. Immunogenicity Assessments

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 10 mL each will be collected to determine antibody production against dulaglutide. Additional samples may be collected if there is a possibility that an AE is immunologically mediated.

Immunogenicity will be assessed by a validated assay designed to detect anti-drug antibodies (ADA) in the presence of dulaglutide at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of dulaglutide.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and ethical review boards (ERBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to dulaglutide. Any samples remaining after 15 years will be destroyed.

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 dulaglutide and to investigate genetic variants thought to play a role in insulin glucose homeostasis. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained for a maximum of 15 years after the last subject 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 or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of dulaglutide or after dulaglutide 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

Approximately 24 subjects may be enrolled in order that at least 18 subjects complete the study. The sample size was based on a within-subject variability (coefficient of variation) of 21% for AUC and C_{max} of dulaglutide from previous studies. Eighteen subjects will provide a 90% probability that the half-width of the 90% confidence interval (CI) of the ratio of the geometric means for AUC and C_{max} is no larger than 14%.

Subjects who are randomized may be replaced to ensure that at least 18 subjects may complete the study.

10.2. Populations for Analyses

10.2.1. Study Participant Disposition

A detailed description of subject disposition will be provided at the end of the study. All subjects 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 subject's age, sex, weight, height, BMI, race/sub-race, tobacco/nicotine habits, or other demographic characteristics will be recorded and may be used in the PK 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.

Pharmacokinetic analyses will be conducted on data from all subjects who receive at least one dose of dulaglutide and have evaluable PK.

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

Additional exploratory analyses of the data will be conducted as deemed appropriate. Study results may be pooled with the results of other studies for population PK analysis purposes to avoid issues with post-hoc analyses and incomplete disclosures of analyses.

10.3.1. Safety Analyses

10.3.1.1. Clinical Evaluation of Safety

All investigational product and protocol procedure 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 investigational product as perceived by the investigator. Symptoms reported to occur prior

to enrollment 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 regulatory dictionary.

The number of investigational product-related SAEs will be reported.

10.3.1.2. Statistical Evaluation of Safety

Safety parameters that will be assessed include safety clinical laboratory parameters and vital signs. The parameters will be listed and summarized using standard descriptive statistics. The change from baseline (Day 1 predose of each period) in vital signs will be analyzed and summarized. The change from baseline (Day -1 of each period) in amylase and lipase will also be summarized. Electrocardiograms and physical examinations will be performed for safety monitoring purposes and will not be presented. Additional analysis will be performed if warranted upon review of the data.

10.3.2. Pharmacokinetic Analyses

10.3.2.1. Pharmacokinetic Parameter Estimation

Pharmacokinetic parameter estimates for dulaglutide will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be C_{max} and AUC from time zero to infinity (AUC[0-∞]), of dulaglutide. Other noncompartmental parameters, such as AUC from time zero to 168 hours (AUC[0-168h]), AUC from time zero to 336 hours (AUC[0-336h]), time to C_{max} (t_{max}), $t_{1/2}$, apparent total body clearance of drug, apparent volume of distribution, and AUC from time zero to time t, where t is the last time point with a measurable concentration (AUC[0-t_{last}]), may be reported.

10.3.2.2. Pharmacokinetic Statistical Inference

The PK parameter estimates will be evaluated to determine the relative bioavailability of dulaglutide administered SC by SDP (test) compared to dulaglutide administered by PFS (reference).

The PK parameters will be summarized using descriptive statistics by treatment.

Log-transformed C_{max} and AUC(0-∞) (primary parameters) and AUC(0-168h) and AUC(0-336h) (secondary parameters) will be evaluated in a linear mixed-effects analysis of variance model with fixed effects for treatment (SDP or PFS), period, and sequence and a random effect for subject within sequence. The ratios of least squares geometric means of SDP compared to PFS, as well as the corresponding 90% CIs, will be estimated and reported.

The t_{max} will be analyzed nonparametrically using the Wilcoxon ranked sum test. Estimates of the median difference and the corresponding 90% CIs will be calculated.

Additional analysis may be conducted if deemed appropriate.

10.3.3. Evaluation of Immunogenicity

The frequency and percentage of subjects with preexisting ADA and with treatment-emergent ADA (TE ADA) to dulaglutide will be tabulated. Treatment-emergent ADA are defined as a change from negative at baseline to positive at endpoint with antibody titer greater or equal to 1:4 or a positive at baseline to a positive at endpoint with greater or equal to 4-fold increases. That is, if a positive antibody titer changes from 1:2 at baseline to 1:8 at endpoint, it is considered treatment emergent. For subjects with TE ADA, the distribution of maximum titers will be described. If a neutralization assay is performed, the frequency of neutralizing antibodies will be tabulated in subjects with TE ADA.

The relationship between the presence (or absence) of antibodies and safety and PK parameters may be assessed.

10.3.4. Interim Analyses

An interim PK analysis (including C_{max} and AUC[0-168h]) will be conducted 1 week after the start of Period 1. The purpose of this analysis is to provide preliminary data to further support Phase 3 development. The PK samples collected predose through 168-hour time point will be analyzed.

11. References

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Appendix 1. Abbreviations and Definitions

Term	Definition
ADA	anti-drug antibodies
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.
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve
AUC(0-168h)	area under the concentration versus time curve from time zero to 168 hours
AUC(0-336h)	area under the concentration versus time curve from time zero to 336 hours
AUC(0-∞)	area under the concentration versus time curve from time zero to infinity
AUC(0-t_{last})	area under the concentration versus time curve from time zero to time t, where t is the last time point with a measurable concentration
BMI	body mass index
CI	confidence interval
C_{max}	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 retested at some defined time point, depending on the steps required to obtain confirmed results.
CP	Clinical Pharmacologist

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.
CRU	clinical research unit
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
GCP	good clinical practice
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
HRT	hormone replacement therapy
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	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.
ISR	injection site reaction

MTC	medullary thyroid cancer
NOAEL	no-observed-adverse-effect level
open-label	A study in which there are no restrictions on knowledge of treatment allocation, therefore the investigator and the study participant are aware of the drug therapy received during the study.
PFS	prefilled syringe
PK	pharmacokinetic(s)
randomize	The process of assigning subjects to an experimental group on a random basis.
SAE	serious adverse event
SC	subcutaneous(ly)
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
SmPC	Summary of Product Characteristics
SUSARs	suspected unexpected serious adverse reactions
$t_{1/2}$	apparent terminal elimination half-life
T2D	type 2 diabetes
TBL	total bilirubin level
TE ADA	treatment-emergent anti-drug antibodies
t_{max}	time to maximum observed drug concentration
ULN	upper limit of normal
USPI	United States Package Insert

Appendix 2. Clinical Laboratory Tests

Safety Clinical Laboratory Tests

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Chloride
Mean cell volume	Calcium
Mean cell hemoglobin	Glucose, random
Mean cell hemoglobin concentration	Blood urea nitrogen
Leukocytes (WBC)	Total protein
Platelets	Albumin
Absolute counts of:	Total bilirubin
Neutrophils	Alkaline phosphatase
Lymphocytes	Aspartate aminotransferase
Monocytes	Alanine aminotransferase
Eosinophils	Creatinine
Basophils	Serum lipase
	Serum amylase
Urinalysis	
Specific gravity	
pH	
Protein	Ethanol testing[a]
Glucose	Urine drug screen (including cotinine)[a]
Ketones	Hepatitis B surface antigen[b]
Bilirubin	Hepatitis C antibody[b]
Urobilinogen	HIV[b]
Blood	Pregnancy test[c] (females only)
Nitrite	FSH[b,d] (females only)

Abbreviations: FSH = follicle-stimulating hormone; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

a Ethanol testing and standard urine drug screen must be performed at screening, and upon admission to the clinical research unit. Drug/ethanol testing may be repeated at the discretion of the investigator.

b Performed at screening only.

c Serum pregnancy test will be performed at screening. Urine pregnancy test will be performed for women of childbearing potential at Day -1 for each period and at early termination/Follow-up.

d To confirm postmenopausal status.

Appendix 3. Study Governance, Regulatory and Ethical Considerations

Informed Consent

The investigator is responsible for:

- ensuring that the subject 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 subject or legal representative. This includes obtaining the appropriate signatures and dates on the informed consent form (ICF) prior to the performance of any protocol procedures and prior to the administration of investigational product.
- answering any questions the subject may have throughout the study and sharing in a timely manner any new information that may be relevant to the subject'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 or its designee is responsible for the central recruitment strategy for subjects. Individual investigators may have additional local requirements or processes. Study-specific recruitment material should be approved by Lilly.

Ethical Review

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

Documentation of ERB approval of the protocol and the ICF must be provided to Lilly before the study may begin at the investigative site(s). Lilly or its representatives must approve the ICF before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on good clinical practice (GCP).

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

- the current Investigator's Brochure or United States Package Insert 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 Organizations of Medical Sciences International Ethical Guidelines
2) applicable ICH GCP Guidelines
3) applicable laws and regulations

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 or designee will sign the clinical study report for this study, indicating agreement with the analyses, results, and conclusions of the report.

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 electronic case report forms (eCRFs), and study procedures.
- make periodic visits to the study site.
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax.
- review and evaluate eCRF data and/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 subject 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 clinical 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 subject personal information collected will be provided in a written document to the subject by the sponsor.

Study and Site Closure

Discontinuation of Study Sites

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

Discontinuation of the Study

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

Appendix 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 subjects in consultation with Lilly or its designee Clinical Research Physician.

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
Direct 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 antibody)[a]**
CK/CPK	

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

a Assayed by Lilly-designated or local laboratory.

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

Appendix 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 H9X-MC-GBGM Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	8	1	8
Clinical laboratory tests[a]	8	5	40
Pharmacogenetics	10	1	10
Pharmacokinetics	4	19	76
Immunogenicity	10	3	30
Total			164
Total for clinical purposes (rounded up to nearest 10 mL)			170

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

Appendix 6. Pancreatic Monitoring

Glucagon-like peptide-1(GLP-1) agonists have been associated with a possible risk of acute pancreatitis. In 2006, the US prescribing information for exenatide was revised to include the event of pancreatitis. In 2007, the US prescribing information for this medication was amended to include pancreatitis under precautions. Epidemiologic studies have indicated that there is an increased incidence and prevalence of pancreatitis in persons with type 2 diabetes (T2D).

To enhance understanding of the natural variability of pancreatic enzymes in the T2D population and to assess for any potential effects of dulaglutide on the exocrine pancreas, amylase and lipase values will be monitored in clinical trials with dulaglutide.

Additional monitoring will be requested for amylase or lipase values ≥3x upper limit of normal (ULN) at any visit after randomization, even in asymptomatic subjects (see figure below). Lipase and amylase may also be obtained at any time during the clinical trials for any subject suspected of having symptoms suggestive of pancreatitis (such as severe gastrointestinal signs and/or symptoms), at the investigator's discretion.

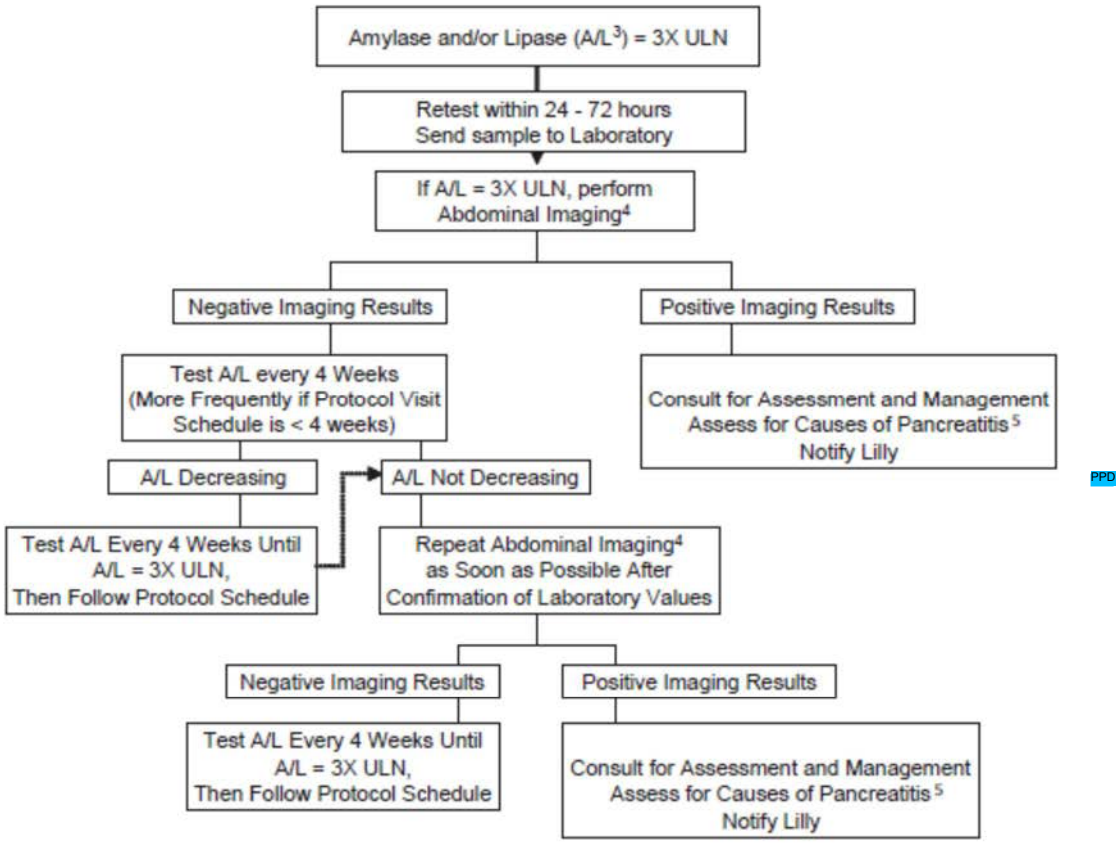
Acute pancreatitis is an adverse event defined as an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems. The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain characteristic of acute pancreatitis
- serum amylase and/or lipase >3x ULN
- characteristic findings of acute pancreatitis on computed tomography scan or magnetic resonance imaging

Most subjects with acute pancreatitis experience abdominal pain that is located generally in the epigastrium and radiates to the back in approximately half the cases. The pain is often associated with nausea and vomiting. However, experience with GLP-1 agonists has demonstrated that some subjects asymptomatic for classic pancreatitis may demonstrate significant elevations of lipase and/or amylase. For subjects considered by investigators to be asymptomatic for pancreatitis, but whose value(s) for lipase and/or amylase are ≥3x ULN, an algorithm is in place to follow these subjects safely and to quickly reach/or not a diagnosis of pancreatitis.

Pancreatic Enzymes: Safety Monitoring Algorithm In Patients without Symptoms of Pancreatitis[1,2]

Follow this algorithm when the value(s) for serum amylase and/or lipase are = 3x upper limit of normal (ULN)



1. Symptomatic – related primarily to abdominal pain consistent with pancreatitis; however, in the opinion of the investigator severe nausea and vomiting plus other symptoms consistent with pancreatitis may be considered symptomatic as well.

2. If in the opinion of the investigator, the patient has symptoms of acute pancreatitis:
   (a) Stop injectable study drug
   (b) Consult for assessment and management
   (c) Assess for causes of pancreatitis
   (d) Notify Lilly

3. A/L = amylase and/or lipase. Either or both enzymes can be used to meet the algorithm criteria.

4. Abdominal imaging is most valuable when performed at the time of elevated enzyme values. If in the opinion of the radiologist or investigator, it is safe for the patient/subject to receive contrast, an enhanced abdominal CT is preferred. MRI is also an acceptable imaging modality.

5. At a minimum, order a CBC and a pancreatic panel (which includes LFTs, calcium and triglycerides). Record all concomitant medications.

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