J1D-MC-GZAA Protocol (e)

# A Randomized, Placebo-Controlled, Subject- and Investigator-Blind, Single and Multiple Dose, Safety, Tolerability, and Pharmacokinetics Study of LY3463251 in Healthy and Overweight Healthy Subjects

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LY3463251


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# 1. Protocol Synopsis

**Title of Study:**

A Randomized, Placebo-Controlled, Subject- and Investigator-Blind, Single and Multiple Dose, Safety, Tolerability, and Pharmacokinetics Study of LY3463251 in Healthy and Overweight Healthy Subjects

**Rationale:**

New antihyperglycemic agents for the treatment of type 2 diabetes mellitus (T2DM) offering significant improvements in glycemic control, which would result in improved health outcomes, are highly desired. LY3463251 is being developed to improve glycemic control in adult patients with T2DM, as an adjunct to diet and exercise.

This is the first-in-human study of LY3463251, which will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3463251 in healthy subjects after a single dose and overweight healthy subjects after multiple doses. Additionally, the pharmacodynamic (PD) effects of multiple doses of LY3463251 on glycemic parameters (including fasting plasma glucose, fasting serum insulin, glucose and insulin during an oral glucose tolerance test [OGTT]), gastric emptying using acetaminophen, appetite (measured using a visual analog scale), and body weight in overweight healthy subjects will be explored.

**Objectives/Endpoints:**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To determine the safety and tolerability of single doses of LY3463251 in healthy subjects and multiple doses of LY3463251 in overweight healthy subjects. | Incidence of treatment-emergent adverse events and serious adverse events.<br>Clinically significant changes in vital signs data, safety laboratory parameters, and electrocardiograms. |
| **Secondary** | |
| To determine the pharmacokinetics of LY3463251 following single doses in healthy subjects and multiple doses in overweight healthy subjects. | Area under the concentration versus time curve from time 0 to infinity (AUC[0-∞]), area under the concentration versus time curve during 1 dosing interval (AUC[0-τ]; multiple doses only), area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration (AUC[0-$t_{last}$]), maximum observed concentration ($C_{max}$), and time of $C_{max}$ ($T_{max}$). |
| To determine the pharmacodynamic effects of LY3463251 following multiple doses of LY3463251 in overweight healthy subjects. | Glycemic effects (including fasting plasma glucose, fasting serum insulin, C-peptide, and glucose and insulin during an OGTT), gastric emptying using acetaminophen, appetite (measured using a visual analog scale), and body weight. |

**Summary of Study Design:**

Study J1D-MC-GZAA is a single-site, randomized, placebo-controlled, dose-escalation study in healthy and overweight healthy subjects. The subjects and investigator will be blinded to the treatment assignment.

**Part A (Single-Ascending Dose [SAD] in Healthy Subjects):** Subjects with a body mass index (BMI) of ≥18.5 and <32 kg/m$^2$ will be randomized to receive a single dose of LY3463251 or placebo on Day 1. Six subjects will be randomized to LY3463251 and 2 subjects will be randomized to placebo in each cohort. It is planned for subjects to be followed for up to approximately 6 weeks post-dose for: safety assessments, including measurements of blood pressure and body weight; and collection of safety laboratory, PK, and immunogenicity samples.

It is planned for 8 single subcutaneous (SC) doses of LY3463251 to be evaluated in 8 dose-escalating cohorts. However, doses may be adjusted and the number of cohorts reduced based on ongoing review of the PK, safety, and tolerability data.

- Cohort 1: 0.01 mg LY3463251 or placebo
- Cohort 2: 0.03 mg LY3463251 or placebo
- Cohort 3: 0.1 mg LY3463251 or placebo
- Cohort 4: 0.3 mg LY3463251 or placebo
- Cohort 5: 1 mg LY3463251 or placebo
- Cohort 6: 3 mg LY3463251 or placebo
- Cohort 7: 10 mg LY3463251 or placebo
- Cohort 8: 24 mg LY3463251 or placebo

Dose-escalation decisions will primarily be based on safety and tolerability data; for Cohorts 1 to 3, decisions will be made based on data obtained up to Day 7 from at least 7 subjects in the previous cohort and all available safety and tolerability data from previous cohorts. For Cohorts 4 to 8, decisions will be made based on data obtained up to Day 14 from at least 7 subjects in the previous cohort and all available safety and tolerability data from previous cohorts. Following completion of Cohorts 1 to 3, an interim PK analysis will be conducted. Depending on those PK results, dose escalation decisions for Cohorts 4 and 5 may be based on data available at 7 rather than 14 days post-dose.

**Part B (Multiple-Ascending Dose [MAD] in Overweight Healthy Subjects):** Subjects with a BMI ≥27 and <40 kg/m$^2$, will be randomized to receive 12 once-weekly (QW) SC doses of LY3463251 or placebo. Nine subjects will be randomized to LY3463251 and 3 subjects will be randomized to placebo in each cohort. It is planned for subjects to be followed for up to 45 (±3) days following their last dose for safety assessments, including measurement of blood pressure; collection of safety laboratory, PK, fasting plasma glucose (PD), fasting serum insulin (PD), OGTT (PD), and immunogenicity samples; and measurements of appetite and body weight (PD).

The dose levels of LY3463251 planned for Part B include 1, 3, 9, and 24 mg, and will be evaluated in 4 dose-escalating cohorts. An additional cohort (Cohort 5) may be initiated after reviewing at least 4 weeks of tolerability data obtained from Cohort 4. If the Cohort 5 is initiated, it will evaluate a dose lower than 24 mg (maximum dose administered in Part A) or assess an alternate dose up-titration scheme that does not exceed 24 mg. Escalation or titration of doses in a cohort may be adjusted based on the safety and tolerability data obtained from at least 7 subjects in the previous cohort.

**Treatment Arms and Planned Duration for an Individual Subject:**

**Part A (SAD):** Subjects will participate in a screening period of up to 28 days prior to Day -1 and it is planned that subjects will be followed for approximately 41 days after receiving a single dose of investigational product. The total study duration for each subject is planned to be approximately 10 weeks.

**Part B (MAD):** Subjects will participate in a screening period of up to 28 days prior to Day 1, will receive multiple doses of investigational product over a period of approximately 12 weeks, and it is planned that subjects will be followed up for 45 (±3) days after the last dose. The total duration for each subject is planned to be approximately 23 weeks.

**Number of Subjects:**

In Part A, up to 75 subjects may be enrolled such that approximately 64 subjects have evaluable data.

In Part B, up to 85 subjects may be enrolled such that approximately 60 subjects have evaluable data.

Subjects who are randomized and who are discontinued from the study (providing that discontinuation did not result from a safety finding) may be replaced to ensure that enough subjects complete the study.

**Statistical Analysis:**

Safety and tolerability: Treatment-emergent adverse events and safety laboratory and vital signs data will be summarized using descriptive statistics.

Pharmacokinetics: The degree of dose proportionality for LY3463251 will be assessed by fitting the power model to area under the concentration versus time curve (AUC) from time 0 to infinity (AUC[0-∞]), area under the concentration versus time curve over a dosing interval (AUC[0-τ]) and maximum observed concentration ($C_{max}$) versus dose for each dose level of LY3463251. The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. In addition, the slope and its 90% confidence interval (CI) and the geometric least-square means for each dose level tested will be produced. The analysis will be performed separately for Parts A and B. In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated. Log-transformed $C_{max}$ and AUC least-squares means, and 90% CI estimates for each dose will be back-transformed to provide the geometric means and the corresponding 90% CIs.

Pharmacodynamics (Part B only): Fasting plasma glucose concentrations, fasting serum insulin concentrations, C-peptide, OGTT-derived parameters, gastric-emptying rate, appetite, and body weight will be summarized using descriptive statistics.

# 2. Schedule of Activities

## 2.1. Part A (Single-Ascending Dose)

| | Screening | Days | | | | | FU[a] | ED[b] | Comments |
|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | Up to 28 days prior to Day 1 | -1 | 1 | 2 to 6 | 8 | 11, 15, 22, 29 | 42 (±3) | | |
| Informed Consent | X | | | | | | | | |
| Subject Admission to CRU | | X | | | | | | | |
| Subject Discharge from CRU | | | | | X | | | | |
| Non-Residential Visit | X | | | | | X | X | X | |
| IP Administration | | | X | | | | | | |
| Medical History | X | | | | | | | | |
| Height | X | | | | | | | | |
| Weight | X | X | X | Days 2 and 5 | | Days 15, 22, 29 | X | X | Body weight will be recorded for safety analysis. |
| Blood Pressure and Pulse Rate (Supine) | X | | P, 6, 12 h | 24, 48, 72, 96, 120 h | 168 h | X | | X | Where possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled timepoint. Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator. |
| Ambulatory Blood Pressure Monitoring | | Day -1 to Day 4 | | | | | | | For 24 h prior to and 72 h post IP administration. Measurements of blood pressure will be collected every 30 min between 0800 and 2200 h and every 60 min between 2201 and 0759 h. |
| Body Temperature and Respiratory Rate | X | | P | 24 | 168 h | X | | X | Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator. |
| Safety Lab Tests[c] | X | X | P | Days 2 and 5 | X | Days 15, 22, 29 | | X | See Appendix 2, Safety Laboratory Tests, for details. |
| Fasting Plasma Glucose[c] | X | X | P | Days 2 and 5 | X | Days 15, 22, 29 | X | X | Fasting plasma glucose will be recorded for safety analysis. |
| Serum Pregnancy Test | X | | | | | | | | Female subjects only. |
| Physical Exam | X | X | | | | | | | After screening, medical assessment only performed to include medical review and targeted examination, as appropriate. |
| 12-Lead ECG | X | | P, 6, 12 h | 24, 48, 72, 96, 120 h | 168 h | X | | X | Single ECGs. Additional single ECGs may be obtained if clinically indicated. |
| Genetic Sample | | | P | | | | | | Single sample for pharmacogenetic analysis taken prior to/on Day 1. |
| Fasting Biomarker Sample | | X | | | | Day 15 | | | Sample for storage only. |
| Adverse Event Recording | X | | | | | | | | |
| Plasma PK samples | | | P, 6, 12 h | 24, 48, 72, 96, 120 h | 168 h | X | X | X | Sampling times are relative to the time of study treatment administration (0 min). |
| Immunogenicity Samples | | | P | | | Days 15 | X | X | All samples for immunogenicity should be taken predose, when |

| | Screening | Days | | | | | FU[a] | ED[b] | Comments |
|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | Up to 28 days prior to Day 1 | -1 | 1 | 2 to 6 | 8 | 11, 15, 22, 29 | 42 (±3) | | |
| | | | | | | and 29 | | | applicable and possible. Also, a time matched PK should be taken at each immunogenicity sample time point. Additional samples may be collected approximately every 3 months for up to 1 year after dose (Section 9.6.6) |

Abbreviations: CRU = clinical research unit; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; h = hour(s); min = minutes; IP = investigational product; P = predose; PK = pharmacokinetics.

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.

[a] Additional FU visits may occur depending upon emerging PK and/or safety data.

[b] At the discretion of the investigator, subjects may be requested to return to the CRU for safety monitoring at additional visits following completion of the ED procedures. At the discretion of the investigator, assessments may include, but will not be limited to, those presented for the FU visit (Day 42) with the addition of safety lab tests.

[c] Samples collected at screening and on Day -1 will be analyzed at a local laboratory. Samples collected at all other time points will be analyzed by a central laboratory.

## 2.2. Part B (Multiple-Ascending Doses)

| | Screening | Days | | | | | | | | | | | | | | FU[a] | ED[b] | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 28 days prior to Day 1** | **-2** | **-1** | **1** | **2 to 7** | **8** | **9** | **15, 22, 29, 36, 43, 50, 57, 64, 71, 78** | **16, 23, 30, 37, 44, 51, 58, 65, 72, 79** | **80** | **81** | **85** | **86** | **92** | **107** | **123 (±3)** | | **The timepoints need to be noted in conjunction with the comments below.** |
| Informed Consent | X | | | | | | | | | | | | | | | | | |
| Subject Admission to CRU | | X | | | | | | X | | X | | X | | | | | | Subjects may be admitted the night before the day of dosing. |
| Subject Discharge from CRU | | | | | | | X | | X | | X | | X | | | | | Subjects may be discharged on any day between Day 4 and Day 7 at the investigator's discretion. |
| Non-Residential Visit | X | | | | Day 6 | | | | | | | | | X | X | X | X | If the subjects are discharged before Day 6, the subjects will attend the non-residential visit on Day 6. |
| IP Administration | | | | X | | X | | X | | | | | | | | | | IP administration on Day 1 indicates time = 0 h. |
| Medical History | X | | | | | | | | | | | | | | | | | |
| Height | X | | | | | | | | | | | | | | | | | |
| Body Weight | X | | X | X | | P | | P | | | | X | | | X | X | X | Body weight will be recorded twice first thing in the morning for PD analysis. See Section 9.4.2. |
| Blood Pressure and Pulse Rate (Supine) | X | | X | P, 6, 12 h | 24, 48, 72, 120 h | P, 6, 12 h | 24 h | P, 6, 12 h | 24 h | X | | X | | X | X | X | X | Where possible, measurements of blood pressure and pulse rate should be performed at approximately the same time of day at each scheduled time point. Time points may be added for each study period, if warranted and agreed upon between Lilly and the investigator. |
| Ambulatory Blood Pressure Measurement | | | Day -1 to Day 2 | | | X | | Days 15, 29, and 57 only | | | | X | | | | | | ABPM will be monitored for 24 h prior to and 24 h following the first dose, and for 24 h following subsequent doses. Measurements of blood pressure will be collected every 30 min between 0800 and 2200 h and every 60 min between 2201 and 0759 h. |
| Body Temperature | X | | X | P | 24 h | P | 24 h | P | 24 h | | | X | | | | X | | |

| | Screening | Days | | | | | | | | | | | | | | FU[a] | ED[b] | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 28 days prior to Day 1** | **-2** | **-1** | **1** | **2 to 7** | **8** | **9** | **15, 22, 29, 36, 43, 50, 57, 64, 71, 78** | **16, 23, 30, 37, 44, 51, 58, 65, 72, 79** | **80** | **81** | **85** | **86** | **92** | **107** | **123 (±3)** | | **The timepoints need to be noted in conjunction with the comments below.** |
| Clinical Laboratory Tests (fasting) | X | | X | P | Day 6 | | | P (Days 15, 22, 29, 36, 43, 57, and 71 only) | | | | X | | | X | X | X | See Appendix 2, Clinical Laboratory Tests, for details. |
| Fasting Plasma Glucose | | | X | | | | | | | | | | | | | | | Samples will be analyzed at a central laboratory. |
| Fasting Serum Insulin | | | | P | | | | P (Day 57 only) | | | | | | | | | X | Samples will be analyzed at a central laboratory. |
| C-Peptide Samples | | | | P | | | | P (Day 57 only) | | | | | | | | | X | Samples will be analyzed at a central laboratory. |
| OGTT (fasting overnight) | | X | | | | | | | Day 30 | | | X | | | | | | Blood sample collected for glucose, C-peptide, and insulin concentrations prior to and at 30, 60, 90, and 120 min after glucose administration.<br>Samples will be analyzed at a central laboratory.<br>OGTT includes samples for FPG, fasting serum insulin, and fasting C-peptide, corresponding to 0 min. |
| Acetaminophen test for gastric emptying | | X | | | Day 3 | | | | | X | | | | | | | | Acetaminophen PK sampling schedule on each day specified in the table: Pre-acetaminophen dose and 0.5, 0.75, 1, 2, 3, 4, 6, 9, 12, and 24 hours after acetaminophen dose. Acetaminophen can be administered after completion of OGTT on Day -2 and after overnight fast on Days 3 and 80. Food is not allowed for 2 hours after acetaminophen dose. |
| Standardized Meal | | | X | | | X | | Days 15, 22, 29, and 57 only | | | | X | | | | | | Standardized breakfast and lunch should be provided at the same time of day on each occasion. |
| Visual Analog Scale (Appetite) (Fasting) | | | X | | | X | | X | | | | X | | | | | | Administered at 30 min (±20 min) prior to the start of standardized breakfast and lunch. |

| | Screening | Days | | | | | | | | | | | | | | FU[a] | ED[b] | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 28 days prior to Day 1** | **-2** | **-1** | **1** | **2 to 7** | **8** | **9** | **15, 22, 29, 36, 43, 50, 57, 64, 71, 78** | **16, 23, 30, 37, 44, 51, 58, 65, 72, 79** | **80** | **81** | **85** | **86** | **92** | **107** | **123 (±3)** | | **The timepoints need to be noted in conjunction with the comments below.** |
| Visual Analog Scale (Postprandial) | | | X | | | X | | Days 15, 22, 29, and 57 only | | | | X | | | | | | Administered at 30 min (±15 min) and 5 h (±30 min) after standardized breakfast and lunch. |
| C-SSRS Baseline and Screening | X | | X | | | | | | | | | | | | | | | |
| C-SSRS Since Last Visit | | | | | | X | | Days 15, 22, 29, 43, and 57 only | | | | X | | | | X | | C-SSRS may be performed around the same time of the day with a time window of ±2 h for a subject before or after dosing, at the discretion of the investigator. |
| Self-Harm Supplement Form and Self-Harm Follow-up Form | X | | X | | | X | | Days 15, 22, 29, 43, and 57 only | | | | X | | | | X | | Self-Harm Follow-up form is required only if triggered by the Self-Harm Supplement Form. |
| Serum Pregnancy Test | X | | | | | | | | | | | | | | | X | | Female subjects only. Additional serum pregnancy tests may be performed at the discretion of investigator. |
| Physical Examination | X | | | | | | | | | | | | | | | | | At screening, complete physical examination (except genital and rectal). After screening, physical examination should be only symptom directed. |
| 12-lead ECG | X | | | P | 24, 48, 72 h | P | | P (Days 15, 29, and 57 only) | Day 79 | X | | X | | | | X | X | Single ECGs. Additional single ECGs may be obtained if clinically indicated. The ECGs should be obtained prior to collection of the PK samples, and closer to the PK sampling time points. |
| Genetic Sample | | | | P | | | | | | | | | | | | | | Single sample for pharmacogenetic analysis taken on Day 1 or Day -1. |
| Fasting Biomarker Sample | | | X | | | | | Day 29 only | | | | X | | | | X | | Biomarker sample for storage. |
| Adverse Event Recording | X | | | | | | | | | | | | | | | | | |
| Plasma PK Samples | | | | P, 6, 12 h | 24, 48, 72, 120 h | P | | P (Days 15, 29, 57, and 78 only) | 24 h postdose on Day 79 | X | | X | | X | X | X | X | Sampling times are relative to the time of the last IP administration (0 min). |

| | Screening | Days | | | | | | | | | | | | | | FU[a] | ED[b] | Comments |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Procedure** | **Up to 28 days prior to Day 1** | **-2** | **-1** | **1** | **2 to 7** | **8** | **9** | **15, 22, 29, 36, 43, 50, 57, 64, 71, 78** | **16, 23, 30, 37, 44, 51, 58, 65, 72, 79** | **80** | **81** | **85** | **86** | **92** | **107** | **123 (±3)** | | **The timepoints need to be noted in conjunction with the comments below.** |
| | | | | | | | | | only | | | | | | | | | |
| Immunogenicity Samples | | | | P | | | | P (Days 15 and 29 only) | | | | X | | | | X | X | All samples for immunogenicity should be taken predose, when applicable and possible. Also, a time-matched PK should be taken at each immunogenicity sample time point. Additional samples may be collected approximately every 3 months for up to 1 year after dose (Section 9.6.6). |

Abbreviations: CRU = clinical research unit; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FU = follow-up; h = hour; IP = investigational product; min = minutes; OGTT = oral glucose tolerance test; P = predose; PD = pharmacodynamic; PK = pharmacokinetic.

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

[a] Additional FU visits may occur depending upon emerging PK, PD, and/or safety data.

[b] At the discretion of the investigator, subjects may be requested to return to the CRU for safety monitoring at additional visits following completion of the ED procedures. At the discretion of the investigator, assessments may include, but will not be limited to, those presented for the FU visit (Day 123).

# 3. Introduction

## 3.1. Study Rationale

With the prevalence of type 2 diabetes mellitus (T2DM) increasing world-wide, new antihyperglycemic agents offering significant improvements in glycemic control and secondary benefits, which would result in improved health outcomes, are highly desired. LY3463251 is a growth and differentiation factor 15 (GDF15) variant that is being developed with an aim to fulfill these unmet needs, potentially leading to improvements in clinical outcomes.

This is the first-in-human study of LY3463251, which will investigate the safety, tolerability, and pharmacokinetics (PK) of LY3463251 in healthy subjects after a single dose and overweight healthy subjects after multiple doses. Additionally, the pharmacodynamic (PD) effects of multiple doses of LY3463251 on glycemic parameters (including fasting plasma glucose, fasting serum insulin, and glucose and insulin during an oral glucose tolerance test [OGTT]), appetite (measured using visual analog scale [VAS]), and body weight in overweight healthy subjects will be explored.

## 3.2. Background

GDF15 (also known as macrophage inhibitory cytokine-1 or MIC-1 or nonsteroidal anti-inflammatory drug-activated gene-1 [NAG-1]) is a cysteine knot protein belonging to the transforming growth factor-beta (TGFβ) superfamily (Bootcov et al. 1997). Among the many reported biological functions of GDF15, the regulation of energy homeostasis has gained significant attention due to its potential for the treatment of obesity and T2DM (Tsai et al. 2016).

The connection between GDF15 and alterations in body weight was initially postulated based on the observation that increasing serum GDF15 levels correlate with weight loss in individuals with advanced prostate cancer (Johnen et al. 2007). Increasing GDF15 levels in mice through administration of recombinant protein or via secretion from tumor xenografts illustrated that GDF15 induces weight loss via its ability to decrease food intake and enhance energy expenditure (Johnen et al. 2007; Tsai et al. 2018). Furthermore, transgenic mice overexpressing GDF15 were found to be resistant to diet-induced obesity and to exhibit improved glucose tolerance (Macia et al. 2012; Chrysovergis et al. 2014), whereas GDF15 knockout mice had increased body weight and fat mass (Tsai et al. 2013).

Recent work indicates that GDF15 elicits these effects through action on the brainstem, localized to the area postrema (Tsai et al. 2014). The area postrema is a circumventricular organ and has been specifically shown to be involved in the control of food intake and body weight (Young 2012). The orphan receptor glial cell derived neurotrophic factor receptor alpha–like (GFRAL) was identified as the ligand binding receptor for GDF15 (Emmerson et al. 2017; Mullican et al. 2017; Yang et al. 2017; Hsu et al. 2017). GDF15 was found to induce signaling by stimulating the interaction of GFRAL with a coreceptor rearranged during transfection (RET; Mullican et al. 2017; Hsu et al. 2017). GFRAL was found to be expressed specifically in the area postrema located outside the blood-brain barrier and the neighboring nucleus tractus solitarius.

Furthermore, GFRAL localization was shown to be highly conserved across species including mouse, rat, monkey, and human (Emmerson et al. 2017; Mullican et al. 2017).

LY3463251 was CCI found to demonstrate significantly prolonged PK profile relative to the native form, supporting potential once-weekly (QW) administration.

CCI

There are no nonclinical safety assessment findings precluding clinical development.

As of 11 July 2019, 64 healthy subjects entered Part A; 48 subjects received single ascending subcutaneous (SC) doses of 0.01, 0.03, 0.1, 0.3, 1, 3, 10, or 24 mg LY3463251, and 16 subjects received placebo.

In Part A, there were no deaths, serious adverse events (SAEs), or discontinuations due to adverse events (AEs). Single doses of LY3463251 through 3 mg were well tolerated (Cohorts 1 through 6). At doses of 10 mg (Cohort 7) and 24 mg (Cohort 8), LY3463251 treatment was commonly associated with manageable and reversible treatment-emergent adverse events (TEAEs) of nausea and vomiting. These TEAEs were of mild or moderate severity and required treatment with ondansetron in 4 of 6 subjects receiving 24 mg LY3463251.

The main laboratory finding was an increase in serum transaminase levels, observed in 9 out of 48 subjects receiving LY3463251 and 1 out of 16 subjects receiving placebo, without any indication of a dose-response relationship. These findings were observed within Cohorts 1 through 6 but were not detected in Cohorts 7 or 8. None of these changes were associated with abnormalities in total bilirubin level (TBL) or alkaline phosphatase (ALP), and no subject had clinical signs or symptoms suggestive of liver injury or other medical conditions. Two subjects in Cohort 4 (LY3463251 0.3 mg) had increased alanine aminotransferase (ALT) beyond 2-fold the upper limit of normal (ULN), peaking at 3.8× ULN for 1 subject, and 2.5× ULN for the other subject. In both subjects, peaks were observed at only 1 time point and had reversed by the next visit.

No relevant treatment-emergent abnormalities were noted for blood pressure, pulse rate, body temperature, blood pressure assessed by ambulatory monitoring, or electrocardiograms (ECGs). Dose-dependent body weight decreases were noted for subjects receiving LY3463251 in Cohorts 7 and 8, with a nadir generally on Day 5, reversing on subsequent days. Subjects in Cohorts 7

and 8 lost an average of approximately 1 kg body weight compared with subjects who received placebo who gained approximately 0.1 kg and 0.85 kg body weight, respectively. The loss of body weight in subjects who received LY3463251 was generally associated with the gastrointestinal (GI) TEAEs observed in Cohorts 7 and 8. Another TEAE of interest is a case of moderate generalized urticaria without any associated signs of anaphylaxis, that occurred 106 minutes after dosing, and resolved within 2 days after it started, following a single dose of antihistamine. The subject did not have detectable baseline or treatment-emergent anti-drug antibodies.

Based on the preliminary PK data available from Cohorts 1 to 6 (all days) and Cohort 7 (up to Day 15), the exposures to LY3463251 (maximum observed concentration [$C_{max}$] and area under the concentration versus time curve (AUC) appeared to increase proportionally in the dose range evaluated. The median time to maximum observed concentration ($T_{max}$) occurred between 48 and 96 hours after dose administration. The mean half-life of LY3463251 was approximately 7 days, thus supporting once-weekly administration. More details about these preliminary clinical and laboratory results can be found in the Investigator's Brochure (IB).

## 3.3. Benefit/Risk Assessment

Based on the available nonclinical and single-ascending dose (SAD) clinical data, LY3463251 continues to be considered a low-risk compound. Anticipated risks are those associated with GI events, mainly nausea and vomiting, elevations of liver enzyme levels, and urticarial allergic reactions. These risks are considered to be monitorable and manageable at the planned dose range of 1 to 24 mg in Part B and with updated discontinuation criteria based on the SAD results.

Analyses of the frequency and magnitude of the cluster of differentiation (CD4)+ T-cell responses indicated that LY3463251 is predicted to have a very low to low risk of clinical immunogenicity. Results from SAD assessments confirm this status.

Based on observations from the SAD study, subjects may benefit from a therapeutic weight loss.

More information about the known and expected benefits, risks, SAEs and reasonably anticipated AEs of LY3463251 is to be found in the IB.

# 4. Objectives and Endpoints

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

**Table GZAA.1. Objectives and Endpoints**

| Objectives | Endpoints |
|---|---|
| **Primary** | |
| To determine the safety and tolerability of single doses of LY3463251 in healthy subjects and multiple doses of LY3463251 in overweight healthy subjects. | Incidence of TEAEs and SAEs.<br>Clinically significant changes in vital signs data, safety laboratory parameters, and electrocardiograms. |
| **Secondary** | |
| To determine the pharmacokinetics of LY3463251 following single doses in healthy subjects and multiple doses in overweight healthy subjects. | AUC(0-∞), AUC(0-τ) [Part B only], AUC(0-$t_{last}$), $C_{max}$, and $T_{max}$. |
| To determine the pharmacodynamic effects of LY3463251 following multiple doses of LY3463251 in overweight healthy subjects. | Glycemic effects (including fasting plasma glucose, fasting serum insulin, C-peptide, and glucose and insulin during an oral glucose tolerance test), gastric emptying using acetaminophen, appetite (measured using a VAS), and body weight. |
| **Exploratory** | |
| To determine the immunogenicity of LY3463251 following single and multiple doses. | Incidence of TEADA. |
| To evaluate the pharmacodynamic effect on the lipid profile of multiple doses of LY3463251 in overweight healthy subjects. | Low- and high-density lipoproteins, cholesterol, and triglycerides. |

Abbreviations: AUC(0-∞) = area under the concentration versus time curve from time 0 to infinity; AUC(0-τ) = area under the concentration versus time curve during 1 dosing interval; AUC(0-$t_{last}$) = area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration; $C_{max}$ = maximum observed concentration; SAE = serious adverse event; TEADA = treatment-emergent antidrug antibodies; TEAE = treatment-emergent adverse event; $T_{max}$ = time of maximum observed concentration; VAS = visual analog scale.

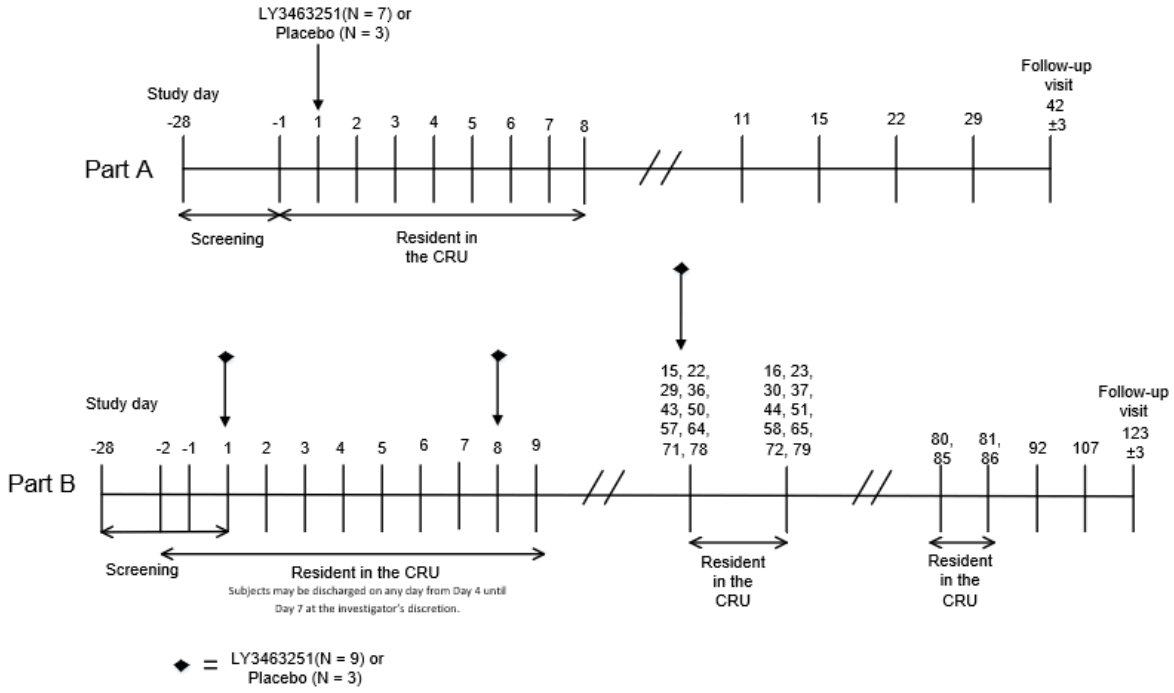
# 5. Study Design

## 5.1. Overall Design

This is a single-site, randomized, placebo-controlled, dose-escalation study in healthy and overweight healthy subjects to evaluate the safety, tolerability, and PK of LY3463251 following single doses in healthy subjects and multiple doses in overweight healthy subjects. Additionally, the PD effects of multiple doses of LY3463251 on glycemic effects (including fasting plasma glucose, fasting serum insulin, and glucose and insulin during an OGTT), appetite, and body weight in overweight healthy subjects will be explored. The subjects and investigator will be blinded to the treatment assignment; the sponsor will not be blinded. The study will be conducted in 2 parts: Part A (SAD) and Part B (multiple-ascending dose [MAD]).

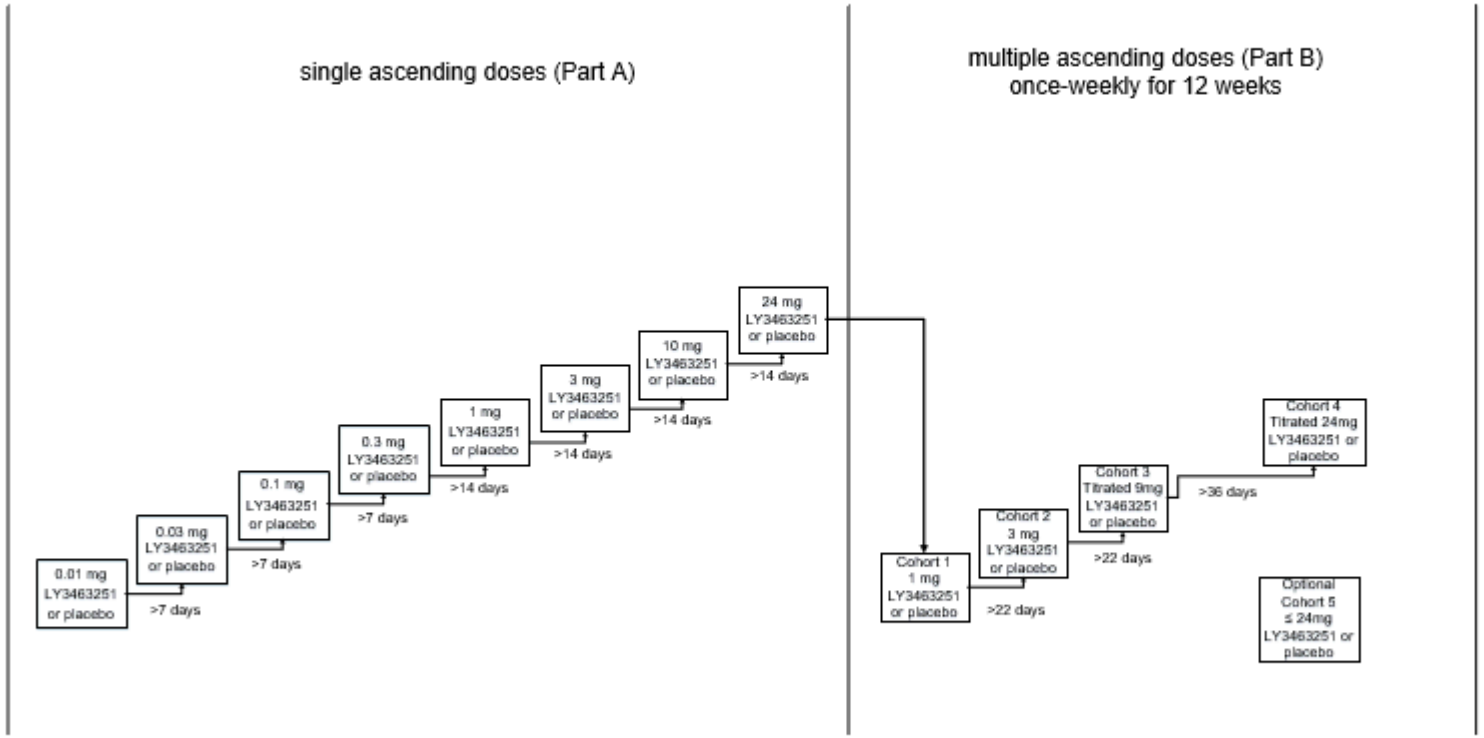
Screening will occur up to 28 days prior to Day 1 in both parts of the study.

Study governance considerations are described in detail in Appendix 3. Schematic representations of the study are presented in Figure GZAA.1.




Abbreviation: CRU = clinical research unit.

**Figure GZAA.1. Planned treatment periods.**




Part B may be initiated following review of all available safety data up to Day 14 post-dose from the last cohort, and of all safety data available at this time (including antidrug antibody data) from the preceding cohorts. An optional Cohort 5 may be initiated after reviewing at least 4 weeks of tolerability data obtained from Cohort 4. The number of cohorts in both parts may be reduced based on review of PK, safety, and/or tolerability data.

**Figure GZAA.2. Dose-escalation.**

### 5.1.1. Part A (Healthy Subjects)

Subjects, with a body mass index (BMI) of ≥18.5 and <32 kg/m$^2$, will be admitted to the clinical research unit (CRU) on Day -1 and will be randomized to receive a single dose of LY3463251 or placebo on Day 1. Six subjects will be randomized to LY3463251 and 2 subjects will be randomized to placebo in each cohort. At the discretion of the investigator, subjects may be discharged from the CRU on Day 8 after all study procedures have been completed. Subjects will return to the CRU as outpatients at predetermined visits for up to approximately 6 weeks post-dose for: safety assessments, including measurements of blood pressure and body weight; and collection of safety laboratory, PK, and immunogenicity samples. Sampling schedules may be adjusted and the duration of the residential period may be increased (but not decreased) based on ongoing review of the PK and/or safety data. Additional follow-up visits may occur depending upon the PK and/or safety data.

It is planned for 8 single SC doses of LY3463251 to be evaluated in 8 dose-escalating cohorts. However, doses may be adjusted and the number of cohorts reduced based on ongoing review of the PK, safety, and tolerability data.

- Cohort 1: 0.01 mg LY3463251 or placebo
- Cohort 2: 0.03 mg LY3463251 or placebo
- Cohort 3: 0.1 mg LY3463251 or placebo
- Cohort 4: 0.3 mg LY3463251 or placebo
- Cohort 5: 1 mg LY3463251 or placebo
- Cohort 6: 3 mg LY3463251 or placebo
- Cohort 7: 10 mg LY3463251 or placebo
- Cohort 8: 24 mg LY3463251 or placebo

Data to be reviewed prior to dose-escalation decisions, including the timing and scope of these reviews, are described in Section 7.4.1.

Safety and tolerability will be assessed throughout Part A of the study by means of vital sign measurements, safety laboratory tests, ECGs, physical examinations, and AE recording.

### 5.1.2. Part B (Overweight Healthy Subjects)

Subjects, with a BMI ≥27 and <40 kg/m$^2$, will be admitted to the CRU on Day -2 and will be randomized to receive QW SC doses of LY3463251 or placebo on Days 1, 8, 15, 22, 29, 36, 43, 50, 57, 64, 71, and 78. Nine subjects will be randomized to LY3463251 and 3 subjects will be randomized to placebo in each cohort.

Subjects will receive their first dose of LY3463251 or placebo on Day 1.

Subjects may be discharged from the CRU on Day 4 after all study procedures have been completed or remain until Day 9 at the discretion of the investigator.

Subjects will return to the CRU for a series of residential visits over a period of approximately 12 weeks for administration of LY3463251 or placebo, and will subsequently return as outpatients at predetermined visits for up to 45 (±3) days following their last dose for:

- safety assessments, including measurements of blood pressure; collection of safety laboratory,
- pharmacokinetics,
- pharmacodynamics: fasting plasma glucose, insulin, OGTT, C-peptide, gastric emptying and measurement of appetite and body weight, and
- immunogenicity samples.

Sampling schedules may be adjusted, and the duration of the residential period may be increased (but not decreased) based on ongoing review of the PK, PD, and/or safety data. Additional follow-up visits may occur depending upon the PK, PD, and/or safety data.

The target dose levels of LY3463251 planned for Part B include 1, 3, 9, and 24 mg, and will be evaluated in 4 dose-escalating cohorts. Cohorts 2 and 3 will be initiated following review of all available data from the previous cohort through at least 22 days and Cohort 4 to be initiated after at least 36 days.

An additional cohort (Cohort 5) may be initiated after reviewing at least 4 weeks of tolerability data obtained from Cohort 4. If the Cohort 5 is initiated, it will evaluate a dose lower than 24 mg (maximum dose administered in Part A) or assess an alternate dose up-titration scheme that does not exceed 24 mg (Table GZAA.2).

Escalation or titration of doses in a cohort may be adjusted based on the safety and tolerability data from at least 7 subjects in the previous cohort.

**Table GZAA.2. Dosing Scheme in Part B**

| Study Day | 1 | 8 | 15 | 22 | 29 | 36 | 43 | 50 | 57 | 64 | 71 | 78 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Dose (mg) | | | | | | | | | | | |
| **Cohort 1** | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| **Cohort 2** | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| **Cohort 3** | 3 | 3 | 6 | 6 | 9 | 9 | 9 | 9 | 9 | 9 | 9 | 9 |
| **Cohort 4** | 3 | 3 | 9 | 9 | 15 | 15 | 24 | 24 | 24 | 24 | 24 | 24 |
| **Cohort 5 (Optional)** | Dose level(s) to be determined after reviewing 4-week data from Cohort 4. | | | | | | | | | | | |

The timing for initiation of Part B of the study and the data to be reviewed prior to dose-escalation decisions, including the timing and scope of these reviews, are described in Section 7.4.1.

Safety and tolerability will be assessed throughout Part B of the study by means of vital sign measurements, safety laboratory tests, ECGs, physical examinations, and AEs.

## 5.2. Number of Participants

It is planned to enroll 64 subjects into Part A and 60 subjects into Part B. For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities have been finished.

Subjects who are randomized and who are discontinued from the study (providing that discontinuation did not result from a safety finding) may be replaced to ensure that enough subjects complete the study. To allow for replacement in case of discontinuation, up to 75 subjects may be enrolled into Part A and up to 85 subjects may be enrolled into Part B.

## 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 the study in healthy subjects mitigates the potential confounding effects of the disease state and concomitant medications in patients, and therefore provides the most unbiased assessment of the safety and tolerability in this first-in-human study. Overweight healthy subjects have been chosen for Part B in order to conduct a preliminary PD evaluation of change in fasting plasma glucose, fasting serum insulin, OGTT-derived parameters, appetite, and body weight.

In Part B, gastric emptying rate will be assessed using acetaminophen to evaluate if the observed GI intolerability after single dose of LY3463251 in Part A was associated with delay in gastric emptying.

A subject- and investigator-blinded, randomized, placebo-controlled design has been chosen to minimize bias in the primary objective of the study. A parallel-group design was chosen because a crossover design is impractical for compounds that have long half-lives. Additionally, a crossover design could confound PK data if subjects developed neutralizing antidrug antibodies (ADA).

The study is intended to estimate a maximum tolerated dose (MTD) or establish that doses exceeding the expected therapeutic dose are tolerated. Safety, tolerability, PK, immunogenicity and preliminary PD data in healthy subjects and overweight healthy subjects will assist in identifying an appropriate dose range for subsequent clinical studies.

The 12-week duration of the treatment period in the Part B has been planned

- to evaluate the safety and tolerability of LY3463251, considering the time needed to up-titrate doses >3 mg (~1 month or longer), while potentially decreasing the extent of nausea and vomiting observed in study subjects,
- for a reliable assessment of changes in body weight and insulin sensitivity in the presence of LY3463251, and
- for a more predictive assessment of a potential hepatic safety risk compared with a study of a shorter duration (FDA 2009; Hoofnagle and Björnsson 2019).

Periodic trial-level safety reviews during the MAD (in addition to the SAD) will ensure that any subject can be discontinued early, or the dose escalation can be terminated, in case of any AE requiring such a decision.

While recently published European Medicines Agency (EMA) guideline (EMA 2017) recommends use of sentinel dosing in first-in-human studies, it also allows for flexibility in a proposed dosing approach based on the available scientific data and preclinical assessment of a given molecule. The intended and exaggerated pharmacological responses of LY3463251 have been well characterized in multiple preclinical pharmacology models. LY3463251 was evaluated in the whole blood cytokine release assay indicating that LY3463251 does not activate blood innate immune cells, thus suggesting a low risk of a cytokine release syndrome. Moreover, toxicology studies have suggested that clinically unmanageable concerns would be unlikely to occur in humans treated with LY3463251. Based on the available data on the LY3463251 molecule, it does not present an uncertainty profile necessitating a sentinel dosing approach. Furthermore, sentinel dosing with low-risk compounds, such as LY3463251, may lead to inability to interpret data due to false positive AE findings in the absence of data from all cohorts or placebo-treated subjects.

CCI [redacted]

## 5.5. Justification for Dose

Human efficacious doses were estimated by scaling LY3463251 PK in monkeys to humans and using weight loss data in diet-induced obese mice and lean rats. CCI [redacted]

CCI [redacted]

CCI [redacted] The safety margins for the maximum anticipated human dose in Phase 1 studies are approximately 0.09-fold (rats) and 525-fold (monkeys), based on administered doses (dose multiples) and nonclinical NOAEL data (Table GZAA.3). Although the rat exposure margins at the NOAEL dose do not cover the complete dosing range planned, adverse findings in the rat study were limited to decreases in body weight and food consumption, which are expected pharmacological effects of LY3463251, and should not restrict the planned clinical doses.

CCI [redacted] Planned doses up to 24 mg will allow evaluation of PD effects across a wide range of LY3463251 exposures. This evaluation will aid in performing dose-exposure-response analyses and selecting doses for future clinical studies. Experience with other drugs has shown that slower dose escalation has improved tolerability (Petrone et al. 1999; Kim et al. 2015; Nauck et al. 2016); therefore, inclusion of dose up-titration steps in Cohorts 3 and 4 may potentially mitigate the GI tolerability issues observed for higher doses in Part A. Doses in Part B may be titrated or adjusted before each dose escalation based on the available safety, tolerability, and PK data during the study.

In addition, data from recently completed 3-month rat and monkey toxicology studies provide appropriate safety margins for the doses proposed in Part B (Table GZAA.5).

**Table GZAA.3. Margin of Safety for Subcutaneous Administration of LY3463251 in Part A Based on Administered Doses in 1-Month Toxicity and Toxicokinetic Studies**

| Species/Dose | Dose (mg/kg) | Margin of Safety[a] | |
|---|---|---|---|
| | | Starting Dose | Maximum Dose |
| **Human**[b] | | | |
| Starting dose (0.01 mg) | 0.00014[c] | | |
| Maximum dose (24 mg) | 0.343[c] | | |
| **Rat** | | | |
| NOAEL[d] | 0.03 | 214× | 0.09× |
| High dose[d] | 1 | 7,143× | 2.9× |
| **Monkey** | | | |
| NOAEL[e] | 180 | 1,285,714× | 525× |

Abbreviation: NOAEL = no-observed-adverse-effect level.

[a] The margin of safety is the administered dose in animals/administered dose in humans on a mg/kg basis.

[b] The human doses shown are the anticipated starting dose and the maximum dose for Part A.

[c] Human doses were adjusted for body weight assuming a 70-kg person.

[d] The rat NOAEL and high dose are from a 1-month repeat-dose toxicology study (Study Number 130-655).

[e] The monkey NOAEL was determined in a 1-month repeat-dose toxicology study (Study Number 130-657).

**NOTE:** Although the rat NOAEL was 0.03 mg/kg, adverse findings in rats at the mid and high doses (0.3 and 1 mg/kg, respectively) were limited to excessive decreases in body weight and food consumption. These are expected pharmacologic effects of LY3463251. There were no other adverse findings in rats that would affect clinical dosing limits.

**Table GZAA.4. Exposure Multiples for Subcutaneous Administration of LY3463251 in Part A Based on Exposures Measured in 1-Month Toxicity and Toxicokinetic Studies and Predicted Human Exposures**

| Species/Dose | AUC (µg•hr/mL) | Margin of Safety[a] | |
|---|---|---|---|
| | | Starting Dose | Maximum Dose |
| **Human**[b] | | | |
| Starting dose (0.01 mg) | 0.147[c] | | |
| Maximum dose (24 mg) | 352[c] | | |
| **Rat** | | | |
| NOAEL[d] | 14.95[e] | 102× | 0.04× |
| High dose[d] | 392.5[e] | 2,670× | 1.1× |
| **Monkey** | | | |
| NOAEL[f] | 93,100[g] | 633,333× | 264× |

Abbreviation: AUC = area under the plasma concentration versus time curve; $AUC_{0-\infty}$ = area under the concentration versus time curve from time 0 to infinity; $AUC_{0-168h}$ = area under the concentration versus time curve from time 0 to 168 hours post-dose; NOAEL = no-observed-adverse-effect level.

[a] The exposure multiple is calculated as the $AUC_{0-168h}$ in animals/$AUC_{0-\infty}$ in humans.

[b] The human doses shown are the anticipated starting dose and the maximum dose for Part A.

[c] Human exposures are predicted values.

[d] The rat exposure values are from the NOAEL (0.03 mg/kg) and high dose (1 mg/kg) in a 1-month repeat-dose toxicology study (Study Number 130-655).

[e] Rat $AUC_{0-168h}$ values are the mean male + female exposures on Day 29 in Study 130-655.

[f] The monkey NOAEL (180 mg/kg) was determined in a 1-month repeat-dose toxicology study (Study Number 130-657).

[g] The monkey $AUC_{0-168h}$ value is the mean male + female exposure on Day 29 in Study 130-657.

**NOTE:** Although the rat NOAEL was 0.03 mg/kg, adverse findings in rats at the mid and high doses (0.3 and 1 mg/kg, respectively) were limited to excessive decreases in body weight and food consumption. These are expected pharmacologic effects of LY3463251. There were no other adverse findings in rats that would affect clinical dosing limits.

**Table GZAA.5. Exposure Multiples for Subcutaneous Administration of LY3463251 in Part B Based on Exposures Measured in 3-Month Toxicity and Toxicokinetic Studies and Human Exposures from Part A**

| Species/Dose | AUC (µg•hr/mL) | Margin of Safety[a] | |
|---|---|---|---|
| | | Starting Dose | Maximum Dose |
| **Human**[b] | | | |
| Starting dose (1 mg) | 17.6[c] | | |
| Maximum dose (24 mg) | 590[c] | | |
| **Rat** | | | |
| NOAEL[d] | 29.9[e] | 1.7× | 0.1× |
| High dose[d] | 221[e] | 12.6× | 0.4× |
| **Monkey** | | | |
| NOAEL[f] | 83200[g] | 4727× | 141× |

Abbreviations: AUC = area under the plasma concentration versus time curve; $AUC_{0-\infty}$ = area under the concentration versus time curve from time 0 to infinity; $AUC_{0-168h}$ = area under the concentration versus time curve from time 0 to 168 hours postdose; NOAEL = no-observed-adverse-effect level.

[a] The exposure multiple is calculated as the $AUC_{0-168h}$ in animals/$AUC_{0-\infty}$ in humans.

[b] The human doses shown are the starting dose and the maximum dose for Study GZAA Part B.

[c] Steady state human exposures based on the preliminary PK data from Study GZAA Part A.

[d] The rat exposure values are from the NOAEL (0.1 mg/kg) and high dose (1 mg/kg) in a 3-month repeat-dose toxicology study (Study Number 130-695).

[e] Rat $AUC_{0-168h}$ values are the mean male + female exposures on Day 85 in Study 130-695.

[f] The monkey NOAEL (180 mg/kg) was determined in a 3-month repeat-dose toxicology study (Study Number 130-694).

[g] The monkey $AUC_{0-168h}$ value is the mean male + female exposure on Day 85 in Study 130-694.

**NOTE:** Although the rat NOAEL was 0.1 mg/kg, adverse findings in rats at the high doses (1 mg/kg) were limited to excessive decreases in body weight and food consumption. These are expected pharmacologic effects of LY3463251. There were no other adverse findings in rats that would affect clinical dosing limits.

# 6. Study Population

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

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 28 days prior to enrollment. Subjects who are not enrolled within 28 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 must agree to adhere to contraception restrictions specified in Section 6.3.4

[1b] female subjects must be of non-childbearing potential, and include those who are:

- infertile due to surgical sterilization (hysterectomy, bilateral salpingectomy, or bilateral oophorectomy), congenital anomaly such as mullerian agenesis, or
- those who are post-menopausal, defined in Part A as either:
    - a woman at least 50 years of age with an intact uterus, not on hormone therapy, who has had cessation of menses for at least 1 year, or at least 6 months of spontaneous amenorrhea with a follicle-stimulating hormone of >40 mIU/Ml
    - a woman of at least 55 years of age not on hormone therapy who has had at least 6 months of spontaneous amenorrhea
    - a woman of at least 55 years of age who has a diagnosis of menopause before starting hormone replacement therapy
- those who are post-menopausal, defined in Part B as either:

- a woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND with a follicle-stimulating hormone of >40 mIU/mL; women in this category must test negative in pregnancy test prior to study entry.
- a woman 55 years of age or older not on hormone therapy who has had at least 12 months of spontaneous amenorrhea; or
- a woman of at least 55 years of age with a diagnosis of menopause before starting hormone replacement therapy.

[2] are aged between 18 and 65 years, inclusive

[3] have a BMI of ≥18.5 and <32 kg/m$^2$ (Part A [SAD]) or a BMI ≥27 and <40 kg/m$^2$ (Part B [MAD])

[4] have had a stable weight for the 3 months prior to screening and enrollment (<5% body weight change), and have not received dietary intervention in the 3 months prior to screening and enrollment

[5] have safety 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

[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

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

[9] 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

[10] are Lilly or Covance employees

[11] 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

[12] 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

[13] have previously completed or withdrawn from this study and have previously received the investigational product

[14] have known allergies to related compounds of LY3463251 or any components of the formulation, or history of significant atopy

[15] have clinically significant abnormal ECG results constituting a risk when taking the investigational product, as determined by the investigator

[16] have clinically significant abnormal blood pressure and/or pulse rate constituting a risk when taking the investigational product, as determined by the investigator

[17] have a history or presence of cardiovascular (including hypertension), respiratory, hepatic, renal, GI, 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. Appendectomy is permitted.

[18] have been diagnosed with type I diabetes mellitus or TD2M, or have any of the following at screening:

- a fasting plasma glucose concentration ≥126 mg/dL (7.0 mmol/L)
- glycated hemoglobin ≥6.5% (48 mmol/mol)

Note: assessments performed on Day 1 will not be used to confirm eligibility.

[19] have a history or presence of psychiatric disorders. Attention deficit disorder (ADD)/attention deficit hyperactivity disorder (ADHD) is permitted provided it is not severe, does not require treatment, and does not jeopardize the ability to adhere to the study requirements. At least 5 half-lives following discontinuation of any treatment for ADD/ADHD should have passed

- For Part B only:
    - in the judgment of the investigator, subjects are actively suicidal and deemed to be at significant risk for suicide
    - have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the Columbia Suicide Severity Rating Scale (C-SSRS)

[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, hepatitis B core antibody, and/or positive hepatitis B surface antigen

[24] are women who are lactating

[25] intend to use over-the-counter medication in the 7 days, or prescription medications in the 14 days prior to dose administration (including any medications for the treatment of obesity), with the exception of vitamin and mineral supplements and occasional use of acetaminophen. If the situation arises, an otherwise suitable subject may be included following agreement between the investigator and the sponsor

[26] have donated blood of more than 500 mL within the previous 3 months of study screening, or intend to donate blood during the course of the study

[27] have an average weekly alcohol intake that exceeds 21 units per week (males up to age 65) and 14 units per week (females and males aged 65), or are unwilling to stop alcohol consumption from 48 hours prior to admission to and while resident at the CRU (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] have used any tobacco product within 3 months of Day -1, or are unwilling to refrain from the use of tobacco during the study. Results from cotinine tests performed as part of the urine drug screen that are consistent with passive smoking are not exclusionary

[29] are immunocompromised

[30] have received treatment with biologic agents (such as monoclonal antibodies, including marketed drugs) within 3 months or 5 half-lives (whichever is longer) prior to dosing.

[31] have significant allergies to humanized monoclonal antibodies

[32] have clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe post treatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, or exfoliative dermatitis)

[33] have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years

[34] have had breast cancer within the past 10 years

[35] are unwilling to abide by the lifestyle and dietary requirements in Section 6.3

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

[37] have a history or presence of a GI disorder that impacts gastric emptying (for example, relevant esophageal reflux or gall bladder disease, gastric bypass surgery, pyloric stenosis).

[38] prior (within 5 years) or planned (during the study) surgical treatment or device-based treatment use for obesity.

[39] have obesity induced by other endocrinologic disorders (for example, Cushing syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader Willi syndrome)

[40] have evidence of acute or chronic liver disease or Gilbert's disease, including any of the following:

- aspartate aminotransferase (AST) or ALT >1.5× ULN; or
- ALP >1.5× ULN; or
- TBL >2× ULN.

## 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*

Subjects will be provided with standardized meals while resident at the CRU, and the same standardized breakfast and lunch will be provided on each day for all subjects when appetite will be assessed by VAS (Section 9.6.4). The macronutrient composition of the standardized meals should be targeted to provide approximately 50% of the calories from carbohydrate, 30% of the calories from fat, and 20% of the calories from protein. Subjects will be instructed to consume meals within approximately 30 minutes. Detailed guidance related to meal standardization will be provided to the investigative site.

Subjects should be fasted for 8 hours prior to blood sampling, performing ECGs, and dose administration. Post-dose ECG measurements should be taken prior to any food intake.

Subjects should maintain adequate carbohydrate intake for the 3 days before the scheduled OGTT and will be fasted for at least 10 hours before administration of the 75-g oral glucose dose.

On days where assessment of subjects' appetite is to be measured (Section 2), standardized breakfast and lunch will be provided approximately 30 minutes after the first VAS assessment. Additional food should not be consumed until after the 5-hour VAS assessment. With the exception of water, drinks are not permitted until after the 5-hour VAS assessment. If the subject is unable to consume the standardized meal completely, the leftover amount (as percentage of total meal) will be recorded in the electronic case report form (eCRF).

At all other times, subjects should maintain their standard diet.

### *6.3.2. Caffeine, Alcohol, and Tobacco*

Subjects will be allowed to maintain their regular caffeine consumption.

Tobacco use is not permitted for 3 months prior to Day -1 and during the study.

Alcohol consumption is not permitted from 48 hours prior to admission to and while resident at the CRU.

### *6.3.3. Activity*

Subjects should avoid exercise during the screening visit, and should avoid strenuous exercise 3 days prior to each admission to and while at the CRU. Subjects should maintain their normal levels of activity at other times.

### *6.3.4. Contraceptive Requirements*

Male subjects (regardless of their fertility status) with non-pregnant female partners of childbearing potential must agree to either remain abstinent (if this is their preferred and usual lifestyle), or to use condoms as well as one additional highly effective (< 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) from the time of first administration of the investigational product until the last study visit or 90 days following the last dose of investigational product, whichever is longer.

Men and their partners may choose to use a double-barrier method of contraception; however, barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception (each barrier method must include use of a spermicide). 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.

Male subjects with pregnant partners should use condoms during intercourse from the time of first administration of the investigational product until the last study visit or 90 days following the last dose of investigational product, whichever is longer. Male subjects should refrain from sperm donation from the time of first administration of the investigational product until the last study visit or 90 days following the last dose of investigational product, whichever is longer.

Male subjects who chose to remain abstinent (if this is their preferred and usual lifestyle) must adhere to the contraception requirements indicated above should their circumstances change.

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

## 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

The investigational product will be administered as a SC injection into the abdomen while the subject is resident at the CRU.

LY3463251 will be provided at a concentration of 3 mg/mL. The doses to be administered are presented in Sections 5.1.1 and 5.1.2.

Placebo will be normal saline (0.9% sodium chloride).

The investigator or designee is responsible for:

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

Note: In some cases, the site 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*

LY3463251 and placebo will be provided to the investigative site as bulk supply in vials by Lilly or its designee.

Clinical trial materials will be labeled according to the country's regulatory requirements, and will be stored, inventoried, reconciled, and destroyed according to applicable regulations. Clinical trial materials are manufactured in accordance with current good manufacturing practices.

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

## 7.2. Method of Treatment Assignment

Subjects will be randomized to a treatment using a computer-generated randomization schedule.

### *7.2.1. Selection and Timing of Doses*

The actual time of all dose administrations will be recorded in the subject's eCRF.

The doses will be administered at approximately the same times on each day in Part B.

## 7.3. Blinding

Blinding will be maintained throughout the conduct of the study as described in the separate blinding plan.

The unblinded pharmacist or designee will prepare the study drug.

Emergency codes will be available to the investigator. A code, which reveals the treatment for a specific study subject, may be opened during the study only if the subject's well-being requires knowledge of the subject's treatment assignment.

If a subject's study treatment assignment is unblinded, the subject must be discontinued from the study, unless the investigator obtains specific approval from a Lilly clinical pharmacologist (CP) 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 subject's emergency code.

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

## 7.4. Dose Modification

### *7.4.1. Dose-Escalation*

By nature of being a dose-escalation study, data will be evaluated on an ongoing basis until the highest planned dose has been administered, or the MTD is determined. If the highest planned dose is not reached, the highest dose level that is tolerated will be designated as the MTD.

Safety and tolerability data will be the primary criteria for the dose-escalation. No dose decision can occur without prior discussion and agreement between the investigator and the Lilly CP/CRP/study team. Safety data, in particular AEs, SAEs, and adverse laboratory abnormalities, will be independently assessed by the investigator, and will be considered related to the investigational product unless there is clear evidence that the event is not related.

Any available PK data may be used to guide dose selection or to determine if the number of doses to be studied may be reduced.

After review of these data, an agreement on the appropriate dose will be made by the investigator and sponsor for the next cohort/dose level. A lower dose may be administered; dose levels may be repeated providing that it is not the result of a safety finding; or the magnitude of dose escalations may be reduced following data review, providing that subsequent escalations do not increase by more than approximately 3-fold (a half-log increment).

#### 7.4.1.1. Part A

Dose-escalation decisions will primarily be based on safety and tolerability data obtained up to Day 7 (in Cohorts 1 through 3) or Day 14 (in Cohorts 4 through 8) from at least 7 subjects in the previous cohort, and all safety and tolerability data from previous cohorts. Additionally, any available PK data may be used to guide dose selection or to determine if the number of doses to be studied may be reduced.

If any of the following scenarios occur, dosing at the current level and further dose-escalation will be discontinued:

- Five or more subjects develop AEs within 7/14 days (depending on the cohort; see Section 10.3.5) of dosing that are considered to be related to study treatment and graded as at least moderate, clinically significant and not responsive to supportive care
- One or more subjects develop AEs within 7/14 days (depending on the cohort; see Section 10.3.5) of dosing that are considered to be related to study treatment and graded as severe
- One or more subjects develop SAEs that are considered to be related to study treatment

#### 7.4.1.2. Part B

**Dose-escalation at the cohort level**

Part B may be initiated following review of all available safety and tolerability data up to Day 14 post-dose from all subjects in the last cohort of Part A, and all safety and tolerability data available at this time (including ADA data) from the previous cohorts.

Dose-escalation decisions in Part B will primarily be based on safety and tolerability data obtained from at least 7 subjects up to and including Day 22 for Cohorts 2 and 3, and up to and including Day 36 for Cohort 4. Additionally, any available PK data may be used to guide dose selection or to determine if the number of doses to be studied may be reduced.

If any of the following scenarios occur, dosing at the current level and further dose-escalation will be interrupted:

- Four or more subjects develop AEs that are considered to be related to study treatment and graded as at least moderate and not responsive to supportive care
- One or more subjects develop AEs that are considered to be related to study treatment and graded as severe
- One or more subjects develop SAEs that are considered to be related to study treatment

**Dose-escalation at the individual subject level**

In case a subject interrupted the study drug and

- more than 2 doses were missed, the subject should be discontinued from the study – this would be at least 25% of doses missed and may compromise data reliability.
- the number of consecutive missed doses is ≤2, the treatment can be restarted at the same dose, if the drug was well tolerated prior to interruption.
- the number of consecutive missed doses is ≤2, then the treatment should be restarted at 3 mg irrespective of the dose the subject was receiving if the dose was not well tolerated before the interruption and subsequently follow the assigned dose escalation scheme.

Every effort should be made for a subject to adhere to the protocol dose escalations within a cohort. However, it is possible that some subjects may not tolerate higher doses of the study drug.

All dose adjustments discussed below may only occur following agreement between the investigator and sponsor medical monitor. The dose administered to the subjects each week should be recorded on the case report form during titration and throughout the study.

**Dose modification for Cohort 4**

Subjects who do not tolerate the 3 mg or 9 mg doses of study drug for at least 2 weeks will be discontinued from study drug but should continue to be monitored for safety for the duration of the study.

If after 2 weeks at 15 mg, a subject still has gastrointestinal symptoms preventing dose escalation to 24 mg, the subject may be kept at 15 mg for 1 to 3 additional doses before escalating to 24 mg.

Subjects who cannot tolerate the 15 mg dose after at least 2 doses due to moderate or severe gastrointestinal symptoms may be discontinued from study treatment but should continue to be monitored for safety for the duration of the study.

If after at least 2 doses of 24 mg a subject has poorly tolerated nausea, vomiting, or diarrhea, and the investigator does not believe that the subject will tolerate additional injections of 24 mg despite the possibility of tachyphylaxis, then the investigator may reduce the dose to 15 mg. If this dose of 15 mg is tolerated, the subject may remain at that dose level for the duration of the study or the investigator may increase the dose back to 24 mg. Maintenance doses of less than 15 mg will not be allowed.

**Dose Modification for Optional Cohort 5**

In case a subject has poorly tolerated nausea, vomiting, or diarrhea at a given dose, the investigator may decide to decrease the dose to a previous dose level.

## 7.5. Preparation/Handling/Storage/Accountability

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 product 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).

## 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

In general, concomitant medication should be avoided; however, acetaminophen (1 g, maximum 4 g/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 CP or CRP. Any medication used during the course of the study must be documented.

Acetaminophen should not be allowed from the day prior to gastric emptying assessment until 24 hours after acetaminophen dosing.

## 7.8. Treatment After the End of the Study

Not applicable.

# 8. Discontinuation Criteria

Subjects discontinuing from the treatment or study prematurely for any reason should complete early discontinuation procedures per Section 2 of this protocol.

Dose-escalation stopping criteria are presented in Section 7.4.1.

## 8.1. Discontinuation from Study Treatment

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:

- ALT or AST ≥5× ULN on 2 consecutive occasions
- ALT or AST ≥3× ULN and TBL ≥2× ULN or international normalized ratio ≥1.5
- ALT or AST ≥3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- 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%).

The following discontinuation criteria related to abnormal liver tests should be applied during the dose-escalation process. The occurrence of 1 or more cases meeting ***all*** the following criteria should be considered as a dose-limiting toxicity event:

- ALT or AST ≥3× ULN
- TBL ≥2× ULN
- No initial cholestasis (ALP does not exceed 2× ULN), and
- No other cause explaining the abnormality in liver tests.

Subjects who do not tolerate a given dose level due to gastrointestinal symptoms may be discontinued from study drug or may have their dose reduced depending on various parameters as described in Section 7.4.1.2 (dose level, severity of symptoms, investigator's judgement, discussion between investigator and sponsor medical monitor). If they are discontinued from study drug, these subjects should continue to be monitored for safety for the duration of the study.

Additionally, subjects may be discontinued from the investigational product if any of the following occur:

- An AE that is considered to be intolerable
- An abnormal safety laboratory test result, as determined by the investigator

- Corrected QT interval (QTc) >500 msec or an increase from baseline in QTc >60 msec
- The investigator decides that the subject should be discontinued from using the investigational product.

If the subject develops active suicidal ideation with some intent to act with or without a specific plan (yes to Question 4 or 5 on the "Suicidal Ideation" portion of the C-SSRS) or develops suicide-related behaviors as recorded on the C-SSRS, it is recommended that the subject be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the subject is to be discontinued from the study.

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions are described in Section 9.4.6.4. Systemic allergic/ hypersensitivity reactions may possibly lead to a participant's permanent discontinuation of investigational intervention. The investigator, after consultation with the sponsor-designated medical monitor, determines that a clinically significant hypersensitivity reaction has occurred. A clinically significant systemic hypersensitivity reaction is 1 that occurs after administration of the investigational intervention (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) and requires parenteral medication, does not respond to symptomatic medication, results in clinical sequelae, or is an anaphylactic reaction.

### *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 (GCP)
- Investigator decision: the investigator decides that the subject should be discontinued from the study
- Subject decision: the subject 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 laboratory tests that will be performed for this study.

Appendix 6 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 (ICF) 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, 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 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.

See Section 9.4.6.3 for monitoring injection site reactions and Section 9.4.6.4 for monitoring allergic/hypersensitivity events.

### *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 (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 subject or may require intervention to prevent one 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 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 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 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 so that the situation can be assessed.

## 9.3. Treatment of Overdose

For the purposes of this study, an overdose of LY3463251 is considered any dose higher than the dose assigned through randomization. Therapeutic or monitoring measures should be implemented according to clinical presentation at the discretion of the investigator.

## 9.4. Safety

### *9.4.1. Laboratory Tests*

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

Samples collected at screening and on Day -1 will be analyzed at a local laboratory. Samples collected at the remaining time points will be analyzed by a central laboratory. With the exception of safety laboratory test results that may unblind the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor.

#### 9.4.1.1. Fasting Plasma Glucose, Lipoprotein, Cholesterol, and Triglycerides

**Part A:** Fasting plasma glucose, low- and high-density lipoprotein, cholesterol, and triglyceride concentrations will be measured as part of safety assessments. Samples for analysis of low- and high-density lipoprotein, cholesterol, and triglyceride concentrations will be collected as part of the safety laboratory tests, and venous blood samples of approximately 4 mL will be collected to determine plasma concentrations of glucose.

**Part B:** Fasting plasma glucose, low- and high-density lipoprotein, cholesterol, and triglyceride concentrations will be measured for PD analysis (Section 9.6.1).

### *9.4.2. Body Weight*

Body weight will be measured as part of safety assessments in Part A and for PD analysis in Part B.

Body weight will be measured as indicated in the Schedule of Activities (Section 2).

Subjects will be weighed in light clothing at approximately the same time in the morning before dosing, after an overnight fast and evacuation of bowel and the bladder, if possible.

During the treatment period, weight will be measured twice on each scheduled occasion during Part B only, with the subject stepping off the scale between measurements. Both weight measurements will be recorded in the source document and the eCRF. Wherever possible, the same scale will be used for all weight measurements throughout the study and the scale will not be moved or recalibrated.

### 9.4.3. Vital Signs

For each subject, vital signs (including blood pressure, pulse rate, and body temperature in Parts A and B, and respiratory rate in Part A only) 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.

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. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

Ambulatory measurements of blood pressure will be collected every 30 minutes between 0800 and 2200 hours and every 60 minutes between 2201 and 0759 hours according to the Schedule of Activities (Section 2).

### 9.4.4. Electrocardiograms

For each subject, single ECGs should be collected according to the Schedule of Activities (Section 2), and may be obtained at additional times, when deemed clinically necessary. Electrocardiograms must be recorded before collection of any blood samples. Subjects must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection.

Electrocardiograms will be interpreted by a qualified investigator (physician 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 quantitative or qualitative change from baseline is identified after enrollment, the investigator will assess the subjects for symptoms (e.g., palpitations, near syncope, syncope) to 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 (from at least 1 of the replicate ECGs from each timepoint when replicate ECGs are collected). Any new clinically relevant finding should be reported as an AE. Any clinically significant findings from

ECGs that result in a diagnosis and that occur after the subject receives the first dose of the investigational product, should be reported to Lilly, or its designee, as an AE via eCRF.

Digital ECGs will be electronically transmitted to a central ECG laboratory designated by Lilly. The central ECG laboratory will perform a basic quality control check (e.g. demographics and study details) then store the ECGs in a database. At a future time, the stored ECG data may be overread at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report writing purposes unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

### *9.4.5. Physical Examination*

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

### *9.4.6. 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
- adverse events

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

#### 9.4.6.1. Hepatic Safety

**Close hepatic monitoring**

Laboratory tests (Appendix 2), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

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

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

**Comprehensive hepatic evaluation**

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

| If a subject with baseline results of... | develops the following elevation: |
|---|---|
| ALT or AST <1.5X ULN | ALT or AST ≥3X ULN with hepatic signs/symptoms[a], or ALT or AST ≥5X ULN |
| ALP <1.5X ULN | ALP ≥3X ULN |
| TBL <1.5 X ULN | TBL ≥2X ULN (except for patients with Gilbert's syndrome) |
| ALT or AST ≥1.5X ULN | ALT or AST ≥2X baseline with hepatic signs/symptoms[a], or ALT or AST ≥3X baseline |
| ALP ≥1.5X ULN | ALP ≥2X baseline |
| TBL ≥1.5X ULN | TBL ≥1.5X baseline (except for patients with Gilbert's syndrome) |

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

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper-quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined earlier, as well as tests for prothrombin time-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the subject's clinical condition, the investigator should consider referring the subject for a

- hepatologist or gastroenterologist consultation
- magnetic resonance cholangiopancreatography
- endoscopic retrograde cholangiopancreatography
- cardiac echocardiogram, or
- liver biopsy.

**Additional hepatic data collection (hepatic safety CRF) in study subjects who have abnormal liver test results during the study**

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study subjects who meet 1 or more of the following 5 conditions:

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

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

#### 9.4.6.2. Columbia-Suicide Severity Rating Scale

The C-SSRS (Columbia Lighthouse Project [WWW]) captures the occurrence, severity, and frequency of suicide-related thoughts and behaviors during the assessment period. The scale includes suggested questions to solicit the type of information needed to determine if a suicide-related thought or behavior has occurred. The C-SSRS will be administered by appropriately trained site personnel at the time points specified in the Schedule of Activities (Section 2.2).

Subjects with any significant change must be referred to a psychiatrist. If the investigator determines that suicide-related behaviors have occurred, the Lilly Self-Harm Supplement Form will be used to collect additional information to allow for a more complete assessment of these behaviors. As noted earlier, subjects with any clinically significant change, as determined by the investigator, must be referred to a psychiatrist.

#### 9.4.6.3. Injection Site Reactions

If an AE of injection site reaction is reported, the investigator will complete a supplemental injection site reaction form in the eCRF. The injection site reaction form documents the presence of erythema, induration, pain (mild, moderate, or severe), pruritis, and edema. Injection sites may be inspected and photographically documented.

#### 9.4.6.4. Allergic/Hypersensitivity Events

All biologic agents carry the risk of systemic allergic/hypersensitivity reactions. Clinical manifestations of these reactions may include but are not limited to

- skin rash
- pruritus (itching)
- dyspnea

- urticaria (hives)
- angioedema (for example, swelling of the lips and/or tongue)
- hypotension
- anaphylactic reaction

Participants with clinical manifestations of systemic allergic/hypersensitivity reactions should be treated per local standard of care. Additional data describing each symptom should be provided to the sponsor in the eCRF.

In case of anaphylaxis or generalized urticaria, additional blood samples should be collected as close as possible to the onset of the event (see Appendix 3). Follow-up samples should be obtained at the next scheduled visit or 4 weeks after the event, whichever is later. The laboratory results are provided to the sponsor via the central laboratory.

## 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 LY3463251. 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 clock time) of each sampling will be recorded.

Samples from placebo-treated subjects will not be analyzed.

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

### *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 LY3463251 will be assayed using a validated enzyme-linked immunosorbent assay method. Analyses of samples collected from placebo-treated subjects are not planned.

Bioanalytical samples collected to measure investigational product concentrations will be retained for a maximum of 1 year following last subject visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as additional metabolism or exploratory analyses such as bioanalytical assay validation or cross-validation exercises.

## 9.6. Pharmacodynamics

### *9.6.1. Fasting Plasma Glucose, Lipoprotein, Cholesterol and Triglycerides (Part B)*

Fasting plasma glucose, low- and high-density lipoprotein, cholesterol, and triglyceride concentrations will be measured from venous blood samples. Samples for analysis of low- and

high-density lipoprotein, cholesterol, and triglyceride concentrations will be collected as part of the safety laboratory tests, and venous blood samples of approximately 4 mL will be collected to determine plasma concentrations of glucose, as described in Section 9.4.1.

### 9.6.2. Serum Insulin and C-Peptide (Part B)

At the visits and times specified in the Schedule of Activities (Section 2), venous blood samples of approximately 3.5 mL each will be collected to determine C-peptide and serum concentrations of insulin. Samples will be analyzed at a central laboratory.

### 9.6.3. Oral Glucose Tolerance Test (Part B)

Subjects should maintain their regular dietary intake for 3 days before the scheduled OGTT. Subjects will be fasted for at least 10 hours before administration of a 75-g oral glucose dose, which should be consumed within 5 minutes.

Glucose, C-peptide, and insulin will be measured during an OGTT to assess effects of LY3463251 on glycemic control, OGTT index, and insulin sensitivity. Samples will be analyzed at a central laboratory.

### 9.6.4. Gastric Emptying (Part B)

Acetaminophen is a well-established marker for the rate and extent of gastric emptying (Young 2005). It is rapidly absorbed from the duodenum upon release from the stomach. A delay in gastric emptying is reflected in the alterations to the concentration-time profile of acetaminophen, specifically, decreasing its $C_{max}$ and $T_{max}$ without altering the extent (total drug amount) absorbed. A dose of approximately 1 g acetaminophen is considered to be sufficient for bioanalytical detection and will be administered after overnight fast on Day -2 and about 48 hours after first and last LY3463251 doses in Part B (Section 2).

Venous blood samples of approximately 2 mL each will be collected to determine the plasma concentrations of acetaminophen.

#### 9.6.4.1. Bioanalysis

Concentrations of acetaminophen will be assayed using validated liquid chromatography mass spectrometry method. Analyses of samples collected from placebo-treated subjects are not planned.

### 9.6.5. Visual Analog Scale for Assessment of Appetite (Part B)

At the times specified in the Schedule of Activities (Section 2), the subjective rating of appetite sensations will be measured by a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption.

Dietary restrictions related to the measurements of appetite are described in Section 6.3.1.

The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000), and is presented as a 100-mm line, anchored by verbal descriptors, usually “extremely” and “not at all.” Subjects 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 subject 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 (van Can et al. 2014):

satiety + fullness + (100 — prospective food consumption) + (100 — hunger) / 4

A higher overall appetite score indicates less appetite and a lower score indicates more appetite.

### *9.6.6. 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 LY3463251. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of LY3463251. All samples for immunogenicity should be taken predose when applicable and possible. Sampling for drug hypersensitivity reactions is described in Section 9.4.6.4. 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.

Treatment-emergent ADAs (TEADAs) are defined in Section 10.3.4. Subjects who are TEADA positive at the end of the study or at early discontinuation may be followed up with samples taken approximately every 3 months, until they return to 2-fold titer of baseline or for a maximum of 1 year.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3463251 at a laboratory approved by the sponsor. Antibodies may be further characterized and/or evaluated for their ability to neutralize the activity of LY3463251.

Samples will be retained for a maximum of 15 years after the last subject visit, or for a shorter period if local regulations and institutional review boards (IRBs) allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to LY3463251. 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 LY3463251 and to investigate genetic variants thought to play a role in T2DM, diabetic complications, obesity, or the potential mechanism of action of LY3463251. 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 IRBs 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 LY3463251 or after LY3463251 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

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

Blood samples for non-pharmacogenetic biomarker research will be collected at the times specified in the Schedule of Activities (Section 2) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to LY3463251, pathways associated with T2DM, diabetic complications, obesity, or the potential mechanism of action of LY3463251 and/or research method, or for validating diagnostic tools or assay related to T2DM, diabetic complications, obesity, or the potential mechanism of action of LY3463251.

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 IRBs impose shorter time limits, 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 LY3463251 or after LY3463251 is commercially available.

## 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 is customary for Phase 1 clinical studies evaluating safety and PK, and is not powered on the basis of statistical hypothesis testing.

Subjects who are randomized and who are discontinued from the study (providing that discontinuation was not as a result of a safety finding) may be replaced to ensure that enough subjects 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.

### *10.2.2. Study Participant Characteristics*

The subject's age, sex, race, weight, height, and other demographic characteristics will be summarized.

## 10.3. Statistical Analyses

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

Pharmacokinetic and PD analyses will be conducted on data from all subjects who receive at least 1 dose of the investigational product and have evaluable PK and PD data.

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.

### *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, 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 laboratory parameters, C-SSRS scores, Lilly Self-Harm Supplement responses, and vital signs.

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (Columbia Lighthouse Project [WWW]). The parameters will be listed, and summarized using standard descriptive statistics. Electrocardiogram data and physical examination will be performed for safety monitoring purposes and will not be listed or summarized.

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 LY3463251 will be calculated by standard noncompartmental methods of analysis.

The primary parameters for analysis will be AUC from time 0 to infinity (AUC[0-∞]), AUC during 1 dosing interval (AUC[0-τ]), AUC from time 0 to the time of the last quantifiable concentration (AUC[0-$t_{last}$]), maximum drug concentration ($C_{max}$) and time to reach $C_{max}$ ($T_{max}$). Other noncompartmental parameters, such as half-life, apparent clearance, and apparent volume of distribution may be reported. If deemed necessary, additional model based analyses may be performed.

#### 10.3.2.2. Pharmacokinetic Statistical Inference

The degree of dose proportionality for LY3463251 will be assessed by fitting the power model (Smith et al. 2000) to AUC[0-∞], AUC[0-τ] and $C_{max}$ versus dose for each dose level of LY3463251. The estimated ratio of dose-normalized geometric means of PK parameters between the highest and lowest doses will be used to assess dose proportionality. In addition, the slope and its 90% confidence interval (CI) and the geometric least-square means for each dose level tested will be produced. The analysis will be performed separately for Parts A and B. In the event that the power model is not a good representation of the data over the entire dose range tested, alternative models may be investigated. Log-transformed $C_{max}$ and AUC least-squares means, and 90% CI estimates for each dose will be back-transformed to provide the geometric means and the corresponding 90% CIs.

Additional analysis will be conducted if appropriate.

### *10.3.3. Pharmacodynamic Analyses (Part B Only)*

#### 10.3.3.1. Pharmacodynamic Parameter Estimation

The primary parameters for analysis will be fasting plasma glucose concentrations, fasting serum insulin concentrations, OGTT-derived-parameters, gastric emptying rate, appetite, and body weight. Baseline body weight will be computed as the average of the measurements taken on

Days -1 and 1. Pharmacodynamic data will be summarized as reported values and as changes from baseline using descriptive statistics.

#### 10.3.3.2. Pharmacodynamic Statistical Inference

Pharmacodynamic parameters will be summarized with no statistical inference. Additional analysis will be conducted if appropriate.

### *10.3.4. Evaluation of Immunogenicity*

The frequency and percentage of subjects with preexisting ADA and with TEADA to LY3463251 will be tabulated. For subjects who are ADA negative at baseline, TEADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the assay. For subjects who are ADA positive at baseline, TEADAs are defined as those with a 4-fold (2 dilutions) increase in titer compared to baseline. For subjects with TEADA, the distribution of maximum titers will be described. The frequency and percentage of subjects with neutralizing antibodies, if measured, may also be tabulated for subjects with TEADA.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3463251 may be assessed.

### *10.3.5. Data Review During the Study*

Access to safety data is scheduled to occur after Day 7 for Cohorts 1 through 3 in Part A, Day 14 for Cohorts 4 to 8 in Part A, Day 22 for Cohorts 1 and 2, and Day 36 for Cohort 3 in Part B. Following completion of Cohorts 1 to 3 in Part A, an interim PK analysis will be conducted. Depending on those PK results in Part A, dose escalation decisions for Cohorts 4 and 5 may be based on data available at 7 rather than 14 days post-dose.

After the third SAD cohort, all available PK data obtained up to Day 14 from at least 7 subjects in the third cohort, and all available PK data from the preceding cohorts, will be reviewed to confirm the human dose projections established before study start. Depending on these results in Part A, the timing for dose escalation between Cohorts 4 and 5 may be reduced to 7 days.

The purpose of these reviews is to guide dose selection for the next dosing session, and/or to inform the design of subsequent studies. The investigator and the Lilly sponsor team will make the determination regarding dose-escalation, based upon their review of the data. The investigator will remain blinded, and the Lilly sponsor team will be unblinded during these reviews.

Safety and tolerability data up to 14 days post-dose from all subjects in the last cohort of Part A, and all safety and tolerability data available at this time (including ADA data) from the preceding cohorts of Part A will be reviewed prior to initiation of Part B.

Interim access to PK and PD data may be scheduled during Part B to plan for future clinical studies.

### *10.3.6. Interim Analyses*

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the Lilly CP, 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 |
| **ADHD** | attention deficit hyperactivity disorder |
| **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 versus time curve |
| **$AUC_{0\text{-}168h}$** | area under the concentration versus time curve from time 0 to 168 hours post-dose |
| **$AUC_{(0\text{-}\infty)}$** | area under the concentration versus time curve from time 0 to infinity |
| **$AUC_{(0\text{-}\tau)}$** | area under the concentration versus time curve during 1 dosing interval |
| **$AUC_{(0\text{-}t_{last})}$** | area under the concentration versus time curve from time 0 to the time of the last quantifiable concentration |
| **blinding** | A procedure in which one 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.<br><br>A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the subject is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the subject are not. A double-blind study is one in which neither the subject 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 |
| **BMI** | body mass index |
| **CI** | confidence interval |
| **$C_{max}$** | maximum observed 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, GCP requirements, and the applicable regulatory requirements. |

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| **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 |
| **C-SSRS** | Columbia Suicide Severity Rating Scale |
| **ECG** | electrocardiogram |
| **eCRF** | electronic case report form |
| **EMA** | European Medicines Agency |
| **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. |
| **Fc** | fragment crystallization region |
| **GCP** | good clinical practice |
| **GDF15** | growth and differentiation factor 15 |
| **GFRAL** | glial cell derived neurotrophic receptor alpha–like |
| **GI** | gastrointestinal |
| **HIV** | human immunodeficiency virus |
| **IB** | Investigator's Brochure |
| **ICF** | informed consent form |
| **ICH** | International Council for Harmonization |
| **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. |

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|---|---|
| **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. |
| **IRB** | institutional review board |
| **MTD** | maximum tolerated dose |
| **NOAEL** | no-observed-adverse-effects-level |
| **OGTT** | oral glucose tolerance test |
| **PK/PD** | pharmacokinetic/pharmacodynamic |
| **QTc** | corrected QT interval |
| **QW** | once-weekly |
| **randomize** | the process of assigning subjects/patients to an experimental group on a random basis |
| **SAD** | single-ascending dose |
| **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. |
| **SUSAR** | suspected unexpected serious adverse reaction |
| **T2DM** | type 2 diabetes mellitus |
| **TBL** | total bilirubin level |
| **TEADA** | treatment-emergent antidrug antibodies |
| **TEAE** | treatment-emergent adverse event: Any untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment |
| **$T_{max}$** | time to maximum observed concentration |
| **ULN** | upper limit of normal |

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|---|---|
| **VAS** | visual analog scale |

# Appendix 2. Safety Laboratory Tests (Fasting)

### Safety Laboratory Tests

Samples collected at screening and on Day -1 will be analyzed at a local laboratory. Samples collected at all other time points will be analyzed by a central laboratory.

In addition, a 3.5-mL sample will be collected locally on Day 6 for analyzing the levels of AST, ALT, ALP, total bilirubin, and gamma glutamyl transferase during Part B of the study.

| | |
|---|---|
| Hematology | Clinical Chemistry |
| Hematocrit | Sodium |
| Hemoglobin | Potassium |
| | Bicarbonate |
| Erythrocyte count (red blood cells) | Chloride |
| Mean cell volume | Calcium |
| Mean cell hemoglobin | Phosphorus |
| Mean cell hemoglobin concentration | Magnesium |
| Leukocytes (white blood cells [WBC]) | Glucose (fasting) |
| Platelets | Blood urea nitrogen |
| Differential WBC [Absolute counts] of: | Uric acid |
| Neutrophils | Total cholesterol |
| Lymphocytes | Total protein |
| Monocytes | Albumin |
| Eosinophils | Total bilirubin |
| Basophils | Alkaline phosphatase |
| Urinalysis | Aspartate aminotransferase |
| Specific gravity | Alanine aminotransferase |
| pH | Creatinine |
| Protein | Gamma-glutamyl transferase |
| Glucose | Low-density lipoprotein |
| Ketones | High-density lipoprotein |
| Bilirubin | Triglycerides |
| Urobilinogen | Ethanol testing[a] |
| Blood | Urine drug screen (including cotinine)[a] |
| Nitrite | Hepatitis B surface antigen[b] |
| Microscopic examination (if protein, nitrite, or blood is positive) | Hepatitis B core antibody[b] |
| | Hepatitis C antibody[b] |
| | Human immunodeficiency virus[b] |
| | Pregnancy test[c] |
| | Follicle-stimulating hormone[c] |
| | Glycated hemoglobin[b] |

Abbreviation: WBC = white blood cells.

[a] Performed at screening and Day -1. May be repeated at other times, at the discretion of the investigator.

[b] Performed at screening only.

[c] Females only.

# Appendix 3. Hypersensitivity Tests

Selected tests may be obtained in the event of anaphylaxis or generalized urticaria.

**Hypersensitivity Tests[a]**

| | |
|---|---|
| Anti-LY3463251 antibodies (immunogenicity) | Tryptase |
| LY3463251 concentration (PK) | N-methylhistamine |
| | Drugs-specific IgE[b] |
| | Basophil activation test[b] |
| | Complements |
| | Cytokine Panel |

Abbreviations: IgE = immunoglobulin E; PK = pharmacokinetics.

[a] Assayed by Lilly-designated laboratory

[b] Basophil activation test will be performed if a drug-specific IgE assay is unavailable.

# Appendix 4. 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. 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 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 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 IRB was properly constituted and convened as required by International Council for Harmonisation (ICH) guidelines and other applicable laws and regulations.

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

The study site's IRB 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 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 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 laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable IRBs 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 IRB 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 5. 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 CRP.

**Hepatic Monitoring Tests**

| | |
|---|---|
| **Hepatic Hematology[a]** | **Haptoglobin[a]** |
| Hemoglobin | |
| Hematocrit | **Hepatic Coagulation[a]** |
| Red blood cells | Prothrombin Time |
| White blood cells | Prothrombin Time, International Normalized Ratio |
| 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 and direct bilirubin | Hepatitis E antibody, IgG |
| Conjugated bilirubin | Hepatitis E antibody, IgM |
| Alkaline phosphatase | |
| Alanine aminotransferase | **Anti-nuclear antibody[a]** |
| Aspartate aminotransferase | **Alkaline Phosphatase Isoenzymes[a]** |
| Gamma-glutamyl transferase | **Anti-smooth muscle antibody (or anti-actin antibody)[a]** |
| Creatine phosphokinase | |

Abbreviation: Ig = immunoglobulin.

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

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

# Appendix 6. 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 J1D-MC-GZAA Sampling Summary (Part A [Single-Ascending Dose])**

| Purpose | Blood Volume per Sample (mL) | Number of Blood Samples | Total Volume (mL) |
|---|---|---|---|
| Screening tests[a] | 23.5 | 1 | 23.5 |
| Safety laboratory tests[a] | 12.5 | 8 | 100 |
| Fasting plasma glucose | 4 | 9 | 36 |
| Pharmacokinetics | 5 | 14 | 70 |
| Immunogenicity | 10 | 5 | 50 |
| Pharmacogenetics | 10 | 1 | 10 |
| Biomarkers | 10 | 2 | 20 |
| Total | | | 309.5 |
| Total for clinical purposes | | | 310 |

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

**Protocol J1D-MC-GZAA Sampling Summary (Part B [Multiple-Ascending Dose])**

| Purpose | Blood Volume per Sample (mL) | Number of Blood Samples | Total Volume (mL) |
|---|---|---|---|
| Screening tests[a] | 23.5 | 1 | 23.5 |
| Safety laboratory tests[a] | 12.5 | 14 | 175 |
| Liver function tests on Day 6[b] | 3.5 | 1 | 3.5 |
| Fasting plasma glucose | 2 | 1 | 2 |
| Fasting serum insulin and C-peptide | 3.5 | 3 | 10.5 |
| Oral glucose tolerance test[c] | 5.5 | 15 | 82.5 |
| Pharmacokinetics | 3 | 18 | 54 |
| Acetaminophen test for gastric emptying | 2 | 33 | 66 |
| Immunogenicity | 10 | 6 | 60 |
| Pharmacogenetics | 10 | 1 | 10 |
| Biomarkers | 10 | 4 | 40 |
| Total | | | 527 |
| Total for clinical purposes | | | 530 |

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

[b] Analyzed at a local laboratory. Liver function tests include aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and gamma glutamyl transferase.

[c] Includes 2-mL sample for measurement of glucose and 3.5 mL sample for measurement of insulin and C-peptide at a central laboratory.

# Appendix 7. Protocol Amendment J1D-MC-GZAA(e) Summary

## A Randomized, Placebo-Controlled, Subject and Investigator-Blind, Single and Multiple Dose, Safety, Tolerability, and Pharmacokinetics Study of LY3463251 in Healthy and Overweight Healthy Subjects Overview

Protocol J1D-MC-GZAA, A Randomized, Placebo-Controlled, Subject and Investigator-Blind, Single and Multiple Dose, Safety, Tolerability, and Pharmacokinetics Study of LY3463251, has been amended. The new protocol is indicated by Amendment (e) will be used to conduct the study in place of any preceding version of the protocol.

This protocol amendment (e) is not a substantial amendment and will be used to conduct the study in place of any preceding version of the protocol.

**Overall Rationale for the Amendment**

| Section # and Name | Description of Change | Brief Rationale |
|---|---|---|
| 5.2 Number of Participants | The maximum number of subjects to be enrolled in part B was increased from 75 to 85 | Objective is to consider the risk of dropouts due to the COVID-19 pandemic. |
| 7.4.1.2 Part B | Dose escalation at the cohort level and individual subject-level was clarified.<br>Dose modification language was added for subjects in Cohort 4 or in optional Cohort 5. | To allow dose modification in Part B for subjects who do not tolerate or poorly tolerate doses of study drug. |
| 8.1 Discontinuation from Study Treatment | The previous dose modification language was replaced. | This dose modification language was replaced by the changes to Section 7.4.1.2 Part B. |
| 9.4.6.1. Hepatic Safety | The previous hepatic safety language was replaced with newer language. | The language was updated to stay current with hepatic safety monitoring procedures. |

The revisions are as follows:

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

# 1. Protocol Synopsis

**Number of Subjects:**
~~It is planned to enroll 64 subjects into Part A and 60 subjects into Part B.~~

In Part A, up to 75 subjects may be enrolled such that approximately 64 subjects have evaluable data.

In Part B, up to 85 subjects may be enrolled such that approximately 60 subjects have evaluable data.

Subjects who are randomized and who are discontinued from the study (providing that discontinuation did not result from a safety finding) may be replaced to ensure that enough subjects complete the study. ~~To allow for replacements in case of discontinuation, up to 75 subjects may be enrolled into Part A and up to 75 subjects may be enrolled into Part B.~~

## 5.2. Number of Participants

It is planned to enroll 64 subjects into Part A and 60 subjects into Part B. For purposes of this study, a subject completes the study when all scheduled procedures shown in the Schedule of Activities have been finished.

Subjects who are randomized and who are discontinued from the study (providing that discontinuation did not result from a safety finding) may be replaced to ensure that enough subjects complete the study. To allow for replacement in case of discontinuation, up to 75 subjects may be enrolled into Part A and up to ~~75~~ 85 subjects may be enrolled into Part B.

### 7.4.1.2. Part B

**Dose-escalation at the cohort level**

Part B may be initiated following review of all available safety and tolerability data up to Day 14 post-dose from all subjects in the last cohort of Part A, and all safety and tolerability data available at this time (including ADA data) from the previous cohorts.

Dose-escalation decisions in Part B will primarily be based on safety and tolerability data obtained from at least 7 subjects up to and including Day 22 for Cohorts 2 and 3, and up to and including Day 36 for Cohort 4. Additionally, any available PK data may be used to guide dose selection or to determine if the number of doses to be studied may be reduced.

If any of the following scenarios occur, dosing at the current level and further dose-escalation will be interrupted:

- Four or more subjects develop AEs that are considered to be related to study treatment and graded as at least moderate and not responsive to supportive care
- One or more subjects develop AEs that are considered to be related to study treatment and graded as severe
- One or more subjects develop SAEs that are considered to be related to study treatment

**Dose-escalation at the individual subject level**

In case a ~~participant~~ subject interrupted the study drug and

- more than 2 doses were missed, the subject should be discontinued from the study – this would be at least 25% of doses missed and may compromise data reliability.
- the number of consecutive missed doses is ≤2, the treatment can be restarted at the same dose, if the drug was well tolerated prior to interruption.
- the number of consecutive missed doses is ≤2, then the treatment should be restarted at 3 mg irrespective of the dose the subject was receiving if the dose was not well tolerated before the interruption and subsequently follow the assigned dose escalation scheme.

Every effort should be made for a subject to adhere to the protocol dose escalations within a cohort. However, it is possible that some subjects may not tolerate higher doses of the study drug.

All dose adjustments discussed below may only occur following agreement between the investigator and sponsor medical monitor. The dose administered to the subjects each week should be recorded on the case report form during titration and throughout the study.

**Dose modification for Cohort 4**

Subjects who do not tolerate the 3 mg or 9 mg doses of study drug for at least 2 weeks will be discontinued from study drug but should continue to be monitored for safety for the duration of the study.

If after 2 weeks at 15 mg, a subject still has gastrointestinal symptoms preventing dose escalation to 24 mg, the subject may be kept at 15 mg for 1 to 3 additional doses before escalating to 24 mg. Subjects who cannot tolerate the 15 mg dose after at least 2 doses due to moderate or severe gastrointestinal symptoms may be discontinued from study treatment but should continue to be monitored for safety for the duration of the study.

If after at least 2 doses of 24 mg a subject has poorly tolerated nausea, vomiting, or diarrhea, and the investigator does not believe that the subject will tolerate additional injections of 24 mg despite the possibility of tachyphylaxis, then the investigator may reduce the dose to 15 mg. If this dose of 15 mg is tolerated, the subject may remain at that dose level for the duration of the study or the investigator may increase the dose back to 24 mg. Maintenance doses of less than 15 mg will not be allowed.

**Dose modification for optional Cohort 5**

In case a subject has poorly tolerated nausea, vomiting, or diarrhea at a given dose, the investigator may decide to decrease the dose to a previous dose level.

## 8.1. Discontinuation from Study Treatment

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:

- ALT or AST ≥5× ULN on 2 consecutive occasions

- ALT or AST ≥3× ULN and TBL ≥2× ULN or international normalized ratio ≥1.5
- ALT or AST ≥3× ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- 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%).

The following discontinuation criteria related to abnormal liver tests should be applied during the dose-escalation process. The occurrence of 1 or more cases meeting ***all*** the following criteria should be considered as a dose-limiting toxicity event:

- ALT or AST ≥3× ULN
- TBL ≥2× ULN
- No initial cholestasis (ALP does not exceed 2× ULN), and
- No other cause explaining the abnormality in liver tests.

Subjects who do not tolerate a given dose level due to gastro-intestinal symptoms may be discontinued from study drug or may have their dose reduced depending on various parameters as described in Section 7.4.1.2 (dose level, severity of symptoms, investigator's judgement, discussion between investigator and sponsor medical monitor). If they are discontinued from study drug, these subjects should continue to be monitored for safety for the duration of the study.

~~In the presence of GI events, subjects~~

- ~~from 1-mg and 3-mg dose groups who are unable to tolerate their assigned dose level for ≥2 weeks (have persistent vomiting or moderate to severe nausea) should be discontinued from using the study drug~~
- ~~in the remaining dose groups who have reached their target dose for ≥2 weeks and are still unable to tolerate that dose level (present persistent vomiting or moderate to severe nausea) may have the dose reduced to the previous dose and remain on the reduced dose for the remainder of the study. The dose administered to the subjects each week should be recorded on the case report form during titration and throughout the study.~~

### 9.4.6.1. Hepatic Safety

~~If a study subject experiences elevated ALT or AST ≥3× ULN, ALP ≥2× ULN, or elevated TBL ≥2× ULN, liver tests (Appendix 5) should be repeated within 48 to 72 hours including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine phosphokinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator 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~~
- ~~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.~~

**Close hepatic monitoring**

Laboratory tests (Appendix 2), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

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

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

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

**Comprehensive hepatic evaluation**

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

| If a subject with baseline results of... | develops the following elevation: |
|---|---|
| ALT or AST <1.5X ULN | ALT or AST ≥3X ULN with hepatic signs/symptoms[a], or ALT or AST ≥5X ULN |
| ALP <1.5X ULN | ALP ≥3X ULN |
| TBL <1.5 X ULN | TBL ≥2X ULN (except for patients with Gilbert's syndrome) |
| ALT or AST ≥1.5X ULN | ALT or AST ≥2X baseline with hepatic signs/symptoms[a], or ALT or AST ≥3X baseline |
| ALP ≥1.5X ULN | ALP ≥2X baseline |
| TBL ≥1.5X ULN | TBL ≥1.5X baseline (except for patients with Gilbert's syndrome) |

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

[a] Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper-quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined earlier, as well as tests for prothrombin time-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (e.g., ultrasound or computed tomography scan).

Based on the patient's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- serum phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the subject's clinical condition, the investigator should consider referring the subject for a

- hepatologist or gastroenterologist consultation
- magnetic resonance cholangiopancreatography
- endoscopic retrograde cholangiopancreatography
- cardiac echocardiogram, or
- liver biopsy.

**Additional hepatic data collection (hepatic safety CRF) in study subjects who have abnormal liver test results during the study**

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study subjects who meet 1 or more of the following 5 conditions:

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

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

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