Statistical Analysis Plan: J1I-MC-GZBU (Version 3)

A Phase 2b, Double-Blind Study to Investigate the Effect of Retatrutide on Renal Function in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes

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Statistical Analysis Plan (J1I-MC-GZBU): A Phase 2 Study to Investigate of Effect of LY3437943 on Renal Function in Participants with Overweight or Obesity and Chronic Kidney Disease with or without Type 2 Diabetes

Protocol Title: A Phase 2b, Double-blind Study to Investigate the Effect of LY3437943 on Renal Function in Participants with Overweight or Obesity and Chronic Kidney Disease with or without Type 2 Diabetes

Protocol Number: J1I-MC-GZBU

Compound Number: LY3437943

Short Title: Effect of LY3437943 on Renal Function in Participants with Overweight or Obesity and Chronic Kidney Disease with or without Type 2 Diabetes

Sponsor Name: Eli Lilly and Company

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Registry	ID
EU trial number:	2023-504583-42-00

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Version history

This SAP for study J1I-MC-GZBU (GZBU) is based on the protocol amendment (c) dated 17 June 2024.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	26-Mar-2024	Not Applicable	Original version
2	01-Apr-2025	• Updated ANHECOVA model to ANCOVA throughout the SAP	• Use ANCOVA model in anticipation to reduce the complexity in the modeling
		• Updated Primary Multiple Imputation to (PMI) Multiple Imputation	• In anticipation of the relatively small sample size, reduce the different scenarios needed to be considered in the PMI method.
		• MRI tests will be analyzed with MMRM, removed reference for ANHECOVA under the efficacy estimand	• MRI test results will be available with multiple post-baseline measurements and MMRM method should be applied instead of ANHECOVA
		• Updated MMRM model	• Reduce the complexity of the MMRM model
		• Removed KM plots of study/treatment discontinuation, removed patient flow listing and discontinued due to inadvertent enrollment listing and others in the disposition section	• Not considered necessary
		• Revised planned ECG analyses	• Align with planned ECG analyses in the protocol

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SAP Version	Approval Date	Change	Rationale
3	See date on Page 1	• Use JBM correction instead of BM correction in Section 3.3	• Recommendation from the scientific committee

1. Introduction

This SAP is intended to describe the analyses of primary and secondary objectives, as well as safety assessments for Study GZBU. Exploratory analyses are also included.

Pharmacokinetic/pharmacodynamic (PK/PD) analyses will be documented in a separate plan.

Changes to the protocol-planned analyses are described in Section 3.9.

1.1. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To compare the effect of LY3437943 to placebo on mGFR from baseline to Week 24	Change in GFR (mL/min/1.73 m^2) using iohexol clearance
Secondary	
To compare the effect of LY3437943 to placebo on mGFR from baseline to Week 16	Change in GFR (mL/min/1.73 m^2) using iohexol clearance
To compare the effect of LY3437943 to placebo from baseline to Week 16 and baseline to Week 24 for • glomerular and tubular functional measurements	Change in • UACR • creatinine-corrected FENa • filtration fraction
• renal hemodynamic measurements by MRI	Change in • mean arterial flow (MAF) • renal artery resistive index (RARI) • renal blood flow velocity (peak systolic velocity [PSV] and end diastolic velocity [EDV]) • global renal perfusion
• renal volumetric measurements assessed by MRI	Change in • total renal parenchyma volume • renal cortex volume
• renal injury and function by MRI	Change in • renal cortex T_1 (ms) • medulla T_1 (ms)
• renal oxygenation measured by kidney BOLD MRI	Change in • renal cortex R_2* • medulla R_2*

Objectives	Endpoints
• body weight	Percent change in body weight
To compare the effect of LY3437943 to placebo on glomerular and tubular functional measurements from baseline to Week 24	Change • 24-hr UAE (mg/24 h) • 24-hr urinary electrolytes (mg/24 h)
Exploratory	
To compare the effect of LY3437943 to placebo from baseline to Week 16 and baseline to Week 24 for • renal fat metrics measured by MRI	Change in • renal sinus fat and perirenal fat volumes • parenchymal proton density fat fraction (PDFF)
• renal cortex and medulla diffusion measured by MRI	Change in apparent diffusion coefficient (ADC)
• aortic flow by PC-MRI	Change in • mean aortic flow • aortic peak systolic velocity (PSV) • aortic end diastolic velocity (EDV)
• abdominal visceral/subcutaneous adipose tissue	Change in • volumes of abdominal visceral adipose tissue • volumes of subcutaneous adipose tissue
• estimate glomerular filtration rate	Change in • eGFR from creatinine • eGFR from cystatin C • eGFR from creatinine-cystatin C

Abbreviations: BOLD = blood oxygenation level dependent; FENa = fractional excretion of sodium; GFR = glomerular filtration rate; mGFR = measured glomerular filtration rate; MRI = magnetic resonance imaging; PC = phase contrast; UACR = urine albumin-creatinine ratio; UAE = urinary albumin excretion.

Primary estimand

The efficacy estimand is the primary estimand for this study and will be used for the primary objectives planned in the study. The efficacy estimand addresses intercurrent events (ICE) using the hypothetical strategy (ICH 2019).

Hypothetical strategy for the efficacy estimand

A scenario is envisaged in which the ICE would not occur. The value of the variable to reflect the clinical question of interest is the value that the variable would have taken in the hypothetical scenario defined.

Efficacy estimand

The clinical question of interest for the efficacy estimand is:

> *What is the treatment difference in mGFR change from baseline to 24 weeks between LY3437943 and placebo in participants who meet the eligibility criteria if they would remain on their randomly assigned treatment for 24 weeks and would not initiate new SGLT2 inhibitor, ACE inhibitor, or ARB?*

Efficacy estimand attributes

Population: Participants who are randomly assigned a study intervention and take at least 1 dose of study intervention.

Measure: Change in GFR from baseline to 24 weeks.

Treatment condition: The randomized treatment with allowance for potential dose interruptions and modifications.

Intercurrent events: ICEs include permanent discontinuation of study intervention and initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB, which are handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned treatment for 24 weeks and would not initiate new SGLT2 inhibitor, ACE inhibitor, or ARB. Dose modification and interruption will not be considered as ICEs because they are part of the treatment condition.

Population-level summary and treatment effect of interest: Difference in mean change in mGFR from baseline to 24 weeks between LY3437943 and placebo.

Rationale for efficacy estimand

This estimand aims to study the mechanism of action of LY3437943 under the ideal condition that all participants adhere to their randomly assigned treatment without being confounded by the initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB medications.

Secondary estimand

The treatment regimen estimand will be used as the secondary estimand for the primary objective of this study.

Treatment policy strategy for the treatment regimen estimand

The occurrence of the ICE is considered irrelevant in defining the treatment effect of interest; the values for the variable of interest are used regardless of whether the ICE occurs.

Treatment regimen estimand

The primary clinical question of interest is:

> *What is the treatment difference in mGFR change from baseline to 24 weeks between LY3437943 and placebo in participants who meet the eligibility criteria regardless of adherence to study intervention or initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB?*

Treatment regimen estimand attributes

Population: Participants who are randomly assigned a study intervention and take at least 1 dose of study intervention.

Measure: Change in glomerular filtration rate (GFR) from baseline to 24 weeks.

Treatment condition: The randomized treatment with allowance for potential dose interruptions and modifications.

Intercurrent events: No ICEs since treatment adherence and the initiation of new sodium-glucose cotransporter-2 (SGLT2) inhibitor, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin receptor blocker (ARB) are part of the treatment condition.

Population-level summary and treatment effect of interest: Difference in mean change in measured glomerular filtration rate (mGFR) from baseline to 24 weeks between LY3437943 and placebo.

Rationale for treatment regimen estimand

This estimand aims to evaluate the efficacy of LY3437943 that reflects the real-life behavior of the target population.

1.2. Study Design

Study GZBU is a Phase 2b, double-blind, 24-week study that will investigate the effects of LY3437943 compared with placebo on renal function, in participants with overweight or obesity and established chronic kidney disease (CKD) with or without type 2 diabetes (T2D).

Approximately 120 participants are planned to be randomly assigned to study intervention in a 1:1 ratio of 60 participants to LY3437943 and 60 participants to placebo. After screening, participants will be randomly assigned to receive either LY3437943 (12 mg) or placebo and will be administered their dose once weekly (QW) by subcutaneous injection for up to approximately 24 weeks. The LY3437943 dose will be initiated at 2 mg QW and increased every 4 weeks until the 12 mg dose is reached. The target maintenance dose is 12 mg. If 12 mg is not tolerated, the 4 mg, 6 mg, or 9 mg dose is allowed.

This study includes a:

- screening period
- dose escalation treatment period, and
- maintenance treatment period.

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The study duration will be approximately 33 weeks including screening and follow-up. The treatment duration will be approximately 24 weeks, and the visit frequency will be every 4 weeks. The study schema is shown in Figure GZBU.1.1.

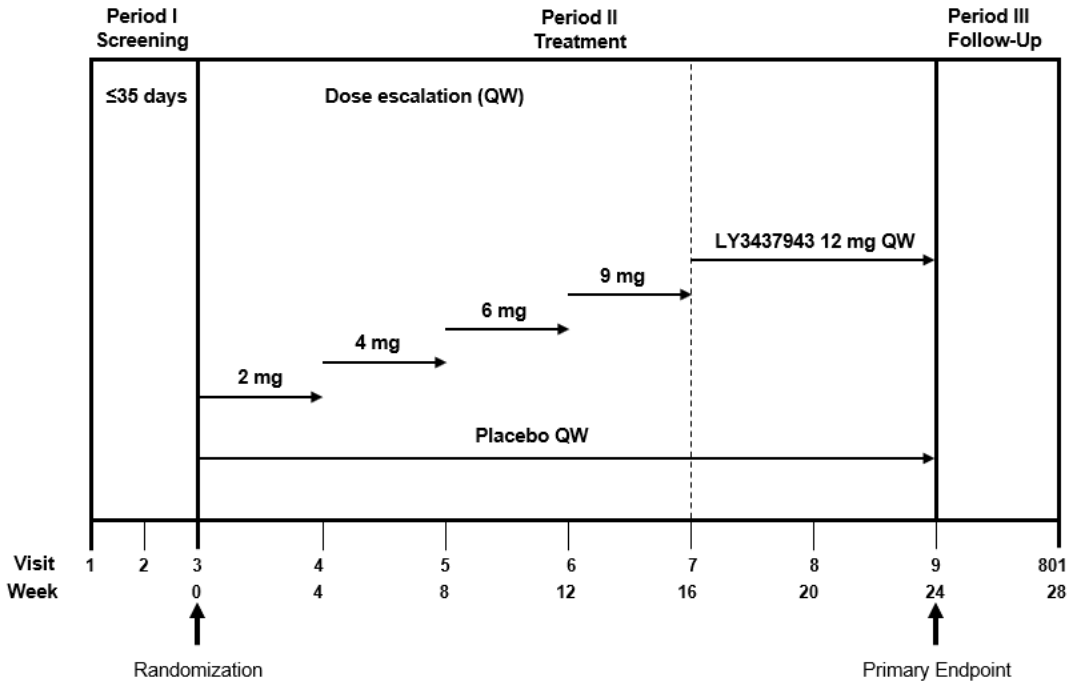
The iohexol clearance procedure will be used to measure the GFR. The procedure will occur on Week 0, Week 16, and Week 24. If a participant discontinues the study early, the investigator will decide if it is safe and medically appropriate to perform the procedure during an early discontinuation (ED) visit.

Renal imaging procedures include multimodal magnetic resonance imaging (MRI) and will be conducted to measure the secondary objectives. The MRI will occur on screening at Visit 2, then at Week 16 and Week 24. The MRI procedure should occur within 7 days before or after the visit and within 7 days of dosing. If a repeat scan is required to obtain measures for secondary objectives, it can be performed outside of the visit window and would not be considered a protocol violation. If a participant discontinues the study early, an MRI procedure on an ED visit should only be performed if it has been 4 weeks or more after the initial study intervention administration and if an MRI procedure has not been performed during the treatment period. If the MRI procedures cannot be performed on the same day as other activities planned for the ED visit, it can be conducted on different days. However, all procedures should be completed within 7 days of the ED visit (±7 days).

A safety follow-up visit will occur approximately 4 weeks following the last treatment period visit or final treatment visit. All participants are required to complete a posttreatment safety follow-up visit.

Participants discontinuing the study early and performing an ED visit will also be asked to perform the posttreatment safety follow-up visit.

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Abbreviation: QW = once weekly.

Figure GZBU.1.1. Illustration of study design for Study J1I-MC-GZBU.

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2. Analysis Sets

For the purposes of analysis, the following analysis sets are defined:

Analysis Set	Description
Enrolled participant	All participants who sign informed consent.
Randomized participant	All participants who are randomly assigned to study intervention.
Safety participant	All participants who are randomly assigned to a study intervention and take at least 1 dose of double-blind study intervention.
Completed participant	All participants who are randomly assigned to a study intervention, remain on treatment, and have evaluable data collected at 24 weeks, without discontinuation of study intervention or initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; SGLT2 = sodium-glucose cotransporter-2.

Participants will be analyzed according to the treatment group to which they were randomly assigned for all the defined populations except for the safety analyses. In the safety analyses, participants will be analyzed according to the treatment they received.

For the purpose of analysis, the following data points sets are defined:

Data Points Sets	Description
Efficacy estimand data points set	Data points obtained during the treatment period at or after randomization up to the earliest date of discontinuation of study intervention or initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB.
Treatment regimen estimand data points set	Data points obtained during the treatment period at or after randomization regardless of discontinuation of study intervention or initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB.

Abbreviations: ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; SGLT2 = sodium-glucose cotransporter-2.

The primary analysis and key secondary analyses will be conducted on safety participants with efficacy estimand. Selected endpoints will also be analyzed under the treatment regimen estimand.

The completed participants with efficacy estimand data points sets will be used for the supplementary analysis on the primary objective of change in GRF (iohexol) from baseline to 24 weeks between LY3437943 and placebo. The details can be found in Section 3.3.4.

In general, safety assessments will be guided by an estimand comparing the safety of LY3437943 doses with placebo irrespective of adherence to the study. Thus, safety analyses will be conducted using the safety participants on the basis of data observed during treatment period plus posttreatment follow-up period, that is, the period from the first dose of treatment to the end of the safety follow-up visit or the date of study withdrawal. It is noted that for some safety endpoints, such as, injection site reaction, treatment discontinuation because of AE, and so on, the analyses will be based on data observed during treatment period only.

3. Statistical Analyses

3.1. General Considerations

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

Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data (for example, too few events to justify conducting an analysis). Not all analyses described in this SAP will necessarily be included in the CSR. Any analysis described in this SAP and not provided in the CSR would be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of or in addition to a static display.

Unless otherwise noted in statistical summaries and analyses, the statistical treatment comparisons will only be performed between LY3437943 and placebo. All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) will be calculated at 95%, 2-sided.

The randomization of this study is stratified by a T2D status at baseline (with T2D, without T2D), estimated glomerular filtration rate (eGFR) category (≥25 to <45, ≥45 to <60, and ≥60 to ≤75 mL/min/1.73 m^2), and use of SGLT2 inhibitor at baseline (yes or no). A strata variable is defined for statistical modeling to consist of the joint levels of stratification factors:

- with T2D, eGFR ≥25 to <45 mL/min/1.73 m^2
- with T2D, eGFR ≥45 to <60 mL/min/1.73 m^2
- with T2D, eGFR ≥60 to ≤75 mL/min/1.73 m^2
- without T2D, eGFR ≥25 to <45 mL/min/1.73 m^2
- without T2D, eGFR ≥45 to <60 mL/min/1.73 m^2, or
- without T2D, eGFR ≥60 to ≤75 mL/min/1.73 m^2.

Note: SGLT2 inhibitor use of yes or no is not considered because of low SGLT2 inhibitor use in the randomized participants. When modeling GFR related parameters, e.g. mGFR and eGFR, baseline continuous GFR values instead of baseline GFR stratum will be included in the model.

Data may exist at visits where the variable is not scheduled to be collected, because of, for example, ED visits. In these situations, data from the ED visit that does not correspond to the planned collection schedule will be excluded from the mixed model for repeated measures (MMRM) analysis (Andersen and Millen 2013).

3.1.1. Definition of Baseline

Baseline for efficacy assessments is defined as the last non-missing measurement prior to the first dosing of study intervention, which in most cases will be the measurement recorded at

Week 0 (Visit 3). If there are no doses of study intervention, baseline will be defined as the last non-missing measure on or prior to randomization. In cases where the measurement is taken on the same day (where time is not collected or not reliable) as the first injection, this measurement will be used as the baseline values for data analysis.

Baseline period for safety assessment starts at screening and ends prior to the first dose (typically at Week 0). For safety assessments, the baseline value will be the last non-missing measure on or prior to the first dosing date. When multiple measurements were taken on the same date, the average of the measurements will be used.

3.1.2. Analysis Methods

3.1.2.1. Analysis Methods for Treatment Regimen Estimand

3.1.2.1.1. ANCOVA

The analysis of covariance (ANCOVA) model will be used to analyze continuous measurements at Week 24 visit (or at Week 16 visit) guided by the treatment regimen estimand. The model will include:

- treatment group as a factor variable
- strata as a factor variable (as defined in Section 3.1)
- baseline value (of the dependent variable)

The estimated treatment group effect and comparison between LY3437943 (12 mg) and placebo will be reported. The associated 2-sided 95% CI and corresponding p-values will also be reported.

3.1.2.1.2. Multiple Imputation Method

If there are occurrences of missing data despite the best precautions, missing data should be imputed using the jump-to-reference (placebo) imputation approach.

3.1.2.2. Analysis Methods for Efficacy Estimand

3.1.2.2.1. Mixed Model for Repeated Measure

The MMRM will be used to analyze continuous measurements with multiple postbaseline measures at each postbaseline visit guided by efficacy estimand. Participant dose modification and interruption will not disqualify their measurements from being included into the model. The ED visits will be mapped to the closest visit on the basis of the visit window rule per protocol Section 10.12. The visits that are out of the visit window will not be included in the MMRM model. The MMRM model will include the following terms:

- treatment group as a factor variable
- visit as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)

- interaction between treatment group and visit, and
- interaction between baseline value and visit.

The estimated treatment group effect and comparison between LY3437943 (12 mg) and placebo at the scheduled visits will be reported. The associated 2-sided 95% CI and corresponding p-values will also be reported. An unstructured covariance matrix by each treatment group will be used to model the within-participant errors, assuming heteroscedasticity and the measurements for different participants are independent.

If the model fails to converge, the following covariance structures will be tested in order:

- first-order autoregressive and
- compound symmetry.

The first covariance structure that converges will be used.

For urine albumin-creatinine ratio, both the postbaseline response variables and baseline variable will be log-transformed before fitting the MMRM. The treatment group estimates will be the percent change (%) from baseline while the treatment contrasts will be the relative change in LY3437943 (12 mg) compared with the placebo over the scheduled visits.

3.1.2.2.2. ANCOVA

The ANCOVA model will be used to analyze the continuous measurements with only one post-baseline measurements at Week 24 visit guided by the hypothetical estimand. The model will include:

- treatment group as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)

The estimated treatment group effect and comparison between LY3437943 (12 mg) and placebo will be reported. The associated 2-sided 95% CI and corresponding p-values will also be reported.

3.1.2.2.3. Multiple Imputation Strategy

To handle the possible missing data that may have occurred under the hypothetical strategy in the efficacy estimand, a multiple imputation will be conducted in a way consistent with what the values would likely have been had they been collected. For ANCOVA guided by the efficacy estimand, the missing data will be imputed using nonmissing data within the same treatment group at the same visit under the missing at random assumption.

3.1.2.3. Analysis Methods for Safety

Fisher's exact tests will be used for treatment comparisons of percentages. The risk differences and 95% CIs will be provided.

The MMRM analysis will be used for selected continuous safety data with multiple postbaseline measurements. The MMRM model will include the following terms:

- treatment group as a factor variable
- visit as a factor variable
- baseline value (of the dependent variable)
- interaction between treatment group and visit

The logistic regression model will be used for severe hypoglycemia incidence for postbaseline treatment comparisons. The model will include the fixed effects of treatment and strata variable.

3.2. Participant Dispositions

The participant dispositions for the screen period, the study intervention/treatment, the treatment period and/or the follow-up period will be collected in case report forms with the corresponding primary reason. The study completion for a participant is defined as the participant completing both the treatment period and the follow-up period, regardless of completion of study treatment.

The planned listings and summary tables for dispositions are provided in Table GZBU.3.1. No inferential analysis will be performed.

Table GZBU.3.1. Listings and Summary Tables Related to Dispositions

Analysis	Population/Period
Summary of study and study treatment disposition	Randomized/TP + FP (TP for study treatment disposition)
Listing of randomization	Randomized
Listing of randomized participants not receiving study treatment	Randomized
Listing of study and study treatment disposition	Randomized

Abbreviations: AE = adverse event; FP = follow-up period; TP = treatment period.

3.3. Primary Endpoint/Estimands Analysis

3.3.1. CCI




CCI



3.3.2. Main Analytical Approach

The analytical approaches are specified in Section 3.1.2.1.2 (ANCOVA with primary imputation) and Section 3.1.2.2.1 (MMRM).

3.3.3. Sensitivity Analyses

No sensitivity analyses are planned.

3.3.4. Supplementary Analyses

The completed participants with efficacy estimand data points sets will be used for the supplementary analysis on the primary objective of change in GRF (iohexol) from baseline to 24 weeks between LY3437943 and placebo.

Analyses of change from baseline in eGFR from baseline to 16 and 24 weeks based on the efficacy estimand will be conducted. The eGFR used will be derived based on cystatin only, creatinine only, and cystatin- creatinine.

3.4. Secondary Endpoints/Estimands Analyses

Table GZBU.3.2 includes the description and derivation of all the primary and secondary endpoints for the efficacy measures and patient-reported outcomes.

Table GZBU.3.3 provides the detailed analyses including endpoint, estimand, data points sets, method and imputation, population, and time point for the primary and some of the secondary endpoints.

Table GZBU.3.2. Description and Derivation of Primary and Secondary Endpoints for Efficacy Measures and Patient-reported Outcomes

Measure	Description	Variable	Derivation/Comment	Handling Missing Components
Measured GFR using iohexol clearance	Per protocol Section 8.5.1: • The iohexol clearance procedure will be used to measure the GFR. A single injection of iohexol will be followed by multiple blood sample collections for iohexol measurement and GFR calculation.	mGFR BSA indexed (mL/min/1.73m^2)	See Section 3.3.1	Single item, missing if missing
		Change from baseline in mGFR BSA indexed (mL/min/1.73 m^2)	Calculated as: postbaseline mGFR (mL/min/1.73 m^2) – baseline mGFR (mL/min/1.73 m^2)	Missing if baseline or postbaseline value is missing
		mGFR non-indexed (mL/min)	See Section 3.3.1	Single item, missing if missing
		Change from baseline in mGFR non-indexed (mL/min)	Calculated as: postbaseline mGFR (mL/min) – baseline mGFR (mL/min)	Missing if baseline or postbaseline value is missing
Estimated GFR		Cystatin-C based eGFR (mL/min/1.73 m^2)	As provided	Single item, missing if missing
		Creatinine based eGFR (mL/min/1.73 m^2)	As provided	Single item, missing if missing
		Cystatin-Creatinine based eGFR (mL/min/1.73 m^2)	Calculate using 2021 CKD-EPI Creatinine-cystatin C Equation	Single item, missing if missing
		Change from baseline in eGFR (mL/min/1.73 m^2)	postbaseline eGFR (mL/min/1.73 m^2) – baseline eGFR (mL/min/1.73 m^2), repeat for all three eGFR tests	Missing if baseline or postbaseline value is missing
Glomerular and tubular functional measurements	Per protocol Section 8.5.3: • The central laboratory will calculate UACR using urinary albumin and creatinine values from the clinical chemistry samples.	UACR	As provided Log transformation before the analysis	Single item, missing if missing
		Change from baseline in UACR (%)	Calculated as: log (postbaseline UACR) – log (baseline UACR) then will transform back to percent change.	Missing if baseline or postbaseline value is missing

Measure	Description	Variable	Derivation/Comment	Handling Missing Components
	• Sponsor statisticians will calculate the creatinine-corrected FENa using creatinine and sodium values from blood and urine sample collections summarized in the SoA using the equation (Espinel 1976). • Filtration fraction is estimated from mGFR and MRI-assessed renal arterial flow, corrected by hematocrit. Sponsor statisticians will calculate the filtration fraction using the equation (Villa et al. 2020). • Sponsor statisticians will calculate 24-hr UAE using the 24-hour urine sample collected. • Sponsor statisticians will calculate 24-hr urine electrolytes using the 24-hour urine sample collected.	Creatinine-corrected FENa	100 × ([serum creatinine (mg/dL) × urine sodium (mEq/L)] / [serum sodium (mEq/L) × urine creatinine (mg/dL)])	Single item, missing if missing
		Change in creatinine-corrected FENa	Postbaseline FENa – baseline FENa	Missing if baseline or postbaseline value is missing
		Filtration fraction	mGFR non-indexed (mL/min) / renal plasma flow (RPF) (mL/min) where RPF is MRI-measured RBF x (1 - hematocrit)	Single item, missing if missing
		Change in filtration fraction	Postbaseline filtration fraction – baseline filtration fraction	Missing if baseline or postbaseline value is missing
		24-hr UAE (mg/24 h)	As provided	Single item, missing if missing
		Change in 24-hr UAE (mg/24 h)	Postbaseline 24-hr UAE – baseline 24-hr UAE	Missing if baseline or postbaseline value is missing
		24-hr urinary electrolytes (mg/24 h)	As provided	Single item, missing if missing
		Change in 24-hr urinary electrolytes (mg/24 h)	Postbaseline 24-hr urinary electrolytes – baseline 24-hr urinary electrolytes	Missing if baseline or postbaseline value is missing
Renal Hemodynamic measurements by MRI	Per protocol Section 8.5.2: • MAF is the mean blood flow (mL/min) in the renal arteries calculated using PC-MRI. • PSV is the highest velocity (cm/s) measurement within the systole of the cardiac cycle. EDV is the lowest measured velocity (cm/s) within the diastole of the cardiac cycle. Both parameters will be measured using PC-	Mean arterial flow (MAF) (mL/min)	As measured	Single item, missing if missing
		Change in MAF (mL/min)	Postbaseline MAF – baseline MAF	Missing if baseline or postbaseline value is missing
		Renal blood flow velocity PSV (cm/s)	As measured	Single item, missing if missing
		Change in PSV (cm/s)	Postbaseline PSV – baseline PSV	Missing if baseline or postbaseline value is missing

Measure	Description	Variable	Derivation/Comment	Handling Missing Components
	MRI and cardiac gating to time systole and diastole. • RARI (no units) will be calculated using the equation below: RARI = (PSV – EDV) / PSV PSV and EDV will be measured using PC-MRI. A high RARI value might indicate the presence of renal artery stenosis or other renal vascular diseases. • Global renal perfusion will be assessed as the mean renal flow per 100 g of kidney tissue as measured by MRI (mL/min/100 g).	Renal blood flow velocity EDV (cm/s)	As measured	Single item, missing if missing
		Change in EDV (cm/s)	Postbaseline EDV – baseline EDV	Missing if baseline or postbaseline value is missing
		Renal artery resistive index (RARI)	RARI = (PSV – EDV) / PSV	If any component is missing, then the index is missing
		Change in RARI	Postbaseline RARI – baseline RARI	Missing if baseline or postbaseline value is missing
		Global renal perfusion (mL/min/100 g)	As measured	Single item, missing if missing
		Change in global renal perfusion (mL/min/100 g)	Postbaseline global renal perfusion – baseline global renal perfusion (mL/min/100 g)	Missing if baseline or postbaseline value is missing
Renal volumetric measurements by MRI	Per protocol Section 8.5.2: Total kidney, cortical, and medulla volume (cm3) will be measured by delineating corresponding region-of-interests from T1 maps.	Total renal parenchyma volume (cm^3)	As assessed	Single item, missing if missing
		Change in total renal parenchyma volume (cm^3)	Postbaseline total renal parenchyma volume – baseline total renal parenchyma volume	Missing if baseline or postbaseline value is missing
		Renal cortex volume (cm^3)	As assessed	Single item, missing if missing
		Change in renal cortex volume (cm^3)	Postbaseline renal cortex volume – baseline renal cortex volume	Missing if baseline or postbaseline value is missing
Renal injury and function by MRI	Per protocol Section 8.5.2: Renal function and renal injury will be assessed using T1 mapping scans. Renal microstructural changes will be assessed for cortex and medulla separately using image	Renal cortex T1 (ms)	As assessed	Single item, missing if missing
		Change in cortex T1 (ms)	Postbaseline renal cortex T1 (ms) – baseline renal cortex T1 (ms)	Missing if baseline or postbaseline value is missing

Measure	Description	Variable	Derivation/Comment	Handling Missing Components
	masks. Higher T1 (ms) values and lesser corticomedullary differentiation on T1 maps were associated with worsened renal function (Wolf et al. 2018). An indirect assessment of renal oxygenation will be conducted based on the paramagnetic properties of endogenous deoxyhemoglobin on the basis of BOLD MRI-measured R^2* parameter (s-1). R^2* increases with the increase in deoxyhemoglobin levels and associates with reduced tissue oxygenation. Cortex and medulla oxygenation will be assessed separately from BOLD images.	Medulla T1 (ms)	As assessed	Single item, missing if missing
		Change in medulla T1 (ms)	Postbaseline medulla T1 (ms) – baseline medulla T1 (ms)	Missing if baseline or postbaseline value is missing
		Renal cortex R^2* (s^{-1})	As assessed	Single item, missing if missing
		Change in renal cortex R^2* (s^{-1})	Postbaseline renal cortex R^2*(s^{-1}) – baseline renal cortex R^2*(s^{-1})	Missing if baseline or postbaseline value is missing
		Medulla R^2* (s^{-1})	As assessed	Single item, missing if missing
		Change in Medulla R^2* (s^{-1})	Postbaseline Medulla cortex R^2*(s^{-1}) – baseline Medulla R^2*(s^{-1})	Missing if baseline or postbaseline value is missing
Renal fat metrics	Per protocol Section 8.5.2: Increased renal sinus fat and perirenal fat are associated with metabolic disease, CKD, impaired renal function, and blood hypertension (Favre et al. 2017; Notohamiprodjo et al. 2020). Renal sinus fat and perirenal fat volumes (cm^3) will be measured utilizing MRI scans acquired. using Dixon technique (Ma 2008). Parenchymal proton density fat fraction (PDFF) will be assessed using MRI-PDFF maps to measure the relative amount of fat in renal parenchyma (%). The region-of-interests will be placed on parenchymal tissues to calculate PDFF values.	Sinus fat volume (cm^3)	As assessed	Single item, missing if missing
		Change in Sinus fat volume (cm^3)	Postbaseline sinus fat volume (cm^3) – baseline sinus fat volume (cm^3)	Missing if baseline or postbaseline value is missing
		Perirenal fat volume (cm^3)	As assessed	Single item, missing if missing
		Change in Perirenal fat volume (cm^3)	Postbaseline perirenal fat volume (cm^3) – baseline perirenal fat volume (cm^3)	Missing if baseline or postbaseline value is missing
		Parenchyma PDFF (%)	As assessed	Single item, missing if missing
		Change in Parenchyma PDF	Postbaseline PDFF – baseline PDFF	Missing if baseline or postbaseline value is missing
Renal cortex and medulla diffusion	Renal diffusion will be assessed by ADC maps obtained from DWI-MRI. ADC estimates the water molecule motion in the tissue and is associated with changes in renal microstructure, renal fibrosis, cellular	ADC (mm^2/s)	As assessed	Single item, missing if missing

Measure	Description	Variable	Derivation/Comment	Handling Missing Components
	infiltration (inflammatory or tumorous) or edema, and changes in renal perfusion. A decrease in ADC values (mm^2/s) in cortex and medulla might reflect a decrease in renal function, increase in tissue fibrotic changes, and inflammation (Caroli et al. 2018).	Change in ADC (mm^2/s)	Postbaseline ADC (mm^2/s) – baseline ADC (mm^2/s)	Missing if baseline or postbaseline value is missing
Abdominal visceral/subcutaneous adipose tissue	Volumes of abdominal visceral adipose tissue and subcutaneous adipose tissue will be measured using MRI scans acquired using Dixon technique.	Volume of abdominal visceral adipose tissue (cm^3)	As measured	Single item, missing if missing
		Change in volume of abdominal visceral adipose tissue (cm^3)	Postbaseline abdominal visceral adipose tissue volume (cm^3) – baseline abdominal visceral adipose tissue volume (cm^3)	Missing if baseline or postbaseline value is missing
		Volume of abdominal subcutaneous adipose tissue (cm^3)	As measured	Single item, missing if missing
		Change in volume of abdominal subcutaneous adipose tissue	Postbaseline abdominal visceral adipose tissue volume (cm^3) – baseline abdominal visceral adipose tissue volume (cm^3)	Missing if baseline or postbaseline value is missing
Body weight	Per protocol Section 10.7: Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms to 1 decimal place. All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents. Body weight should be measured in fasting state.	Body weight (kg)	As measured	Single item, missing if missing
		Percent change in body weight (kg)	Calculated as: 100% × (postbaseline body weight [kg] – baseline body weight [kg]) / baseline body weight (kg)	Missing if baseline or postbaseline value is missing

Abbreviations: ADC = apparent diffusion coefficients; CKD = chronic kidney disease; DWI-MRI = diffusion-weighted imaging MRI; EDV = early discontinuation visit; ESV = end systolic volume; FENa = fractional excretion of sodium; GFR = glomerular filtration rate; mGFR = measured glomerular filtration rate; MRI = magnetic resonance imaging; PC-MRI = phase contract MRI; PSV = peak systolic velocity; SoA = Schedule of Activities; UACR = urine albumin-creatinine ratio; UAE = urinary albumin excretion.

Table GZBU.3.3 Description of Efficacy/Health Outcomes Analyses

Measure	Endpoint	Estimand Data Points Sets / Population[a]	Analysis Method	Time Point[b]	Analysis Type
Measured GFR using iohexol clearance	Change from baseline in • mGFR BSA-indexed (mL/min/1.73 m^2) • mGFR non-indexed (mL/min)	Efficacy	MMRM	Week 24 visit	Primary endpoint, main analysis
		Treatment regimen	ANCOVA with MI	Week 24 visit	Primary endpoint, secondary analysis
				Week 16 visit	Primary endpoint, secondary analysis
		Efficacy with completed participants	MMRM	Week 24 visit	Primary endpoint, supportive analysis
Estimated GFR	Change from baseline in • Cystatin-C based eGFR • Creatinine based eGFR • Cystatin-Creatinine based eGFR	Efficacy	MMRM	Week 24 visit	Primary endpoint, supportive analysis
Glomerular and tubular functional measurements	Percent change from baseline in UACR (%)	Efficacy	MMRM (log transformation)	Week 24 visit	Secondary, main analysis
	Change in filtration fraction	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in 24-hr UAE (mg/24 h)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in 24-hr urinary electrolytes (mg/24 h)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
Renal Hemodynamic measurements by MRI	Change in MAF (mL/min)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in PSV (cm/s)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in EDV (cm/s)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis

Measure	Endpoint	Estimand Data Points Sets / Population[a]	Analysis Method	Time Point[b]	Analysis Type
	Change in RARI	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in global renal perfusion (mL/min/100 g)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in total renal parenchyma volume (cm^3)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in renal cortex volume (cm^3)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
Renal volumetric measurements by MRI	Change in total renal parenchyma volume (cm^3)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in renal cortex volume (cm^3)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
Renal injury and function by MRI	Change in cortex T1 (ms)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in medulla T1 (ms)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in renal cortex R^{2*} (s^{-1})	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in medulla R^{2*} (s^{-1})	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
Renal fat metrics	Change in sinus fat volume (cm^3)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in perirenal fat volume (cm^3)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in parenchyma PDF	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
Renal cortex and medulla diffusion	Change in ADC (mm^2/s)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
Abdominal visceral/subcutaneous adipose tissue	Change in volume of abdominal visceral adipose tissue (cm^3)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis
	Change in volume of abdominal subcutaneous adipose tissue	Efficacy	MMRM	Week 24 visit	Secondary, main analysis

Measure	Endpoint	Estimand Data Points Sets / Population[a]	Analysis Method	Time Point[b]	Analysis Type
Body weight	Percent change in body weight (kg)	Efficacy	MMRM	Week 24 visit	Secondary, main analysis

Abbreviations: ADC = apparent diffusion coefficient; ANCOVA = Analysis of heterogeneous covariance; BSA = body surface area; GFR = glomerular filtration rate; MAF = mean arterial flow; mGFR = measured glomerular filtration rate; MI = multiple imputation; MMRM = mixed model for repeated measures; PDF = proton density fat fraction; PSV = peak systolic velocity; RARI = renal artery resistive index; UACR = urine albumin-creatinine ratio; UAE = urinary albumin excretion.

3.5. Tertiary/Exploratory Analysis

These analyses will be described in the supplementary statistical analysis plan.

3.6. Safety Analyses

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3437943 doses with placebo irrespective of adherence to study drug. Thus, safety analyses will be conducted using the safety analysis set.

Descriptions of the safety analyses are provided in this SAP; however, some details are in compound level safety standards.

3.6.1. Extent of Exposure

Duration of exposure to study treatment will be summarized by treatment group for safety participants. The following exposure will be calculated:

Duration of treatment exposure will be calculated as:

$$Last\ treatment\ dose\ date - first\ treatment\ dose\ date + 7\ days$$

Descriptive statistics for participant weeks (or days) of exposure and total participant years in exposure will be provided.

The frequency of participants falling into different exposure ranges will be summarized:

- >0 weeks
- ≥4 weeks
- ≥8 weeks
- ≥12 weeks
- ≥16 weeks
- ≥20 weeks, and
- ≥24 weeks.

No p-values will be reported.

Participants with dose modification and/or reduction will be summarized with reasons.

Participants overdosed with the study treatment will be summarized. Overdose is defined as any total dose of study intervention within a 72-hour period greater than the dose assigned by the interactive web-response system.

3.6.2. Adverse Events

The planned summaries for adverse events are provided in Table GZBU.3.4 and are described fully in compound level safety standards.

Table GZBU.3.4. Summary Tables Related to Adverse Events

Analysis	Method	Population/Period
Overview of AEs, including • TEAE • SAE • death, and • discontinuation from study drug due to an AE.	Fisher's exact	Safety/TP + FP (TP for study treatment discontinuation due to an AE)
TEAEs by PT within SOC	Fisher's exact	Safety/TP + FP
Maximum severity TEAEs by PT	Fisher's exact	Safety/TP + FP
Common TEAEs by PT	Fisher's exact	Safety/TP + FP
SAEs by PT within SOC	Fisher's exact	Safety/TP + FP
SAEs by PT	Fisher's exact	Safety/TP + FP
Primary AEs leading to permanent discontinuation of study drug by PT within SOC	Fisher's exact	Safety/TP
AEs leading to study treatment interruption by PT within SOC	Fisher's exact	Safety/TP
Listing of SAEs		Randomized/TP + FP
Listing of primary AEs leading to permanent discontinuation of study drug		Randomized/TP
Listing of deaths		Randomized/TP + FP
Narratives for participants with at least 1 notable event		Safety/TP + FP

Abbreviations: AE = adverse event; FP = follow-up period; PT = Preferred Term; SAE = serious adverse event; SOC = System Organ Class; TEAE = treatment-emergent adverse event; TP = treatment period.

3.6.3. Clinical Laboratory Evaluation

The planned summaries for clinical laboratory evaluations are provided in Table GZBU.3.5 and are described fully in compound level safety standards.

Table GZBU.3.5. Summary Tables Related to Clinical Laboratory Evaluations

Analysis	Method	Population/Period
Box plots and mean/SD (or 95% CI) for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plots and mean/SD (or 95% CI) for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Summary for participants with elevated or low values meeting specified levels	Descriptive statistics	Safety/TP + FP
Listing of abnormal laboratory findings		Safety/TP + FP

Abbreviations: CI = confidence interval; FP = follow-up period; SD = standard deviation; TP = treatment period.

3.6.4. Vital Signs and Physical Characteristics

The planned summaries for vital signs (systolic blood pressure, diastolic blood pressure, and pulse rate) are provided in Table GZBU.3.6, and are described fully in compound level safety standards. When multiple vital sign measurements were collected at the same visit; the mean of these measurements will be used for the analysis.

Table GZBU.3.6. Summary Tables Related to Vital Signs

Analysis	Method	Population/Period
Box plots for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plots for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Analysis of vital signs (SBP, DBP, and pulse rate) and change from baseline	MMRM	Safety/TP + FP
Summary for elevated or low values meeting specified levels	Descriptive statistics	Safety/TP + FP

Abbreviations: DBP = diastolic blood pressure; FP = follow-up period; SBP = systolic blood pressure; TP = treatment period.

3.6.5. Electrocardiograms

Single ECG will be collected and interpreted by the investigator locally. The available abnormal ECG data will be listed and tabulated.

3.6.6. Adverse Events of Special Interest and Other Safety Topics

This section includes safety topics of interest whether because of observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, safety topics of interest will be identified by one or more standardized Medical Dictionary for Regulatory Activities (MedDRA) query(ies) (SMQ), by a Lilly defined MedDRA Preferred Term listing based upon the review of the most current MedDRA version, or by relevant laboratory changes.

The planned analyses for safety topics of interest are provided in Table GZBU.3.7 and are described fully in compound level safety standards.

Table GZBU.3.7. Description and Analyses of Special Safety Topics including Adverse Events of Special Interest

Special Safety Topic	Short Description	Analysis	Method	Population/Period
Major adverse cardiovascular events	Death and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. See protocol Section 8.3.4.1 for the list of MACE.	Positively adjudicated MACE by category/subcategory and PT	Fisher's exact	Safety/TP + FP
		Listing of MACE reported by investigator (whether or not positively adjudicated)		Safety/TP + FP
Arrhythmia and *Cardiac conduction disorders*	The treatment-emergent (TE) arrhythmias and cardiac conduction disorders events will be derived using the MedDRA PTs contained in certain SMQs.	TE arrhythmias and cardiac conduction disorders by PT nested within SMQ	Fisher's exact	Safety/TP + FP
		Listing of TE arrhythmias and cardiac conduction disorders		Safety/TP + FP
Hypoglycemia	The 2023 American Diabetes Association position statement on glycemic targets (ElSayad et al. 2023) will be used to define: • Level 1 hypoglycemia • Level 2 hypoglycemia • Level 3 hypoglycemia (severe/serious hypoglycemia) Per protocol Section 8.3.4.3, site staff should ONLY record hypoglycemia as an AE if the event meets serious criteria. A hypoglycemic event meets serious criteria if it meets the Level 3 severe definition.	Incidence (percent of patients experiencing 1 or more episode) and the rate (episodes/patient/year) of Level 3 (severe/serious) hypoglycemia	Logistic regression	Safety/TP + FP excluding events after initiation of new antihyperglycemic therapy as defined in Table GZBU.5.5.
		Listing of severe hypoglycemia events		
Severe gastrointestinal (GI) adverse events	Severe GI AEs using *Gastrointestinal disorder* SOC will be captured. The events of *Nausea, vomiting, and diarrhea* will be analyzed.	Severe/Serious TE GI events by PT	Fisher's exact	Safety/TP + FP
		Listing of severe or serious TE GI events		Safety/TP + FP
		Incidence and severity of TE *Nausea, vomiting, and diarrhea*, and combined	Fisher's exact	Safety/TP + FP
		Prevalence over time for severe/serious TE *Nausea, vomiting, and diarrhea*, and combined		Safety/TP + FP

Special Safety Topic	Short Description	Analysis	Method	Population/Period
Acute renal events	Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of *Acute renal failure* or worsening of preexisting CKD. LY3437943 may cause severe GI AEs. These events may lead to *Dehydration*, which could cause a deterioration in renal function, including acute *Renal failure*.	TE acute renal events by PT nested within SMQ	Fisher's exact	Safety/TP + FP
		TE *Dehydration* events by PT	Fisher's exact	Safety/TP + FP
Pancreatitis	The pancreatic enzyme data (p-amylase and lipase) will be observed through laboratory testing. All suspected cases of acute or chronic *Pancreatitis* and AEs of severe or serious *Abdominal pain* of unknown etiology will be sent for adjudication by an independent clinical endpoint committee.	Summary of maximum postbaseline pancreatic enzyme value exceeding the thresholds		Safety/TP + FP
		MMRM analysis for pancreatic enzymes: p-amylase and lipase (log transformation)	MMRM	Safety/TP + FP
		Pancreatitis events by PT for both investigator-reported events and subsequently confirmed adjudicated events	Fisher's exact	Safety/TP + FP
Thyroid malignancies and *Thyroid C-cell hyperplasia*	TE thyroid malignancies and *Thyroid C-cell hyperplasia* will be identified using MedDRA HLT and PT. The purpose of calcitonin measurements is to assess the potential effect of LY3437943 on thyroid C-cell function. Data will be captured in specific eCRFs.	TE *Thyroid C-cell hyperplasia* and malignancies by PT	Fisher's exact	Safety/TP + FP
		Listing of TE *Thyroid C-cell hyperplasia* and *Thyroid neoplasm*		Safety/TP + FP
		Summary of maximum postbaseline calcitonin value in the thresholds		Safety/TP + FP
		MMRM analysis for calcitonin (log transformation)	MMRM	Safety/TP + FP
Malignancies	The malignancy events will be derived using the MedDRA PTs contained certain SMQs.	TE malignancy by PT	Fisher's exact	Safety/TP + FP

Special Safety Topic	Short Description	Analysis	Method	Population/Period
Hepatic disorder	Hepatic laboratory results include alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum alkaline phosphatase (ALP), total bilirubin (TBL), direct bilirubin (DBL), international normalized ratio (INR), and gamma-glutamyltransferase (GGT). When criteria are met for hepatic evaluations, investigators will conduct close monitoring of hepatic symptoms and liver tests, perform a comprehensive evaluation for alternative causes of abnormal liver tests, and complete follow-up hepatic safety eCRFs.	Abnormal postbaseline categories for hepatic safety parameters: ALT, AST, ALP, TBL, DBL, and GGT		Safety/TP + FP
		Hepatocellular *Drug-induced liver injury* screening plot (TBL vs ALT or AST)		Safety/TP + FP
		Hepatocellular *Drug-induced liver injury* screening table		Safety/TP + FP
		Listing of potential hepatocellular *Drug-induced liver injury*		Safety/TP + FP
		Cholestatic *Drug-induced liver injury* screening plot (TBL vs ALP)		Safety/TP + FP
		Cholestatic *Drug-induced liver injury* screening table		Safety/TP + FP
		Listing of potential cholestatic *Drug-induced liver injury*		Safety/TP + FP
		Participant profiles for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the protocol)		Safety/TP + FP
Gallbladder disorder and *Biliary tract disorder*	All events of TEAE biliary colic, cholecystitis, or other suspected events related to *Gallbladder disease* will be identified by using certain SMQs.	TE *Gallbladder disorder* and *Biliary tract disorder* by PT nested within SMQ	Fisher's exact	Safety/TP + FP
Hypersensitivity reaction	Two main analyses are performed in support of assessment of potential immediate *Hypersensitivity*, including *Anaphylaxis*, as well as potential nonimmediate *Hypersensitivity*.	Potential immediate TE *Hypersensitivity reaction* by PT within scope and category	Fisher's exact	Safety/TP + FP
		Potential nonimmediate TE *Hypersensitivity reaction* by PT within scope and category	Fisher's exact	Safety/TP + FP
		Severe/serious TE *Hypersensitivity reaction* - potential immediate by PT within scope and category	Fisher's exact	Safety/TP + FP
		Severe/serious TE *Hypersensitivity reaction* - potential nonimmediate by PT within scope and category	Fisher's exact	Safety/TP + FP

Special Safety Topic	Short Description	Analysis	Method	Population/Period
Injection site reaction (ISR)	ISRs will be derived using the MedDRA PTs in MedDRA HLTs. *Injection site reaction* and related information will be reported via "Injection Site Reactions" eCRF.	TE ISRs by PT within each category	Fisher's exact	Safety/TP
		ISRs - participant-based analysis		Safety/TP
		ISRs - event-based analysis		Safety/TP
		Severe/serious TE ISRs by PT within each category	Fisher's exact	Safety/TP
		Listing of TE severe/serious ISRs		Safety/TP
Depression, *Suicidal ideation*, and *Suicidal behavior*	AEs will be searched using MedDRA PTs from certain SMQs.	TE *Depression*, *Suicidal ideation*, and *Suicidal behavior* events by PT nested within SMQ	Fisher's exact	Safety/TP + FP
		Listing of TE *Depression*, *Suicidal ideation*, and *Suicidal behavior* events		Safety/TP + FP
	Suicide-related thoughts and behaviors will be collected based on the C-SSRS.	Summary of C-SSRS categories and composite measures		Safety/TP + FP
		Listing of *Suicidal ideation*, *Suicidal behavior*, or *Self injurious behavior without suicidal intent*		Safety/TP + FP
		Summary of C-SSRS TE events		Safety/TP + FP
	Patient health questionnaire-9 (PHQ-9) will be collected to assesses the specific diagnostic symptoms that determine the presence of a clinical *Depressive disorder*. The PHQ-9 total scores will be categorized as none (not depressed), mild, moderate, moderately severe, and severe.	Shift of each baseline category (maximum value) versus each postbaseline category (maximum value)		Safety/TP + FP
		Shift of categories based on the maximum values during baseline and postbaseline: • any increase in depression category (that is, worsening of depression) • increase from No or Mild Depression to Moderate, Moderately Severe, or Severe Depression • increase from Mild or Moderate Depression to Moderately Severe or Severe Depression		Safety/TP + FP
Abuse potential	The *Abuse* potential events will be derived according to FDA guidance and compound level safety standards.	TE *Abuse* potential events by PT	Fisher's exact	Safety/TP + FP

Special Safety Topic	Short Description	Analysis	Method	Population/Period
CCI				

Abbreviations: AE = adverse event; C-SSRS = Columbia Suicide Severity Rating Scale; CKD = chronic kidney disease; CRF = case report form; CV = cardiovascular; eCRF = electronic case report form; FDA = United States Food and Drug Administration; FP = follow-up period; HLT = High Level Term; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; PT = Preferred Term; SAE = serious adverse event; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event; TP = treatment period.

Note: Listings and participant profiles may be provided through interactive display tools instead of a static display.

Approved on 18 Nov 2025 GMT

3.7. Other Analyses

3.7.1. Immunogenicity

Immunogenicity analyses are exploratory and may alter from those outlined here, though they will minimally follow the analyses specified in the retatrutide program immunogenicity SAP.

The frequency and percentage of participants with preexisting anti-drug antibody (ADA) and with LY3437943 treatment-emergent (TE) ADA may be reported.

TE ADAs are defined as

- treatment-induced ADA: those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline, or
- treatment-boosted ADA: those with a 4-fold (2 dilutions) increase in titer compared the with baseline if ADAs were detected at baseline.

For the TE ADA positive (ADA+) participants, the distribution of maximum titers may be reported.

The frequency of neutralizing antibodies against LY3437943, if performed, may be reported in TE ADA+ participants.

If cross-reactivity to native glucagon-like peptide-1 (GLP-1), glucagon-like peptide (GIP), and glucagon, or neutralizing antibodies against native GLP-1 and GIP, and glucagon assays are performed, the frequency of each may be reported.

The relationship between the presence of antibodies and the LY3437943 concentrations and PD response, including safety and efficacy to LY3437943, may be assessed.

3.7.2. Subgroup Analyses

Subgroup analyses will be conducted for the primary endpoint of change in mGFR from baseline at Week 24 visit using the efficacy estimand:

The variables for subgroup analysis are specified in Table GZBU.5.1.

The following analyses will be conducted:

- For efficacy estimand: the ANCOVA model or MMRM model described in Section 3.1.2.2 with the addition of the subgroup factor and the interaction term of treatment group with the subgroup variable.

If the subgroup factor is part of the strata variable, a new strata variable that excludes the subgroup categories will be used.

If any category within the subgroup (for example, status of yes or no) is <5% of the total population, only descriptive statistics will be provided for that category (that is, no inferential testing within the subgroup category).

Additional subgroup evaluations may be conducted as exploratory analyses.

3.8. Interim Analyses

3.8.1. Assessment Committee

An internal Assessment Committee (AC) will be formed to review the interim analyses (if applicable) in Study GZBU for the safety and PD assessments in an unblinded manner. A statistical analysis center independent from the study team will perform the data analysis for the AC. Based on the projected enrollment, 2 interim safety analyses are planned, when 25% and 50% of participants have completed Week 24 or have discontinued intervention. Changes in the number of interim safety analyses and the timing of conducting the interim safety analyses due to the change of enrollment rate will not require a protocol amendment.

The study team will not have access to the unblinded data. Only the AC is authorized to evaluate unblinded interim analyses. Study sites will receive information about interim safety results only if they need to know for the safety of their participants.

The database lock will occur after all randomized participants complete the 24-week treatment period and the posttreatment safety follow-up period of the study or discontinue the study early. The primary objective of the study will be assessed following this database lock.

Details of the AC are described in the AC charter. Details regarding maintaining the blind during the conduct of this study will be specified in the blinding and unblinding plan document.

3.9. Changes to Protocol-Planned Analyses

No change from the planned analyses listed in the protocol.

4. Sample Size Determination

Approximately 120 participants are planned to be randomly assigned to study intervention in a 1:1 ratio of 60 participants to LY3437943 and 60 participants to placebo. Assuming a 15% dropout rate, approximately 51 participants will complete each of the LY3437943 and placebo arms.

Sample size selection is guided by the objective of establishing a significantly different change in mGFR, of LY3437943 compared to placebo, from baseline to Week 24. The chosen sample size provides at least 80% power to establish a significant difference in change of GFR between LY3437943 and placebo, based on a 2-sided 2-sample t-test with significance level of 0.05, a standard deviation (SD) of 8.1 and a mean change in GFR of 4.56 mL/min/m_2 at Week 24 from baseline compared to placebo.

The effect size is calculated from Phase 2 studies of LY3437943 assuming 50% T2D participants and 50% non-T2D participants based on the estimand with hypothetical strategy, where the mean change in eGFR was 1.50 mL/min/m^2 for T2D participants and 7.61 mL/min/m^2 for non-T2D participants yielding a mean across all participants of 4.56 mL/min/m^2. In these same studies, the SD of eGFR change was 7.1 in the T2D population and 8.9 in the non-T2D population, yielding an average of 8.0 for the 2 groups combined. To leverage the use of a measured GFR endpoint which is known to be less prone to variability than estimated GFR, the more conservative SD of 8.1 was adopted from the results of external trial, MB102035, comparing the effect of SGLT2 inhibitor dapagliflozin on measured GFR in participants with T2D (Lambers Heerspink et al. 2013).

Sample size calculations were conducted using nQuery Version 8.

5. Supporting Documentation

5.1. Appendix 1: Demographic and Baseline Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for randomized participants. The listing of basic demographic characteristics (that is, age, sex, ethnicity, race, country, baseline body weight, and so on) for randomized participants will be provided.

The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline demographics and characteristics across treatment groups will be performed.

Table GZBU.5.1 describes the specific variables and how they will be summarized. The last column specifies variables used for the subgroup analysis described in Section 3.7.2.

Table GZBU.5.1. Demographics and Baseline Characteristics with Variables for Subgroup Analysis

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]
Demographics			
Age[b]	Yes	<65, ≥65 years	X
		<75, ≥75 years	
		<65, ≥65 and <75, ≥75 and <85, ≥85 years	
Sex	No	Male, Female	X
Menopausal status (for females)	No	Premenopausal, Perimenopausal, Postmenopausal	
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino	X
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	X
Country	No	By each country	
Geographic region	No	North America, Europe, Other	X
	No	North America, Europe, Asia, Australia, or Central/South America	
Height (cm)	Yes		
Baseline waist circumference (cm)	Yes		
Baseline body weight (kg)	Yes		
Baseline BMI	Yes	<35 kg/m^2 ; ≥35 and <40 kg/m^2 , ≥40 kg/m^2	X
Alcohol use	No	Never, Current, Former	
Tobacco use	No	Never, Current, Former	
Recreational drug use - methamphetamine	No	Never, Current, Former	
Recreational drug use - cocaine	No	Never, Current, Former	
Baseline therapy			
SGLT2 inhibitor use[c]	No	Yes, No	X
Baseline disease characteristics			
Baseline systolic blood pressure (mm Hg)	Yes		

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]
Baseline diastolic blood pressure (mm Hg)	Yes		
Baseline pulse rate (beats/min)	Yes		
Baseline eGFR(mL/min/1.73 m^2)	No	≥45 and <45 mL/min/1.73 m^2	
Baseline eGFR category per IWRS (mL/min/1.73 m^2)	No	≥25 to <45, ≥45 to <60, ≥60 to ≤75 mL/min/1.73 m^2	X
Baseline UACR (mg/g)	Yes	<30, ≥30 mg/g	X
Baseline triglycerides (mg/dL)	Yes		
Baseline total cholesterol (mg/dL)	Yes		
Baseline VLDL-cholesterol (mg/dL)	Yes		
Baseline non-HDL-cholesterol (mg/dL)	Yes		
Baseline LDL-cholesterol (mg/dL)	Yes		
Baseline HDL-cholesterol (mg/dL)	Yes		
Baseline HbA1c (%)	Yes	≤5.7% (≤39 mmol/mol), >5.7% (>39 mmol/mol)	
		≤8.5% (≤69 mmol/mol), >8.5% (>69 mmol/mol)	
Baseline HbA1c (%) for participants with T2D	Yes	≤8.5% (≤69 mmol/mol), >8.5% (>69 mmol/mol)	
Baseline HbA1c (mmol/mol)	Yes		
Baseline HbA1c (mmol/mol) for participants with T2D	Yes		
Baseline fasting glucose (mg/dL)	Yes		
Baseline fasting glucose (mg/dL) for participants with T2D	Yes		
Baseline fasting glucose (mmol/L)	Yes		
Baseline fasting glucose (mmol/L) for participants with T2D	Yes		
Diabetes status	No	Yes, No	X
Duration of diagnosis for T2D (years) for participants with T2D	Yes	≤5, >5 and ≤10, >10 years	
Duration of obesity (years)	Yes		

Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HDL = high-density lipoprotein; IWRS = ; LDL = low-density lipoprotein; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; VLDL = very low-density lipoprotein.

[a] Subgroup analyses are defined in Section 3.7.2 with more details.

[b] Age in years will be calculated as length of the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the informed consent date.

[c] SGLT2 inhibitor use is defined in Section 5.3, Table GZBU.5.4.

5.2. Appendix 2: Historical Illnesses and Preexisting Conditions

Historical illness is defined as the condition/event with an end date prior to the date of informed consent.

Preexisting condition is defined as the condition/event with a start date prior to the first dose of the study drug and stop date that is at or after the informed consent date or has no stop date (that is, ongoing). Randomization date will be used if a participant has not been dosed.

The planned summaries for historical illness and preexisting conditions are provided in Table GZBU.5.2. No inferential analysis will be performed.

Table GZBU.5.2. Summary Tables Related to Historical Illness and Preexisting Conditions

Analysis	Population/Period
Historical illness by PT within SOC	Randomized
Preexisting conditions by PT within SOC	Randomized

Abbreviations: PT = Preferred Term; SOC = System Organ Class.

5.3. Appendix 3: Concomitant Medications

Medications that start before or at the last date of treatment period or follow-up period and are ongoing or ended during the treatment period or follow-up period will be classified as concomitant medication. Medications that start and end before first dose date of study intervention will be classified as prior therapy.

Baseline is defined as the corresponding medication taken on the day of the first dose of study intervention.

If there are no doses of study intervention, the randomization date will be used instead of the first dose date.

The planned summaries for concomitant medications are provided in Table GZBU.5.3.

Table GZBU.5.3. Summary Tables Related to Concomitant Medications

Analysis	Method	Population/Period
CMs by PN	Fisher's exact	Safety/TP + FP
Antihypertensive CMs at baseline by PN within ATC code		Safety
Lipid-lowering CMs at baseline by PN within ATC code		Safety
Antihyperglycemic CMs at baseline by PN within ATC code		Safety
SGLT2 inhibitor medications at baseline by PN		Safety
Status change of antihypertensive, lipid-lowering, and antihyperglycemic CMs		Safety/TP
Antihyperglycemic CM initiated after baseline by PN	Fisher's exact	Safety/TP
Prohibited concomitant medication on weight management treatment by PN		Full participants/TP
Prohibited concomitant medication on glycemic therapy among participants with T2D by PN		Full participants/TP

Abbreviations: ATC = Anatomical Therapeutic Chemical; CM = concomitant medication; PN = preferred name; FP = follow-up period; SGLT2 = sodium-glucose cotransporter-2; T2D = type 2 diabetes; TP = treatment period.

Table GZBU.5.4 provides protocol-specified concomitant medications of interest.

Table GZBU.5.4. Protocol-specified Concomitant Medication

Category	Preferred Name / ATC Code
Antihypertensive medication	All medications with ATC code containing C01, C03, C07, C08, or C09
Lipid-lowering medication	All medications with ATC code containing C10
Antihyperglycemic medication	All medications with ATC code containing A10, except for A10XA
SGLT2 inhibitor medication	All medications with ATC code of A10BK

Abbreviations: ATC = Anatomical Therapeutic Chemical; SGLT2 = sodium-glucose cotransporter-2.

Table GZBU.5.5 provides the protocol-specified prohibited concomitant medication rules.

Table GZBU.5.5. Prohibited Concomitant Medication Rules

Timing	Preferred Name / ATC Code	ATC Classification	Rule
Prohibited Concomitant Medication that May Affect the Primary Objective Measure (mGFR)			
Postbaseline	IBUPROFEN		Not to be used chronically, no incidental use within 48 hours prior to MRI or iohexol procedures
	NAPROXEN		Not to be used chronically, no incidental use within 48 hours prior to MRI or iohexol procedures
	DICLOFENAC		Not to be used chronically, no incidental use within 48 hours prior to MRI or iohexol procedures
	CELECOXIB		Not to be used chronically, no incidental use within 48 hours prior to MRI or iohexol procedures
	MEFENAMIC ACID		Not to be used chronically, no incidental use within 48 hours prior to MRI or iohexol procedures
	ETORICOXIB		Not to be used chronically, no incidental use within 48 hours prior to MRI or iohexol procedures
	INDOMETHACIN		Not to be used chronically, no incidental use within 48 hours prior to MRI or iohexol procedures
	ASPIRIN		Doses higher than 325 mg are prohibited
	EPHEDRINE		No incidental use within 48 hours prior to iohexol procedures
	PHENYLEPHRINE		No incidental use within 48 hours prior to iohexol procedures
	PSEUDOEPHEDRINE		No incidental use within 48 hours prior to iohexol procedures
	PHENYLPROPANOL AMINE		No incidental use within 48 hours prior to iohexol procedures
	PHENOTHIAZINE DERIVATIVES		No incidental use within 48 hours prior to iohexol procedures

Timing	Preferred Name / ATC Code	ATC Classification	Rule
Prohibited Concomitant Medication on Weight Management Treatment[a]			
Postbaseline	All medications with ATC code of A08AA	Centrally acting antiobesity products	Any initiation is prohibited during treatment period
	All medications with ATC code of A08AB	Peripherally acting antiobesity products	Any initiation is prohibited during treatment period
	All medications with ATC code of A08AX	Other antiobesity drugs	Any initiation is prohibited during treatment period
	LIRAGLUTIDE		Any initiation is prohibited during treatment period
	SEMAGLUTIDE		Any initiation is prohibited during treatment period
	TIRZEPATIDE		Any initiation is prohibited during treatment period
	TOPIRAMATE		Any initiation is prohibited during treatment period if taken with PHENTERMINE
	BUPROPION		Any initiation is prohibited during treatment period if taken with NALTREXONE
	NALTREXONE		Any initiation is prohibited during treatment period if taken with BUPROPION
Prohibited Concomitant Medication on Glycemic Therapy among Participants with T2D[a,b]			
Postbaseline	All medications with ATC code of A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Any initiation is prohibited during treatment period
	All medications with ATC code of A10BJ	Glucagon-like peptide-1 (GLP-1) analogues	Any initiation is prohibited during treatment period
	TIRZEPATIDE		Any initiation is prohibited during treatment period
	PRAMLINTIDE		Any initiation is prohibited during treatment period
	CAGRILINTIDE		Any initiation is prohibited during treatment period
	PRAMLINTIDE		Any initiation is prohibited during treatment period
	DULAGLUTIDE		Any initiation is prohibited during treatment period
	LIRAGLUTIDE		Any initiation is prohibited during treatment period
	LIXISENATIDE		Any initiation is prohibited during treatment period
	SEMAGLUTIDE		Any initiation is prohibited during treatment period
	U-500 INSULIN		Any initiation is prohibited during treatment period
	LISPRO		Any initiation is prohibited during treatment period
	ASPART		Any initiation is prohibited during treatment period

Timing	Preferred Name / ATC Code	ATC Classification	Rule
	GLULISINE		Any initiation is prohibited during treatment period
	HUMAN INSULIN R		Any initiation is prohibited during treatment period

Abbreviations: ATC = Anatomical Therapeutic Chemical; ICE = intercurrent event; mGFR = measured glomerular filtration rate; MRI = magnetic resonance imaging; T2D = Type 2 diabetes.

[a] Use of these medications will be reviewed by the study team (blinded to study treatment) on a case-by-case basis to assess the clinical significance of the change in medication. After review, if deemed to be not clinically significant, the case will not be considered as an ICE.

[b] Include participants who develop T2D during the study.

5.4. Appendix 4: Treatment Compliance

Treatment compliance is defined as taking at least 75% and no more than 125% of required injections of study intervention during the treatment period. Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment group using the safety participants during treatment period. No inferential analysis will be performed.

5.5. Appendix 5: Important Protocol Deviations

Important protocol deviations are identified in the trial issues management plan. A listing and summary of important protocol deviations by treatment group will be provided for all randomized participants. No inferential analysis will be performed.

5.6. Appendix 6: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry requirements.

These will be included in later SAP versions as required by the regulatory bodies.

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