Protocol W8M-MC-CWMM(d)

A Master Protocol for a Randomized, Controlled Clinical Trial of Multiple Interventions for Chronic Weight Management in Adult Participants with Obesity or Overweight

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Approval Date: 12-Dec-2025

Title Page

Master Protocol Title:

A Master Protocol for a Randomized, Controlled Clinical Trial of Multiple Interventions for Chronic Weight Management in Adult Participants with Obesity or Overweight

Protocol Number: W8M-MC-CWMM

Amendment Number: CWMM (d)

Compound: Multi-molecule code LY900038

Brief Title:

Chronic Weight Management Master Protocol

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number:

IND: 163848

Document ID: VV-CLIN-077527

Approval Date: Protocol Amendment (d) Electronically Signed and Approved by Lilly on date provided below.

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	*04-Feb-2025*
Amendment b	*18-Jul-2024*
Amendment a	*13-Aug-2023*
Original Protocol	*04-May-2023*

Amendment [d]

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The protocol was amended to update the exclusion criteria related to hepatitis B and C to align with current guidelines.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Deleted secondary objective "To compare the effect of the primary intervention versus the primary control for weight reduction at [redacted]" and the corresponding endpoint "percent change from baseline in body weight"	To retain consistency with Section 3.
	Deleted "[redacted]" throughout the section	
1.3.2. Visit 401 – Screening	Added a statement that if HCV antibody test is positive, HCV RNA test needs to be performed.	To clarify the laboratory tests to be done and provide guidance on how to interpret them.
	Added a row "Obtain patient number using IWRS" at the time of first study consent	To ensure participant identification and linkage to IWRS for randomization and dosing.
	Placed "Register visit with IWRS" below "Obtain patient number using IWRS" and	To retain the sequence of events and to enhance clarity

Section # and Name	Description of Change	Brief Rationale
	retained it only for screening visit.	
	Removed "Includes obtaining participant identifier from IWRS. Only 1 participant number is required"	To avoid repetition
	Removed "X" from prescreening visit in "Register visit with IWRS"	Updated for clarity
3. Objectives, Endpoints, and Estimands	Deleted secondary objective "To compare the effect of the primary intervention versus the primary control for weight reduction at CCI " and the corresponding endpoint "percent change from baseline in body weight"	To avoid duplication with the primary endpoint.
	Modified estimand language to remove the mention of "percent change in body weight from baseline at CCI "	
	Deleted "CCI " throughout the section	To allow flexibility for ISAs to assess the primary endpoint at their protocol-specified primary time points, which may differ from CCI .
	CCI [redacted]	Clarification for consistency with other sponsor-run studies.
5.2. Exclusion Criteria	Modified Exclusion Criterion 29	Updated per the latest Lilly protocol guidance

Section # and Name	Description of Change	Brief Rationale
	Modified Exclusion Criterion 37 to add "with the exception of highly effective contraceptive methods if applicable and as stated within the respective ISA"	Clarification to support ISA individualized contraception guidance.
	Modified exclusion criterion 41 to add "Adderall"	Clarification
5.4. Screen Failures	Clarified that screen failures from an ISA undergoing CWMM master protocol rescreening may not require repeating all V401 screening activities if prior procedures were completed within CCI [redacted] of the participant's randomization to a treatment in an ISA and that the original laboratory data from previous Patient ID will be transferred over to the new Patient ID.	Clarification to prevent unnecessary blood draws or procedures in instances where a screen failure from 1 ISA is eligible for rescreening under CWMM.
8.2.11. Hepatitis B and Hepatitis C Testing and Monitoring	Added hepatitis C testing and monitoring details	Updated per the latest Lilly protocol guidance
9.3.3.1. Efficacy Analysis.	Deleted the first secondary endpoint "mean percent change of body weight (kg) from randomization at CCI [redacted]"	To align with changes made at the Objectives, Endpoints and Estimands section
	Deleted "CCI [redacted]" throughout the section	
10.2. Appendix 2: Clinical Laboratory Tests	Added content for hepatitis virus test in serology	Updated for clarity
Throughout the protocol	Minor editorial and document formatting revisions were made.	Minor; therefore, have not been summarized.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Master Protocol Title:

A Master Protocol for a Randomized, Controlled Clinical Trial of Multiple Interventions for Chronic Weight Management in Adult Participants with Obesity or Overweight

Master Protocol Brief Title:

Chronic Weight Management Master Protocol

Regulatory Agency Identifier Number(s):

IND: 163848

Rationale:

The purpose of this CWMM Phase-2 master protocol is to create a framework to evaluate the safety and efficacy of various investigational interventions for chronic weight management as hypotheses emerge.

Objectives and Endpoints:

The objectives stated in the table below are applicable to all intervention-specific appendices (ISA) under this CWMM master protocol. If applicable, additional objectives and endpoints unique to the ISA are stated in the ISA.

It is anticipated that most of the ISAs under CWMM will have a [redacted]-week treatment period. If treatment duration is longer or shorter than [redacted] weeks, secondary and exploratory objectives and endpoints will be adjusted accordingly and will be specified in the relevant ISA.

Objectives	Endpoints
Primary	
To compare the effect of the primary intervention versus the primary control for weight reduction at the primary analysis time point	• Percent change from baseline in body weight

Secondary	

To compare the effect of the primary intervention versus the primary control for weight reduction at the primary analysis time point	• Change from baseline in body weight (kg)
	• Incidence of participants who achieve:
	  ○ ≥5% body weight reduction
	  ○ ≥10% body weight reduction
	• Change from baseline in BMI

To assess safety and tolerability of study interventions	• TEAEs overall • SAEs • AEs leading to discontinuation • AEs for special safety topics • Laboratory parameters • Electrocardiogram • Vital signs

Abbreviations: AUC = area under the curve; BMI = body mass index; C_{max} = maximum concentration.

Overall Design

This is a randomized, double-blind, controlled, platform-type clinical trial to investigate the safety and efficacy of multiple interventions for chronic weight management simultaneously and/or sequentially.

The overall protocol design consists of 2 components which, when combined, define the investigations to be conducted in this platform trial. For convenience, the functional combination of the CWMM plus an ISA will be simply described as "the study."

- CWMM master protocol explains the master protocol
  - study concept
  - overall structure and governance
  - pre-screening activities (Visit 601)
  - screening activities (Visit 401)
  - study entry and discontinuation criteria
  - objectives and endpoints
  - safety monitoring activities, and,
  - statistical analyses methods applicable to all ISAs.

  The master protocol contains a Schedule of Activities (SoA) that lists activities that will be common to all studies undertaken using the master protocol.

- Individual ISAs provide information defining features that are specific or tailored to a given intervention, such as
  - specific interventions to be evaluated under the ISA, including intervention-specific background information, benefit/risk information, and dose justification
  - ISA-specific screening activities (Visit 401)
  - ISA-specific study entry and discontinuation criteria

- ISA-specific objectives and endpoints
- ISA-specific safety monitoring activities, and
- ISA-specific outcomes measurements and statistical analyses methods.

Each ISA includes an SoA applicable from baseline through the time of the participant's last planned study visit. Any ISA-specific screening activities will be included in the relevant ISA SoA.

Brief Summary:

Study participants will be adults with obesity or overweight. Each ISA provides a brief summary of the health measurements or outcomes, study interventions, treatment durations, and overall study duration for that ISA.

Study Population:

Individuals included in this study will be at least 18 years old with obesity or overweight.

Additionally, participants will have had a stable body weight for the 3 months prior to randomization.

Number of Participants:

An upper limit of CCI will be enrolled within each ISA to ensure CCI .

Intervention Groups and Duration:

Each ISA specifies the intervention groups and study duration for that ISA.

Ethical Considerations of Benefit/Risk:

Each ISA provides intervention-specific benefit/risk information for that ISA.

Data Monitoring Committee: No

These committees will be established to support the master protocol and ISA teams:

- Internal Assessment Committee, and
- Clinical Event Committee.

1.2. Schema

1.3. Schedule of Activities (SoA)

The activities applicable to all interventions studied under the CWMM master protocol are described or cross-referenced in the following subsections. Additional ISA-specific items that may need to be simultaneously undertaken are addressed in the relevant ISAs SoA, as applicable.

1.3.1. Visit 601 – Prescreening

An optional prescreening Visit 601 will enable key eligibility factors associated with screen failures to be assessed at the earliest time point. The earliest a participant may repeat Visit 601 prescreening is CCI

1.3.2. Visit 401 – Screening

The following are activities to be completed to determine a participant's eligibility for assignment to any ISA conducted under this master protocol.

Additional screening procedures and laboratory testing will be listed in an ISA when applicable.

Timing: approximately [redacted] weeks prior to randomization to treatment (Week CCI

	Prescreening (optional)	Screening (required)	Comment
CRF Visit Number	**601**	**401**	
Weeks		CCI	
Visit Interval Tolerance (± days)	**N/A**	**N/A**	
Fasting Visit	**N/A**	**X**	Fasting not required for Visit 601
Consent and Demographics			
Prescreening informed consent	X		The pre-screening informed consent grants consent only for procedures and assessments marked under V601. For general information about the ICF process, see Section 10.1.3.
Master protocol and relevant ISA informed consent		X	ICF for the master protocol and relevant ISAs must be signed before any protocol-specific tests or procedures are performed.
Inclusion and exclusion criteria/confirmation of eligibility		X	Check criteria specified in the master protocol and relevant ISAs; an ISA may have additional criteria to be checked at a subsequent visit.

	Prescreening (optional)	**Screening** (required)	**Comment**
CRF Visit Number	**601**	**401**	
Weeks		CCI	
Visit Interval Tolerance (± days)	**N/A**	**N/A**	
Fasting Visit	**N/A**	**X**	Fasting not required for Visit 601
Demographics	X	X	Include ethnicity (United States and outside of the US as allowable by local law), year of birth, gender (sex), and race. If demographics have been collected at V601, do not repeat collection at V401.
Preexisting conditions and medical history, including relevant surgical history		X	All ongoing conditions and relevant past medical history should be collected.
Prespecified medical history (indication and history of interest)		X	Prespecified medical history may include assessment of preexisting conditions, such as cardiovascular disease, type-2 diabetes, osteoarthritis, hypertension, sleep apnea.
Substance use (alcohol, caffeine, tobacco, nicotine)		X	
Concomitant medication		X	Data will be collected for all medications.
Adverse events	X	X	AEs are any events that occur after signing an ICF. Full set of AEs will be documented as part of the CWMM Protocol.
Physical evaluation			
Height		X	Height should be obtained per guidance in Section 10.8.
Prescreening height	X		Measured or self-reported.

	Prescreening (optional)	**Screening** (required)	**Comment**
CRF Visit Number	**601**	**401**	
Weeks		CCI	
Visit Interval Tolerance (± days)	**N/A**	**N/A**	
Fasting Visit	**N/A**	**X**	Fasting not required for Visit 601
Weight		X	Weight should be obtained per guidance in Section 10.8 and must be measured in the fasting status. If the participant is not fasting, the participant should return later within the visit window to have the fasting body weight measured.
Prescreening weight	X		Measured or self-reported.
Waist circumference		X	Waist circumference should be obtained per guidance in Section 10.8.
Vital signs		X	Vital sign measurements (includes 2 measurements for pulse rate, blood pressure) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, per the instruction in Section 10.8.
Complete physical examination		X	**Excludes** pelvic, rectal, and breast examinations unless clinically indicated.
12-lead ECG (local)		X	ECGs collected as instructed in Section 8.2.3. ECGs should be obtained prior to collection of blood samples for laboratory testing.
Patient-Reported Outcomes			

	Prescreening (optional)	Screening (required)	Comment
CRF Visit Number	**601**	**401**	
Weeks		CCI	
Visit Interval Tolerance (± days)	**N/A**	**N/A**	
Fasting Visit	**N/A**	**X**	Fasting not required for Visit 601
Patient Health Questionnaire-9 (PHQ-9)		X	Collected electronically via eCOA device. AE collection should occur prior to the collection of the PHQ-9.
Clinician-Administered Assessments			
C-SSRS Screening/Baseline		X	Adapted for the assessment of suicidal ideation and behavior categories only. AE collection should occur prior to the collection of the C-SSRS.
Laboratory tests and sample collections			
Hematology		X	
Clinical chemistry		X	
Lipids		X	
Urinalysis		X	
Hemoglobin A1c (HbA1c)	X	X	See Section 10.2. Participants are not restricted from donating blood between V601 and V401.
Serum pregnancy		X	For all female participants, regardless of childbearing potential.
Cystatin-C		X	
Calcitonin		X	
Pancreatic amylase		X	
Lipase		X	
Urinary Albumin/Creatinine Ratio (UACR)		X	
Estimated glomerular filtration rate (eGFR)		X	Calculated using the CCI method
Thyroid-stimulating hormone (TSH)		X	
Follicle-stimulating hormone (FSH)		X	Collect FSH in females whose menopausal status

	Prescreening (optional)	Screening (required)	Comment
CRF Visit Number	**601**	**401**	
Weeks		CCI	
Visit Interval Tolerance (± days)	**N/A**	**N/A**	
Fasting Visit	**N/A**	**X**	Fasting not required for Visit 601
			needs to be determined. For participants known to be either premenopausal or postmenopausal, these tests do not need to be collected. For definition of postmenopausal, see Section 10.4.1.
HIV screening test		X	
Hepatitis B virus (HBV) screening tests		X	
Hepatitis C virus (HCV) screening tests		X	If HCV antibody test is positive, perform an HCV RNA test.
Assessment of criteria to Proceed to Visit 401			
Confirm whether participant should proceed to Visit 401	X		
Randomization and Dosing			
Obtain patient number using IWRS	X		Obtain at time of first study consent
Register visit with IWRS		X	
Randomization via IWRS to ISA		X	Randomization to an ISA occurs as the last step of IWRS master protocol visit processing after confirming participant eligibility for both this master protocol and the relevant ISAs.

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; HIV = human immunodeficiency virus; ICF = informed consent form; ISA = intervention-specific appendix; IWRS = interactive web-response system.

1.3.3. Activities Conducted after Randomization to a Study Intervention

See the relevant ISA for procedures and activities to be conducted after a participant's randomization to a particular intervention within an ISA. Section 10.13 includes requirements for all ISAs that are part of the CWMM master protocol.

2. Introduction

Study W8M-MC-CWMM (CWMM) is a Phase-2 master protocol to accelerate the development of novel treatments for chronic weight management. This platform trial provides a framework to enable the evaluation of safety and efficacy of different interventions through the use of intervention-specific appendices (ISAs). See Sections 2.2 and 4 for details on study structure and design.

Obesity epidemiology

Obesity is a global epidemic that is associated with increased morbidity and mortality (Sarma et al. 2021). Obesity is associated with over 200 health complications, including conditions that significantly impact morbidity and mortality and contribute to excess health care costs (Wilding and Jacob 2021). In 2014, obesity-related health care costs globally were estimated at approximately 2 trillion dollars (US) (Tremmel et al. 2017). These prior values likely underestimate current costs owing to the continued increase in prevalence of obesity worldwide.

Excess body weight is associated with significant morbidity and mortality. In 2015, excess body weight accounted for approximately 4 million deaths and 120 million disability-adjusted life years worldwide (GBD 2015 Obesity Collaborators et al. 2017). Increases in mortality are driven by both cardiovascular (CV) and non-CV causes, including cancer (Berrington de Gonzalez et al. 2010).

Obesity-related complications and conditions

The impact of excess body weight on morbidity is through a large number of obesity-associated conditions (Machado et al. 2006; Van Thiel and Ramadori 2011; Lashinger et al. 2014; Garofalo et al. 2017; Chalasani et al. 2018; Müller et al. 2022; Kivimäki et al. 2022) including

- atherosclerosis
- ischemic heart disease
- heart failure
- stroke
- diabetes mellitus
- chronic kidney disease
- nonalcoholic fatty liver disease, nonalcoholic steatohepatitis, cirrhosis, and hepatocellular carcinoma
- cancer, including breast, colorectal, kidney, endometrial, and pancreatic
- obstructive sleep apnea, and
- osteoarthritis.

Effect of weight loss on clinical outcomes

A reduction in body weight could potentially improve or reverse conditions frequently associated with increased morbidity and mortality.

Observational studies show that weight loss by metabolic surgery is associated with a reduction in coronary artery events, cerebrovascular events, heart failure, atrial fibrillation, nephropathy, overall cancer risk, and all-cause mortality, compared with non-surgical controls (Aminian et al. 2019, 2020; Mentias et al. 2022; Tao et al. 2020; Khalid et al. 2022). These benefits could reflect direct relationships between change in weight and the observed outcome or be indirect via improvements in associated risk factors (Sutanto et al. 2021).

Pharmacological treatments and unmet need

FDA-approved weight loss medicines have been historically capable of providing weight loss of <10% (Srivastava and Apovian 2018), with some classes of agents carrying risks for adverse neurocognitive, psychiatric, or cardiovascular effects. The current generation of incretin-based medications provides superior weight loss (Wilding et al. 2021; Jastreboff et al. 2022) but still falls short of the weight loss achieved with surgical approaches to weight loss. Modest weight loss yields important medical benefits but has not been shown to produce the full spectrum of benefits observed with obesity surgery treatments. Further, achieving durable weight loss and realizing the full potential benefits remain a challenge, in particular for pharmacological approaches to weight loss.

Therefore, there remains a significant unmet need for efficacious and durable weight loss therapies with a favorable safety profile.

2.1. Study Rationale

The purpose of this CWMM Phase-2 master protocol is to create a framework to evaluate the safety and efficacy of various investigational interventions for chronic weight management as hypotheses emerge.

2.2. Background

2.2.1. Intervention Selection: Adding or Stopping Intervention-Specific Appendices

The CWMM master protocol defines a platform trial that will permit the evaluation of multiple investigational interventions for chronic weight management by the means of the introduction of new Phase-2 ISAs over time. Adding new ISAs will be based on

- adequate safety, tolerability, and pharmacokinetic (PK) properties supportive of an intervention's entry into development for a chronic weight management indication (see Section 2.2.2), and
- regulatory and Ethical Review Boards or Institutional Review Boards (IRB) approval to add the new ISAs and new interventions to the platform trial.

Future ISAs with new investigational drugs will cross-reference the IND for that investigational drug.

The platform design is not an adaptive design, therefore, there is no plan to discontinue ISAs based on interim analyses or external new data.

2.2.2. Governance

Selection of new interventions for investigation in this platform trial

Eli Lilly and Company (Lilly) will be responsible for the selection of interventions to be added to, or removed from, clinical development on this platform trial.

Periodic assessment of safety data in this platform trial

An Internal Assessment Committee (IAC) may be established for the purpose of making periodic prespecified or ad hoc assessments of safety data in an unblinded fashion and to make recommendations for protocol modifications or other actions. This internal committee will be independent of the Lilly study teams.

In addition, an external (independent) Clinical Event Committee (CEC) may be established, if specified in an ISA, for the purpose of adjudicating defined clinical events, in a blinded, consistent, and unbiased manner throughout the course of an ISA study.

These and other governance considerations are further described in Section 10.1.5.

Considerations for use of a common database in this platform trial

Data collected for each ISA of this platform trial will be stored in a common database. To be considered for inclusion in this platform trial, investigations of other interventions must be amenable to trial designs conformable to the preestablished standardized structure of this common database. Section 10.13 outlines the minimum standards for the SoA for each ISA.

2.3. Benefit/Risk Assessment

Study interventions are not administered during CWMM Visit 401 (screening), and the screening procedures generally present little risk. Participants may benefit by receiving personal health information from the physical examination and other safety assessments.

Intervention-specific benefit/risk information is provided in the relevant ISA.

In addition, information about the known and expected benefits and risks and reasonably expected AEs of the study intervention may be found in the Investigator's Brochure (IB) for each intervention evaluated in an ISA.

3. Objectives, Endpoints, and Estimands

The purpose of this CWMM Phase-2 master protocol is to create a framework to evaluate the safety and efficacy of various investigational interventions for chronic weight management as multiple molecules and some of their combinations emerge. The primary, secondary, and exploratory objectives stated in the table below are applicable to all ISAs under this CWMM master protocol. If applicable, additional objectives and endpoints unique to the ISA are stated in Section 3 of the ISA.

The primary analysis time point, primary control (for example, placebo or active comparator), and comparator (when applicable) will be identified within the ISA.

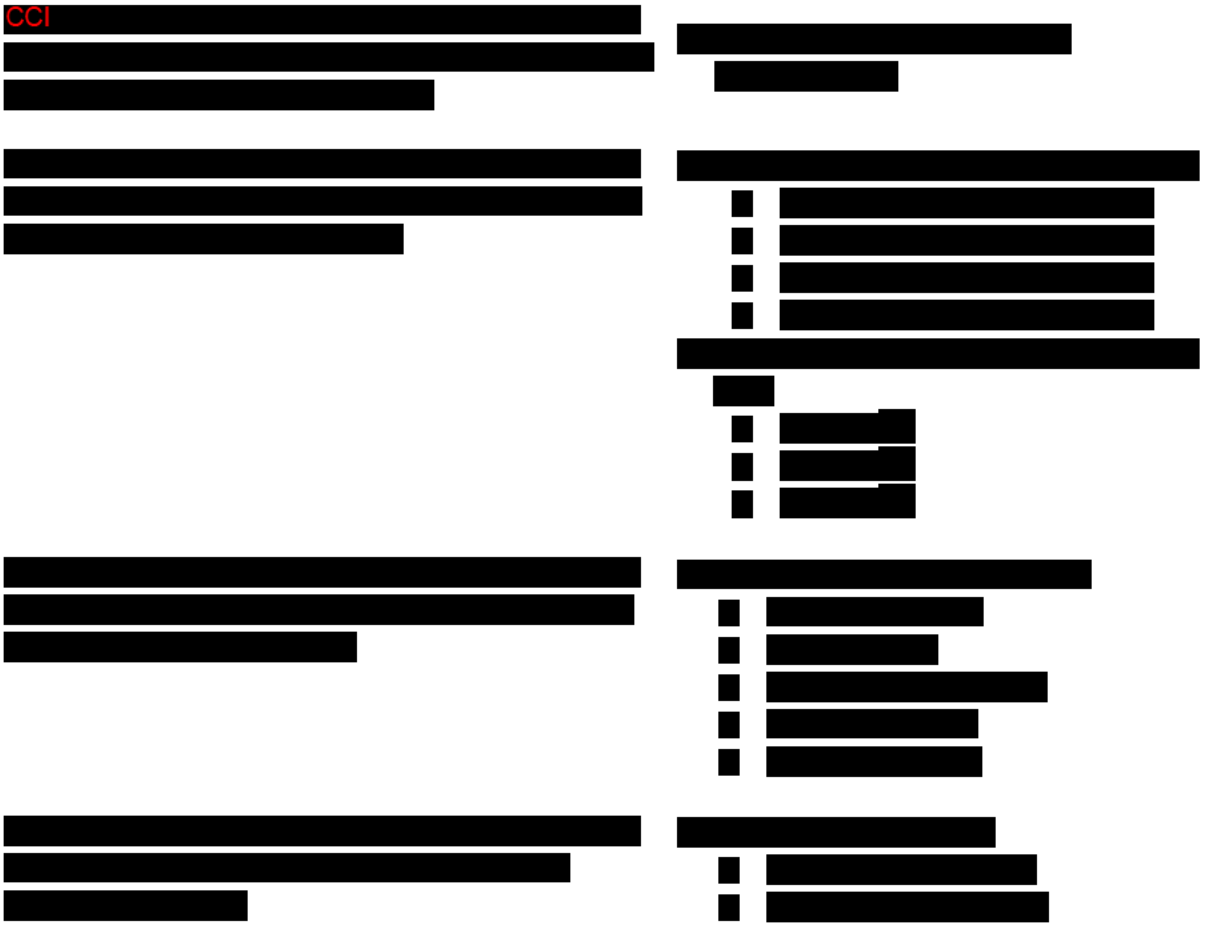
It is anticipated that most of the ISAs under CWMM will have a CCI-week treatment period. If treatment duration is longer or shorter than CCI weeks, secondary and exploratory objectives and endpoints will be adjusted accordingly and will be specified in the relevant ISA.

Objectives	Endpoints
Primary	
To compare the effect of the primary intervention versus the primary control for weight reduction at the primary analysis time point	• Percent change from baseline in body weight
Secondary	

To compare the effect of the primary intervention versus the primary control for weight reduction at the primary analysis time point	• Change from baseline in body weight (kg)
	• Incidence of participants who achieve:
	  ○ ≥5% body weight reduction
	  ○ ≥10% body weight reduction
	• Change from baseline in BMI

To assess safety and tolerability of study interventions	• TEAEs overall • SAEs • AEs leading to discontinuation • AEs for special safety topics • Laboratory parameters • Electrocardiogram • Vital signs

Exploratory



Abbreviations: AE = adverse event; AUC = area under the curve; BMI = body mass index; BP = blood pressure; C_{max} = maximum concentration; CCI ; SAE = serious adverse event; TEAE = treatment-emergent adverse event

Estimands for primary objective

An efficacy estimand is used as the primary estimand for CWMM's primary objective.

The primary clinical question of interest is:

> *What is the treatment difference, in percent change in body weight, between the primary intervention and primary control at the primary analysis time point in participants with study condition/disease if they would remain on their randomly assigned treatment?*

In the efficacy estimand, the intercurrent event (ICE) is addressed under hypothetical strategy (ICH E9[R1] 2021). In the hypothetical strategy, a scenario is envisaged in which the ICE would not occur.

The "efficacy" estimand is defined by the following attributes:

- Population: participants who meet the inclusion criteria. Further details can be found in Sections 5 and 9.
- Endpoint: percent change in body weight from baseline to the primary time point.
- Treatment condition: the randomized treatment with allowance for down-titration based on gastrointestinal (GI) tolerability, unless otherwise specified in the ISA.
- Population-level summary: Mean percent changes in body weight between the primary intervention and primary control. ICEs include permanent discontinuation of any study drug or specified in the ISA, which is handled by the hypothetical strategy. Additional ICEs may be specified in an ISA-specific protocol when appropriate. Dose modification and interruption will not be considered as ICEs because dose modification and interruption are part of the treatment condition. Down-titration will not be considered as ICEs for the estimand definition, unless otherwise specified in the ISA.

Rationale for use of an "efficacy" estimand: This Phase 2 chronic weight management platform trial aims to study the efficacy of various investigational agents under the ideal condition that all participants adhere to the randomized treatment.

Additional estimands may be explored for the primary objective.

Estimands for secondary objective

The estimand strategy applied to the primary objective will also be used for the secondary objectives, including:

Difference between primary intervention and primary control as well as difference between the primary intervention and comparator (when applicable) in

- change in body weight (kg) from baseline at the primary time point
- incidence of study participants who achieve ≥5% body weight reduction at the primary time point
- incidence of study participants who achieve ≥10% body weight reduction at the primary time point, and
- change in body mass index (BMI) (kg/m^2) from baseline at the primary time point Unless specified otherwise, safety and tolerability assessments will be guided by an estimand comparing the primary intervention doses with primary control irrespective of adherence to study drug, including data collected during the treatment period plus safety follow-up from participants who are randomly assigned and are exposed to at least 1 dose of study drug.

4. Study Design

4.1. Overall Design

Study design overview

This is a randomized, double-blind, controlled, platform-type clinical trial to investigate the safety and efficacy of multiple interventions for chronic weight management simultaneously and/or sequentially. Section 1.2 illustrates the general schema.

Master protocol and Intervention-Specific Appendices (ISAs)

The overall protocol design consists of 2 components which, when combined, define the investigations to be conducted in this platform trial.

- CWMM master protocol explains the master protocol
    - study concept
    - overall structure and governance
    - screening activities (Visit 401)
    - study entry and discontinuation criteria
    - objectives and endpoints
    - safety monitoring activities, and
    - statistical analyses methods applicable to all ISAs.

  The master protocol contains an SoA that lists activities that will be common to all studies undertaken using the master protocol (see Sections 1.3.1 and 10.13).

- Individual ISAs provide information defining features that are specific or tailored to a given intervention, such as
    - specific interventions to be evaluated under the ISA, including intervention-specific background information, benefit/risk information, and dose justification
    - ISA-specific screening activities (Visit 401)
    - ISA-specific study entry and discontinuation criteria
    - ISA-specific objectives and endpoints
    - ISA-specific safety monitoring activities, and
    - ISA-specific outcomes measurements and statistical analyses methods.

Each ISA includes an SoA applicable from baseline through the time of the participant's last planned study visit. Any ISA-specific screening activities will be included in the relevant ISA SoA. See Section 10.13.1 for activities and specific visits during an ISA Treatment Period.

4.1.1. Design Outline

Pre-screening and Screening period

Informed consent process

To participate in studies using the master protocol, a participant must provide informed consent for the procedures described in this master protocol and in the relevant ISAs prior to initiating any screening procedures. This will mean signing more than 1 ICF, as illustrated in Section 1.2

- a CWMM prescreening ICF, which grants consent only for procedures and assessments marked under V601.
- a CWMM master protocol ICF, which describes the study objective and high-level design, and the required screening procedures, and
- at least 1 ISA-specific ICF, which describes the ISA objective and design, the intervention risk and benefit information, required ISA treatment and posttreatment procedures, including risks associated with these procedures, and the approximate probability of being randomly assigned to investigational, comparator control(s) (if applicable), or placebo group.

The ICF(s) must meet the regulatory and ethical requirements stated in Section 10.1, Appendix 1 of this master protocol.

Visit numbering

There are up to 3 visits prior to randomization into a treatment group. The visits are designated as Visits 601, 401, and 402. On-treatment visit numbers are designated by the week of study treatment. The visit of randomization and first dose of study drug is Visit 0 (Week [redacted]), and if the next visit would be scheduled [redacted] weeks later, for example, then that visit would be designated as Visit [redacted] rather than Visit [redacted] The first posttreatment visit is designated as Visit 801.

Prescreening

An optional prescreening Visit 601 may be conducted at a traditional investigator site or other location associated with the investigator. HbA1c measurement may be performed through the central laboratory or at a local laboratory or via point-of-care testing, if permissible by local regulations and requirements. Local laboratories performing testing must be qualified in accordance with applicable local regulations. Registration of the visit with IWRS is required to obtain a participant identifier. The prescreening visit must be recorded in the CRF with the associated participant identifier.

Confirm the participant meets applicable eligibility criteria before proceeding to Visit 401. It is recommended that the prescreening visit be performed within [redacted] weeks of Visit 401. Certain activities will be repeated at Visit 401 for confirmation of study eligibility, including collection of height and weight to calculate BMI and HbA1c measurement via the central laboratory.

Screening (Visit 401)

The screening period of the CWMM master protocol and ISAs may begin approximately [redacted] weeks before a participant receives study intervention in an ISA. All screening procedures for the CWMM master and relevant ISAs will be completed during Visit 401. Sections 5.1 and 5.2

of the CWMM master protocol provide the criteria by which participants will be screened for inclusion in, or exclusion from, the master protocol. Sections 5.1 and 5.2 of the relevant ISAs provide ISA-specific eligibility criteria.

If the time between Visit 401 and randomization (Visit 0) takes more or less time than [redacted] weeks, it will not be considered a protocol deviation for any ISA. However, if this interval is greater than [redacted] weeks, the participant should be rescreened.

Participants who have not fasted for Visit 401 will need to return to the site for collection of fasting parameters. This return visit will be considered part of Visit 401.

Randomization to ISAs

Participants found eligible according to all CWMM master protocol trial entry criteria, and all entry criteria of at least 1 available ISA, will be randomized or assigned to an ISAs during Visit 401. The assignment to an ISA will not be blinded.

Treatment and posttreatment periods

The treatment period of an ISA begins at the end of the ISA-specific screening/lead-in period and starts with randomization to a treatment group. The duration of the treatment period may vary across ISAs. Participants will be randomly assigned to a treatment arm within an ISA at Visit 0. When the treatment period ends, participants in every ISA will have at least 1 posttreatment follow-up visit (Visit 801).

Some aspects of the treatment period are defined in this master protocol, as required features common to all studies (ISAs) performed under the master protocol/ISA structure. See the ISAs for procedures conducted during ISA-specific treatment and posttreatment study periods.

Early discontinuation of study intervention

Participants who permanently discontinue the study intervention early are encouraged to remain in the study for safety monitoring through the end of the study treatment period and to participate in posttreatment follow-up visits as specified in the master protocol and/or the relevant ISA (Section 7).

4.2. Scientific Rationale for Study Design

The following are rationales for key elements of the CWMM master protocol design. Rationales for endpoints, trial duration, and other key elements of study design are provided in the ISAs.

Appropriateness of study population

Adult participants who have BMI ≥27 kg/m^2. This population will help elucidate the benefit/risk profile of the intervention and allow comparison across interventions.

Use of control(s)

A double-blind, randomized, controlled design limits bias for investigator assessments and for patient-reported outcomes and enables a clearer interpretation of the effects of an active intervention.

Each ISA will have a concurrent control arm. Most ISAs will include a placebo control, serving this purpose as well as offering the opportunity for partial placebo borrowing (sharing of data

from placebo participants across ISAs), which over time can limit the number of patients exposed to inactive therapy. There is also a possibility for active-controlled trials comparing 2 investigational interventions or comparing an investigational intervention to an approved product. As data accumulate, there is a similar opportunity for borrowing of data from active intervention arms, to be evaluated within the context of each ISA.

The CWMM master protocol is designed to maintain consistency in the population across ISAs, within reason, to enable such efficiencies in the use of trial participant data.

Optional prescreening

Optional prescreening is included in the study design to reduce the number of screen failures.

Race and ethnicity

In this study, collection of demographic information includes ethnicity (in the United States and outside of the US as allowable by law) and race. The scientific rationale is based on the need to assess response in safety and/or efficacy based on race or ethnicity. Such a need can be addressed only if the relevant data are collected.

4.3. Justification for Dose

Justifications for doses of investigational interventions are provided in the relevant ISA.

4.4. End of Study Definition

The end of the master protocol will occur when all ISAs are complete, and no new ISAs are planned to be conducted under this master protocol.

For each ISA, the end of the study is defined as the date of the last scheduled procedure of the last participant assigned to treatment in that ISA.

5. Study Population

The study population is defined by the inclusion and exclusion criteria detailed here in the master protocol, together with any additional criteria defined in the concurrently evaluated ISA(s).

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before receiving a dose of study intervention as part of an ISA.

Participant eligibility under the master protocol must be met to be eligible for randomization to an ISA. Additional eligibility criterion may apply for each particular ISA.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

For rescreening and retesting activities within the screening period, see Section 5.4.

5.1. Inclusion Criteria

Participants are eligible to be included in ISAs under the master protocol only if all of the following criteria apply:

Age

1. Participant must be 18 or the legal age of consent in the jurisdiction in which the study is taking place to 75 years of age inclusive, at the time of signing the informed consent.

Weight

2. Have a BMI of
   - ≥30 kg/m^2, or
   - ≥27 kg/m^2 and <30 kg/m^2, with at least 1 weight-related comorbidity (for example hypertension, type 2 diabetes, dyslipidemia, cardiovascular disease, obstructive sleep apnea, hyperuricemia/gout, PCOS, urinary incontinence, osteoarthritis, chronic lower back pain/knee pain, metabolic dysfunction-associated steatotic liver disease [MASLD] or metabolic dysfunction-associated steatohepatitis [MASH], or chronic kidney disease).
3. Have had a stable body weight for the 3 months prior to randomization (<5% body weight gain and/or loss).

Informed consent

4. Capable of giving signed informed consent as described in Section 10.1.3, Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this master protocol and in the relevant ISAs.

   Note: Contraceptive use should be consistent with local regulations regarding the methods of contraception for persons participating in clinical studies. For contraception requirements, see the relevant ISA.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

Obesity related

5. Have a prior or planned surgical treatment for obesity (except prior liposuction or abdominoplasty, if performed >1 year prior to screening).
6. Have obesity induced by other endocrinologic disorders (for example, Cushing's syndrome) or diagnosed monogenic or syndromic forms of obesity (for example, Melanocortin 4 Receptor deficiency or Prader–Willi Syndrome).
7. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening, including but not limited to

   - mucosal ablation
   - gastric artery embolization
   - intragastric balloon, and
   - duodenal-jejunal endoluminal liner.

Other medical

8. Have Type 1 diabetes mellitus, latent autoimmune diabetes in adults, or history of ketoacidosis or hyperosmolar coma.
9. Have a history of significant active or unstable major depressive disorder or other severe psychiatric disorder, for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder, within the last 2 years.

   Note: Participants with major depressive disorder or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.
10. Have a lifetime history of suicide attempt.
11. Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 401 or Visit 0, prior to randomization within an ISA.
12. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.

13. On the Columbia Suicide-Severity Rating Scale (C-SSRS) at Visit 401 or Visit 0, prior to randomization, have
    - answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **and** the ideation occurred within the past month.

    OR
    - answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS **and** the behavior occurred within the past month.
14. Have poorly controlled hypertension (that is, mean seated systolic BP ≥160 mm Hg or mean seated diastolic BP ≥100 mm Hg) at screening, renal artery stenosis, or evidence of labile BP including symptomatic postural hypotension.
15. Have an elevated resting pulse rate (PR) (mean >100 bpm) or reduced resting pulse rate (mean <50 bpm) at screening.
16. Have any of the following cardiovascular conditions within 3 months prior to Screening:
    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina, or
    - hospitalization due to congestive heart failure.
17. Have ongoing or a history of frequent intermittent or chronic tachyarrhythmia syndromes, such as atrial fibrillation, supraventricular tachycardia, and positional orthostatic tachycardia syndrome.
    Note: Participants with a history of premature atrial contractions or premature ventricular contractions may be included.
18. Have ongoing or a history of bradyarrhythmias other than sinus bradycardia.
19. Have a history of NYHA Functional Classification III or IV congestive heart failure (see Section 10.7).
20. Have a screening electrocardiogram (ECG) with abnormalities that may interfere with the interpretation of changes in ECG intervals as determined by the investigator.
21. Have a personal or family history of long QT syndrome, a family history of sudden death in a first-degree relative (parents, siblings, or children) before the age of 40 years, or a personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications known to significantly prolong the QT or corrected QT interval (QTc) interval at screening.
22. Have a history of symptomatic gallbladder disease within the past 2 years, defined by the presence of gallstones on an imaging study and abdominal pain attributed to the gallstones by the participant's physician; subjects who had a procedure to remove the gallstones and/or the gallbladder (cholecystectomy), with no long-term complications, are eligible for participation if the procedure was completed at least 3 months prior to screening.
23. Have signs and symptoms of any liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory during screening:

- alanine aminotransferase (ALT) level >3.0x upper limit of normal (ULN) for the reference range
- alkaline phosphatase (ALP) level ≥1.5x ULN for the reference range, or
- total bilirubin (TBL) ≥1.5x ULN for the reference range, except for cases of known Gilbert's Syndrome.

24. Have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to patient safety. Subjects on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.
25. Have evidence of a significant, uncontrolled endocrine abnormality, for example, thyrotoxicosis or adrenal crisis, in the opinion of the investigator.
26. Have a history of an active or untreated malignancy or are in remission from a malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years.
27. Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies historically or at screening.
28. Have evidence of hepatitis B and/or positive hepatitis B surface antigen (Section 8.2.11).
29. Have hepatitis C as defined by a positive hepatitis C virus (HCV) RNA test
30. Have a history of any other condition, such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder, that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.
31. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) (1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits).
32. Have a history of frequent use of marijuana or tetrahydrocannabinol (THC-containing products) within 3 months of enrollment or unwillingness to abstain from marijuana or THC-containing products use during the trial. Patients should refrain from using during study participation.
    Note: If a participant has used cannabidiol oil during the past 3 months but agrees to refrain from use for the duration of the study, the participant can be enrolled.
33. Have had a transplanted organ (corneal transplants [keratoplasty] are allowed) or are awaiting an organ transplant.
34. Have had a blood donation of greater than 500 mL within 8 weeks prior to study screening, or a blood transfusion or severe blood loss within the prior 3 months, or have known hemoglobinopathy (for example, hemolytic anemia and sickle cell anemia), or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females) at screening.

    Note: Blood donation criteria should be consistent with local regulations.
35. Have evidence of a significant active, uncontrolled medical condition, or a history of any medical problem capable of constituting a risk when taking the study medication or

interfering with the interpretation of data, as judged by the screening investigator at screening.

36. Have evidence of a significant, active autoimmune abnormality, for example, lupus or rheumatoid arthritis, that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 9 months.

Prior/concomitant therapy

37. Unless otherwise specified, all concomitant medications should be at a stable dose for at least 3 months prior to randomization (with the exception of highly effective contraceptive methods if applicable and as stated within the respective ISA).
38. Are receiving or have received within 3 months prior to screening chronic (>2 weeks) systemic glucocorticoid therapy, excluding topical, intraocular, intranasal, inhaled, or single intraarticular injection.
39. Have current treatment with or a history of treatment with (within 3 months prior to screening) medications that may cause significant weight gain including, but not limited to, tricyclic antidepressants, atypical antipsychotics, and mood stabilizers. However, participants at a stable dose (greater than 6 months and with no expectation that the dose will change within the next year) and who are weight stable for the last 3 months on these medications may be included in the study.
    Examples of such medications
    - imipramine
    - amitriptyline
    - mirtazapine
    - paroxetine
    - phenelzine
    - chlorpromazine
    - thioridazine
    - clozapine
    - olanzapine
    - valproic acid and its derivatives, and
    - lithium.
40. Within 3 months prior to screening, have taken medications (prescribed or over the counter) or alternative remedies (including herbal or nutritional supplements) that promote weight loss

    Examples include, but are not limited to

    - Saxenda® (liraglutide 3.0 mg) or other GLP-1 RA
    - Xenical®/alli® (orlistat)
    - Meridia® (sibutramine)

- Acutrim (phenylpropanolamine)
- Sanorex® (mazindol)
- Adipex-P® or Lomaira™ (phentermine)
- BELVIQ® (lorcaserin)
- Qsymia® (phentermine/topiramate combination)
- Contrave® (naltrexone/bupropion)
- Zepbound® or Mounjaro® (tirzepatide)
- Wegovy® or Ozempic® (semaglutide), and
- other similar body weight loss medication, including over-the-counter medications.

41. Are taking a central nervous system stimulant, for example, Ritalin-SR®, Adderall XR®, with the exception of caffeinated beverages.
42. Evidence of regular use, in the opinion of the investigator, of known drugs of abuse.

Prior/concurrent clinical study experience

43. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
44. Have participated, within the last 3 months, in a clinical study and received pharmacologic treatment, whether active or placebo. If the study involved an IP, at least 5 elimination half-lives or 3 months, whichever is longer, should have passed.
45. Have participated, within the last 12 months, in a clinical study of weight loss medication and received pharmacologic treatment, whether active or placebo.

Other exclusions

46. Are females who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks or 5 half-lives, whichever is longer, after receiving the last dose of study intervention.
47. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
48. Are employees of Lilly or are employees of a third-party organization involved in the study that requires exclusion of their employees.
49. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), site personnel will provide diet and physical activity counseling and will encourage the participants to be compliant with diet and physical activity recommendations.

Diet – Participants should follow the diet recommendations provided by the study site or given in Section 10.9.1.

For most assessments, the participants will be required to come to the site in a fasting state, after an overnight fast (except for water) of at least 8 hours.

Caffeine, alcohol, and tobacco – Except when fasting is required, participants will be allowed to maintain their regular caffeine consumption throughout the study period.

Alcohol will not be permitted at least 24 hours prior to the study site visits, until the participant has been discharged from the clinical research site.

Participants should not consume more than 10 cigarettes or equivalent per day.

Physical activity – Participants may be advised by the study site to increase their regular levels of physical activity during the study per suggestions in Section 10.9.2. Participants will be advised to avoid strenuous physical activity within 24 hours prior to each study site visit if possible.

Blood donation – Study participants should be instructed not to donate blood or blood products during the study and for [redacted] weeks following the study.

5.4. Screen Failures

Consenting to, and screening for the CWMM master protocol and relevant ISAs will occur prior to participants being randomized or assigned to an ISA.

A screen failure occurs when a participant who consents to screening as above but is not subsequently randomized to any ISA or is randomized to an ISA but is not randomized to treatment. A minimal set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who are not eligible for participation in this master protocol or are ineligible for relevant ISAs (screen failure) may be rescreened. If a participant does not complete screening procedures within [redacted] weeks of signing the informed consent forms to confirm eligibility for the master and applicable ISAs, the participant is considered a screen failure. Individuals may rescreen 2 times.

Rescreened participants should be assigned a new participant number. Each time master protocol or ISA rescreening is performed, the individual must sign a new master protocol ICF and ISA ICF(s), as applicable. A screen failure from an ISA who undergoes rescreening under the CWMM master protocol may not require repeating all V401 screening activities if the activities have been completed within [redacted] weeks of the participant's randomization to a treatment in an ISA. The original laboratory data from the previous participant number will be transferred to the new participant number in instances where this is applicable.

Repeating laboratory tests during the screening period or repeating screening tests to comply with the protocol-designated screening period does not constitute rescreening.

5.5. Criteria for Temporarily Delaying Randomization of a Participant

This section is not applicable to this master protocol. All entry criteria must be met within the specified intervals in the SoA.

A study site could experience a period of time in which no ISA is active at that site. During that time period, screening for the master protocol may continue, but the allowed screening duration of the master protocol, defined in Section 1.3.1 in weeks relative to Week [redacted] must still be observed. Participants who have not been assigned to an active ISA before the end of the master protocol screening visit (Visit 401) must undergo rescreening if they wish to continue their study participation.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Study interventions and, if applicable, investigational medical devices are described in the ISAs.

6.2. Preparation, Handling, Storage, and Accountability

See the relevant ISA.

6.3. Measures to Minimize Bias: Randomization and Blinding

Blinding will be maintained throughout the conduct of studies performed under this master protocol. Instances where unblinding may be undertaken are described in the separate Unblinding Plan.

Method of treatment assignment

Assignment to the ISAs and to the treatment groups within the ISAs will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). The randomization ratios are specified in the individual ISAs. ISAs will have randomization ratio details which will depend on anticipated timing of ISA entry, number of active ISAs, required number of participants to be assigned to an active treatment group in the ISA, and desired number of placebo participants to maintain the blind and minimize bias.

Emergency unblinding

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All actions resulting in an unblinding event are recorded and reported by the IWRS.

The investigator has the sole responsibility for determining if unblinding of a participants' intervention assignment is warranted in case of an emergency. Participant 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 the sponsor as soon as possible.

Discontinuation after unblinding

If an investigator, site staff performing assessments, or participant is unblinded, the participant must be permanently discontinued from study intervention but should continue in the study for efficacy and safety endpoint evaluations and monitoring for all visits.

Additional measures to minimize bias

Additional measures to minimize bias may be described in the ISAs.

6.4. Study Intervention Compliance

This CWMM master protocol section describes compliance for all ISAs. If there are additional ISA-specific measures to assure or assess compliance or adherence, these measures will be described in an individual ISA.

Participant compliance with ISA study interventions should be assessed at each visit.

In addition to the assessment of a participant's compliance with administration of study interventions, other aspects of compliance with the study treatments should be assessed at each visit based on the participant's adherence to the visit schedule, completion of study diaries when applicable, and any other parameters the investigator considers necessary.

Participants considered to be poorly compliant with their study intervention and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol. Additionally, any specific management of treatment exposures required as a result of poor compliance will be guided by language in the ISAs.

6.5. Dose Modification

Dose modifications, if allowed, are described in the relevant ISA.

6.6. Continued Access to Study Intervention after the End of the Study

Study intervention will not be available at the end of any ISA.

6.7. Treatment of Overdose

See the relevant ISA.

6.8. Prior and Concomitant Therapy

Newly prescribed medications

Investigative site staff will inform participants they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the screening period or following assignment to an ISA. This may not be possible when initiated for treatment of medical emergencies, in which case, the participant will inform the investigator or a designated site staff member as soon as possible.

If the need for additional concomitant medication arises, the participant may be continued in the study and on study intervention if, in the investigator's opinion, the addition of the new medication does not pose a safety risk and the medication is not excluded. If an additional concomitant medication is started, the sponsor should be informed as soon as possible.

Permitted medications

Participants will be permitted to use concomitant medications that they require during the study, except certain medications, for example, other medications for weight management, that may interfere with the assessment of safety and efficacy characteristics of the study treatments.

Doses of other prescription medications for treatment of concurrent medical conditions should remain constant during the study unless an adjustment is medically indicated. For example, doses of antihypertensive medication may be reduced if the participant's BP declines significantly during the study.

Any medication or vaccine (including over the counter or prescription medicines and acetaminophen/paracetamol), vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded in the case report form (CRF). Nonsteroidal anti-inflammatory medications (including ibuprofen and aspirin), acetaminophen, cough suppressants, antihistamines, antibiotics, and topical ointments may be used on an as-needed basis without notifying the sponsor and are not restricted by the stable dosing requirements listed earlier.

Prohibited medications

Treatment with, or initiation of, medications that are excluded in the entry criteria (Section 5.2 in this master protocol and, if applicable, in the relevant ISA) may not be used during the study. Some medications required for the management of incident diabetes or incident heart failure (sodium-glucose cotransporter-2 [SGLT2] inhibitors) may be allowed in some ISAs. Specific details may be found in the ISA.

Hormone replacement therapy in postmenopausal females and contraceptives containing an estrogen and a progestin (oral or transdermal system) in premenopausal females should not be started after entering the study. If initiation of such hormonal therapies during the course of the study is deemed necessary by the participant's clinical care team, this may be allowable after consultation with the study medical monitor.

The sponsor should be contacted if a participant starts treatment with a medication that is prohibited by the protocol.

Prescription or over-the-counter medications that are indicated for weight loss are exclusionary if used within 3 months prior to screening or between screening and randomization. These medications are also not allowed at any time during the treatment period. If started after randomization, the medications should be immediately withdrawn. Participants who refuse to withdraw the weight loss medications must be discontinued from study intervention (see Section 7.1).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

The following sections describe reasons for

- temporary or permanent discontinuation of a participant's dosing (discontinuation of study intervention), and
- discontinuation (withdrawal) of a participant from the study.

For discontinuation of study sites, of ISAs, or of this master protocol as a whole, see Section 10.1.9.

7.1. Discontinuation of Study Intervention

Continuing in the study after discontinuation of study intervention

When necessary, a participant may be **permanently discontinued from study intervention**. If so, the participant should discontinue the study intervention (treatment) and remain in the study and follow select procedures for all remaining study visits, as shown in the SoA of the ISA.

See this master protocol (Section 8) and the relevant ISA (Section 1.3 [SoA] and Section 8) for data to be collected at the time of discontinuation from the study intervention and for activities in the posttreatment follow-up period and for any further evaluations that need to be completed.

Contact the relevant ISA's Lilly-designated medical monitor to determine procedures that may not be necessary for participants who discontinue the study intervention early.

Possible reasons for discontinuation of study intervention

The following reasons for early **permanent** discontinuation of study intervention apply to any ISA conducted under this master protocol.

- Participant decision
  - the participant or the participant's designee, for example, parents or legal guardian, requests to discontinue investigational product.
- Investigator decision
  - the investigator decides that the participant should be discontinued from the study medication.
- If participants answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS or answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS. A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.
- If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the Lilly-designated medical monitor should be notified. If the investigator is uncertain about whether a systemic

hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

- Any non-study medication for weight loss is given for more than 1 week, or more than 1 dose of weekly medication.
- Participants will be discontinued from the investigational product in the following circumstances:
  - diagnosis of cirrhosis after randomization
  - diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
  - any treatment-emergent adverse event (TEAE), SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
  - a female participant becomes pregnant, and
  - diagnosis of Type 1 diabetes mellitus or latent autoimmune diabetes in adults.
- If the participant develops any exclusion criterion during the course of the study, the investigator should call the sponsor to determine whether discontinuation of study drug is necessary, and
- Significant noncompliance with the protocol.

7.1.1. Hepatic Criteria for Study Drug Interruption or Discontinuation

Refer to Section 8.2.10 for hepatic criteria for study drug interruption or discontinuation.

7.1.2. QTc Stopping Criteria

If a clinically significant finding is identified, including but not limited to changes from baseline in QT interval corrected using Fridericia's formula (QTcF) after enrollment, the investigator or qualified designee will determine if the participant can continue the study intervention and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an adverse event (AE).

7.1.3. Temporary Interruption of Study Intervention

During the treatment period of an ISA, the investigator may interrupt a participant's study intervention, for example, due to an AE or a clinically significant laboratory value. The dates of study intervention interruption and restart must be documented.

Details regarding temporary discontinuation or interruption and re-introduction of study intervention, if applicable, are described in the ISAs.

7.1.4. Rechallenge

Details regarding restarting study intervention, if applicable, are described in the ISAs.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the master protocol or ISA

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee (for example, parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, and
- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and posttreatment follow-up, if applicable, as shown in the SoA of the relevant ISA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the CWMM master protocol SoA (Section 1.3) and in the SoA of the relevant ISA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Adherence to the CWMM and relevant study design elements, including those specified in the SoA and the inclusion and exclusion criteria, is essential and required for proper study execution.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria, including establishing eligibility for the CWMM master protocol and all currently available ISAs at the time of screening. Additionally, participant eligibility for a given ISA will be confirmed at the time of randomization to treatment within the ISA.

Unless otherwise specified in the relevant ISA, safety and efficacy assessments and sample collections should be completed prior to dosing at the dosing visits.

8.1. Efficacy Assessments

Efficacy-related assessments occur at visits specified in the CWMM master protocol SoA (Section 1.3) and in the relevant ISA.

Efficacy endpoints are described in this master protocol and the relevant ISA.

Primary

The primary efficacy measure is percent change body weight from baseline at the primary time point. Body weight measurements will be collected at specific clinic visits as summarized in the CWMM SoA (Section 1.3.1) and the SoA of the relevant ISA. Methods for measuring body weight are described in CWMM Section 10.8.

Secondary

The following secondary efficacy measure will be collected or calculated at the times shown in the CWMM SoA (Section 1.3.1) and the SoA of the relevant ISA:

- body weight, and
- BMI

Exploratory

CCI

8.1.1. Bioelectrical Impedance Analysis

A whole-body bioelectrical impedance analyzer will be used to assess endpoints related to body composition, as detailed in Section 10.13.

8.2. Safety Assessments

Visits and safety assessments

Safety assessments occur at visits specified in this master CWMM master protocol SoA (Section 1.3) and in the SoA of the relevant ISA.

Data collection and reporting

The AE data collection and reporting requirements are described in Section 8.3 and Section 10.3, Appendix 3.

For some interventions studied under this master protocol, there may be predefined adverse events of special interest (AESIs) or safety topics for monitoring beyond what is specified in this Master Protocol. If so, appropriate additional sample or data collections for AESIs or safety topics for monitoring will be specified in the ISAs.

Safety data monitoring

Each site's principal investigator will monitor safety data from their site throughout the study. Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

Sponsor safety monitoring

The sponsor will monitor the safety data, including AEs and SAEs, discontinuations, vital signs, and clinical laboratory results by means of periodic blinded reviews and by other appropriate methods. The SAE reports will be reviewed in real time and across studies and will include review of applicable clinical safety and epidemiological publications from the literature. If this safety monitoring activity uncovers an issue that needs to be addressed by unblinding at the individual or group level, members of the IAC can conduct additional analyses of the safety data. The IAC is an advisory group for this study formed to protect the integrity of the study in unblinded safety data reviews. See Section 10.1, Appendix 1, Section 10.1.5.

Appropriateness of safety assessments

The safety assessments used in this study are routine elements of clinical health assessment and Phase 2 drug development.

Safety assessments described in this master protocol and in ISAs

The following sections describe safety assessments applicable to all ISAs.

See the ISAs for any additional safety assessments that may be applicable to a particular ISA.

8.2.1. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations for performing these measurements included in Section 10.8.

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

8.2.2. Physical Examinations

For each participant, measurements including height and weight should be conducted according to the master protocol SoA and the ISA-specific SoA and following the study-specific recommendations for performing these measurements included in Section 10.8.

A complete physical examination will include, at a minimum, assessments of the

- skin, including feet
- cardiovascular system
- respiratory system
- GI system
- neurological system, and
- thyroid.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.3. Electrocardiograms

Prior to collecting any blood samples, 12-lead ECGs will be collected for each participant as specified in the CWMM master protocol SoA (Section 1.3) and ISA SoA.

ECGs may also be collected at visits specified in the relevant ISA and at additional visits or time points when deemed clinically necessary.

- All V401 screening ECGs are to be collected locally.
- All digital single and triplicate ECGs, as applicable in an ISA, will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory.
- 12-lead ECGs should be obtained after the participant has rested in a supine (or semi-supine) position for at least 10 minutes.

ECGs should be collected prior to collection of blood samples for laboratory testing, including PK samples.

For ECGs recorded in triplicate, consecutive replicate ECGs will be obtained at approximately 1-minute intervals and within 30 minutes prior to PK collection.

ECGs may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

ECGs will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria or for immediate participant management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant

receives the first dose of the investigational treatment should be reported in the CRF and to Lilly or its designee as an AE. The investigator (or qualified designee) must document their review of the ECG printed at the time of evaluation.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified by the investigator, the participant will be assessed by the investigator for symptoms (for example, palpitations, near syncope, or syncope) and to determine whether the participant can continue in the study. The investigator or qualified designee is responsible for determining if any change in participant management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) of the digital ECG and then store the ECGs in a database. At a future time, the stored ECG data may be over-read by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

ECGs will also be machine read for central evaluation of ECG parameters. The machine-read ECG intervals and HR may be used for data analyses and report-writing purposes, unless a cardiologist over-reading of the ECGs is conducted prior to completion of the final study report (in which case, the over-read data will be used).

8.2.4. Clinical Safety Laboratory Tests

Section 10.2 and the SoA (Section 1.3) lists the clinical laboratory tests to be performed during the screening period of this master protocol. See the relevant ISA for clinical laboratory tests to be performed during the study periods of an ISA.

All protocol-required laboratory assessments, as defined in the ISAs and in this master protocol, must be conducted in accordance with the SoAs, standard collection requirements, and the laboratory manuals.

Report the information as an AE if laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE or AE or dose modification.

Reviewing and recording test results

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition.

Repeat testing after a clinically significant abnormal finding

All laboratory tests with values considered clinically significantly abnormal during participation in the study or after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or Lilly-designated medical monitor.

If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

8.2.5. Major Adverse Cardiovascular Events

Nonfatal and fatal cardiovascular AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment. The nonfatal and fatal cardiovascular AEs to be adjudicated include

- myocardial infarction
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack deaths due to cardiovascular or unexplained causes
- hospitalization for unstable angina or heart failure, and
- coronary interventions, such as coronary artery bypass graft or percutaneous coronary intervention.

8.2.6. Deaths

All deaths will be adjudicated by a committee of physicians external to Lilly. This committee will be blinded to treatment assignment.

8.2.7. Hepatobiliary Disorders

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver laboratory tests, hepatic monitoring should be initiated as outlined in this CWMM master protocol.

8.2.8. 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 chronic renal failure.

8.2.9. Pregnancy Testing

Pregnancy testing at Visit 401

Serum pregnancy testing will be performed using a central study laboratory during the screening period of this master protocol (Sections 1.3 and 10.2).

Pregnancy testing after Visit 401

Urine pregnancy testing after Visit 401 will be performed locally according to the SoA of the relevant ISA if required. If a urine pregnancy test is not available, a serum pregnancy test performed by a local laboratory is an acceptable alternative.

If a urine pregnancy test is inconclusive at any visit, an additional serum pregnancy test should be performed. If the specified visit includes administration of study intervention, the pregnancy test must be "negative" within 24 hours before the study intervention is administered.

Pregnancy testing at any time during the study

Additional pregnancy testing may be performed at any time in the study, at the discretion of the investigator, if the participant's menstrual period is missed or there is clinical suspicion of pregnancy, or as required by local law or regulation.

Discontinuation of participants who are pregnant

Participants who are pregnant will be permanently discontinued from the study intervention (Section 7.1).

8.2.10. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Drug Interruption or Discontinuation

The following tables summarize actions to take based on abnormal hepatic laboratory or clinical changes.

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study drug
ALT or AST ≥3x ULN	X		
ALP ≥2x ULN	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥5x ULN	X	X	
ALP ≥2.5x ULN	X	X	
ALT or AST ≥3x ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥5x ULN for more than 2 weeks	X	X	X
ALT or AST ≥8x ULN	X	X	X
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x ULN	X	X	X
ALP ≥2.5x ULN and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x ULN with hepatic signs or symptoms[a]	X	X	X

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study drug
ALT or AST ≥2x baseline	X		
ALP ≥2x baseline	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5x baseline	X	X	
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x baseline	X	X	X
ALP ≥2.5x baseline and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x baseline with hepatic signs or symptoms[a]	X	X	X

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study drug
ALT or AST ≥2x baseline	X		
ALP ≥2x baseline	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5x baseline	X	X	
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR≥1.5	X	X	X
ALP ≥3x baseline	X	X	X
ALP ≥2.5x baseline and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x baseline with hepatic signs or symptoms[a]	X	X	X

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome, the threshold for TBL may be higher.

8.2.10.1. Close Hepatic Monitoring

If a participant develops any 1 of these changes, initiate close hepatic monitoring:

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)
ALT or AST ≥3x ULN **or**	ALT or AST ≥2x baseline
ALP ≥2x ULN **or**	ALP ≥2x baseline
TBL ≥2x ULN[a]	TBL ≥2x ULN[a]

[a] In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests (Section 10.2), including ALT, AST, ALP, TBL, D. Bil, GGT, CK, and CBC with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.
- In addition to lab tests, basic evaluation for possible causes of abnormal liver tests 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 current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

8.2.10.2. Comprehensive Hepatic Evaluation

If a participant develops any 1 of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation.

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)
ALT or AST ≥5x ULN **or**	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) **or**
ALP ≥2.5x ULN **or**	ALP ≥2.5x baseline **or**

ALT or AST ≥3x ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR ≥1.5

a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).
- Based on the participant'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 blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.10.3. Study Drug Interruption or Discontinuation

If a participant develops any 1 of the following laboratory or clinical changes, interrupt the study drug and continue close monitoring and comprehensive hepatic evaluation as described in Sections 8.2.10.1 and 8.2.10.2.

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	**Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)**
ALT or AST ≥3x ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥5x ULN for more than 2 weeks **or**	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks **or**
ALT or AST ≥8x ULN **or**	ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first) **or**

ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5 **or** ALP ≥3x ULN **or** ALP ≥2.5x ULN and TBL ≥2x ULN[b] **or** ALP ≥2.5x ULN with hepatic signs or symptoms[a]	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR ≥1.5 **or** ALP ≥3x baseline **or** ALP ≥2.5x baseline and TBL ≥2x ULN[b] **or** ALP ≥2.5x baseline with hepatic signs or symptoms[a]

[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Interruption or discontinuation of study drug should include these actions:

- While the participant is not receiving the study drug, clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study (that is, data lock) the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, data lock date).
- All the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study drug after interruption for a hepatic reason can be considered only in consultation with the Lilly designated medical monitor and only if the liver test results returned to near baseline and if a self-limited, non-study drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

8.2.11. Hepatitis B and Hepatitis C Testing and Monitoring

Hepatitis B testing

As specified in the SoA (Section 1.3), initial testing for HBV infection includes HbsAg and hepatitis B core antibody (HbcAb).

- If HbsAg is negative and HbcAb is negative, the participant is not excluded.
- If HbsAg is positive, the participant is excluded.
- If HbsAg is negative and HbcAb is positive, further testing for HBV DNA is required.
    - If the screening HBV DNA is positive, the participant is excluded.

If screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study.

Hepatitis C testing

As specified in the SoA (Section 1.3), initial testing for HCV infection includes testing for anti-HCV.

- If anti-HCV is positive, a test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded (see Section 5.2).

Participants who have had HCV infection and have been successfully treated, defined as a sustained virologic response (HCV RNA by PCR negative for at least 24 weeks following treatment completion), are not excluded on the basis of HCV as long as HCV RNA test is negative at screening.

8.2.12. Mood Changes, Suicidal Ideation, and Suicidal Behavior Risk Monitoring

Participants who have obesity or are overweight are at increased risk for depression (Luppino et al. 2010). Depression can increase the risk for suicidal ideation and behavior. Therefore, study participants will be screened at trial entry and monitored during the study for depression, suicidal ideation, and suicidal behavior.

Participants should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases. Consideration should be given to discontinuing the study medication in who experience signs of suicidal ideation or behavior, following a risk assessment.

Baseline and treatment-emergent assessment of depression, suicidal ideation, and suicidal behavior will be monitored during the study using the C-SSRS and PHQ-9. Scores of the questionnaires must be reviewed by the investigator at the time of each visit, and appropriate actions as described below should be taken.

8.2.12.1. C-SSRS

Columbia Suicide-Severity Rating Scale (C-SSRS) is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

See Section 8.3.1.1 for the collection of the C-SSRS relative to nonleading (spontaneous) AE collection.

8.2.12.2. PHQ-9

The PHQ-9 questionnaire is a validated, participant-completed 9-item depression module of the Patient Health Questionnaire, which is used as a diagnostic instrument for common mental

disorders. The PHQ-9 consists of 9 items each scored on a scale of 0 = "not at all" to 3 = "nearly every day" with a recall period of "the last 2 weeks." Major depression is diagnosed if 5 or more of the 9 depressive symptom criteria have been present at least "more than half the days" in the past 2 weeks, and 1 of the symptoms is depressed mood or anhedonia. As a severity measure, a higher score indicates greater severity (Kroenke et al. 2001).

Participants will be referred to a Mental Health Professional if in the opinion of the investigator it is necessary for the safety of the participant or if at any time the participant has a PHQ-9 score ≥15.

8.2.13. Additional Safety Data and Sample Collections

For some interventions, additional data or sample collections may be necessary when certain AEs occur. See the ISAs for any additional data or sample collections for such AEs and additional instructions, if applicable.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Section 10.3:

- AEs
- SAEs, and
- Product complaints (PCs).

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest (as defined in the ISAs) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE-related to prescreening study procedure	Signing of the pre-screening ICF	Participation in the study has ended	As soon as possible upon site awareness	AE CRF	N/A
AE	Signing of the ICF	Participation in the study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	At least 5 half-lives plus CCI days (female partners of male participants) and 5 half-lives plus CCI days (female participants) after the last dose or, until study participation has ended, whichever is later.	Within 24 hours (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint Form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint Form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint Form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint Form	

[a] SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.1.1. Adverse Event Monitoring with a Systematic Questionnaire

Nonleading AE collection should occur prior to the collection of the C-SSRS.

If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After learning of a pregnancy in the female partner of a study participant, the investigator
  - will obtain a consent to release information from the pregnant female partner directly, and
  - within 24 hours after obtaining this consent, will record pregnancy information on the appropriate form and submit it to the sponsor.

  The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will discontinue study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

See the relevant ISA.

8.4. Pharmacokinetics

See the relevant ISA.

Sample retention is described in Section 10.1.12.

8.5. Pharmacodynamics

See the relevant ISA.

Sample retention is described in Section 10.1.12.

8.6. Genetics

See the relevant ISA.

Sample retention is described in Section 10.1.12.

8.7. Biomarkers

See the relevant ISA.

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Immunogenicity may be evaluated in the ISAs governed by this protocol. Information on immunogenicity sample collection and assessment will be described in the ISA as applicable.

Refer to Section 10.1.12, Appendix 1 for details on sample retention.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

If applicable, see the relevant ISA.

9. Statistical Considerations

The statistical analysis plan (SAP) for the CWMM master protocol and each respective ISA will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the common endpoints shared across all the ISAs.

9.1. Statistical Hypotheses

For each ISA of the CWMM master protocol, the primary null hypothesis is that there is no difference between the intervention and primary control on the primary endpoint and time point. The null hypothesis for secondary objectives is that there is no difference between the intervention and primary control for secondary endpoints at time points of interest. Intervention-specific details regarding hypotheses and statistical testing will be detailed in the respective ISAs.

9.1.1. Multiplicity Adjustment

No adjustments or control for multiplicity will be performed unless specified in the ISA SAP.

9.2. Analysis Sets

This table describes the populations and data points that will be used for statistical analyses within each ISA of the CWMM master protocol. Additional intervention-specific populations for analyses may be described in the ISAs:

Participant Analysis Set	Description
Full analysis set (FAS)	All randomized participants who meet the inclusion criteria.
Safety analysis set (SAS)	All participants who are exposed to investigational intervention.

The following data point sets are defined:

Data Point Sets	Description
DPS1	Data points obtained during treatment period at or after randomization up to the date of discontinuation of any study drug or intercurrent events (ICEs) specified in respective ISAs.
DPS2	Data points obtained during treatment period at or after randomization regardless of adherence to study drug.
DPS3	Data points obtained during treatment period plus safety follow-up period regardless of adherence to study drug.

Abbreviation: DPS = data point set.

FAS and DPS1 will be used to estimate the primary estimand (efficacy estimand) for primary and secondary objectives.

FAS and DPS2 may be used to estimate the additional estimands for the primary and secondary objectives.

SAS and DPS3 will be used to present safety data.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analyses of the CWMM master protocol and ISAs will be the responsibility of the sponsor or its designee. Multiple SAPs will be defined and used throughout the duration of the entire CWMM master protocol. A single CWMM master protocol SAP will be developed, as well as an ISA SAP, for each ISA. The CWMM master protocol SAP describes the statistical analyses that are common across the entire CWMM master protocol, and the analyses will be conducted within each ISA. The analyses in the CWMM master protocol SAP will include

- disposition reports
- AE analyses
- laboratory analyses
- vital signs analyses
- PK parameters analyses, and
- efficacy analyses that do not depend on borrowing of comparator and primary control information from other ISAs.

The ISA SAP will contain the statistical analyses unique for each ISA and may include

- the proposed strategy of borrowing comparator and primary control information from other ISAs
- if any partial borrowing of placebo information is implemented, the model used for the primary and secondary analyses, and
- details of analyses that are unique to the ISA or analyses that may differ from what is specified in the CWMM master protocol SAP.

If there is a discrepancy between the CWMM master protocol SAP and the ISA SAP, the methodology in the ISA SAP will be used.

Changes to the CWMM master protocol data analyses methods will require an amendment only if they change a principal feature of the master protocol. Any other change to the data analyses methods, and the justification for making the change, will be described in the SAP and the clinical study report for each respective ISA.

The initial ISA will not have an opportunity to prospectively borrow control information from other ISAs; borrowing control information may occur in subsequent ISA analyses when appropriate. Bayesian hierarchical modeling and other modeling approaches will be considered for borrowing information. Analysis details and impact on sample size will be provided in the ISA and its respective SAP.

The CWMM master protocol SAP will be finalized prior to the unblinding of the first ISA. The ISA SAP will be finalized prior to the first unblinding of the respective ISA.

The specific baseline definitions for each analysis will be provided in the CWMM master protocol SAP.

All tests of treatment effects will be conducted at a 2-sided alpha level of CCI, unless otherwise stated, and all confidence intervals will be given at a 2-sided CCI% level. Unless otherwise stated in an ISA, the primary estimand of interest in comparing efficacy of primary intervention doses with the primary control is the “efficacy” estimand, which represents the effect of treatment in the hypothetical scenario where the patient did not discontinue study drug. The primary efficacy assessment, guided by the “efficacy” estimand, will be conducted using the FAS and DPS1 dataset (see Analyses Sets table in Section 9.2). For the efficacy estimand, the hypothetical strategy is used to handle the ICEs (permanent discontinuation of study drug), so only data collected before the occurrence of any ICEs will be used in the mixed model for repeated measures (MMRM) analysis (Section 9.3.1). Efficacy measures will be implicitly imputed for visits occurring after the ICEs.

The summary statistics for continuous measures will include sample size, mean, standard deviation, median, minimum, and maximum. Unless stated otherwise in an ISA's SAP, the analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time, in addition to the baseline and end of treatment measurements, will be an MMRM. Analysis of Heterogeneous Covariance (ANHECOVA) (Ye et al. 2022) may be used to make comparisons among treatment groups for continuous measurements with only 1 postbaseline assessment.

Summary statistics for categorical measures, including categorized continuous measures, will include sample size, frequency, and percentages. Fisher's exact test will be used to examine the treatment difference in categorical outcomes.

Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. The negative binomial regression model may be used for the treatment comparison of discrete count measures if deemed appropriate.

9.3.2. Primary Endpoint Analysis

The primary efficacy assessment, guided by the "efficacy estimand," will be conducted using the FAS and DPS1 dataset for the primary endpoint (percent change from baseline in body weight at the primary time point).

The primary efficacy comparison will be based on the contrast between each treatment group (group of cohorts with the same target dose) of primary intervention and primary control at the ISA-specified primary time point from the MMRM analysis of percent change from baseline in body weight using the FAS and DPS1 dataset (Section 9.2). The analysis model and selection of covariance structure will be described in each ISA.

Treatment comparisons will be performed for the primary objective at the full significance level of CCI

9.3.3. Secondary Endpoint(s) Analysis

9.3.3.1. Efficacy Analyses

The following secondary endpoints will be analyzed on the FAS and DPS1 dataset:

- mean change from baseline in body weight (kg) from randomization at the primary time point
- incidence of study participants who achieve the following criteria from randomization at the primary time point:
  - ≥5% body weight reduction
  - ≥10% body weight reduction, and
- mean change in BMI (kg/m^2) from randomization at the primary time point.

Analyses of continuous endpoints, including change in body weight (kg), BMI (kg/m^2), will be conducted in a manner similar to the primary efficacy analyses discussed in Section 9.3.2.

Analyses for incidence of participants reaching ≥5% body weight reduction and ≥10% body weight reduction from baseline at the ISA-specified primary time point will be conducted using a

longitudinal logistic regression analysis. The analysis model, covariates, and selection of covariance structure will be described in the CWMM master protocol SAP and each ISA's SAP. Additional secondary efficacy analyses may be performed, if deemed necessary and specified in master and/or the respective ISA SAP.

9.3.4. Exploratory Endpoint(s) Analysis

Details of the analyses will be provided in the CWMM master protocol SAP as well as each ISA SAP.

9.3.5. Safety Analyses

All safety analyses will be conducted on the safety analysis set and DPS3 (Section 9.2) for each ISA. Safety assessments will be guided by an estimand comparing safety of primary intervention to the primary control irrespective of adherence to study drug.

For each ISA, AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, study drug discontinuation due to AEs, deaths, and other CV endpoints. Counts and proportions of participants experiencing AEs will be reported for each treatment group and each dose escalation subgroup, and Fisher's exact test will be used to compare the primary intervention dose groups with the primary control.

9.3.5.1. Central Laboratory Measures, Vitals and Electrocardiograms

Values and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized for each treatment group at each scheduled visit. The details will be provided in the respective ISA SAP.

9.3.5.2. Analysis of C-SSRS Data

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 (C-SSRS WWW).

9.3.6. Other Analyses

Other safety analyses may be conducted. Details will be provided in the master SAP and each ISA's SAP.

9.3.6.1. Participant Disposition

A detailed description of participant disposition will be provided, including a summary of the number and percentage of participants entered into the study and randomized, and number and percentage of participants who complete the study or discontinue, both overall and by reason for discontinuation for each ISA at the end of the study. Intervention-specific analyses are described in the respective ISAs' SAP. A summary of important protocol deviations will be provided for each ISA. The percentage of participants discontinuing from each treatment will be compared using the Fisher's exact test. Kaplan–Meier analyses of time from randomization to premature

discontinuation from study and premature discontinuation from study drug by treatment group will be provided.

9.3.6.2. Participant Characteristics

Demographics, baseline characteristics, medical history, and concomitant illness will be summarized by treatment group using the FAS.

Additional intervention-specific analyses may be specified in each respective ISA.

9.3.6.3. Concomitant Therapy

Previous and concomitant medications will be summarized by drug class and each treatment group using the FAS for each ISA and will be presented by Anatomical Therapeutic Chemical drug classes using the latest version of the WHO drug dictionary.

9.3.6.4. Treatment Compliance

Treatment compliance with investigational product will be summarized by treatment for each ISA. Intervention-specific analyses are described in the relevant ISAs SAP.

9.3.6.5. Pharmacokinetic/Pharmacodynamic Analyses

Intervention-specific PK/PD analyses are described in the relevant ISAs. Details will be specified in a separate PK/PD analysis plan.

9.3.6.6. Evaluation of Immunogenicity

Immunogenicity assessments will be described in the ISAs as applicable.

9.4. Interim Analysis

The CWMM master protocol does not require or specify interim analyses for an ISA. If an interim analysis is planned for an ISA, the details (for example, timing, rationale, use of participants in other ISAs) will be provided in the ISA or ISA SAP. Unblinding details will be specified in a master unblinding plan document; ISA-specific unblinding plan documents will be developed as needed.

9.5. Sample Size Determination

An upper limit of approximately CCI % enrollment of females will be enrolled within each ISA to ensure a sufficiently large sample of males. The sample size and power for each ISA will be provided and justified in the ISA. Sample size determination based on the primary endpoint will be carried out as follows: When the primary control is placebo, ISA sample size will be evaluated through a test of superiority to placebo conducted for each of the intervention doses at 2-sided significance levels of CCI using a 2-sample t-test. In other cases, the sample size justification may depend on a superiority or non-inferiority test to the primary control.

Borrowing information from placebo or other active or investigational treatment arms from other ISAs will be justified and detailed within the respective ISA and SAP, as necessary. Sample size for control arms may vary by ISA, and an ISA that enters the CWMM master protocol later in calendar time may randomize fewer participants, since there may be a sufficient set of placebo or

active or investigational treatment participants from which information may be borrowed and used in the primary efficacy analysis. Operating characteristics may also vary for the ISAs that enter later in calendar time for the same reason.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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

- consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- International Organization for Standardization (ISO) 14155, and
- applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents, for example, advertisements, must be submitted to an IRB/Independent Ethics Committees (IEC) by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures stablished by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant or the potential participant's legally authorized representative and answer all questions regarding the CWMM master protocol and relevant ISAs.

Potential participants must be informed that their participation is voluntary. Participants or their legally authorized representatives will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy and data protection requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered into the CWMM master protocol and any ISA, and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative and is kept on file.

A participant who is rescreened for the CWMM master protocol must sign a new ICF, along with ICFs for currently available ISAs.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.5. Committees Structure

Internal Assessment Committee (IAC)

In addition to the safety reviews routinely performed by the blinded study team as described in Section 8.2, an IAC may exist for the purpose of reviewing safety data in an unblinded fashion periodically or on an ad hoc basis if needed. The IAC may determine whether any changes to the study, for example, dose reductions or other protocol modifications, should be made (Section 10.1.5.1).

The IAC will be independent from the study team and include, at a minimum, a Lilly medical physician, a statistician, and a representative from the Lilly Global Patient Safety organization. Details about IAC membership, purpose, responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

If an efficacy interim analysis is conducted, the IAC will be responsible for review of the efficacy data. See Section 9.4 for general information about interim analyses. Details of interim analyses will be provided in the SAP.

Investigator sites will receive information about interim analyses results only if such information is relevant regarding the safety of their study participants.

Clinical Event Committee (CEC)

An external (independent), blinded CEC may be used to adjudicate select clinical events in ISAs. If applicable, the CEC will be defined in the relevant ISA.

10.1.5.1. Stopping Rules

Each ISA may specify study stopping rules as appropriate for the study intervention.

The IAC may convene periodically but also when the accumulated safety data triggers one of the stopping rules if specified in an ISA. Further enrollment in that ISA, or further dosing in that ISA, or both may be stopped, pending a decision of the IAC.

10.1.6. Dissemination of Clinical Study Data

Clinical study reports

A clinical study report will be provided for each ISA.

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results

will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, SAP, clinical study report, and blank or annotated CRF, will be provided in a secure data-sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRFs or electronic clinical outcome assessment (eCOA) unless transmitted to the sponsor or designee electronically, for example, laboratory data. The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Data monitoring and management

When applicable, quality tolerance limits may be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters may be monitored during the study and important excursions from the quality tolerance limits and remedial actions taken may be summarized in the clinical study report.

Monitoring details describing strategy (for example, risk-based initiatives in operations and quality, such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals, for example, CROs.

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records retention and audits

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the Clinical Trial Agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

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

Data capture system

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

Electronic data capture system

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Clinical outcome assessments

Clinical outcome assessment (COA) data (patient-focused outcome instrument) will be collected by authorized study personnel, via a paper source document or eCOA.

Additionally, any eCOA data (patient-focused outcome instrument) will be directly recorded by the participant or investigator site personnel, into a device, for example, hand-held smart phone or tablet. The eCOA data will serve as the source documentation and the investigator will not maintain a separate written or electronic record of these data.

Data storage and access

Data collected via the sponsor-provided data capture systems will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

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

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in Section 10.1.7.

10.1.9. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study or site termination

Either the CWMM master protocol as a whole or only a particular ISA may be discontinued at the discretion of the sponsor if the sponsor judges' discontinuation to be necessary for medical, safety, regulatory, futility, lack of benefit/efficacy, or discontinuation of study intervention development, or other reasons consistent with applicable laws, regulations, and GCP.

The sponsor or sponsor's designee reserves the right to close the study site or terminate either the CWMM master protocol as a whole or an ISA, at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to

For study termination:

- discontinuation of further study intervention development

For site termination:

- failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- inadequate recruitment (evaluated after a reasonable amount of time) of participants by the investigator, and
- total number of participants included earlier than expected.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s)

used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of the ISAs conducted as part of this CWMM master protocol will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical trial.

10.1.12. Sample Retention

Sample retention 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 the intervention or after the intervention becomes commercially available.

This table describes the retention period for potential sample types collected for the CWMM master protocol and ISAs.

Sample Type	Custodian	Retention Period After Last Patient Visit[a]
Nonpharmacogenomic	Sponsor or Designee	up to 15 years
CCI [redacted]		[redacted]
Pharmacokinetic	Sponsor or Designee	1 year
Genetics/PD	Sponsor or Designee	up to 15 years
Immunogenicity	Sponsor or Designee	15 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

Use of central or local laboratories

The tests detailed in the table below will be performed by the central laboratory or by a local laboratory as indicated by the tables in this appendix.

Local laboratory results are only required in the event that the central laboratory results are not available for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time if possible. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be recorded.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Laboratory tests for inclusion/exclusion of potential study participants

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of this CWMM master protocol and each ISA.

Allowance for additional laboratory testing

Additional tests may be performed at any time during the study as determined necessary by the investigator, Lilly-designated medical monitor, or required by local regulations.

Investigator responsibilities

Investigators must document their review of the laboratory safety results.

Provision of laboratory test results

Laboratory test results that could unblind the study will not be reported to investigative sites or other blinded personnel.

Pregnancy testing

Pregnancy testing is described in the SoA (Section 1.3), in Section 8.2.9, and in the table below, as well as in the relevant ISA.

10.2.1. Clinical Laboratory Tests

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs – red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs – white blood cells)	

Platelets	
Differential	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Cell morphology (RBCs and WBCs) (performed only if clinically indicated)	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Lipid Panel	Assayed by Lilly-designated laboratory
High-density lipoprotein (HDL)	
Low-density lipoprotein (LDL-C)	This value will be calculated. If triglycerides are >400 mg/dL, the direct LDL will be assayed
Very low-density lipoprotein (VLDL-C)	
Total cholesterol	
Triglycerides	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	

Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment (performed only if clinically indicated)	
Hormones	Assayed by Lilly-designated laboratory
Thyroid-stimulating hormone (TSH)	
Hormones (females only)	
Serum pregnancy (beta-HCG)	
Follicle-stimulating hormone (FSH)	
Calculations	Generated by Lilly-designated Laboratory
Urinary albumin/creatinine ratio (UACR)	
EGFR [redacted]	
Serology	Assayed by Lilly-designated laboratory
HIV screening test	
Hepatitis B virus (HBV) testing:	
Hepatitis B surface antigen (HBsAg)	
Hepatitis B core antibody total (anti-HBc)	
HBV DNA	Performed only for participants who test negative for HBsAg and test positive for anti-HBc.
Hepatitis C virus (HCV) testing:	
HCV antibody	
HCV RNA	Performed only for participants who test positive for HCV antibodies.
Additional Testing	Assayed by Lilly-designated laboratory
Cystatin-C	
Calcitonin	
Pancreatic amylase	
Lipase	
HbA1c	Testing may be performed locally for Visit 601. All other visits assayed by Lilly-designated laboratory.

10.3. Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Information for ISAs having devices

The definitions and procedures detailed in this appendix are in accordance with ISO 14155.

Both the investigator and the sponsor will comply with all local medical device reporting requirements.

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 6.1.1 of the relevant ISA for the list of sponsor medical devices.

10.3.1. Definition of AE

AE definition

- For drug-only clinical studies: An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
- For clinical studies that include a medical device: An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device used in an ISA. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, and vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent preexisting condition, including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

- Results in death
- Is life-threatening
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability or incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.

  - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

- Is a congenital anomaly or birth defect
  - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations
  - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
  - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

10.3.3. Definition of Product Complaints

Product complaint

- A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:
  - deficiencies in labeling information, and
  - use errors for device or drug-device combination products due to ergonomic design elements of the product.
- PCs related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and product complaint recording

- When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation, for example, hospital progress notes, laboratory reports, and diagnostics reports, related to the event.
- The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page, and PC information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.
- There may be instances when copies of medical records for certain cases are requested by sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide sponsor or designee with a copy of any postmortem findings, including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the SAE paper form (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on an SAE paper form (see next section) or to the sponsor or designee by telephone.

- Contacts for SAE reporting can be found in the Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

SAE reporting via paper form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in Global Patient Safety Clinical Trial SAE Transmission Cover Sheet and Form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information, for example, summary or listing of SAEs, from the sponsor will review and then file it along with the IB or state other documents and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

This table defines postmenopausal state for screening purposes in the CWMM master protocol. For additional definitions, see the relevant ISA.

Word/Phrase	Definition
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Females should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen-receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

See the relevant ISA.

10.5. Appendix 5: Genetics

Use/analysis of DNA

- Genetic or epigenetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic or epigenetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to primary intervention or obesity, diabetes mellitus, related traits or complications, including nonalcoholic steatohepatitis and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to primary intervention or comparators, study interventions related to this drug class and/or obesity, diabetes mellitus, related traits or complications, including nonalcoholic steatohepatitis. Genetic or epigenetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic or epigenetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The samples may be analyzed as part of a multi-study assessment of genetic or epigenetic factors involved in the response to primary intervention or comparators, or study interventions related to this class to understand study disease or related conditions.
- The results of genetic or epigenetic analyses may be reported in the clinical study report or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on the primary intervention or study interventions related to this class or research on obesity, diabetes mellitus, related traits or complications, including nonalcoholic steatohepatitis continues but no longer than 15 years or other period as per local requirements.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Hepatic evaluation testing

See CWMM master protocol Section 8.2.10 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management.

The local laboratory must be qualified in accordance with applicable local regulations.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[b]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[b]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	HDV IgM antibody
Direct bilirubin	**Hepatitis E virus (HEV) testing:**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine aminotransferase (ALT)	HEV IgM antibody
Aspartate aminotransferase (AST)	HEV RNA[b]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)**[a]
Hepatic Coagulation Panel	**Anti-actin antibody**[c]
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[b]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology Culture:**
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV antibody	
EBV DNA[b]	

[a] Not required if anti-actin antibody is tested.

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

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

10.7. Appendix 7: New York Heart Association Functional Classification of Heart Failure

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

10.8. Appendix 8: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs

The following information has been adapted from standardized physical measurement protocols for the WHO's STEPwise approach to Surveillance (STEPS) (WHO 2017).

Measuring height

Step 1. Ask the participant to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when their height is measured).

Step 2. Ask the participant to stand on the calibrated height measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the backboard, the stadiometer, or the wall.

Step 3. Ask the participant to look straight ahead without tilting their head up.

Step 4. Ask the participant to breathe in and stand tall. Measure the participant's height in centimeters, and measure and record to 1 decimal place.

Measuring weight

- 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 must be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

Step 1. Ask the participant to empty their pockets and remove their footwear, outerwear (coat, jacket, etc.), and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when weight is measured).

Step 2. Make sure the scale is placed on a firm, flat, even surface (not on carpet, on a sloping surface, or a rough, uneven surface).

Step 3. Ask the participant to step onto the scale with 1 foot on each side of the scale.

Step 4. Ask the participant to stand still with arms by sides and then record weight in kilograms to the nearest one-tenth kilogram.

Measuring waist circumference

- Waist circumference should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Measurements should be taken at the end of a normal expiration using a non-stretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.

- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the CRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Step 1: Ask the participant to wear little clothing (if available, garments could also be used).

Step 2: Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.

Step 3: Ask the participant to relax and measure the participant's waist circumference.

Vital sign measurements

- Vital sign measurements (BP and HR, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- The participant should sit quietly for 5 minutes before vital sign measurements are taken.
- For each parameter, 2 measurements will be taken using the same arm, preferably the nondominant arm.
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and BP needs to be recorded in the CRF.
- BP must be taken with an automated BP instrument.
- If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

Note: In the event pulse measurement cannot be taken via an automated BP instrument, the preferred location for measurement of pulse is the radial artery.

10.9. Appendix 9: Diet and Physical Activity Suggestions for Sites without Programs

10.9.1. Diet

Diet recommendations are based on the World Health Organization (WHO 2020a) for everyone which is based on a Mediterranean eating pattern.

The Mediterranean eating pattern for a healthy diet consists of

- legumes (for example, lentils and beans)
- nuts
- whole grains (for example, unprocessed wheat, maize, millet, oats, and brown rice)
- at least 5 portions of fruit and vegetables per day (excluding potatoes, sweet potatoes, cassava, and other starchy roots)
- less than 10% of total energy intake from free sugars (equivalent to 50 g or 12 level teaspoons), but ideally less than 5% of total energy intake. Free sugars are sugars added to foods and drinks, as well as sugars present in honey, syrups, fruit juices, and fruit juice concentrates
- less than 30% of total energy intake from fats. Unsaturated fats are preferred over saturated fats. Unsaturated fats are found in fish, avocado, nuts, sunflower, canola, and olive oils. Consumption of saturated fats, which are fats in fatty meat, butter, palm and coconut oil, cream cheese, ghee, and lard, should be reduced to less than 10% of total energy intake. Trans fats, which are found in industrially produced foods, should be avoided, and
- salt intake should not be more than 5 g (about 1 teaspoon) per day and should be iodized.

10.9.2. Physical Activity

Regular physical activity can improve a participant's health. Moving more and sitting less benefits everyone, regardless of age, sex, race, ethnicity, or current fitness level. Benefits accumulate with even small amounts and start immediately.

To safely engage in physical activity, types of physical activity appropriate for the participant's current fitness should be chosen. Furthermore, the amount and duration of physical activity should be gradually increased over time. Participants with chronic conditions and symptoms should be under the care of a health care provider about the types and amounts of physical activity that are appropriate for the participant.

Physical activity recommendations are based on WHO recommendations (WHO 2020b) and with the US Health and Human Services (HHS 2020) recommendations.

- Any physical activity is better than none. Adults should move more and sit less.
- Adults should do 150 minutes (2 hours 30 minutes) to 300 minutes (5 hours) of moderate-intensity aerobic physical activity throughout the week or 75 minutes (1 hour 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and

vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.

- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond the equivalent of 300 minutes (5 hours) of moderate-intensity physical activity a week.
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.
- Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week, as well as aerobic and muscle-strengthening activities. They should be as physically active as their abilities and conditions allow. When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.

10.10. Appendix 10: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs), and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-up, and Reporting

Refer to Appendix 3 (Section 10.3) for definitions and procedures for recording, evaluating, follow-up, and reporting of all events.

10.11. Appendix 11: Country-Specific Requirements

For sites in EU Member States

Sponsor has processes that are compliant with General Data Protection Regulation (GDPR) data privacy regulations and the European Clinical Trial Regulation (CTR) (Articles 56, 57, 58).

For sites outside of EU Member States

Country-specific requirements, if any, will be described in a separate protocol addendum or an ISA.

10.12. Appendix 12: Provisions for Changes in Study Conduct during Exceptional circumstances

The following provisions are applicable to all ISAs unless otherwise specified.

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators or participants, or both, to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, for example, upon implementation and suspension of changes. All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for

- participation in remote visits, as defined in Section "Remote Visits"
- a change in the method of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

See the relevant ISA for the additional informed consent requirements, if any, specific to that ISA.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Types of remote visits for Visit 401 (CWMM master protocol screening period)

Telemedicine:

Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner may include, but are not limited to

1. medical history
2. concomitant medications
3. AEs
4. explain diet and physical activity plan, and
5. mental health questionnaires, for example, PHQ-9.

Mobile healthcare:

Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits may include, but are not limited to

- height, weight, and waist measurements
- vital signs
- symptom-directed physical assessments
- ECGs
- administration of patient-reported outcomes
- collection of blood and urine samples, and
- collection of health information.

Other alternative locations:

During exceptional circumstances, laboratory samples, and ECGs may be collected locally, if needed outside of mobile healthcare visits.

Types of remote visits for Visit 402 and thereafter

See the relevant ISA.

Data capture

In source documents and the CRF, the study site should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and PCs remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the site staff.

Local laboratory testing option for Visit 401 (CWMM master protocol screening period)

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

Local laboratory testing option for Visit 402 and thereafter

See the relevant ISA. A local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf
- arranging delivery of study supplies, and
- if applicable, working with the sponsor to determine how study intervention that is typically administered on site will be administered to the participant; for example, during a mobile healthcare visit or at an alternate location such as an infusion center.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site, for example, participant's home, the investigator or sponsor, or both, should ensure oversight of the shipping process to ensure accountability and product quality, that is, storage conditions maintained and intact packaging upon receipt.
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, these additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer study intervention.
- See the relevant ISA for any intervention-specific instructions.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visits are valid for a maximum of [redacted] weeks. The following rules will be applied for active, nonrandomly assigned participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than [redacted] weeks from screening to randomization, the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within [redacted] weeks from first screening visit.
  - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
  - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than [redacted] weeks from screening to randomization, the participant may be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. This rescreen is in addition to the one allowed by the main protocol. The screening procedures per the usual SoA should be followed, starting at screening Visit 401 to ensure participant eligibility at randomization Visit 0.

Adjustments to visit window for Visit 401

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

	Screening (SoA)
For this visit…	**Visit Interval Tolerance**
Screening (Visit 401)	The visit window "Weeks" are described in the SoA, and there is no specific visit interval tolerance stated, but flexibility can be considered following consultation with, and with prior approval by, the sponsor.

For participants whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Adjustments to visit windows for Visit 402 and thereafter

See relevant ISA.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing or shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.13. Appendix 13: Requirements for ISA Design

The ISAs associated with this CWMM master protocol will use a common clinical trial database. The common database is built on a standard visit structure, and certain activities are expected to occur at the standard visits.

This appendix describes these standards. A study team developing an SoA for a new ISA may add visits and activities as needed to support molecule-specific objectives and endpoints, but the standards described in this appendix must be incorporated into the SoA for a new ISA to support use of the common database.

10.13.1. Activities during an ISA Treatment Period

The visit structure of the treatment period must include a visit at

- baseline/randomization (Visit 0/Week CCI
- Week CCI
- Week CCI and
- Week CCI

It is anticipated that most of the ISAs under CWMM will have a CCI -week treatment period. If treatment duration is longer or shorter than CCI weeks, visits, and procedure frequency will be adjusted accordingly and will be specified in the relevant ISA.

This table lists the frequency of the standard activities for visits in the treatment period.

Activity	Frequency in an ISA	Comment
Inclusion/exclusion criteria; confirmation of eligibility	At treatment randomization visit	Confirm ISA inclusion and exclusion criteria prior to randomization to treatment and administration of first dose of study intervention
Concomitant medications	All visits	
Adverse events (AEs)	All visits	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3. Additional data are collected for certain AEs
Weight	All onsite visits	Weight measurements should be obtained per the detailed protocol guidance in Section 10.8. Body weight must be measured in the fasting status. If the participant is not fasting, the participant should return at a later date within the visit window to have the fasting body weight measured
Waist circumference	All onsite visits	Waist circumference should be obtained per guidance in Section 10.8

Vital signs (includes 2 measurements for pulse rate, blood pressure)	All onsite visits	Vital sign measurements (includes 2 measurements for pulse rate, blood pressure) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, per the instruction in Section 8.2.1 and Section 10.8
Symptom-directed physical assessment	As needed	Symptom-directed physical assessment may be conducted at the discretion of the PI or qualified personnel as indicated per local regulations based on participant status and standard of care
ECG 12-lead (central) – see comments	As specified in ISA	Single or Triplicate ECG measurements should be obtained per the instructions in Section 8.2.3. ECGs should be obtained prior to collection of blood samples for laboratory testing
Dispense participant diary	At frequency as listed in the ISA **IF** dosing occurs outside of the site	
Diary review	At frequency as listed in the ISA **IF** dosing occurs outside of the site	
Diary return	At frequency as listed in the ISA **IF** dosing occurs outside of the site	
Bioelectrical Impendence Analysis (BIA)	At Weeks [redacted] and [redacted]	
Patient Health Questionnaire-9 (PHQ-9)	At Weeks [redacted] and [redacted]	
C-SSRS Since Last Assessed (Category Version)	At Weeks [redacted] and [redacted]	AE collection should occur prior to the collection of the C-SSRS. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed
Explain diet and physical activity plan	At frequency as listed in the ISA **IF** dosing occurs outside of the site	
Review diet and physical activity Goals	At frequency as listed in the ISA **IF** dosing occurs outside of the site	
Hematology	At Weeks [redacted] and [redacted]	
Hemoglobin A1c (HbA1c)	At Weeks [redacted] and [redacted]	
Clinical chemistry	At Weeks [redacted] and [redacted]	
Urinalysis	At Weeks [redacted] and [redacted]	
Lipids	At Weeks [redacted] and [redacted]	
Cystatin-C	At Weeks [redacted] and [redacted]	
Calcitonin	At Weeks [redacted] and [redacted]	
Pancreatic amylase	At Weeks [redacted] and [redacted]	
Lipase	At Weeks [redacted] and [redacted]	

Urinary albumin/creatinine Ratio (UACR)	At Weeks [redacted], [redacted] and [redacted]	
EGFR [redacted]	At Weeks [redacted] [redacted] and [redacted]	
Genetic sample (pharmacogenetic storage sample)	At treatment randomization visit	
Exploratory biomarker samples (Non-pharmacogenetic stored sample)	At Weeks [redacted] [redacted] [redacted] and [redacted]	
Register visit with IWRS	All onsite visits	
Randomization via IWRS	At treatment randomization visit	
Dispense study intervention via IWRS	At Weeks [redacted] [redacted] and [redacted]	Other dispensing time points will be called out in the relevant ISA
Participant returns unused study intervention	At Weeks [redacted] [redacted] and [redacted]	
Assess study intervention compliance	At frequency as listed in the ISA **IF** dosing occurs outside of the site	

Abbreviations: AE = adverse event; [redacted]; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; EGFR = estimated glomerular filtration rate; HIV = human immunodeficiency virus; ICF = informed consent form; ISA = intervention-specific appendix; IWRS = interactive web-response system; PK = pharmacokinetics.

Dispensing and dosing frequency is specific to the study intervention and will be described in the ISAs.

10.13.2. Activities during a Posttreatment Follow-up Period

An ISA under this CWMM master protocol is required to have a posttreatment follow-up period consisting of at least 1 visit. The duration of posttreatment follow-up is typically equal to, or greater than, [redacted] half-lives of a study intervention. Therefore, the timing of this visit relative to the last administered dose of study intervention will vary across the ISAs.

An ISA under this CWMM master protocol may include additional visits within this period. The number of added visits, if any, and the intervals between them will be determined by each ISA team.

This table lists the timing and/or frequency of the standard activities for visits in this period.

Activity	Comment
Concomitant medications	
Adverse events (AEs)	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3. Additional data are collected for certain AEs
Weight	Weight measurements should be obtained per the detailed protocol guidance in Section 10.8. Body weight must be measured in the fasting status. If the participant is not fasting, the participant should return at a later date within the visit window to have the fasting body weight measured
Waist circumference	
Vital signs (includes 2 measurements for pulse rate, blood pressure)	Vital sign measurements (includes 2 measurements for pulse rate, blood pressure) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, per the instruction in Section 8.2.1 and Section 10.8
ECG 12-lead (central)	ECG measurements should be obtained per the instructions in Section 8.2.3
Patient Health Questionnaire-9 (PHQ-9)	
C-SSRS Since Last Assessed (Category Version)	AE collection should occur prior to the collection of the C-SSRS. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed
Hematology	
Clinical chemistry	
Exploratory biomarker samples (Nonpharmacogenetic stored sample)	
Register visit with IWRS	

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; IWRS = interactive web-response system.

10.13.3. Activities during an Early Discontinuation Visit

An ISA under this CWMM master protocol must specify which activities are to be performed at an early discontinuation visit. Some early discontinuation activities will be standard for all ISAs, but an ISA may include additional activities.

This table lists the standard activities for an early discontinuation visit.

Activity	Comment
Concomitant Medications	
Adverse events (AEs)	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3. Additional data are collected for certain AEs
Weight	Weight measurements should be obtained per the detailed protocol guidance in Section 10.8. Body weight must be measured in the fasting status. If the participant is not fasting, the participant should return at a later date within the visit window to have the fasting body weight measured
Waist circumference	
Vital signs (includes 2 measurements for pulse rate, blood pressure)	Vital sign measurements (includes 2 measurements for pulse rate, blood pressure) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, per the instruction in Section 8.2.1 and Section 10.8
ECG 12-lead (central)	Single ECG measurements should be obtained per the instructions in Section 8.2.3
Diary review	
Diary return	
Patient Health Questionnaire-9 (PHQ-9)	
C-SSRS Since Last Assessed (Category Version)	AE collection should occur prior to the collection of the C-SSRS. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed
Review diet and physical activity Goals	
Hematology	
Hemoglobin A1c (HbA1c)	
Clinical chemistry	
Lipids	
Pharmacokinetics (PK) samples (details in ISA)	
Exploratory biomarker samples (Non-pharmacogenetic stored sample)	
Register visit with IWRS	
Participant returns unused study intervention	
Assess study intervention compliance	

Abbreviations: AE = adverse event; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; IWRS = interactive web-response system.

10.14. Appendix 14: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
AST	aspartate aminotransferase
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an auxiliary medicinal product
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant 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
BP	blood pressure
CBC	complete blood count
C-SSRS	Columbia Suicide-Severity Rating Scale
CEC	Clinical Event Committee
CFR	Code of Federal Regulations

CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
COA	clinical outcome assessment
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 study-related, good clinical practice (GCP), and applicable regulatory requirements
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant
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
CV	cardiovascular
D. Bil	direct bilirubin
Device deficiencies	equivalent to product complaint
eCOA	electronic clinical outcome assessment
EDC	electronic data capture system
ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
GI	gastrointestinal
HbcAb	hepatitis B core antibody
HbsAg	hepatitis B surface antigen
HBV	hepatitis B virus

HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committees
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial
IND	Investigational New Drug
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant'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 or locked
Investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IRB	Institutional Review Boards
ISA	intervention-specific appendix
ISO	International Organization for Standardization
IWRS	interactive web-response system
LDL	low-density lipoprotein

medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involves a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling, for example, Summary of Product Characteristics, IB, local label, and protocol, or • shared use of cartridges or prefilled pens, or both
Misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen or indication, or both, or is obtained without a prescription
NIMP	Non-investigational medicinal product. See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment
Participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT-INR	prothrombin time
QTc	corrected QT interval
QTcF	corrected QT interval (Fridericia)
QTL	quality tolerance limit
SAE	serious adverse event
SAP	statistical analysis plan

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
SoA	schedule of activities
TBL	total bilirubin
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
ULN	upper limit of normal

10.15. Appendix 15: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment [c]: 04-Feb-2025

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The main purpose of this amendment is to provide clarification and expand on specified components that will apply across future ISAs.

Section # and Name	Description of Change	Brief Rationale
5.1. Inclusion Criteria	The inclusion criterion 2 has been modified, reinstating the requirement for participants with overweight (a BMI of ≥27 to <30 kg/m^2) to have a weight-related comorbidity.	In response to feedback from the FDA, Lilly has reinstated the requirement for participants with overweight to have a weight-related comorbidity.

Amendment [b]: 18-July-2024

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The main purpose of this amendment is to provide clarification and expand on specified components that will apply across future ISAs.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Objectives and Endpoints subheader revised to remove estimands.	Correction.
	Revised secondary endpoint from "proportion" to "incidence" of participants achieving ≥5% or ≥10% body weight reduction.	Description updated.
	Study population: removed comorbidity (high blood pressure, dyslipidemia, cardiovascular disease, OSA) requirement for participants with obesity or overweight	FDA expectations for CWM populations have changed.
	Specified that an upper limit of approximately [redacted]% of participants will be female.	To ensure sufficient representation of both sexes.

Section # and Name	Description of Change	Brief Rationale
	Data Monitoring Committee revised to "No."	There is no DMC for CWMM; there is an IAC and Clinical Events Committee.
1.3.2. Visit 401 - Screening	Indicated master protocol and relevant ISA ICFs are signed at V401 in left column.	Clarification.
	Removed "report any procedure related events prior to V401" from adverse event row	Clarification
	Indicated that PHQ-9 is collected electronically via eCOA device.	To clarify PHQ-9 collection after identifying sites completing PHQ-9 on paper. All scales (except C-SSRS) are to be completed electronically via eCOA.
3. Objective, Endpoints, and Estimands	Clarified primary objective estimand to align with current definition	Clarification and correct description for accuracy.
	Revised secondary endpoint from "proportion" to "incidence" of participants achieving ≥5% or ≥10% body weight reduction.	Description updated.
	Revised exploratory endpoint from "CCI " to "CCI " CCI	Description updated.
	Revised exploratory BMI endpoint from "CCI " to "CCI " and CCI	Correction.
	Aligned description for secondary objective from "percentage" to "incidence" of participants achieving ≥5% or ≥10% body weight reduction.	Description updated.
4.2. Scientific Rationale for Study Design	Redefined study population to include adults who have a BMI ≥27 kg/m^2 without weight-related diseases (hypertension, dyslipidemia, cardiovascular disease, or obstructive sleep apnea). .	FDA expectations for CWM populations have changed.
5.1. Inclusion Criteria	IC 2: removed weight-related comorbidities requirement for participants with a BMI ≥27 kg/m^2.	FDA expectations for CWM populations have changed.
5.2. Exclusion Criteria	EC 5: revised to better indicate that prior liposuction or abdominoplasty is permitted if performed >1 year before screening.	Clarification.

Section # and Name	Description of Change	Brief Rationale
	EC 15: revised as follows: Have an elevated resting pulse rate (PR) (mean >100 bpm) or reduced resting pulse rate (mean <50 bpm) at screening ~~and baseline.~~	Expansion of the exclusion criteria.
	EC 18: revised as follows: Have ongoing or a history of bradyarrhythmias other than sinus bradycardia.	To provide clarification.
	EC 40: addition of tirzepatide (Zepbound®, Mounjaro®) and Ozempic® to medications prohibited within 3 months prior to screening.	Clarification.
7.1.1. Hepatic Criteria for Study Drug Interruption or Discontinuation	Revised header from "Liver Chemistry Stopping Criteria" and removed section content as this is addressed in section 8.2.10.	Update per Lilly Safety guidelines.
8.1.1. Bioelectrical Impedance Analysis	Added BIA section to efficacy assessments.	New CWM assessment tool.
8.2.3. Electrocardiograms	Added bullet indicating that all V401 screening ECGs are to be collected locally.	Clarification.
	Revised to indicate that changes from baseline in QT/QTc should be identified by the investigator.	Clarification.
8.2.10.1. Close Hepatic Monitoring 8.2.10.2 Comprehensive Hepatic Evaluation 8.2.10.3. Study Drug Interruption or Discontinuation	Revised section and added updated content based on Lilly Safety guidelines. Changes in criteria affecting the following sections: • close hepatic monitoring • comprehensive hepatic evaluation • study intervention interruption or discontinuation	Update per Lilly Safety guidelines.
8.2.11. Hepatitis B Testing and Monitoring	Added hepatitis B safety monitoring section.	Update per Lilly Safety guidelines.
8.2.12. Mood Changes, Suicidal Ideation, and Suicidal Behavior Risk Monitoring	Revised section header to include mood changes.	The wording of the header needed to be corrected.
9.2. Analysis Sets	In the data point set table, DPS1 description revised to indicate data obtained up to the date of discontinuation of any study drug or intercurrent events (ICEs) specified in respective ISAs.	Clarification.

Section # and Name	Description of Change	Brief Rationale
	In the data point set table, DPS2 description revised to include during treatment period at or after randomization regardless of adherence to study drug.	Clarification.
9.3.3.1. Efficacy Analysis	Aligned description for secondary efficacy analysis from "proportion" to "incidence" of participants achieving ≥5% or ≥10% body weight reduction.	Alignment with secondary endpoint.
9.5. Sample Size Determination	Specified that an upper limit of approximately [redacted]% of participants will be female.	Reflecting decision for limits on enrollment.
10.2.1. Clinical Laboratory Tests	In hematology section of table removed "segmented" from differential neutrophils.	Clarification.
	In additional testing section of table, comment added to HbA1c indicating testing may be performed locally for V601 and all other visits assay by Lilly-designated laboratory.	Clarification.
10.8. Appendix 8: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs	Measuring height section Step 4 revised to clarify the participant's height must be directly measured in centimeters	To provide clarification and ensure accuracy in measurements captured.
10.13.1. Activities during an ISA Treatment Period	Addition of BIA at Weeks [redacted] and [redacted]	Alignment with secondary endpoint.
Throughout	Minor editorial corrections/clarifications.	Clarification.

Amendment [a]: 13-August-2023

Overall Rationale for the Amendment:

The main purpose of this protocol amendment is to clarify placebo borrowing as partial across ISAs in response to regulatory feedback.

Changes specific to certain protocol sections and a brief rationale are provided in this table.

Section # and Name	Description of Change	Brief Rationale
1.2. Schema	Revised the schema to change "randomize to an ISA" to "randomize to one ISA" and removed "option to add ISAs for other intervention"	Clarification
2.2.1. Intervention Selection: Adding or Stopping	Added the following:	To address regulatory feedback

Section # and Name	Description of Change	Brief Rationale
Intervention-Specific Appendices	"Future ISAs with new investigational drugs will cross-reference the IND for that investigational drug. The platform design is not an adaptive design, therefore, there is no plan to discontinue ISAs based on interim analyses or external new data."	
4.2. Scientific Rationale for Study Design	Added the following: • each ISA will have a concurrent control arm. • 'partial' next to placebo borrowing	To specify that only a specified proportion of placebo participants would be borrowed across ISAs
9.3.1. General Considerations	Added "any partial" next to borrowing of placebo information	
9.2. Analysis Sets	Added the following to DPS2 description, "Data points also includes those collected after the discontinuation likely due to efficacy and safety reason."	Clarification
10.13.1. Activities during an ISA Treatment Period	Revised ECG requirement to state "as specified in ISA" and added "single" in comment Removed ECG 12-lead (central) for postdose	Alignment with ISA
Throughout	Minor editorial and formatting changes	Minor, therefore, not detailed

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Approval	PPD Medical Director 12-Dec-2025 14:01:30 GMT+0000

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