Protocol: W8M-MC-OXA1 (b)

A Phase 2, Parallel-Group, Double-Blind, 4-Arm Study to Investigate Weight Management with LY3305677 Compared with Placebo in Adult Participants with Obesity or Overweight

NCT06124807

Approval Date: 28-Oct-2024

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

ISA Title: A Phase 2, Parallel-Group, Double-Blind, 4-Arm Study to Investigate Weight Management with LY3305677 Compared with Placebo in Adult Participants with Obesity or Overweight

ISA Number: W8M-MC-OXA1

ISA Amendment Number: b

Compound: Mazdutide (LY3305677)

ISA Brief Title:

A Study to Investigate Weight Management with LY3305677 Compared with Placebo in Adult Participants with Obesity or Overweight

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

IND for CWMM master protocol: 163848

EU trial number: 2022-502816-35-00

Document ID: VV-CLIN-117989

Approval Date: Protocol Amendment (b) 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 a	*13-Aug-2023*
Original Protocol	*30-May-2023*

Amendment [b]

Overall Rationale for the Amendment:

The main objective of this ISA amendment is to incorporate changes to the objectives as it relates to treatment effects on liver fat. The population of interest in secondary endpoint was specified to be those with elevated liver fat at baseline, and additional endpoints evaluating change in liver fat were added.

Changes specific to certain ISA sections and a brief rationale are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3. Objectives, Endpoints and Estimands	Secondary and exploratory endpoints related to liver fat content (LFC): Modified population in secondary endpoint related to liver fat content to subset the population to include participants with baseline LFC ≥5% and baseline LFC . Added the following secondary and exploratory endpoints for participants with baseline LFC ≥5% and baseline LFC ≥10% as measured by MRI-PDFF at Weeks 32 and 48: • Incidence of ≥30% relative reduction in LFC (secondary) • Incidence of LFC<5% (exploratory) • Incidence of ≥50% relative reduction in LFC (exploratory)	Additional liver fat analyses added for comparison with similar endpoints from other studies.
	Added “24-hour mean” to each ABPM endpoint.	Clarification
	Added time points of “Week 32” and “Week 48” to HRQoL, function, and appetite objective	Clarification
	Added “Change from baseline in:” to body composition endpoints	Clarification

Section # and Name	Description of Change	Brief Rationale
	Liver fat objective: specified MRI measurement as MRI-PDFF	Clarification
1.1 Synopsis	Data monitoring committee changed from "Yes" to "Not applicable; refer to CWMM master protocol."	Correction
1.3 Schedule of Activities (SoA) for OXA1 ISA and CWMM Master Protocol	Subsection "Early discontinuation (ED) visits": removed "from study intervention or"	Correction
	Removed "intervention" from Visit 801 description	Correction
	Added return of actigraphy device (AX6) row (V0, V40, and V48)	Clarification
	Specified EGC 12-lead (central) is triplicate for all applicable visits	Correction
	Added "2 to 6 hours postdose at Visits 1, 12, and 24" and "as applicable" to postdose ECG row comments	Clarification
	Removed "paper or" from PRO section	Correction
2.2 Background	Added summary of Phase 1 study OXAG data	Provide clinically relevant information to investigators
4.1.1 Overview of Study Periods	Subsection "Prescreening": removed "via the central laboratory" regarding HBA1c measurement	Correction
5.2 Exclusion Criteria	Added new exclusion criterion #126; mean resting pulse rate >100 bpm or <60 bpm	Correction
7.1 Discontinuation of Study Intervention	BMI discontinuation criterion revised from "18 kg/m^2" to "18.5 kg/m^2."	Correction
8.1 Efficacy Assessments	Exploratory endpoint "MRI": revised to "Body composition (assessed by MRI)"	Correction
	Added new exploratory endpoint: "Liver fat content (assessed by MRI-PDFF)"	Alignment with additional endpoint
8.1.1.1 PROMIS Short Form Pain Interference 4a v1.1	Added, "; higher scores indicate better levels of function and/or better health"	Clarification
8.1.3 Magnetic Resonance Imaging (MRI)	Subsection "MRI procedures": Added that local MRI over-reads should be completed	To ensure participant safety
9.1 Statistical Hypotheses	Added "at Week 32" to null hypotheses and modified subscripts	Clarification

Section # and Name	Description of Change	Brief Rationale
9.3.1 General Considerations	Additional considerations for OXA1: added secondary endpoint analyses for TE ADA, pharmacokinetics of the primary intervention, and liver fat content	To align with changes in Objectives/endpoints
	Added exploratory endpoint analyses for body composition and liver fat content	To align with changes in Objectives/endpoints
10.8 Appendix 8: Abbreviations and Definitions	Addition of LFC and WC	Editorial
Throughout	Minor editorial clarifications	Clarification

Table of Contents

1. Protocol Summary

1.1. Synopsis

ISA Title:

A Phase 2, Parallel-Group, Double-Blind, 4-Arm Study to Investigate Weight Management with LY3305677 Compared with Placebo in Adult Participants with Obesity or Overweight

ISA Brief Title:

A Study to Investigate Weight Management with LY3305677 Compared with Placebo in Adult Participants with Obesity or Overweight

Regulatory Agency Identifier Numbers:

IND for CWMM master protocol: 163848

EU trial number: 2022-502816-35-00

Rationale:

LY3305677 is an oxyntomodulin analog that has demonstrated acceptable safety and the possibility of weight loss efficacy in early phase trials. It is being developed as a potential once-weekly injection treatment for chronic weight management. The current study is the first Phase 2 trial testing LY3305677, aimed at evaluating safety and efficacy across a wide dose range in the target population. This study will inform the further clinical development of LY3305677.

Objectives, Endpoints, and Estimands:

The CWMM master protocol contains objectives and endpoints that will be evaluated for all study interventions evaluated under the CWMM master protocol.

OXA1 includes the following LY3305677-specific features:

- Primary analysis time point occurs at Week 32
- Intervention is LY3305677
- Control is placebo

In addition to the objectives and endpoints stated in the CWMM master protocol, the secondary objectives and endpoints specific to OXA1 are listed in this table. Exploratory objectives are listed in the main body of OXA1.

Objective	Endpoint
Secondary	
To evaluate the development of treatment-emergent antidrug antibodies to LY3305677	Treatment-emergent antidrug antibodies (TE ADA)
To characterize the pharmacokinetics (PK) of the primary intervention	PK parameters AUC and C_{max}
To compare the effect of LY3305677 versus placebo on liver fat content (LFC) as measured by MRI-PDFF at Week 32 and Week 48	For participants with baseline LFC ≥5% and baseline LFC ≥10%: • change and percent change from baseline in LFC, and • incidence of ≥30% relative reduction in LFC •

Abbreviations: AUC = area under the concentration versus time curve; C_{max} = maximum observed drug concentration; MRI-PDFF = magnetic resonance imaging proton density fat fraction.

Overall Design:

OXA1 is a Phase 2, parallel-group, double-blind, 4-arm study to investigate weight management with LY3305677 subcutaneously administered once weekly compared with placebo.

The study consists of a 6-week screening/lead-in period, a 48-week treatment period, and a posttreatment follow-up period of approximately 8 weeks after the last visit in the treatment period.

The primary endpoint will be at Week 32.

Brief Summary:

The purpose of this study is to measure weight loss with LY3305677 administered subcutaneously once weekly compared with placebo in participants with obesity or overweight with weight-related comorbidities.

Study details include:

- The total study duration will be up to approximately 62 weeks including the screening/lead-in, treatment, and posttreatment follow-up periods.
- The treatment duration will be approximately 48 weeks.
- The visit frequency will be
  - weekly - Visit 0 to Visit 2
  - every 2 weeks - Visit 2 to Visit 24 (Visits 2, 6, 10, 14, 18, and 22 are telephone visits), and

- every 4 weeks - Visit 24 to Visit 48 (Visits 28, 36 and 44 are telephone visits).

Study Population:

In addition to meeting the entry criteria specified in the CWMM master protocol, participants are adult males and females who have not been diagnosed with diabetes mellitus, that is T2DM, or rare forms of diabetes mellitus, except gestational diabetes. Participants also agree to abide by the reproductive and contraceptive requirements provided in OXA1.

Number of Participants:

Approximately 165 participants will be randomly assigned in a 3:2:3:3 ratio with

- 45 participants allocated to placebo
- 30 participants to LY3305677 3/6 mg
- 45 participants to LY3305677 10 mg and
- 45 participants to LY3305677 16 mg

Assuming a 20% dropout rate, this results in approximately 132 total completers with 24 completers on the LY3305677 3/6 mg arm and 36 completers for placebo, and each of the 10 mg and 16 mg LY3305677 arms.

Intervention Groups and Duration:

This study includes a 6-week screening/lead-in period, a 48-week double-blind treatment period, and an 8-week posttreatment follow-up period.

Participants will self-administer study intervention subcutaneously once weekly.

Intervention Name	**LY3305677**	**LY3305677 Placebo**
Dosage Level(s)	1.5 mg 3 mg (target dose) 6 mg (target dose) 8 mg 9 mg 10 mg (target dose) 12 mg 16 mg (target dose)	Matched
Route of Administration	Subcutaneous using a syringe	Subcutaneous using a syringe
Frequency of Administration	Once weekly	Once weekly
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU

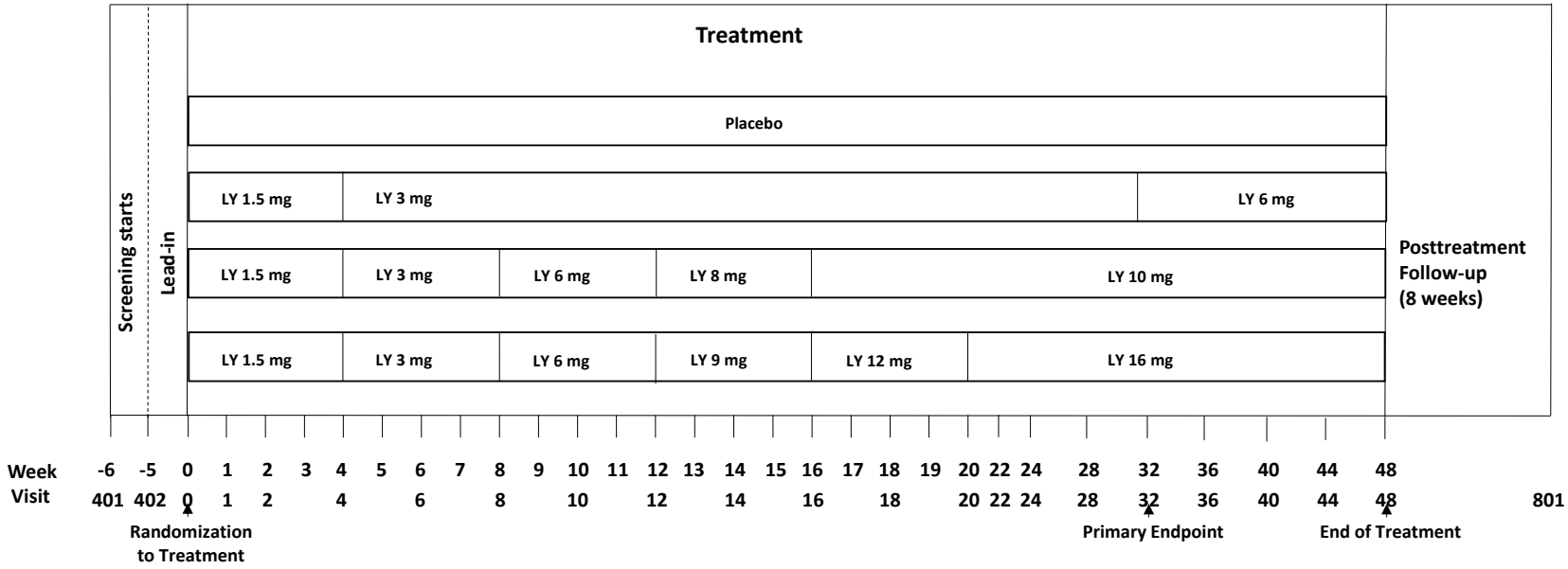
Abbreviation: EU = European Union.

Ethical Considerations of Benefit/Risk:

LY3305677 is being investigated as a subcutaneously administered, once weekly therapy as an adjunct to diet and physical activity to improve weight management in participants with obesity, or overweight if accompanied by weight-related comorbidities. At this time, no safety or efficacy issues have been identified which would constitute undue risk to study participants. The safety profile continues to be refined as more clinical safety data become available. The overall benefit–risk profile supports further development of LY3305677.

Data Monitoring Committee: Not applicable; refer to CWMM master protocol.

1.2. Schema



Abbreviation: LY = LY3305677.

1.3. Schedule of Activities (SoA) for OXA1 ISA and CWMM Master Protocol

In addition to activities required by the CWMM master protocol, this SoA shows visits and procedures unique to the intervention-specific appendix (ISA), which is Study W8M-MC-OXA1 (OXA1) for the study intervention, LY3305677. Please refer to the CWMM master protocol SoA Section 1.3 for information pertaining to screening (Visit 401).

Visit 402 (Lead-in)
Visit 402 may be used to accomplish OXA1-specific activities (such as magnetic resonance imaging [MRI]) requiring significant time to schedule and/or perform. If this visit takes shorter or longer than 5 weeks, it will not be considered a protocol deviation.

Visit 0 (Randomization to treatment)

Participants will be randomly assigned to an OXA1 treatment arm at Visit 0 and will receive their first dose of study intervention.

Unscheduled visits

Unscheduled visits may occur as needed. The SoA reflects some of the procedures that may occur during these visits. Perform additional procedures per investigator's discretion.

Early discontinuation (ED) visits

ED visits will be completed by participants permanently discontinuing early from the study. These participants should also complete posttreatment follow-up. The SoA reflects the procedures that may occur during these visits.

Visit 801 (Posttreatment follow-up)

Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention. The SoA reflects the procedures that may occur during these visits.

Fasting visits

Participants should not eat or drink anything but water for a minimum of 8 hours before a fasting visit.

If a participant attends these visits in a non-fasting state, they should return in a fasting state for body weight measurement and sample collection. If they return within the visit interval tolerance specified in the SoA, it is not a protocol deviation.

Telephone/Telemedicine visits

Visits 2, 6, 10, 14, 18, 22, 28, 36, and 44 may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
Visit Interval Tolerance (+/- days)	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-	±3	
Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Consent and Demographics																									
Inclusion/exclusion criteria; confirmation of eligibility		X																							Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the ICF are considered AEs per CWMM master protocol, Section 8.3.1.
Physical Evaluation																									
Weight		X	X		X		X		X		X		X		X		X		X		X		X	X	Weight should be obtained per guidance in CWMM master protocol, Section 10.8 and must be measured in

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																									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		X	X		X		X		X		X		X		X		X		X		X		X	X	Waist circumference should be obtained per guidance in CWMM master protocol, Section 10.8.
Vital signs (includes 2 measurements for pulse rate and blood pressure)		X	X		X		X		X		X		X		X		X		X		X		X	X	Vital sign measurements (includes 2 measurements for pulse rate and blood pressure) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing, per the instruction in CWMM

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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																									master protocol, Section 10.8.
Symptom-directed physical assessment				X																					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. Does not apply for telephone visits.
ECG 12-lead (central) (triplicate) – See comments		X			X												X				X		X	X	Predose at Visits, 0, 4, 32, 48. ECG measurements should be obtained per the instructions in CWMM master protocol Section 8.2.3. ECGs should be obtained prior to collection of blood samples.

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
ECG 12-lead (central) for postdose – See comments			X						X						X										Triplicate: prior to postdose PK collection at Visits 12 and 24. ECG measurements should be obtained per the instructions in CWMM master protocol Section 8.2.3. ECGs should be obtained 2 to 6 hours postdose at Visits 1, 12, and 24 and **within** 30 min prior to PK sampling, as applicable.
Ambulatory Blood Pressure Monitoring (ABPM) Device																									
ABPM training	X																X				X				
Initiate ABPM	X																X				X				
Return ABPM	X																X				X				
Validity check of collected ABPM data	X																X				X				A 24-hour session of ambulatory monitoring produces technically acceptable measurements if ≥70%

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																									of the readings are valid. See Section 8.2.12.1.
Actigraphy																									
Dispense actigraphy device (AX6)	X																X		X						
Remind participant to wear actigraphy device (AX6)																				X					Device worn for 2 weeks
Participant wears actigraphy device (AX6)	X																X			X					Device worn for 2 weeks and returned at next visit. Device should be placed on participant at Visits 402 and 32. Device given to participant at Visit 40 and instructed to start wearing at Visit 44. See Section 8.1.2.
Return actigraphy device (AX6)		X																	X		X				

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Magnetic Resonance Imagining																									
Magnetic resonance imaging (MRI)	X																X				X		X		Participants MUST have baseline MRI. Fasting is required for MRI measurements. Visit 32 MRI should occur within ± 2 weeks. Visit 48 MRI should be scheduled and performed anytime between Visits 44 and 48.
Participant Diary (Paper or Electronic)																									
Dispense and explain participant diary	X																								Study intervention administration data (date and time of each dose administered) will be recorded in the diary
Diary review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		
Diary return																					X		X		

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Patient-Reported Outcomes (Electronic) *Complete prior to any clinician-administered assessments*																									
Patient Health Questionnaire-9 (PHQ-9)		X							X								X				X		X	X	AE collection should occur prior to the collection of the PHQ-9.
PROMIS SF Pain Interference 4a v1.1		X															X				X		X		AE collection should occur prior to the collection of PROMIS.
PGIS – Physical Function due to Weight		X															X				X		X		AE collection should occur prior to the collection of the PGIS.
PGIC – Physical Function due to Weight																	X				X		X		AE collection should occur prior to the collection of the PGIC.
Short Form-36 version 2 Health Survey acute form (SF-36 v2, Acute)		X															X				X		X		AE collection should occur prior to the collection of the SF-36.
Fasting Appetite VAS (4 item)		X							X						X		X				X				AE collection should occur prior to the collection of the Appetite VAS.

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Clinician-Administered Assessments (Paper)																									
C-SSRS Since Last Assessed (Category Version)		X	X		X		X		X		X		X		X		X		X		X		X	X	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.

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
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Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Participant Education																									
Explain symptoms of hypoglycemic and hypotension events	X																								
Explain diet and physical activity plan	X	X																							
Review diet and physical activity goals					X				X						X				X						
Review preparation of injection and injection technique		X	X		X		X		X		X		X		X		X		X			X			
Laboratory Tests and Sample Collections																									
Hematology		X							X						X		X				X		X	X	
Hemoglobin A1c (HbA1c)		X							X						X		X				X		X	X	
Clinical chemistry		X			X		X		X		X		X		X		X		X		X		X	X	
Urinalysis		X			X		X		X		X		X		X		X		X		X		X	X	
Urine pregnancy (local)		X					X				X				X		X		X		X		X		Only in women of child-bearing potential.

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
Visit Interval Tolerance (+/- days)	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-	±3	
Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Immunogenicity		X			X				X						X						X		X	X	In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional unscheduled samples should be collected as detailed in Section 8.2.12.6 (Hypersensitivity Reactions). Immunogenicity samples and PK samples for immunogenicity must be taken prior to drug administration.
Cystatin-C		X							X						X		X				X		X	X	
Calcitonin		X													X		X				X		X	X	
Pancreatic amylase		X			X		X		X						X		X				X		X	X	
Lipase		X			X		X		X						X		X				X		X	X	
Longitudinal biomarkers		X							X		X		X		X		X				X		X	X	

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
Visit Interval Tolerance (+/- days)	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-	±3	
Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Serum beta-hydroxybutyrate		X			X		X		X		X		X		X		X		X		X		X	X	
Endpoint biomarkers		X															X				X		X	X	
Fatty liver index		X							X						X		X				X		X	X	
Fibrosis 4 (FIB-4)		X							X						X		X				X		X	X	
Urinary albumin/creatinine ratio (UACR)		X							X						X		X				X		X	X	
eGFR (CKD-EPI) calculated using cystatin-C		X							X						X		X				X		X	X	
Pharmacokinetics (PK) Samples																									
Predose		X			X		X		X						X		X				X				
Postdose (2 to 6 hr after dosing)		X							X						X										Collect 2 to 6 hr postdose. Does not need to be fasting.
Random (any time during visit)																							X	X	Collection anytime during the visit.

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
Visit Interval Tolerance (+/- days)	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-	±3	
Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Stored Samples																									
Genetic sample (pharmacogenetic storage sample)		X																							
Exploratory biomarker samples (non-pharmacogenetic stored sample)		X							X		X		X		X		X				X		X	X	
Epigenetic Sample		X															X				X			X	Sample for epigenetics analyses
Randomization and Dosing																									
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Randomization via IWRS to treatment group (within ISA)		X																							
Dispense study intervention via IWRS		X	X		X		X		X		X		X		X		X		X						
Observe participant administer study intervention		X	X		X		X		X		X		X		X		X		X						

CRF Visit Number	402	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48	UnSch (997)	ED	801	
Week	-5 to 0	0	1	2	4	6	8	10	12	14	16	18	20	22	24	28	32	36	40	44	48			56*	*Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention but could occur prior to Week 56 for participants discontinuing study early.
Visit Interval Tolerance (+/- days)	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	-	-	±3	
Fasting Visit		X	X		X		X		X		X		X		X		X		X		X		X	X	
Visit Detail				T		T		T		T		T		T		T		T		T					T =The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Dispense injection supplies		X	X		X		X		X		X		X		X		X		X						
Participant returns unused study intervention					X		X		X		X		X		X		X		X		X		X		
Assess study intervention compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		Injection confirmation (compliance) will be performed by site personnel at Visit 0. Participant diary will be used for all remaining compliance visits.

Abbreviations: ADA = antidrug antibodies; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; ISA = intervention-specific appendix; IWRS = interactive web-response system; MRI = magnetic resonance imaging; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of Severity; PROMIS SF = Patient-Reported Outcome Measurement Information System short form; UnSch = unscheduled visit; VAS = visual analog scale.

2. Introduction

LY3305677 (mazdutide) is a long-acting, synthetic peptide oxyntomodulin (OXM) analog currently being developed as a once-weekly, subcutaneously administered injection for use as an adjunct to diet and physical activity for weight management in participants who have a BMI ≥30 kg/m^2 or ≥27 kg/m^2 if accompanied by weight-related comorbidities.

2.1. Study Rationale

LY3305677 is an OXM analog that has demonstrated acceptable safety and weight loss efficacy in early phase trials. It is being developed as a potential once-weekly injection treatment for chronic weight management. The current study is the first Phase 2 trial testing LY3305677, aimed at evaluating safety and efficacy across a wide dose range in the target population. This study will inform the further clinical development of LY3305677.

2.2. Background

OXM is a gut-derived peptide hormone released in response to food intake. OXM activates both glucagon-like peptide-1 (GLP-1) and glucagon receptors resulting in reduced food intake, improved glucose and lipid metabolism, increased energy expenditure, and body weight loss. When administered exogenously, OXM can improve glucose control and increase weight loss (Pocai 2013).

LY3305677 is a long-acting, synthetic peptide analog of OXM and contains a fatty acyl side chain to extend time of action, allowing once-weekly dosing.

Phase 1 data from the LY3305677 multiple-ascending dose study I8P-MC-OXAD (OXAD) in patients with type 2 diabetes mellitus (T2DM) demonstrated significant decreases in body weight in all treatment groups (up to a mean of 10.73 kg [-12.7%] in the high-dose group at approximately 4 months). LY3305677 significantly reduced HbA1c in all treatment groups and improved insulin sensitivity in mixed-meal tolerance tests, as demonstrated by Matsuda index increases of approximately 2-fold in the high-dose group. Treatment with LY3305677 significantly reduced fasting cholesterol, LDL cholesterol, and triglyceride levels, with reductions in triglycerides of approximately 50% and in LDL cholesterol of approximately 30% in the high-dose group at approximately 4 months.

Phase 1 data from the LY3305677 multiple dose titration study I8P-MC-OXAG (OXAG) in participants with obesity or overweight demonstrated the maximum LS mean difference of weight loss was approximately 19 kg or 20% of body weight compared to placebo. The LS mean difference in absolute decrease and percent decrease from baseline in WC were approximately 12 cm or 11% of WC compared to placebo in Cohort 1 and 16 cm or 16% of WC compared to placebo in Cohort 2.

A detailed description of the chemistry, pharmacology, safety, and efficacy of LY3305677 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

This section summarizes the key observations from the completed or ongoing Phase 1 trials with LY3305677.

More detailed information about the known and expected benefits and risks and reasonably expected AEs/SAEs with LY3305677 may be found in the IB.

Information on serious adverse events (SAEs) that are expected in the study population independent of drug exposure will be assessed by the sponsor in aggregate, periodically during the course of the study, and may be found in Section 7 (Reference Safety Information for Assessment of Expectedness of Serious Adverse Reactions) of the IB.

2.3.1. Risk Assessment

Study intervention

LY3305677

The most common AEs observed in the LY3305677 clinical trials in healthy participants and participants with T2DM have been GI effects. These GI AEs have been mild to moderate in severity and none was severe.

Based on preclinical and clinical observations with LY3305677, with GLP-1 receptor agonists, and with GLP-1 containing multifunctional agonists, potential risks associated with LY3305677 include

- acute pancreatitis
- cardiovascular effects
- GI effects
- hypoglycemia
- hypersensitivity
- thyroid C-cell tumors
- liver and biliary effects, and
- developmental effects.

As LY3305677 actions include GLP-1 agonism, these will be safety topics for LY3305677. Refer to Section 8.3.5 for further details about safety topics for monitoring in the current development program in Phase 2. Please refer to the IB, Section 6 for more details.

Management of risks for the study

All identified risks from preclinical and clinical studies to date are associated with on-target pharmacology and are considered monitorable and manageable at the planned dose range of 3 to 16 mg of LY3305677. These risks are similar to those noted during development of marketed GLP-1 RAs.

OXA1 Sections 5.1, 5.2, and 8.3 address known potential risks associated with LY3305677.

After signing the ICF, participants will be educated about signs and symptoms of hypoglycemia and how to treat hypoglycemia. Hypoglycemia may be identified by spontaneous reporting of symptoms from participants or by blood glucose (BG) samples collected during study visits.

Study site PI will provide education on signs and symptoms of low blood pressure and when to seek medical care. Hypotension events may be identified by spontaneous reporting of symptoms (for example, dizziness, blurred vision, and fainting) and blood pressure levels. If systolic blood pressure persisted below 90 mmHg or diastolic blood pressure persisted below 60 mmHg or recurrent symptomatic hypotension has occurred, the PI should consider reducing antihypertensive medication dose level or inform participants to consult with their physician. Changes of antihypertensive medication will be recorded in CRF.

Participants will be closely monitored with scheduled medical assessments, vital signs, laboratory evaluations, and triplicate electrocardiogram (ECG) measurements.

Section 6.5 addresses dose modification based on participant safety and tolerability.

2.3.2. Benefit Assessment

LY3305677 is a dual agonist of the GLP-1 and glucagon receptors that is currently in early clinical development. Full assessment of its potential benefits has not been completed. The purpose of this Phase 2 trial is to provide an initial efficacy assessment in participants who have a BMI ≥30 kg/m^2 or ≥27 kg/m^2 if accompanied by weight-related comorbidities, in addition to safety and pharmacokinetics/pharmacodynamics (PK/PD) assessments.

Participants may benefit by receiving personal health information, routine safety assessments, and frequent engagement with health care providers during the study, which provide opportunities for coaching and support.

Once-weekly administration of LY3305677 has the potential to offer improved weight management.

2.3.3. Overall Benefit Risk Conclusion

LY3305677 is being investigated as a subcutaneously administered, once-weekly therapy as an adjunct to diet and physical activity to improve weight management in participants with BMI ≥30 kg/m^2 or ≥27 kg/m^2 if accompanied by comorbidities. At this time, no safety or efficacy issues have been identified which would constitute undue risk to study participants. The safety profile continues to be refined as more clinical safety data become available. The overall benefit–risk profile supports further development of LY3305677.

3. Objectives, Endpoints, and Estimands

The CWMM master protocol contains objectives and endpoints that will be evaluated for all study interventions evaluated under the CWMM master protocol.

OXA1 includes the following LY3305677-specific features:

- primary analysis time point occurs at Week 32
- intervention is LY3305677, and
- control is placebo.

As specified in the CWMM master protocol, the OXA1 treatment period is 48 weeks in duration, and therefore, endpoints will be evaluated at the primary time point (Week 32) and Week 48. In addition to the primary, secondary, and exploratory objectives and endpoints stated in the CWMM master protocol, secondary and exploratory objectives and their respective endpoints specific for OXA1 are listed in this table.

Objectives	Endpoints
Secondary (in addition to secondary objectives listed in the CWMM master protocol)	
To evaluate the development of treatment-emergent antidrug antibodies to LY3305677	Treatment-emergent anti-drug antibodies (TE ADA)
To characterize the pharmacokinetics (PK) of the primary intervention	PK parameters AUC and C_{max}
To compare the effect of LY3305677 versus placebo on liver fat content (LFC) as measured by MRI-PDFF at Week 32 and Week 48	For participants with baseline LFC ≥5% and baseline LFC ≥10%: • Change and percent change from baseline in LFC • Incidence of ≥30% relative reduction in LFC •
Exploratory (in addition to exploratory objectives listed in the CWMM master protocol)	
To compare the effect of LY3305677 versus placebo on BP and heart rate at Week 32 and Week 48	Change from baseline in: • 24-hour mean systolic BP (mmHg) measured by ABPM • 24-hour mean diastolic BP (mmHg) measured by ABPM • 24-hour mean heart rate measured by ABPM

To compare the effect of LY3305677 versus placebo on physical activity at Week 32 and Week 48	Change from baseline in physical activity measured by: • Daily steps count • M10 (activity intensity of most active 10 hours during 24-hour period) • MVPA (moderate to vigorous physical activity in minutes during 24-hour period)
To compare the effects of LY3305677 versus placebo on HRQoL, function, and appetite at Week 32 and Week 48	Change from baseline in: • PROMIS SF Pain Interference 4a v1.1 • PGIS - Physical Function due to Weight • PGIC - Physical Function due to Weight • Domains of SF-36 v2, Acute • Appetite VAS
To compare the effect of LY3305677 versus placebo on glucose regulation at Week 32 and Week 48	Change from baseline in: • Fasting insulin • Fasting glucose • HbA1c • HOMA2-IR • HOMA2-B
To compare the effect of LY3305677 versus placebo on biomarkers at longitudinal time points and at Week 32 and Week 48	Change from baseline in longitudinal and endpoint biomarkers
To assess the relationships between LY3305677 dose and/or exposure and key safety and efficacy measures, as applicable	Dose-response or exposure-response analyses for key safety and efficacy endpoints, as applicable
To compare the effect of LY3305677 versus placebo on body composition as measured by MRI at Week 32 and Week 48	Change from baseline in: • Adipose tissue volumes • Muscle volumes • Additional MRI-derived measures may be explored

To compare the effect of LY3305677 versus placebo on liver fat content (LFC) as measured by MRI-PDFF at Week 32 and Week 48	For participants with baseline LFC ≥5% and baseline LFC ≥10%: • Incidence of LFC< 5% • Incidence of ≥50% relative reduction in LFC

Abbreviations: ABPM = ambulatory blood pressure monitoring; BP = blood pressure; HbA1c = hemoglobin A1c; HOMA2-B = homeostasis model of beta-cell function; HOMA2-IR = homeostasis model assessment of insulin resistance; HRQoL = health-related quality of life; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of Severity; PROMIS = Patient-Reported Outcome Measurement Information System; SF-36 = Short Form 36; VAS = visual analog scale.

Primary and additional estimands

Please refer to the CWMM master protocol for a description of the primary estimand and additional estimands that will be used for the primary and secondary efficacy objectives for comparisons between LY3305677 and placebo.

4. Study Design

4.1. Overall Design

OXA1 is a Phase 2, parallel-group, double-blind, 4-arm study to investigate weight management with LY3305677 subcutaneously administered once weekly compared with placebo. For convenience, the functional combination of the CWMM master protocol plus the OXA1 ISA will be simply described as "the study".

The study consists of a 6-week screening/lead-in period, a 48-week treatment period, and a posttreatment follow-up period of approximately 8 weeks after the last visit in the treatment period.

The primary endpoint will be at Week 32.

The study schema is presented in Section 1.2.

4.1.1. Overview of Study Periods

Prescreening

An optional prescreening Visit 601 which includes assessment of abbreviated eligibility criteria as outlined in the SoA may be conducted at a traditional investigator site or other location associated with the investigator. 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 8 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.

Screening period

The screening period consists of Visit 401 (screening) and Visit 402 (lead-in) and is split across the CWMM master protocol and OXA1; Visit 401 occurs as part of the CWMM master protocol and Visit 402 occurs as part of OXA1. Signing informed consent forms (ICFs), completing screening procedures, and randomization to the ISA all take place during Visit 401.

Visit 402 will be used to complete any OXA1-specific baseline procedures including baseline procedures for OXA1 appendices.

If the time between Visit 401 and randomization (Visit 0) takes more or less time than 6 weeks, it is not a protocol deviation.

Visit 401

Participant screening for the CWMM master protocol and OXA1 occurs during CWMM master protocol Visit 401 and is described in CWMM master protocol Sections 1.3 (SoA) and 4.1.

Participants who successfully pass screening procedures and are assigned to participate in OXA1 will proceed with Visit 402 as detailed below.

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

Visit 402 (Start of OXA1 procedures)

Prior to Visit 402, all screening results, including laboratory results, will be reviewed to confirm participant eligibility for CWMM master protocol and OXA1.

Participants will complete procedures as indicated in the SoA (Section 1.3).

Participants will receive education on recognizing the symptoms of hypoglycemic events.

Participant diaries will be dispensed and their use explained.

Participants will meet with site personnel to discuss diet and physical activity goals (see Section 5.3 of CWMM master protocol).

Participants will be registered in interactive web-response system (IWRS).

Ambulatory blood pressure monitoring (ABPM)

At Visit 402, participants will begin to undergo a baseline 24-hour ABPM session. Upon return of the ABPM device, the recordings must be transmitted to the core laboratory and analyzed before the participant leaves the site.

If the session provides technically satisfactory results (≥70% of readings are valid), this measurement will serve as the baseline value.

If a technically satisfactory result is not achieved, the investigator should review the device settings and placement and the participant's ABPM device in attempt to correct any user error or device malfunctions. Then another 24-hour ambulatory monitoring session should be conducted prior to Visit 0, and this measurement will serve as the baseline value.

If the second session also provides technically unsatisfactory results, the participant should not participate in additional ABPM collections.

See Section 8.2.12.1 for addition information on ABPM.

Actigraphy

A wrist worn AX6 device will be dispensed to participants and placed on the non-dominant wrist at Visit 402 to collect activity data for at least 2 weeks before being returned to the site at Visit 0.

See Section 8.1.2 for addition information on actigraphy.

Magnetic Resonance Imaging

After the participant has given consent, and meets all ISA eligibility requirements, MRI measurements at baseline should be performed between Visit 402 and Visit 0 (randomization) in OXA1, before the participant receives the first dose of study intervention.

Participants are required to report for the MRI after approximately 8 hours without eating, drinking (except water), and without performing any significant physical activity. Participants can take normal maintenance medications with water if medications are not required to be administered with food.

Treatment period

Visit 0 (randomization to treatment arm)

Study participants are required to report to the study site after approximately 8 hours without eating or drinking (except water) and should not have performed any significant physical activity.

At Visit 0, eligible participants, those who meet all applicable inclusion criteria and none of the applicable exclusion criteria for the CWMM master protocol and for OXA1, will perform all required study procedures prior to randomization to a treatment arm (see SoA).

Participant diaries will be reviewed.

Patient-reported outcomes questionnaires should be administered according to the SoA. The preferred administration order of these questionnaires is

1. PROMIS SF Pain Interference 4a v1.1
2. PGIS – Physical Function due to Weight
3. SF-36 v2 acute form, and
4. Appetite visual analog scale (VAS).

The mental health questionnaires (PHQ-9 and C-SSRS [since last assessed]) should be completed after the assessment for AEs.

Participants will return wrist worn AX6 device at this visit.

All study Visit 0 baseline measurements and assessments must be completed prior to the first dose of study intervention. Furthermore, triplicate ECGs should be collected prior to blood sample collection.

Study intervention dispensing and dosing

Beginning at randomization, all participants will receive study intervention according to the randomized treatment arm for the duration of the 48-week treatment period (primary endpoint at 32 weeks) as per the SoA (Section 1.3).

Following randomization, study site personnel will discuss the treatment group assignment with the participant and explain the dose escalation process and change in dose volume for the LY3305677 dose. Site personnel should distribute the treatment group dosing handout to the participant and explain that study intervention should be administered in the abdomen in different quadrants, rotating over time. Participants should be instructed to not inject in the same place every time.

Study site personnel will either demonstrate LY3305677 (or matching placebo) study intervention preparation and injection technique using a vial and syringe or coach the participant through study intervention preparation. They will then coach and observe the study participant inject the first dose of LY3305677 or matching placebo.

The date and time of the first dose of study intervention will be recorded on eCOA device (either provisioned or participant's own device).

Visits 1 to 20 (dose escalation)

Visits 2, 6, 10, 14, and 18 will be telephone visits; onsite visits are permitted at these times if necessary or preferred.

For all onsite visits (except PK specific visits), study participants are required to report to the study site after approximately 8 hours without eating or drinking (except water) and should not have performed any significant physical activity within that same period.

Study procedures will be performed according to the SoA (Section 1.3).

ECGs should be performed in triplicate during these visits as indicated in the SoA.

Appetite VAS should be completed after the assessment for AEs during visits as indicated in the SoA.

The mental health questionnaires (PHQ-9 and C-SSRS [since last assessed]) should be completed after the assessment for AEs during visits as indicated in the SoA.

Safety and efficacy assessments and laboratory sample collections will be performed as specified in the SoA and as described in the CWMM master protocol.

Study intervention dosing

Injections of the study intervention on study visit days should only occur after all other site procedures have been completed. Dose escalation will occur in certain treatment groups up through Week 20 of treatment. See Section 6.5.1 for detailed dose escalation information.

After the initial study visits to acquaint participants with dilution and self-administration of LY3305677, visits are every 2 weeks from Visits 2 to 24; after Visit 24, visits are every 4 weeks.

Site personnel should observe the participant to check the participant is correctly diluting and injecting LY3305677. Sites may have participants return to the site for unscheduled visits to assist participants with study intervention dilution and injections as needed.

The date and time of the doses of study intervention will be recorded on the eCOA device.

Visits 22 to 48 (maintenance)

After Visit 24 during the maintenance period, visits will occur approximately every 4 weeks until Week 48 visit procedures should be conducted according to the SoA (Section 1.3).

Visits 22, 28, 36 and 44 will be telephone visits; onsite visits are permitted at these times if necessary or preferred.

Actigraphy

At Visit 32 the AX6 device will be dispensed to participants, placed on the non-dominant wrist, wear device continuously for at least 2 weeks, and return to site at Visit 40. At Visit 40, the AX6 device will be dispensed to participants, they will be instructed to begin wearing the device on their non-dominant wrist at Visit 44, wear continuously for at least 2 weeks, and return to site at Visit 48.

See Section 8.1.2 for addition information on actigraphy.

Ambulatory blood pressure monitoring

Within 1 week of Visit 32 (Week 32) and Visit 48 (Week 48), the participant will undergo one 24-hour ambulatory monitoring session. Upon return of the ABPM device, the recordings must be transmitted to the core laboratory and analyzed before the participant leaves the site. If the session provides technically satisfactory results (≥70% of readings are valid), this measurement will serve as the final value. If a technically satisfactory result is not achieved, the investigator should review the device settings and placement and the participant's ABPM device in an attempt to correct any user error or device malfunctions. Another 24-hour ambulatory monitoring session should be conducted (within 7 days after the previous collection), and this measurement will serve as the final value. If the second session also provides technically unsatisfactory results, the data will be considered missing but will not be considered a protocol deviation.

See Section 8.2.12.1 for addition information on ABPM.

Magnetic Resonance Imaging

The postbaseline MRI measurements at Visit 32 should occur within ± 2 weeks. MRI measurement Visit 44 may be performed anytime between Visits 44 and 48. Both MRI measurements should be performed after a fast of at least 8 hours.

Patient-reported outcomes

Patient-reported outcomes questionnaires should be administered according to the SoA.

1. PROMIS SF Pain Interference 4a v1.1
2. PGIS – Physical Function due to Weight
3. PGIC – Physical Function due to Weight
4. SF-36 v2 acute form, and
5. Appetite VAS.

The mental health questionnaires (PHQ-9 and C-SSRS [since last assessed]) should be completed after the assessment for AEs.

The date and time of the doses of study intervention will be recorded on the eCOA device.

Safety and efficacy assessments and laboratory sample collections will be performed as specified in the SoA (Section 1.3) and as described in the CWMM master protocol.

Participants are also required to return any remaining diaries to the study site at Week 48.

Early discontinuation (ED) visit

Participants who discontinue study intervention but remain in the study do not need to undergo ED procedures, but rather should continue to follow regularly scheduled visit procedures.

Participants unable or unwilling to continue the study for any reason will perform an ED of treatment visit (Section 7.1 of the CWMM master protocol). If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as an ED visit. Procedures should be completed according to the SoA (Section 1.3).

Participants who withdraw from the study after signing the informed consent but who have not taken a dose of study intervention prior to randomization do not need to complete ED procedures.

Magnetic Resonance Imaging

The postbaseline MRI measurements at ED may be performed within ±7 days of the date of the study visit. MRI measurements should be performed after a fast of at least 8 hours.

Patient-Reported Outcomes

Patient-reported outcomes questionnaires should be administered according to the SoA.

1. PROMIS SF Pain Interference 4a v1.1
2. PGIS – Physical Function due to Weight
3. PGIC – Physical Function due to Weight
4. SF-36 v2 acute form.

The mental health questionnaires (PHQ-9 and [C-SSRS since last assessed]) should be completed after the assessment for AEs.

Posttreatment follow-up period

Visit 801

Visit 801, a posttreatment follow-up visit, will occur approximately 8 weeks following the last treatment period visit. All participants who have taken at least 1 dose of study intervention should complete Visit 801, according to the SoA (Section 1.3).

For participants who discontinue from the study early (regardless of whether they discontinue study intervention at the same time they discontinue from the study, or if they have discontinued study intervention at an earlier visit), an ED visit followed by the posttreatment follow-up visit (Visit 801) should be completed as per the SoA.

4.2. Scientific Rationale for Study Design

OXA1 is a Phase 2 study designed to examine the body weight-lowering efficacy and safety of LY3305677 QW (planned dose range: 3 mg to 16 mg) compared with placebo during the 48-week treatment period (with the primary endpoint at Week 32), in participants who have a BMI ≥30 kg/m^2 or ≥27 kg/m^2 if accompanied by overweight associated comorbidities.

Phase 1 data in healthy participants, and participants with obesity and overweight or T2DM demonstrated that LY3305677 has potential to produce clinically meaningful weight loss and improve glycemic control with an acceptable safety and tolerability profile consistent with other incretin classes such as GLP-1 RAs and dual GLP-1/GIP RAs.

In OXA1, a placebo arm is included to determine if any LY3305677 safety or efficacy effects are different from no treatment.

A primary study endpoint at Week 32 is considered sufficient duration for an early understanding of drug effect on body weight. The study will continue for an additional 16 weeks, for a total treatment duration of 48 weeks, to collect additional data on weight loss.

At the higher LY3305677 target doses of 10 mg QW and 16 mg QW, each study arm is further randomly assigned into 2 different dose-escalation strategies to investigate the impact on GI tolerability. These data will be used to optimize dose-escalation strategies for future clinical development.

Consistent with current guidelines for weight management, all participants will receive diet and physical activity counseling throughout the study. Clinical sites that have their own diet and physical activity programs may use those programs. However, for sites without specific diet and physical activity programs, a suggested diet and physical activity program is provided in CWMM master protocol Section 10.9.

In CWMM master protocol Section 10.9.1, the diet recommendations are based on the World Health Organization (WHO 2020a) diet for everyone and are based on a Mediterranean Diet eating pattern. In CWMM master protocol Section 10.9.2, physical activity recommendations are based on WHO recommendations (WHO 2020b) and with the US Health and Human Services (HHS 2020) recommendations.

The primary efficacy measure, mean percent change in body weight, is an accepted Phase 2 endpoint for investigational drugs being developed for weight management (FDA 2007).

In addition, the study includes other parameters relevant to assessment of the effects of LY3305677 on safety, BP, lipids, PK and PD parameters, and patient-reported outcomes. Further, safety and tolerability over a wide dose range of LY3305677 versus placebo will be assessed to enable robust benefit–risk characterizations in treatment of participants who have a BMI ≥30 kg/m^2 or ≥27 kg/m^2 if accompanied by weight-related comorbidities.

4.3. Justification for Dose

4.3.1. LY3305677

The LY3305677 planned target doses of 3, 6, 10, and 16 mg, administered subcutaneously QW, were selected for OXA1 based on the following:

- Safety and tolerability of LY3305677 in healthy participants and T2DM participants in the Phase 1 single ascending dose study I8P-MC-OXAA (0.03 to 5 mg dose range), multiple ascending dose studies I8P-MC-OXAB (0.05 to 1.5 mg QW dose range) and I8P-MC-OXAD (4.5 to 10 mg QW dose range). Preliminary safety, tolerability, and weight loss data from the multiple ascending dose study OXAG provide the additional clinical data to support dosing for the top dose of 16 mg QW.
- PK/PD modeling of dose-exposure-response data from Study OXAD.
- Acceptable margin of safety for the 16 mg maximum dose in this study relative to the no observed adverse-effect level in monkeys in the 6-month toxicology studies.

- The lowest maintenance dose of 3 mg QW is anticipated to provide modest weight loss benefit but will be necessary for robust characterization of the LY3305677 dose-exposure-response relationship for weight change. For participants randomly assigned to the 3 mg dose, a dose-escalation to 6 mg is planned after the primary endpoint (Week 32) and will be maintained at 6 mg until the end of the study.
- Maintenance doses of 6 mg, 10 mg, and 16 mg QW are expected to provide clinically meaningful weight loss relative to placebo in a dose-related manner. To reach these higher doses, a starting dose not exceeding 2 mg QW will be used for initiation of treatment, followed by gradual dose escalation to reach the targeted higher doses to mitigate any GI tolerability issues.
- The selected dose range is anticipated to be wide enough to support robust dose-exposure-response analyses of multiple key safety, tolerability, and efficacy endpoints to provide a comprehensive benefit-risk assessment and dose selection rationale for further clinical development of LY3305677 in weight management.

4.4. End of Study Definition

A participant is considered to have completed OXA1 if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

The end of OXA1 is defined as the date of the last visit of the last participant in OXA1 or last scheduled procedure shown in the SoA for the last participant in OXA1 globally.

5. Study Population

Eligibility for participation is based on inclusion and exclusion criteria specified in the CWMM master protocol, with additional criteria specific to the OXA1 as detailed below. Participants must first meet all criteria for the CWMM master protocol, and then must meet all criteria for OXA1 to be eligible to participate in OXA1.

5.1. Inclusion Criteria

In addition to meeting the inclusion criteria specified in the CWMM master protocol, OXA1 participants must meet the following inclusion criteria at the time of screening:

Sex and contraceptive/barrier requirements

100. Are males and females who agree to abide by the reproductive and contraceptive requirements provided in OXA1, Section 10.3.

5.2. Exclusion Criteria

In addition to meeting the exclusion criteria specified in the CWMM master protocol, OXA1 participants will be excluded if any of the following apply at the time of screening:

Medical conditions

Diabetes related

101. Have any prior diagnosis of diabetes mellitus, that is T2DM, or rare forms of diabetes mellitus, except gestational diabetes.
102. Have at least 1 laboratory value suggestive of diabetes during screening, including 1 or more of HbA1c ≥6.5% (48 mmol/mol), fasting serum glucose ≥126 mg/dL (7.0 mmol/L), or random glucose ≥200 mg/dL (11.1 mmol/L).

Other medical

103. Have any of the following cardiovascular conditions **within 6 months** prior to screening:
    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina, or
    - hospitalization due to congestive heart failure (CHF).

    Note: This supersedes CWMM master protocol Section 5.2, exclusion criterion 15.
104. Have a history of New York Heart Association (NYHA) Functional Classification I-IV CHF.

    Note: This supersedes CWMM master protocol Section 5.1, inclusion criterion 2.
105. Have renal impairment measured as estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2, calculated per Chronic Kidney Disease Epidemiology Consortium (CKD-EPI) as determined by the central laboratory during screening.

106. Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction), or chronically take drugs that directly affect GI motility.
107. Have a history of acute or chronic pancreatitis. A participant with a history of acute pancreatitis caused by gallstones may be included in the study if the participant has had a cholecystectomy.
108. Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma.
109. Have a serum calcitonin level (at screening) of
    - ≥20 ng/L, if eGFR ≥60 mL/min/1.73 m^2, or
    - ≥35 ng/L if eGFR <60 mL/min/1.73 m^2, as determined by central laboratory at screening.
110. Have fasting triglycerides >500 mg/dL (5.7 mmol/L).
111. Have had any exposure to GLP-1 analogs, or other incretin receptor agonist compounds within the prior 3 months or any prior history of hypersensitivity/allergies to these medications.
112. Have contraindications for MRI scanning, such as persons with cardiac pacemaker and implants made out of metal (for example, cochlea implant, nerve stimulators, magnetic vascular clips, and metallic heart valve) or other contraindications for MRI.
113. Have claustrophobia precluding completion of an MRI examination.
114. Any condition or circumstance that, in the opinion of the investigator, would interfere with completion of the MRI examination, such as, but not limited to, body weight or girth that exceeds the MRI scanner capabilities.

Prior/concomitant therapy

115. Have discontinued a GLP-1 receptor agonist treatment due to lack of efficacy or intolerability.
116. Use of metformin, or any other glucose-lowering medication such as an SGLT 2 inhibitor, for example, prescribed for polycystic ovarian syndrome, diabetes prevention, or heart failure, is not permitted.

Prior/concurrent clinical study experience

117. Have participated within the last 6 months, whether on active drug or placebo, in a clinical study that contained a selective GLP-1 RA or GIP/GLP-1 or GLP-1/Gcg dual receptor agonists or GLP-1/Gcg/GIP tri-receptor agonists.
118. Have known or suspected hypersensitivity to trial product(s), to selective GLP-1 RAs or GIP/GLP-1 or GLP-1/Gcg dual receptor agonists or GLP-1/Gcg/GIP tri-receptor agonists.

Exclusion criteria specifically for Ambulatory Blood Pressure Monitoring

The following additional exclusions apply only to participation in ABPM collections. A participant who qualifies for the study based on both the CWMM master protocol and the above inclusion/exclusion parameters but does not qualify for ABPM may still participate in the study. Not being able to participate in ABPM procedures is not considered a protocol deviation.

119. Participants with hypertension who do not have well-controlled blood pressure (BP) (>140/90 mmHg), regardless of antihypertensive treatment. Participants receiving treatment for hypertension should be on a stable antihypertensive regimen for at least 3 months prior to screening.

    Note: If the investigator anticipates a need to add antihypertensive medication during the course of the study, the participant should not be included in the ABPM procedures.

120. Participant works in rotation shifts or works during the hours of 2200 to 0700.
121. Participant performs strenuous manual labor that cannot be avoided during the monitoring period.
122. Participant has a nondominant arm circumference of >55 cm at screening.
123. Participant is unable to obtain a valid baseline ABPM reading.
124. Chronic use of nonsteroidal anti-inflammatory agents or cyclooxygenase-2 (COX-2) inhibitors, as well as other agents, prescription or over-the-counter, known to affect BP, are permitted; however, use of these agents on an as-needed basis during the 48-hour period immediately prior to or during each 24-hour ABPM recording is prohibited. Examples include, but are not limited to, decongestants (pseudoephedrine, ephedrine, phenylephrine, naphazoline, and oxymetazoline) and multi-symptom cold remedies.
125. Male participants must abstain from use of phosphodiesterase type 5 (PDE-5) inhibitors (that is, tadalafil, vardenafil, and sildenafil) or yohimbine (herbal aphrodisiac) during the 48-hour period immediately prior to or during each 24-hour ABPM recording, since these medications may confound the BP measurements.

Additional exclusion criteria

126. Have an elevated resting pulse rate (mean >100 bpm) or reduced resting pulse rate (mean <60 bpm) at screening. Note: This supersedes CWMM master protocol Section 5.2, exclusion criterion 15.

5.3. Lifestyle Considerations

See CWMM master protocol, Section 5.3.

5.4. Screen Failures

See CWMM master protocol, Section 5.4.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

This section is not applicable to this study.

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/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3).

Returned study intervention should not be re-dispensed to the participants.

Detailed dosing instructions for all treatment arms in this study can be found in Section 6.5.1.

This table lists the interventions used in this clinical study.

Intervention Name	**LY3305677**	**LY3305677 Placebo**
Dosage Level(s)	1.5 mg 3 mg (target dose) 6 mg (target dose) 8 mg 9 mg 10 mg (target dose) 12 mg 16 mg (target dose)	Matched
Route of Administration	Subcutaneous using a syringe	Subcutaneous using a syringe
Frequency of Administration	Once weekly	Once weekly
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU

Abbreviation: EU = European Union.

The first injections of study intervention should occur at Visit 0 after the participant has undergone all other study procedures and assessments. Subsequent study intervention administrations should be scheduled on the same day of the week and approximately the same time of the day if possible. If a dose of study intervention is missed, the participant should take it as soon as possible, unless it is within 72 hours of the next dose. If less than 72 hours remains, that dose should be skipped, and the next dose should be taken at the scheduled day and time. The day of weekly administration can be changed, if necessary, as long as the last dose was administered 72 or more hours before.

Participants will inject study intervention SC into the abdominal wall, alternating between 4 sites weekly, that is right and left upper quadrants and right and left lower quadrants, using the injection supplies provided. Furthermore, participants should dilute LY3305677 and inject themselves in the presence of site personnel at each visit to check the participant is correctly diluting and injecting LY3305677.

A caregiver may administer the injection after appropriate training. A new syringe will be used for each injection of LY3305677 study intervention. The actual date and time of all dose administrations will be recorded in the study intervention administration diary by the participant.

Packaging and labeling

Study intervention will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study interventions are provided by the sponsor.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study.

At Visit 0, participants who meet all criteria for enrollment will be randomly assigned to one of the study treatment arms (placebo, LY 3/6 mg, LY 10 mg and LY 16 mg) in a 3:2:3:3 ratio. Participants randomized to placebo will be assigned to follow the injection dose schedule with matching injection volume for 1 of the LY3305677 treatment arms. Although the participant and the investigator will know the injection volume of study drug, they will not know whether the participant is receiving LY3305677 or placebo. Assignment to treatment arms will be determined by a computer-generated random sequence using an IWRS with the following stratification variables:

- BMI ($\leq$30, >30 kg/m^2 at screening)
- Sex (male or female)

To preserve the blinding of the study, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

See the CWMM master protocol Section 6.3 for emergency unblinding and additional information on minimizing bias.

6.4. Study Intervention Compliance

Study intervention administration data (date and time of each dose administered) will be recorded in the diary by the participant and reviewed by the investigator at each study visit.

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

Also, see the CWMM master protocol (Section 6.4) for measures to assure or assess compliance.

6.5. Dose Modification

Study intervention administration in OXA1 should follow the schedule summarized in Section 1.3 (SoA) and detailed in the dose escalation table in Section 6.5.1.

Adjustment in study intervention dose level will be allowed for participants assigned to each of the treatment groups.

Dose modifications of LY3305677 or placebo, will be conducted in a blinded fashion as depicted in the dose escalation table in Section 6.5.1.

Dose modification is allowed for:

- dose escalations
- adverse events
- temporary dose interruption, or
- dose reductions, without dosing interruptions, and
- when appropriate to ensure participant safety or to address tolerability issues.

Dose reductions may occur at unscheduled visits.

See CWMM master protocol Section 7.1 for detailed information about discontinuation of study intervention.

6.5.1. Dose Escalations

This table provides dose escalation schemes for LY treatment arms in OXA1. Patients in placebo arm will be split to sub-groups that match the dosing volume and escalation plan of each LY treatment arms.

Treatment arm (Targeted LY dose)	Escalation Period (all dosing is QW)						Maintenance Period (all dosing is QW)
	Week 0 through Week 3	Week 4 through Week 7 (Escalation 1)	Week 8 through Week 11 (Escalation 2)	Week 12 through Week 15 (Escalation 3)	Week 16 through Week 19 (Escalation 4)	Week 20 through Week 31	Week 32 to Week 48
3/6 mg	LY 1.5 mg	LY 3 mg	LY 3 mg	LY 3 mg	LY 3 mg	LY 3 mg	LY 6 mg
10 mg	LY 1.5 mg	LY 3 mg	LY 6 mg	LY 8 mg	LY 10 mg	LY 10 mg	LY 10 mg
16 mg	LY 1.5 mg	LY 3 mg	LY 6 mg	LY 9 mg	LY 12 mg	LY 16 mg	LY 16 mg

Abbreviations: LY= LY3305677; QW= once weekly.

6.5.2. Temporary Interruption and Restarting of Study Intervention

In certain situations, after randomization, the investigator may need to temporarily interrupt study intervention. See Sections 7.1.3 and 7.1.3.1 for detailed guidance regarding temporary interruptions and restarting study intervention, respectively.

6.5.3. Dose Reductions and Re-escalations

Participants may need to have doses modified due to AEs. Any changes in dosing will be documented in the CRF.

Excessive body weight loss

Although weight loss is desired in the population of participants included in this trial, it is possible that a participant may achieve a level of weight loss that is sufficient for health benefits, with further weight loss being considered undesirable. Therefore, the dose of study intervention should be decreased to 1 dose level lower if BMI decreases to less than or equal to 20 kg/m^2. Participants should be permanently discontinued from study intervention if BMI decreases to less than or equal to 18.5 kg/m^2.

Refer Section 7.1 for guidance on discontinuation of study intervention.

Gastrointestinal adverse events

The most frequent AEs for LY3305677 have been GI-related (nausea, vomiting, diarrhea, or constipation). If a participant has intolerable AEs associated with a dose level of study intervention (for example, moderate-to-severe nausea, vomiting, diarrhea, or constipation) and the investigator does not believe that the participant will tolerate the dose with further exposure, then the investigator may reduce the dose to the previous lower dose based on treatment assignment. Due to expected tachyphylaxis of the GI-related AEs, it is preferable that the participant try the intended dose level 2 times before undergoing a dose modification.

All participants who have had a dose reduction will attempt to dose re-escalate once GI-related symptoms improved and after staying at the lower dose level for 2 to 4 doses. If the participant does not tolerate the dose escalation a second time, the participant will have their dose reduced to the last tolerated level.

Dose modifications will be conducted based on details below. Participants in placebo group will be split to subgroups and follow one of the dose escalation and dose modification plan.

6.5.4. Starting Doses and First Dose Escalation

If participants do not tolerate the starting dose or the first dose escalation will need to discontinue from study treatment.

6.5.5. Subsequent Dose Modifications

The following table provides instructions for dose modification for treatment arm.

Target dose 3/6 mg	***If…***	***Then…***
	LY 1.5 or 3 mg is not tolerated during the first 8 weeks	Discontinue from study intervention.
	If intolerability develops any time after Week 8 and prior to Week 32	Reduce LY dose to 1.5 mg and re-escalate.
	The dose escalation of LY from 3 mg to 6 mg at Week 32 is not tolerated	Reduce the LY dose to 3 mg and re-escalate.
	If the participant does not tolerate the LY 6 mg dose a second time	Remain at LY 3 mg.
Target dose 10 mg	***If…***	***Then…***
	LY 1.5 or 3 mg is not tolerated during the first 8 weeks	Discontinue from study intervention.
	LY 6 mg is not tolerated	Reduce dose to LY 3 mg and re-escalate.
	If LY 6 mg is not tolerated a second time	Maintain at LY 3 mg.
	LY 8 mg is not tolerated	Reduce dose to LY 6 mg and re-escalate.
	If LY 8 mg is not tolerated a second time	Maintain at LY 6 mg.
	LY 10 mg is not tolerated	Reduce the LY dose to 8 mg and re-escalate.
	If LY 10 mg is not tolerated a second time	Remain at LY 8 mg.
Target dose 16 mg	***If…***	***Then…***
	LY 1.5 or 3 mg is not tolerated during the first 8 weeks	Discontinue from study intervention.
	LY 6 mg is not tolerated	Reduce dose to LY 3 mg and re-escalate.
	If LY 6 mg is not tolerated a second time	Maintain at LY 3 mg.

	LY 9 mg is not tolerated If LY 9 mg is not tolerated a second time	Reduce dose to LY 6 mg and re-escalate. Maintain at LY 6 mg.
	LY 12 mg is not tolerated If LY 12 mg is not tolerated a second time	Reduce dose to LY 9 mg and re-escalate. Maintain at LY 9 mg.
	LY 16 mg is not tolerated If LY 16 mg is not tolerated a second time	Reduce the LY dose to 12 mg and re-escalate. Maintain at LY 12 mg.

Abbreviation: LY = LY3305677.

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

LY3305677 will not be made available after conclusion of the study.

6.7. Treatment of Overdose

For this study, any total dose of study intervention within a 72-hour time period over 16 mg will be considered an overdose and should be reported as per criteria described in Section 10.3 of the CWMM master protocol. The amount of study intervention taken will be estimated from the participants scheduled dose at the time of the overdose.

In the event of an overdose, the investigator or treating physician should:

- Contact the Lilly-designated medical monitor immediately.
- Evaluate the participant to determine, in consultation with the Lilly-designated medical monitor, whether study intervention should be interrupted or whether the dose should be reduced.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate. Based on the known AE profile of LY3305677, the following are the possible AEs related to an overdose:
    - severe GI events that lead to dehydration and require medical intervention
    - CV abnormalities, such as increase in heart rate (HR), decrease in BP, and supraventricular arrhythmias/cardiac conduction disorders, and
    - hypoglycemia
- Implement medical intervention/monitoring according to the clinical presentation.
- Obtain a plasma sample for PK analysis as soon as possible.
- Document the event of overdose in the CRF.

6.8. Prior and Concomitant Therapy

See the CWMM master protocol (Section 6.8).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

See the CWMM master protocol (Section 7).

7.1. Discontinuation of Study Intervention

In addition to the reasons stated in the CWMM master protocol Section 7.1, participants in OXA1 should be permanently discontinued from study intervention if

- the participant is diagnosed with pancreatitis
- the participant is diagnosed with multiple endocrine neoplasia type 2 syndrome, or
- the participant's BMI reduces below 18.5 kg/m^2.

7.1.1. Liver Chemistry Stopping Criteria

See CWMM master protocol (Section 7.1.1).

7.1.2. Cardiac Arrhythmia and QTc Stopping Criteria

Discontinuation of study intervention should be considered by the investigator and sponsor if any of the following occurs in a participant:

- QTc ≥ 500 msec or change in QTc ≥ 60 msec from baseline
- Clinically significant arrhythmia (i.e., atrial fibrillation)

See CWMM master protocol (Section 7.1.2).

7.1.3. Temporary Interruption of Study Intervention

In certain situations, after randomization, study intervention may need to be temporarily interrupted. Every effort should be made by the investigator to maintain participants on study intervention and to restart study intervention after any temporary interruption, as soon as it is appropriate to do so. A participant may experience multiple events that require dosing interruption; each event should be addressed individually per guidance provided in this section.

For example, participants may need to temporarily interrupt study intervention due to

- occurrence of intolerable GI AEs
- other AEs that warrant dosing interruption determined by the investigator, or
- reasons unrelated to AEs.

If the reason for temporary dosing interruption is related to poor participant tolerability, for example, when protracted GI events of vomiting and/or diarrhea trigger a request from the participant and/or from the investigator for temporary discontinuation of dosing, 1 weekly dose of study intervention may be omitted. A longer interruption may be needed at the discretion of the investigator.

In other situations when participant safety is compromised, for example due to an SAE, more than 1 dose may need to be skipped.

The decision to interrupt dosing in any of these situations will not be considered a protocol deviation.

If the participant interrupts dosing for other reasons that are not related to the tolerability or safety of the participant, dosing interruption will be considered a protocol deviation.

The dates and number of skipped doses related to temporary interruption of study treatment will be documented.

Other situations of study intervention interruption that are not described in this section should be discussed between the primary investigator or designee and Lilly study physician/research scientist to decide on an appropriate dosing plan for any participant with such events.

7.1.3.1. Restarting Study Intervention after a Temporary Interruption

If the number of consecutive missed doses of study intervention is ≤2, the treatment can be restarted at the same dose if the drug was well tolerated prior to discontinuation.

If the number of consecutive missed doses is ≥3 (or fewer doses if the study intervention was not well tolerated) when the dose interruption occurred, then the treatment should be restarted as described below.

If the dose interruption occurs during the first 4 weeks of dosing (that is, the starting dose level), the participant should be restarted on the first dose level.

If the participant has a dose interruption after the first 4 weeks, restart LY3305677 at 3 mg and stay on 3 mg for 2-4 weeks before continuing to dose escalate every 4 weeks according to the escalation schedule assigned to the participant.

See Section 6.5.3 for guidance on dose escalation/maintenance for participants who do not tolerate a dose level of study intervention.

7.2. Participant Discontinuation/Withdrawal from the Study

See CWMM master protocol (Section 7.2).

7.3. Lost to Follow up

See CWMM master protocol (Section 7.3).

8. Study Assessments and Procedures

See CWMM master protocol (Section 8).

8.1. Efficacy Assessments

Primary

The primary efficacy measure is percent change in body weight from baseline at Week 32. Body weight measurements will be collected at specific clinic visits as summarized in the SoA (Section 1.3). Methods for measuring body weight are described in Section 10.8 of the CWMM master protocol.

Secondary

The following secondary efficacy measures will be collected or calculated at the times shown in the SoA:

- body weight,
- BMI, and
- liver fat (assessed by MRI-PDFF).

Exploratory

See Section 3 of the CWMM master protocol and Section 3 of OXA1 for specific efficacy endpoints. The following exploratory efficacy measures will be collected or calculated at the times shown in the SoA:

- Waist circumference
- Body weight
- BMI
- Fasting lipid profile, consisting of total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol triglycerides, non-HDL cholesterol.
- Systolic and diastolic blood pressure (included in vital signs)
- HbA1c
- Fasting insulin
- Fasting glucose (included in clinical chemistry panel)
- Mechanistic biomarkers: to explore potential mechanism of action modifying glucose, lipid, or nutrient metabolism, markers will be assessed (see Section 10.5 for detailed list of biomarkers) related to
    - insulin sensitivity
    - pancreatic beta or alpha cell function
    - glucagon receptor target engagement
    - lipid metabolism
    - liver fat, inflammation, or fibrosis
    - purine metabolism
    - cardiovascular risk, and
    - inflammation.
- Patient-reported outcomes
    - PROMIS SF Pain Interference 4a v1.1

    - PGIS – Physical Function due to Weight
    - PGIC – Physical Function due to Weight
    - SF-36 v2, acute form, and
    - Appetite VAS.
- Physical activity (assessed with Axivity AX6 actigraphy device)
- Body composition (assessed by MRI)
- Liver fat content (assessed by MRI-PDFF)

8.1.1. Patient-Reported Outcomes

The self-administered questionnaires will be translated into the primary languages of the region and administered at the site during the designated visits in the OXA1 SoA. At these visits, the questionnaires should be completed after AE collection but before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff, if the participant is not adversely affected by their fasting condition.

Preferred administration order of these questionnaires is

1. PROMIS SF Pain Interference 4a v1.1
2. PGIS – Physical Function due to Weight
3. PGIC – Physical Function due to Weight
4. SF-36 v2 acute form, and
5. Appetite VAS.

8.1.1.1. PROMIS Short Form Pain Interference 4a v1.1

The Patient-Reported Outcome Measurement Information System (PROMIS) (Health Measures [WWW]) is a set of patient-completed measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions.

The PROMIS Short Form Pain Interference 4a assesses consequences of pain on relevant aspects of one's life. This includes the extent to which pain interferes with day-to-day, social, and household activities. The PROMIS Short Form Pain Interference 4a consists of 4 items that asks participants to rate their pain interference over the past 7 days on a 5-point scale ranging from "1 – not at all" to "5 – very much." Individual item scores are totaled to obtain a raw score, with higher scores indicating more interference. Raw scores can be converted to a t-score, which is standardized with a mean of 50 and a standard deviation (SD) of 10; higher scores indicate better levels of function and/or better health. Patient Global Impression of Severity - Physical Function due to Weight

The Patient Global Impression of Severity - Physical Function due to Weight (PGIS - physical function weight) questionnaire is designed to assess the participants' overall perception of their condition. This is a single global item that asks participants to rate how their weight limited their ability to perform physical activities in the past 7 days on a 5-point scale ranging from "not at all limited" to "extremely limited."

8.1.1.2. Patient Global Impression of Change - Physical Function due to Weight

The Patient Global Impression of Change – Physical Function due to Weight (PGIC - physical function weight) questionnaire is designed to assess the participant's overall perception of the efficacy of treatment. This is a single global item that asks participants to rate the overall change in their ability to perform physical activities due to their weight since starting the study medication. The responses are based on a 5-point scale ranging from "much better" to "much worse".

8.1.1.3. SF-36 v2, Acute Form

The Short Form-36 version 2 Health Survey acute form (SF-36 v2 acute), 1-week recall version is a 36-item generic, participant-completed measure designed to assess the following 8 domains:

- Physical functioning
- Role-physical
- Bodily pain
- General health
- Vitality
- Social functioning
- Role-emotional, and
- Mental health.

The Physical Functioning domain assesses limitations due to health "now" while the remaining domains assess functioning "in the past week." Each domain is scored individually and information from these 8 domains are further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales). Scoring of each domain and both summary scores are norm based and presented in the form of t-scores, with a mean of 50 and SD of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

8.1.1.4. Appetite Visual Analog Scale

To explore the effects of LY3305677 on meal intake and appetite sensation, participants will be asked to rate their appetite sensations using a 100-mm VAS for parameters of hunger, fullness, satiety, and prospective food consumption in the fasted state (refer to the SoA in Section 1.3).

The VAS is a validated tool to assess appetite sensation parameters (Flint et al. 2000). The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "extremely" and "not at all." Participants are required to rate their subjective sensations on four 100-mm scales combined with questions similar to the following:

Overall appetite score is calculated as the average of the 4 individual scores: satiety + fullness + (100-prospective food consumption) + (100-hunger) / 4 (van Can et al. 2014). The higher overall appetite score indicates less appetite, and the lower score indicates more appetite.

8.1.2. Actigraphy

An actigraphy device (Axivity AX6) will be utilized in OXA1 to objectively evaluate the effect of study intervention on physical activity parameters.

This actigraphy device is a data capture tool capable of recording raw data from a suite of integrated sensors and can be configured to collect movement-relevant data in an uninterrupted fashion for up to 2 months, thus is ideal for collecting longitudinal movement data, for example, physical activity and sleep, in real-world health research and well-defined clinical trials.

This actigraphy device meets the CE (Conformitè Europëenne) mark requirements. Participants should wear the actigraphy device for at least 2 weeks, at 3 separate times during the study, per the SoA.

Lack of participation in actigraphy collections at any time is not considered a protocol deviation.

8.1.3. Magnetic Resonance Imaging (MRI)

Purpose

The collected MRI and biomarker data will be used to explore the effect of study intervention on liver fat content and additional MRI derived measurements.

Collection visits

Collection visits are specified in the SoA (Section 1.3). MRI procedures will be performed and specific circulating biomarkers to be collected.

Participants are required to report for the MRI after approximately 8 hours without eating, drinking (except water), and without performing any significant physical activity. Participants can take normal maintenance medications with water if medications are not required to be administered with food.

MRI procedures

MRI measurements at baseline should be performed between Visit 402 and Visit 0 (randomization) in OXA1, before the participant receives the first dose of study intervention.

The postbaseline MRI measurements at Week 32 should occur within ±2 weeks. Week 48 measurements should be scheduled and performed anytime between Visits 44 and 48 and ED measurements may be performed within ±7 days of the date of the study visit. Both MRI measurements should be performed after a fast of at least 8 hours.

To obtain consistent and quality data for central review, investigators will be provided with detailed instructions on the MRI acquisition protocol to be used.

Scans will be performed at 1.5 Tesla (T) or 3 T. The same scanner and imaging acquisition sequence or procedure should be used for all participant time points. Any exceptions must be approved in advance of scanning by the imaging core laboratory. A standardized imaging acquisition sequence or procedure will be utilized at all MRI centers and details will be provided in MRI Site instructions.

MRI images are transmitted to a central reader for evaluation of the MRI-based efficacy endpoints. To ensure participant’s safety, images should also be over-read locally to exclude underlying liver pathologies.

8.2. Safety Assessments

Planned time points for safety assessments are provided in the OXA1 SoA (Section 1.3).

Lilly will periodically review evolving aggregate safety data within the study. The study team will review safety reports in a blinded fashion (for applicable blinded study period) according to the schedule provided in the Trial-Level Safety Review plan. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly-designated medical monitor will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

See the CWMM master protocol Section 8.2 for safety assessments and safety monitoring activities required for all ISAs.

Procedures specified in the following subsections of OXA1 must be followed in addition to those described in the CWMM master protocol.

8.2.1. Vital Signs

See the CWMM master protocol, Section 8.2.1.

8.2.2. Physical Examinations

See the CWMM master protocol, Section 8.2.2.

8.2.3. Electrocardiograms

See CWMM master protocol, Section 8.2.3.

8.2.4. Clinical Safety Laboratory Tests

Perform laboratory assessments per the SoA (Section 1.3). See CWMM master protocol, Section 8.2.4 for information on reporting, review and recording, and repeating laboratory tests.

See OXA1, Section 10.2 and CWMM master protocol, Section 10.2 for the list of clinical laboratory tests.

8.2.5. Major Adverse Cardiovascular Events

See the CWMM master protocol, Section 8.2.5.

8.2.6. Deaths

See CWMM master protocol, Section 8.2.6.

8.2.7. Hepatobiliary Disorders

See CWMM master protocol, Section 8.2.7.

8.2.8. Acute Renal Events

See CWMM master protocol, Section 8.2.8.

8.2.9. Pregnancy Testing

See CWMM master protocol, Section 8.2.9.

8.2.10. Hepatic Monitoring

See CWMM master protocol, Section 8.2.10.

8.2.11. Suicidal Ideation and Behavior Risk Monitoring

8.2.11.1. Columbia-Suicide Severity Rating Scale

See CWMM master protocol, Section 8.2.11.1.

8.2.11.2. Patient Health Questionnaire-9

See CWMM master protocol, Section 8.2.11.2.

8.2.12. Additional Safety Data and Sample Collections

8.2.12.1. Ambulatory Blood Pressure Monitoring (ABPM)

Ambulatory monitoring device

An ambulatory monitoring device that uses an inflatable cuff attached to a portable device worn around the waist will be used to collect multiple BP and HR readings over a 24-hour period, during both sleep and wake cycles. The multiple readings collected by the ABPM device can be averaged to obtain mean BP and HR values, to detect variations over time, and to compute other distribution patterns.

Study procedures

Participants who give consent and meet all eligibility requirements will receive education about ABPM and will be trained in its use at Visit 402. Ambulatory monitoring of HR and BP will be performed prior to Visit 0 and initiated at Visit 402, in the week prior to Visit 32 (Week 32: primary endpoint), and again in the week prior to Visit 48. It will not be considered a protocol deviation if a participant does not meet all ABPM eligibility requirements to participate in ABPM procedures. Participants that do not have a baseline ABPM measure should not have any subsequent ABPM collections.

Use of the ABPM device

The ABPM device will be attached to the nondominant arm, and participants will be instructed to wear the monitor for a 24- to 27-hour period. Participants will also be instructed to keep track of daily activities throughout the testing period and not to engage in strenuous activity.

Ambulatory blood pressure measurements:

- Should be collected on a typical workday, not on a non-working day
- Will be recorded every 30 minutes during daytime hours (0700 to 2200 hours)
- Will be recorded every 60 minutes during nighttime hours (2200 to 0700 hours).

A 24-hour session of ambulatory monitoring produces technically acceptable measurements if ≥70% of the readings are valid.

If a technically satisfactory result is not achieved, the investigator should review the device settings and placement and the participant's activity track in an attempt to correct any user error or device malfunctions. Another 24-hour ambulatory monitoring session should be conducted prior to Visit 0, and this measurement will serve as the baseline value. If the second session also provides technically unsatisfactory results, the participant should not undergo any further ABPM measures.

8.2.12.2. Hypoglycemia

Upon ICF signing, all participants will be educated about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

Hypoglycemia may be identified by spontaneous reporting of symptoms from participants (whether confirmed or unconfirmed by simultaneous glucose values) or by blood glucose (BG) samples collected during study visits.

All participants who develop incident diabetes during the study will be provided with glucometers (Section 8.3.4). Participants without diabetes may, at the investigator's discretion, be given glucometers to assist in the evaluation of reported symptoms consistent with persistent hypoglycemia. Participants receiving glucometers should be instructed to record relevant information (for example, glucose values and symptoms).

Participants who develop incident diabetes during the study may be started on allowed glucose-lowering medications (Section 6.8). In the event that participants subsequently develop persistent or recurrent unexplained hypoglycemia during the treatment period, participants will be asked to reduce the dose or discontinue any concomitant glucose-lowering medication commonly associated with hypoglycemia (for example, sulfonylurea or insulin).

If a hypoglycemic event meets severe criteria (see definition below), it should be recorded as serious on the AE and SAE CRFs and reported to Lilly as an SAE.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the BG values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips) in accordance with the 2020 American Diabetes Association position statement on glycemic targets (ADA 2020). **Level 2** and **Level 3** hypoglycemia events are considered as safety topics of special interest:

Level 1 hypoglycemia:

> **Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L):** Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2 hypoglycemia:

> **Glucose <54 mg/dL (3.0 mmol/L):** Level 2 hypoglycemia is also referred to as documented or BG-confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose

threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

Nocturnal hypoglycemia is a hypoglycemia event (including severe hypoglycemia) that **occurs at night** and presumably during sleep.

To avoid duplicate reporting, all consecutive BG values <70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

8.2.12.3. Pancreatitis

Diagnosis of acute pancreatitis

Acute pancreatitis is safety topic of interest in all studies with LY3305677, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi et al. 2006):

- abdominal pain, characteristic of acute pancreatitis (that is, epigastric pain radiating to the back, often associated with nausea and vomiting)
- serum amylase (total, pancreatic, or both) and/or lipase ≥3X ULN, and
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, the investigator should ensure that the following steps are taken:

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase, and
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI.

***Note*:** Abdominal ultrasound may be used as an alternative method only if CT and MRI cannot be performed.

- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study intervention. Afterwards, if the case is confirmed as acute pancreatitis by the adjudication committee, study intervention must be permanently discontinued; the participant may continue in the study. If the case is not confirmed, then the participant can restart study intervention, if the investigator deems as clinically appropriate, as described in the Section 7.1.3.1.

Case adjudication and data entry

An independent Clinical Endpoint Committee (CEC) will adjudicate all suspected cases of acute pancreatitis. Relevant data from participants with acute pancreatitis will be entered into a specifically designed CRF page. The adjudication committee representative will enter the results of adjudication in a corresponding CRF page.

Asymptomatic elevation of pancreatic amylase and/or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or pancreatic amylase ≥3X ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

8.2.12.4. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or MEN-2 will be excluded from the study. Participants who are diagnosed with MTC and/or MEN-2 during the study will have study intervention stopped and should continue follow-up with an endocrinologist.

The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy (including MTC, papillary carcinoma, and others) and measurements of calcitonin. These data will be captured in specific CRFs. The purpose of calcitonin measurements is to assess the potential of LY3305677 to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

8.2.12.4.1. Calcitonin Measurements

If an increased calcitonin value (see definitions below) is observed in a participant who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped, and calcitonin levels should be measured after an appropriate washout period.

For participants who require additional endocrine assessment because of increased calcitonin concentration as defined in this section, data from the follow-up assessment will be collected in the specific section of the CRF.

Calcitonin measurements in participants with eGFR ≥60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR ≥60 mL/min/1.73 m^2 is defined below. If a participant's laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE.

- ***Serum calcitonin value ≥20 ng/L and <35 ng/L AND ≥50% increase from the screening value***. These participants will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), the study intervention should be stopped, and the participants encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude any serious adverse effects on the thyroid.
- ***Serum calcitonin value ≥35 ng/L AND ≥50% over the screening value***. In these participants, study intervention should be stopped, and the participants recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

Calcitonin measurement in participants with eGFR <60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a *serum calcitonin value ≥35 ng/L AND ≥50% over the screening value.* If a participant's labs meet these criteria, these clinically significant labs should be recorded as an AE.

In these participants, study intervention should be discontinued (after first confirming the value) and the participants recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.

8.2.12.5. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in CWMM master protocol, Section 10.3 must be reported as SAEs.

8.2.12.6. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study intervention. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.2. Laboratory results are provided to the sponsor via the central laboratory.

8.2.12.7. Injection Site Reactions

Symptoms of a local injection site reaction may include erythema, induration, pain, pruritus, and edema. If an injection site event is reported, the AE will be recorded, and additional data will be provided to the sponsor in the CRF. At the time of AE occurrence of severe or serious types, samples will be collected for measurement of LY3305677 antidrug antibodies (ADAs) and LY3305677 concentration.

8.2.12.8. Antidrug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 8.8.

8.2.12.9. Severe Gastrointestinal Adverse Events

LY3305677 may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the CRF/AE and Concomitant Medications forms, respectively.

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

See the CWMM master protocol, Section 10.3 for AE, SAE, and product complaint definitions.

8.3.1. Timing and Mechanism for Collecting Events

See CWMM master protocol, Section 8.3.1.

8.3.2. Pregnancy

See CWMM master protocol, Section 8.3.2.

8.3.3. Adverse Events of Special Interest

8.3.3.1. Hypotension and Related Neurological Signs and Symptoms

Hypotension, orthostatic hypotension, and related neurological events will be identified by spontaneous reporting of symptoms (for example dizziness, blurred vision, and syncope) and blood pressure levels. See Section 2.3.1 for hypotension assessment.

8.3.3.2. Acute Renal Failure

As hypotension may lead to renal impairment, 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 kidney disease. LY3305677 may cause severe GI AEs, such as nausea, vomiting, and diarrhea, consistent with other GLP-1R agonists (Aroda and Ratner 2011). These events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. To date no cases have been observed related to acute renal failure.

Participants should notify investigators in case of severe nausea, frequent vomiting or diarrhea, or symptoms of dehydration.

8.3.3.3. Skin Burning Sensation and Related Adverse Events

If skin burning sensation and related AEs, for example, hyperesthesia and sensitive skin, are reported, it should be recorded as an AE and a skin assessment CRF should be used to capture additional information about these events.

See Section 8.3.5 for Safety Topic for Monitoring.

8.3.4. Incident Diabetes

Participants may be diagnosed with T2DM in a healthcare setting during the time of their participation in the study. This will be recorded as an AE. Newly added pharmacologic treatments will be recorded as new concomitant medications. Data collected within the course of the study (scheduled HbA1c measurements, concomitant medication records) will be used to provide confirmatory evidence of the diabetes diagnosis but failure to confirm in this way is not required to record the diabetes diagnosis event.

8.3.5. Safety Topics for Monitoring

The following safety topics of interest are specific to OXA1:

These are safety topics of interest that may be anticipated based on published information, potential findings based on drug class even if not observed with the specific investigational molecule (LY3305677), preclinical results, or early clinical results. They can also be events that regulatory bodies recommend be monitored. Such topics would not be recorded as notable, unless fitting one of the notable criteria as defined by the ICH Guidance (E3) on “Structure and Content of Clinical Study Reports”: deaths, SAEs, and AEs leading to permanent discontinuation of the investigational drug.

Based on this definition, safety topics for monitoring include the following:

- Hypoglycemia
- Severe/serious gastrointestinal adverse reactions
- Acute kidney injury
- Pancreatitis events (will be adjudicated by CEC)
- Hepatic disorders
- Biliary disorders
- MACE3 (MI, stroke, CV death) (will be adjudicated by CEC)
- Supraventricular arrhythmias and cardiac conduction disorders
- Malignancies (including medullary and papillary thyroid carcinoma)
- Major depressive disorder/suicidal ideation or behavior
- Abuse/liability potential
- Hypotension and related neurological signs and symptoms
- Hypersensitivity reactions, and
- Injection site reactions.

See Section 8.2.12 for any additional samples and data collections when certain AEs occur.

The details of analysis will be provided in the statistical analysis plan (SAP).

8.4. Pharmacokinetics

See the OXA1 (Section 1.3) for the visits and times of PK sample collection.

The actual date and time (24-hour clock time) of every dose and sample collection must be recorded accurately on the appropriate forms.

Plasma samples will be collected for measurement of plasma concentrations of LY3305677 as specified in the SoA.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data (for example, to obtain data closer to the time of peak plasma concentrations) to ensure appropriate monitoring.

Instructions for the collection and handling of biological samples will be provided by the sponsor.

Samples will be used to evaluate the PK of LY3305677. Samples collected for analyses of LY3305677 plasma concentration may also be used to evaluate safety or efficacy aspects related to concerns arising during or after the study.

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

8.4.1. Bioanalysis

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

Concentrations of LY3305677 will be assayed using a validated liquid chromatography mass spectrometry method. Analyses of samples collected during placebo treatment are not planned.

Bioanalytical samples collected to measure LY3305677 concentrations will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, or bioanalytical method cross-validation.

8.5. Pharmacodynamics

Pharmacodynamic assessments are evaluated as part of the efficacy measures (Section 8.1) and biomarkers (Section 8.7) in this study and will be collected in accordance with the SoA (Section 1.3).

8.6. Genetics

Whole-blood samples will be collected from participants to enable DNA isolation for exploratory pharmacogenetic and/or epigenetic analyses as specified in the SoA (Section 1.3), where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic or epigenetic research either now or in the future. Samples may be used to investigate variable exposure or response to LY3305677 or to investigate genetic variants or epigenetic modifications thought to

play a role in obesity, diabetes mellitus, or related traits or complications including nonalcoholic steatohepatitis. Assessment of variable response may include evaluation of AEs or differences in pharmacodynamic, mechanistic, safety, or efficacy measures.

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

Samples will be retained for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or the Ethical Review Board impose shorter time limits, at a facility selected by Lilly or its designee. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3305677 or after LY3305677 is commercially available.

Molecular technologies are expected to improve during the 15-year storage period and therefore cannot be specifically named. However, existing approaches include whole-genome or exome sequencing, genome-wide association studies, multiplex assays, epigenetic assays, and candidate gene studies. Regardless of technology utilized, data generated will be used only for the specific research scope described in this section.

See CWMM master protocol, Section 10.5 for information regarding genetic research and CWMM master protocol, Section 10.1.12 for details about sample retention and custody.

8.7. Biomarkers

In addition to the planned biomarker research as indicated in the SoA and Sections 8.1 and 10.5, biomarker research on stored nonpharmacogenetic samples may be performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of participant response (including safety) and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules, including, proteins, lipids, and other cellular elements.

Serum and plasma samples for nonpharmacogenetic biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow.

Samples will be used for research on the drug targets, disease process, variable response to LY3305677, pathways associated with obesity, diabetes mellitus, related clinical traits or complications including nonalcoholic steatohepatitis, mechanism of action of LY3305677, and/or research methods, or for validating diagnostic tools or assay(s) related to obesity, diabetes mellitus, related traits or complications.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and ethical review boards (ERBs) impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of LY3305677 or after LY3305677 becomes commercially available.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected and stored for future analysis to determine antibody production against LY3305677. Antibodies may be further characterized for cross-reactive binding to oxyntomodulin and/or their ability to neutralize the activity of the LY3305677 (Section 9.3.6.6).

To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of LY3305677. All samples for immunogenicity should be taken predose when applicable and possible.

If the immunogenicity sample at the last scheduled assessment or discontinuation visit indicates TE ADA, additional samples may be taken until the signal returns to baseline, that is, no longer indicates TE ADA, or for up to 1 year after last dose.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3305677 at a laboratory approved by the sponsor. Samples may be stored for a maximum of 15 years (or according to local regulations). Samples may also be used for development and control of an immunogenicity assay.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP for OXA1 will be finalized prior to the first unblinding. The OXA1 SAP 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 most important endpoints, including primary and key secondary endpoints.

The LY3305677 ISA-specific components related to objectives, endpoints, and estimands are included below:

- Primary analysis time point occurs at Week 32
- Intervention is LY3305677
- Control is placebo

9.1. Statistical Hypotheses

The primary objective is to demonstrate that LY3305677 3 mg, 10 mg, or 16 mg QW administered subcutaneously is superior to placebo with regard to percent change in body weight from baseline to primary time point, in participants with obesity, or overweight plus weight-related comorbidities. Thus, the null hypotheses to be tested in relation to the primary objective are as follows:

- H_{30}: QW LY3305677 3 mg is not different from placebo with respect to percent change in body weight from baseline at Week 32.
- $H_{10,0}$: QW LY3305677 10 mg is not different from placebo with respect percent change in body weight from baseline at Week 32.
- $H_{16,0}$: QW LY3305677 16 mg is not different from placebo with percent change in body weight from baseline at Week 32.

9.2. Analyses Sets

The analysis sets are defined in Section 9.2 of the CWMM master protocol.

9.3. Statistical Analyses

The following subsections are to be read as supplement to the statistical considerations specified in Section 9 of the CWMM master protocol.

9.3.1. General Considerations

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

See the CWMM master protocol (Section 9.3.1) for primary and secondary estimands as well as primary and secondary endpoint analyses.

Additional considerations specific to OXA1 include the following:

- Secondary endpoint analyses for TE ADA, PK of the primary intervention, and LFC.

- Exploratory endpoint analyses for patient-reported outcomes, glucose regulation, biomarkers, dose/exposure-response relationships with safety and efficacy, body composition, and LFC.

Any change to the data analysis method described in OXA1 will require an amendment to this protocol only if it changes a principal feature of OXA1. Any other change to the data analysis methods described in the ISA, and the justification for making the change, will be described in the SAP and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

See the CWMM master protocol (Section 9.3.2) for an outline of the primary endpoint analyses. Details of the analyses will be provided in the OXA1 SAP.

9.3.3. Secondary Endpoint(s) Analysis

The following secondary analyses are to be read as supplementary to those outlined in the CWMM master protocol. Details of the analyses will be provided in the OXA1 SAP.

Refer to Evaluation of Immunogenicity (Section 9.3.6.6) for an outline of TE ADA analysis.

9.3.4. Exploratory Endpoint(s) Analysis

Details of the analyses will be provided in the OXA1 SAP.

9.3.5. Safety Analyses

See CWMM master protocol, Section 9.3.5 for a description of safety analyses.

9.3.5.1. Central Laboratory Measures, Vitals, and Electrocardiograms

See the CWMM master protocol for a description of central laboratory measures, vitals, and ECG data analysis.

9.3.5.2. Analysis of C-SSRS Data

See the CWMM master protocol for a description of C-SSRS data analysis.

9.3.6. Other Analyses

9.3.6.1. Participant Disposition

See the CWMM master protocol for a description of participant disposition analyses.

9.3.6.2. Participant Characteristics

See the CWMM master protocol for a list of participant characteristics to be summarized for OXA1.

9.3.6.3. Concomitant Therapy

See the CWMM master protocol for a description of concomitant therapy data summary for OXA1.

9.3.6.4. Treatment Compliance

Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment group and dose escalation subgroup using the full analysis set. Detailed analyses are described in the SAP.

9.3.6.5. Pharmacokinetic/Pharmacodynamic Analyses

LY3305677 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. The relationships between LY3305677 dose and/or concentration and selected efficacy, tolerability, and safety endpoints will be characterized, where applicable.

Additionally, the impact of intrinsic and extrinsic participant factors such as age, weight, gender, and renal function on PK and/or PD parameters may be examined as needed. If antidrug antibody titers are detected from immunogenicity testing, then the impact of immunogenicity on LY3305677 PK or any relevant PD parameters may also be evaluated via PK/PD analysis or graphically. Additional analyses may also be conducted if they are deemed appropriate. Further details on PK and PK/PD analyses will be provided in the PK/PD analysis plan.

9.3.6.6. Evaluation of Immunogenicity

Upon assay validation, the frequency and percentage of participants with preexisting ADA and with TE ADA may be tabulated. TE ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution, if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared with baseline, if ADAs were detected at baseline (treatment-boosted ADA).

The frequency of cross-reactive binding to endogenous oxyntomodulin and/or neutralizing antibodies may also be tabulated in TE-ADA+ participants, when available.

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

9.4. Interim Analysis

An interim efficacy and safety assessment may occur after 100% of participants complete either Visit 20 (Week 20) or Visit 24 (Week 24) of the treatment period to support planning activities associated with the clinical development program and to aid in the development of PK/PD modeling. An internal assessment committee (IAC) will be formed to review the interim analyses for the safety and efficacy reports in an unblinded manner.

Additional interim analyses may be conducted to monitor safety of study participants. Details on the exact timing of the interim analyses, operational support, and unblinding will be specified in the assessment committee (AC) charter and in the study unblinding plan.

If there are unplanned interim analyses, an IAC will be formed to review the interim analyses in an unblinded manner. The details regarding number of committee members and type(s) of analysis to be undertaken will be provided in the AC charter.

Study team members who have potential contact with the sites will remain blinded throughout the study. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded. Study sites will receive information about interim results only if deemed necessary for the safety of the participants.

The primary database lock and primary data analysis for OXA1 will occur when all participants have completed 32 weeks of treatment. The final database lock and final analyses for this study will be performed after all randomly assigned participants have completed the study. Unblinded data and results (including primary study results at 32 weeks) will not be shared with the study sites to maintain blinding at the sites while the study is still ongoing. Details will be specified in the unified master blinding/unblinding plan and in the AC charter.

Early access to the PK and PD data for OXA1 before the primary database lock may be conducted to allow population PK/PD analysis and model development. If applicable, this early access will be detailed in the Unblinding Plan and the Population PK/PD Analysis Plan.

9.5. Sample Size Determination

Approximately 165 participants will be randomly assigned in a 3:2:3:3 ratio with

- 45 participants allocated to placebo
- 30 to LY3305677 3/6 mg
- 45 to LY3305677 10 mg, and
- 45 to LY3305677 16 mg.

Assuming a 20% dropout rate, this results in approximately 132 total completers with 24 completers on the LY3305677 3/6 mg arm and 36 completers for the placebo, each of 10 mg and 16 mg LY3305677 arms.

An upper limit of 60% enrollment of women will be used to ensure a sufficiently large sample of men.

Sample size determination is based on the evaluation of superiority to placebo that will be conducted for each of the 3 LY3305677 doses at a 2-sided significance level of 0.05 using a 2-sample t-test.

The LY3305677 group mean percentage change in body weight from baseline at Week 32 compared to placebo is assumed to be -8% assuming a common SD of 10%.

The chosen sample size provides at least 91% power to establish superiority of at least one of the LY3305677 doses compared to placebo. No adjustment for multiplicity will be performed.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Committees Structure

10.1.1.1. Internal Assessment Committee

See CWMM master protocol, Section 10.1.5 for information on the IAC.

See Section 9.4 of OXA1 for information on efficacy interim analyses and the IAC.

10.1.1.2. Clinical Endpoint Committee

An independent, blinded CEC with membership external to the sponsor will be responsible for case adjudication in a blinded fashion.

The independent CEC will adjudicate cases noted in Section 8.3.5. The CEC charter will contain the final detailed event definitions used for adjudication.

10.2. Appendix 2: Clinical Laboratory Tests

The CWMM master protocol Sections 1.3 (SoA), 10.2 (Clinical Laboratory Tests), and 10.13 (Requirements for ISA Design) describe laboratory tests that will be performed as noted in the OXA1 SoA (Section 1.3).

This table describes tests unique to OXA1.

10.2.1. Clinical Laboratory Tests

Clinical Laboratory Tests	Comments
Hormones	
Insulin	Results will not be provided to the investigative sites
Hormones (female)	
Urine pregnancy	Evaluated locally
Calculations	Generated by Lilly-designated laboratory
Pharmacokinetics	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
PK samples – LY3305677 concentration	
Biomarkers	Assayed by Lilly-designated laboratory.
Longitudinal biomarkers	Results will not be provided to the investigative sites. See Section 10.5 (Mechanistic Biomarkers) for specific laboratory tests.
Beta-hydroxybutyrate	Results will not be provided to the investigative sites. See Section 10.5 (Mechanistic Biomarkers) for further details.
Endpoint biomarkers	Results will not be provided to the investigative sites. See Section 10.5 (Mechanistic Biomarkers) for specific laboratory tests.
C-Reactive Protein, high-sensitivity	Results will not be provided to the investigative sites.
Genetics	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Genetic sample	
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Exploratory samples:	
Serum	
Plasma (EDTA)	
LTS P800	
Whole blood (EDTA)	

Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Anti-LY3305677 antibodies (ADA)	

Abbreviation: EDTA = ethylenediaminetetraacetic acid.

10.2.2. Laboratory Samples to be Obtained at Time of Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory tests results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

Timing	Laboratory Test [a]
Collect from 30 minutes to 4 hours after the start of the event. ● Note: The optimal collection time is from 1 to 2 hours after the start of event.	total tryptase
Collect only if not already collected on the same day as the event. ● Note: If collecting, collect up to 12 hours after the start of the event.	LY3305677 antidrug antibodies (ADAs) LY3305677 concentration

Abbreviation: ADA = anti-drug antibody.

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified time period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.3. Appendix 3: Contraceptive and Barrier Guidance

10.3.1. Definitions

Postmenopausal state is defined in CWMM master protocol, Section 10.4.1. Definitions of child-bearing potential are provided in this table.

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.

10.3.2. Contraception Guidance for Females Participating in OXA1

Guidance for Women of Childbearing Potential

Women of childbearing potential (WOCBP) who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males, and not plan a pregnancy during the study	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or
	• use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle must do the following:

Topic	Condition
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least 75 days (equivalent to 5 half-lives plus 30 days) after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization[a] (including fallopian tube ligation, and hysteroscopic sterilization) • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices
Effective contraception	• male or female condoms with spermicide • diaphragms with spermicide or cervical sponges • barrier method with use of a spermicide ○ condom with spermicide

	○ diaphragm with spermicide, or ○ female condom with spermicide Note: Male and female condoms should not be used in combination.
Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

[a] Hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, and bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a woman not of childbearing potential.

10.3.3. Contraception Guidance for Males Participating in OXA1

10.3.3.1. Guidance for All Male Participants

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 135 days (equivalent to 5 half-lives plus 90 days) after last dose of the study intervention.
Men with partner(s) who are WOCBP	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms with spermicide and use at least 1 additional highly effective method of contraception for the duration of the study and for 135 days (equivalent to 5 half-lives plus 90 days) after last dose of the study intervention.
Men with partner(s) who are pregnant	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms with spermicide for the duration of the study and for 135 days (equivalent to 5 half-lives plus 90 days) after last dose of the study intervention.
Men in exclusively same-sex relationships, as their preferred and usual lifestyle	are not required to use contraception.

Examples of highly effective, effective, and unacceptable methods of contraception can be found below.

Methods	Examples
Highly effective contraception	• female sterilization[a] (including fallopian tube ligation, hysteroscopic sterilization) • combination oral contraceptive pill and mini-pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide
	Note: Male and female condoms should not be used in combination.

Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post coital douche • lactational amenorrhea

[a] Hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, and bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a woman not of childbearing potential.

10.4. Appendix 4: Genetics

See CWMM master protocol, Section 10.5.

10.5. Appendix 5: Mechanistic Biomarkers

Mechanistic biomarkers will be measured at longitudinal intervals (longitudinal biomarkers) or less frequently to correspond with primary and secondary endpoints (endpoint biomarkers). Results will not be provided to the investigative sites. To explore potential mechanisms of action related to changes in glucose, lipid or nutrient metabolism, the following markers will be assessed:

- Biomarkers related to insulin sensitivity: fasting glucose, fasting insulin, fasting C-peptide, homeostasis model assessment of insulin resistance ([HOMA2-IR] computed with fasting glucose and fasting insulin or C-peptide), total adiponectin, total FGF21, IGFBP-2, and leptin
- Biomarkers related to pancreatic alpha- or beta-cell function: homeostasis model assessment of beta-cell function ([HOMA2-B] computed with fasting glucose and fasting insulin or C-peptide), fasting intact proinsulin, intact proinsulin/C-peptide and intact proinsulin/insulin ratios, and fasting glucagon
- Biomarkers of glucagon receptor target engagement: amino acid panels and fasting glucagon
- Biomarkers of lipid metabolism: fasting lipid panel (total cholesterol, LDL cholesterol, VLDL cholesterol, HDL cholesterol, non-HDL cholesterol, triglycerides), beta-hydroxybutyrate, and free fatty acids
- Biomarker of purine metabolism: uric acid
- Biomarkers related to liver fat, inflammation, or fibrosis: FIB-4, FLI, ELF, NIS4, ferritin, CK-18 (M30), and CK-18 (M65)
- Biomarker related to inflammation: hsCRP, and
- Biomarkers related to cardiovascular risk: ApoB, ApoC3, and ApoA1.

Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Insulin sensitivity	• Fasting glucose • Fasting insulin • Fasting C-peptide **Calculation:** HOMA2-IR (computed with fasting glucose and fasting insulin or fasting C-peptide)	Total adiponectin IGFBP-2 Leptin Total FGF21
Pancreatic alpha- or beta-cell function	• Fasting intact proinsulin • Fasting glucagon **Calculations:** • HOMA2-B (computed with fasting glucose and fasting insulin or fasting C-peptide) • intact proinsulin/C-peptide ratio • intact proinsulin/insulin ratio	

Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Glucagon receptor target engagement	• Amino acid panel[a] • Fasting glucagon	
Lipid metabolism	• Fasting lipid panel: o total cholesterol o LDL cholesterol o HDL cholesterol o non-HDL cholesterol o triglycerides o VLDL cholesterol • Beta-hydroxybutyrate [b] • Free fatty acids	
Purine metabolism	Uric acid (in chemistry panel)	
Liver fat, inflammation, or fibrosis		• Cytokeratin-18 (M30) • Cytokeratin-18 (M65) • ELF • NIS4 • ferritin **Calculations:** • Fatty liver index (FLI) • FIB-4 score
Inflammation	hsCRP	
Cardiovascular risk		• ApoB • ApoC3 • ApoA1

Abbreviations: ApoA1 = apolipoprotein A1; ApoB = apolipoprotein B; ApoC3 = apolipoprotein C3; ELF= enhanced liver fibrosis; FGF21 = fibroblast growth factor 21; FIB-4 = Fibrosis-4; FLI = fatty liver index; HDL = high-density lipoprotein; HOMA2-B = homeostasis model assessment of beta-cell function; HOMA2-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; IGFBP-2 = insulin-like growth factor binding protein-2; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.

[a] Amino acids to be analyzed include alanine, arginine, glutamine, proline, serine, threonine, lysine, asparagine, histidine, isoleucine, leucine, methionine, phenylalanine, tryptophan, and valine.

[b] Beta-hydroxybutyrate will be measured with increased frequency in conjunction with the clinical chemistry panel.

10.6. Appendix 6: Country-specific Requirements

10.6.1. Brazil

This section describes protocol changes applicable to adult participants at study sites in Brazil.

This table describes the changes and provides a rationale for the changes.

Master Protocol or ISA Section Number and Name	Description of the Change	Brief Rationale
CWMM master protocol, Section 5.2. Exclusion Criteria	Exclusion criterion #44, regarding previous clinical trial participation, has been replaced with exclusion criterion #49 in which "last 3 months" is changed to "1 year".	Resolution No. 251 (Brazil 1997). The National ERB Brazil recommends not having a participant enter a new clinical study if less than 1 year has elapsed since participation in another clinical study of an investigational drug or device unless there is a direct benefit to the research participant.
CWMM master protocol, Section 10.1.12. Appendix 1: Sample Retention	Addition specific to Brazil - biological samples will be stored for up to 10 years.	Compliance with Brazilian regulation applicable to sample storage, resolution CNS 441 (Brazil 2011).
OXA1 ISA, Section 10.4. Appendix 4: Genetics	Addition specific to Brazil. Biological samples obtained to evaluate genetic material (DNA/RNA) will follow the Brazilian laws and regulations.	Compliance with Brazilian laws and regulations (CNS 340/2004 and CNS 441/2011).
Patient Access to Project Benefits	New section specific to Brazil.	Clarifies the sponsor responsibilities to comply with Resolution CNS 466 (Brazil 2012) and RDC 38 (Brazil 2013).
OXA1 ISA, Section 11. References	Addition of Brazil-specific references.	The references are specific to the Brazil-specific requirements.

The revised text described below shows the changes applicable to adult participants at study sites in Brazil. Deletions are identified by ~~strikethrough format~~ and additions by <u>underlined text</u>.

CWMM master protocol

5.2. Exclusion Criteria

~~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.~~

<u>50. Are currently enrolled in, discontinued, or completed within a period of 1 year, before inclusion, from a clinical study involving an investigational intervention or nonapproved</u>

use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study unless there is direct benefit to the research subject. A time period of at least 5 elimination half-lives or 90 days, whichever is longer, as indicated by the protocol, must still be followed if a direct benefit to the research participant is identified.

CWMM master protocol

10.1.12. Sample Retention

In Brazil, the biological samples obtained within this study will be stored for up to 10 years, with possibility of renewal under request, followed by appropriate justification and a report with all activities developed with the biological samples (CNS 441/2011). The sample and any data generated from it can be linked back to the participant only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study intervention.

OXA1 ISA

10.4. Appendix 4: Genetics

In Brazil, the biological samples from this study used to evaluate genetic material (DNA/RNA) will follow the Brazilian laws and regulations (CNS 340/2004 and CNS 441/2011). The sample and any data generated from it can be linked back to the participant only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Patient Access to the Project Benefits

In Brazil, at the end of their participation in the study, all participants must have assured access to the best proven prophylactic, diagnostic, and therapeutic methods, which may include LY3305677, identified through the study (CNS 466/2012 and RDC 38/2013).

11. References

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 251/1997 do Conselho Nacional de Saúde/MS: Normas de Pesquisa com Novos Fármacos, Medicamentos, Vacinas e Testes Diagnósticos Envolvendo Seres Humanos.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 466/2012 do Conselho Nacional da Saúde / MS: Diretrizes e Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos. Publicado no Diário Oficial da União em 13 de junho, 2013.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 340/2004 do Conselho Nacional da Saúde/MS: Diretrizes para Análise Ética e Tramitação dos Projetos de Pesquisa da Área Temática Especial de Genética Humana.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 441/2011 do Conselho Nacional da Saúde / MS: Diretrizes para análise ética de projetos de pesquisas que envolvam armazenamento de material biológico humano ou uso de material armazenado em pesquisas anteriores.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução-RDC 38/2013 da Agência Nacional deVigilância Sanitária/MS: Aprova o regulamento para os programas de acesso expandido, usocompassivo e fornecimento de medicamento pós-estudo.

10.7. Appendix 7: Provisions for Changes in Study Conduct During Exceptional Circumstances

Section 10.12 of the CWMM master protocol, which describes provisions for changes in study conducting during exception circumstances, is applicable to OXA1.

In addition, the changes described in this appendix are applicable. These are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

See Section 10.12 of the CWMM master protocol for these topics.

- Exceptional circumstances
- Implementing changes under exceptional circumstances
- Considerations for making a change
- Informed consent

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 402 and thereafter

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

- concomitant medications
- AEs
- review diet and exercise goals
- review of study participant diary (including study intervention compliance)
- administration of PROs, and
- 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

- weight and waist measurements
- vital signs
- symptom-directed physical assessments
- ECGs
- administration of PROs
- 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.

See Section 10.12 of the CWMM master protocol for additional information on data capture, safety reporting, and return to on-site visits.

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing after agreement with the Lilly-designated medical monitor. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

See Section 10.12 of the CWMM master protocol.

Screening period guidance

See Section 10.12 of the CWMM master protocol.

Adjustments to visit windows

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 from Visit 402 through Visit 801.

Visit Number	Tolerance
Visit 402	No adjustment to the visit window described SoA
Visit 0 through Visit 10	Within 7 days before the intended date, or up to 7 days after the intended date
Visit 12 through Visit 48	Within 14 days from the intended date, or up to 14 days after the intended date (can be up to 28 days after the intended date for Visit 48)
Visit 801	Within 14 days from the intended date, or up to 14 days after the intended date

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.

Documentation

See Section 10.12 of the CWMM master protocol.

10.8. Appendix 8: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADAs	antidrug antibodies
AE	adverse event
ALT	alanine aminotransferase
ApoA1	apolipoprotein A1
ApoB	apolipoprotein B
ApoC3	apolipoprotein C3
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 labelling 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 labelling of the medicinal product, which is used as an auxiliary medicinal product
AX6	Axivity 6
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
BG	blood glucose
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 participants are aware of the treatment received.
BMI	body mass index

CHF	congestive heart failure
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.
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.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
Device deficiencies	Equivalent to product complaint
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
ED	early discontinuation
eGFR	estimated glomerular filtration rate
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.
FGF21	fibroblast growth factor 21
FIB-4	Fibrosis-4
FLI	fatty liver index
Gcg	glucagon
GCP	good clinical practice
GIP	glucose-dependent insulinotropic peptide
GIP-1	glucose-dependent insulinotropic peptide-1
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HOMA2-B	homeostasis model assessment of beta-cell function

HOMA2-IR	homeostasis model assessment of insulin resistance
hsCRP	high-sensitivity C-reactive protein
IAC	internal assessment committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IGFBP-2	insulin-like growth factor binding protein-2
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.
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/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."
IWRS	interactive web-response system
LDL	low-density lipoprotein
LFC	liver fat content
MACE3	3-point major adverse cardiovascular events: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke

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 involve a failure to uphold one or more of the five “rights” of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five 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, protocol), or • shared use of cartridges, prefilled pens, or both.
MRI	magnetic resonance imaging
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
PGIC	Patient’s Global Impression of Change
PGIS	Patient’s Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PI	principal investigator
PK/PD	pharmacokinetics/pharmacodynamics
PRO	patient-reported outcomes
PROMIS	Patient-Reported Outcome Measurement Information System
QTc	corrected QT interval
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.

SF-36	Short-Form-36
SGLT2	sodium-glucose cotransporter-2
T2DM	Type 2 diabetes mellitus
TE ADA	treatment-emergent antidrug antibodies
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
VAS	visual analog scale
VLDL	very low-density lipoprotein
WC	waist circumference

10.9. Appendix 9: Protocol Amendment History

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

Amendment [a]: 13 August 2023

Overall Rationale for the Amendment:

The main purpose of this ISA amendment is to incorporate additional measurements to better characterize the effects of LY3305677 (mazdutide) and to provide guidance on safety monitoring in response to regulatory feedback.

Changes specific to certain ISA sections and a brief rationale are provided in the below table.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	Added change in liver fat as a secondary objective and endpoint	To clarify liver fat as an important readout of this trial
1.2. Schedule of Activities (SoA) for OXA1 ISA and CWMM Master Protocol	ECG 12-lead (central) for postdose assessment added at Visit 1 and aligned in the comment. Added "hypotension" to the assessment "Explain symptoms of hypoglycemic and hypotension events" Updated urinalysis assessment to occur at the same time points as clinical chemistry testing Revised time point assessment for urine pregnancy (local) Added and increased frequency of serum beta-hydroxybutyrate as an assessment and will be assessed at the same time points as clinical chemistry testing.	To address regulatory feedback
2.3.1. Risk Assessment	Added information regarding education on signs and symptoms of low blood pressure.	To address regulatory feedback
3. Objectives, Endpoints, and Estimands	Added change in liver fat as a secondary objective and endpoint and removed it from exploratory objectives and endpoints. Revised the endpoint for body composition from • "Absolute change and percent change from baseline: liver fat content by MRI-PDFF • additional MRI-derived measures may be explored" to • "Adipose tissue volumes • Muscle volumes"	To clarify liver fat as an important readout and to provide more details on other body composition endpoints of this trial

Section # and Name	Description of Change	Brief Rationale
4.1.1. Overview of Study Periods	Removed "Lack of participation in ABPM collections at any time is not considered a protocol deviation."	To clarify protocol language and ensure sufficient participants will be enrolled for ABPM assessment
5.2. Exclusion Criteria	Removed "or willing" from participation in Ambulatory Blood Pressure Monitoring (ABPM) procedures from exclusion criteria	To clarify protocol language and ensure sufficient participants will be enrolled for ABPM assessment
6.5.3. Dose Reductions and Re-escalations	Added information for excessive body weight loss and discontinuation criterion	To ensure participant's safety
7.1. Discontinuation of Study Intervention	Added "diagnosis with multiple endocrine neoplasia type 2 syndrome" and "the participant's BMI reduces below 18 kg/m^{2}"	To ensure participant's safety
7.1.2. Cardiac Arrhythmia and QTc Stopping Criteria	Updated the section heading to include "Cardiac Arrhythmia" and added criteria leading to discontinuation of study intervention	To ensure participant's safety
8.1. Efficacy Assessments	Added "liver fat" to secondary assessments	Alignment with Section 3
8.1.3. Magnetic Resonance Imaging (MRI)	Removed the following, "After the participant has given consent, and meets all ISA eligibility requirements" "Participants that do not have a baseline MRI performed, should not have a Week 32 MRI or Week-44 MRI performed."	To clarify protocol language
8.2.12.1. Ambulatory Blood Pressure Monitoring (ABPM)	Removed "or refuses"	To clarify protocol language and ensure sufficient participants will be enrolled for ABPM assessment
8.3.3. Adverse Events of Special Interest	Added the following sections: 8.3.3.1. Hypotension and Related Neurological Signs and Symptoms 8.3.3.2. Acute Renal Failure 8.3.3.3. Skin Burning Sensation and Related Adverse Events Removed "There are no AESIs defined for LY3305677 in OXA1"	To address regulatory feedback
8.3.5. Safety Topics for Monitoring	Added "Hypotension and related neurological signs and symptoms"	To address regulatory feedback
10.2.1. Clinical Laboratory Tests	Revised the heading to remove "Performed Starting at Visit 0" Clarified measurement of beta-hydroxybutyrate	Clarification and to address regulatory feedback
10.3.2. Contraception Guidance for Females Participating in OXA1	Updated contraceptive and barrier guidance	To align with emerging information and to address regulatory feedback

Section # and Name	Description of Change	Brief Rationale
	Revised examples of different forms of contraception	
10.3.3.1. Guidance for All Male Participants	Updated contraceptive and barrier guidance Revised examples of highly effective, and effective methods of contraception	To align with emerging information and to address regulatory feedback
10.5. Appendix 5: Mechanistic Biomarkers	Added footnote b for Beta-hydroxybutyrate, which states the following: [b] Beta-hydroxybutyrate will be measured with increased frequency in conjunction with the clinical chemistry panel.	To address regulatory feedback
Throughout	Minor editorial and formatting changes	Minor, therefore, not detailed

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