This study W8M-MC-LAA1 (NCT06230523) is a sub-study of Master Protocol W8M-MC-CWMM (NCT06143956)

Protocol W8M-MC-LAA1(b)

A Phase 2, Parallel-Group, Double-Blind Study to Investigate Weight Management with LY3841136 Compared with Placebo in Adult Participants with Obesity or Overweight

NCT06230523

Approval Date: 19-Aug-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 Study to Investigate Weight Management with LY3841136 Compared with Placebo in Adult Participants with Obesity or Overweight

ISA Number: W8M-MC-LAA1

Amendment Number: b

Compound: LY3841136

ISA Brief Title:

A Study to Investigate Weight Management with LY3841136 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 Number:

IND for CWMM master protocol: 163848

Document ID: VV-CLIN-125172

Approval Date: Protocol 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	23-Apr-2024
Original Protocol	13-Nov-2023

Amendment [b]

This amendment is considered to be substantial.

Overall rationale for the amendment

The main objectives of this ISA amendment are to modify the maximum study intervention dosage from 12 mg to 9 mg, to incorporate a monthly urine pregnancy test into routine monitoring, and to clarify how treatment overdose is defined. The existing 3/6/9/12 mg and 6/12 mg escalation arms will now have a maximum dose of 9 mg (3/6/9 mg and 6/9 mg).

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	Number of Participants	
	• 6/12 mg arm revised to 6/9 mg arm	Alignment with updated dosing arms
	• 3/6/9/12 mg arm revised to 3/6/9 mg arm	Alignment with updated dosing arms
	Intervention Groups and Duration: 12 mg and associated placebo doses removed from intervention table	Alignment with updated dosing arms
1.2. Schema	Modified 6/12 mg arm to 6/9 mg arm	Alignment with updated dosing arms
	Removed 12 mg from the 3/6/9/12 mg arm at Week 20 to reflect updated 3/6/9 mg arm	Alignment with updated dosing arms
1.3. Schedule of Activities	Treatment period: Added columns to represent Weeks 28, 32, 40, and 44	To signify weeks in which monthly pregnancy testing will take place per regulatory feedback
	Visit Interval Tolerance: Added 3 to columns representing Weeks 28, 32, 40, and 44	To reflect changes in routine monitoring

Section # and Name	Description of Change	Brief Rationale
	Visit detail: Added T to columns representing Weeks 28, 32, 40, and 44	To indicate these visits may be conducted via telemedicine or telephone platforms
	Urine pregnancy test (local): Added note to indicate that monthly test results will be gathered via telemedicine or telephone visits and recorded in participant records	In alignment with regulatory feedback
	Urine pregnancy test (local): Placed Xin columns of Weeks 4, 12, 20, 28, 32, 40, and 44 to indicate 4-weekly pregnancy testing	To indicate monthly pregnancy testing per regulatory feedback
4.1. Overall Design	Removed 12 mg from dose escalation details for 6/12 mg and 3/6/9/12 mg arms to reflect new 6/9 mg and 3/6/9 mg arms	Alignment with updated dosing arms
4.2. Scientific Rationale for Study Design	Decreased uppermost dose from 12 mg to 9 mg	Alignment with updated dosing arms
4.3. Justification for Dose	• Removed 12 mg from dose details • Revised highest selected Phase 2 dose of 12 mg to 9 mg • Revised 6/12 mg and 3/6/9/12 mg arms to 6/9 mg and 3/6/9 mg arms • Removed 12 mg from dose escalation details and replaced with 9 mg • Removed 12 mg from dosing details	Alignment with updated dosing arms
6.1. Study Intervention(s) Administered	12 mg and associated placebo doses removed from intervention table	Alignment with updated dosing arms

Section # and Name	Description of Change	Brief Rationale
6.3. Assignment to Study Intervention	• Removed 12 mg from 6/12 mg arm and revised to 6/9 mg arm • Removed 12 mg from 3/6/9/12 mg arm and revised to 3/6/9 mg arm • Added details to participant allocation	Alignment with updated dosing arms
6.6.1. Temporary Interruption and Restarting of Study Intervention	Revised dose reduction and rechallenge instructions for "TEAEs related to study intervention and other TEAEs" for 6/12 mg and 3/6/9/12 mg arms to 6/9 mg and 3/6/9 mg arms	Alignment with updated dosing arms
	Revised dose reduction and rechallenge instructions for "not related to TEAEs (that is, due to a protocol deviation)" for 6/12 mg and 3/6/9/12 mg arms to 6/9 mg and 3/6/9 mg arms	Alignment with updated dosing arms
6.8. Treatment of Overdose	Revised definition of overdose	Clarification
8.2.9. Pregnancy Testing	Added details of monthly pregnancy testing	In alignment with regulatory feedback
9.1. Statistical Hypotheses	Removed 12 mg from primary hypothesis statement	Alignment with updated dosing arms
9.3.3. Primary Endpoint Analysis	Removed 12 mg from both the 6/12 mg and 3/6/9/12 mg arms at Week 20	Alignment with updated dosing arms
9.5. Sample Size Determination	• Added details about participant allocation	Clarification
	• 6/12 mg arm (25 participants) revised to 6/9 mg arm • 3/6/9/12 mg arm revised to 3/6/9 mg arm at Week 20	Alignment with updated dosing arms
10.2.2. Clinical Laboratory Tests Performed Starting at Visit 0	Added details about pregnancy testing	In alignment with regulatory feedback

Section # and Name	Description of Change	Brief Rationale
10.6.7 Sample Size	• Substudy 3/6/9/12 mg arm revised to 3/6/9 arm • Substudy 6/12 mg arm revised to 6/9 mg arm	Alignment with updated dosing arms
Throughout	Minor editorial corrections and clarifications	Clarification

Table of Contents

1. Protocol Summary

1.1. Synopsis

ISA Title:

A Phase 2, Parallel-Group, Double-Blind Study to Investigate Weight Management with LY3841136 Compared with Placebo in Adult Participants with Obesity or Overweight

ISA Brief Title:

A Study to Investigate Weight Management with LY3841136 Compared with Placebo in Adult Participants with Obesity or Overweight

Regulatory Agency Identifier Number:

IND for CWMM master protocol: 163848

Rationale:

LY3841136 is a potent, selective, long-acting amylin receptor agonist (LAARA) being evaluated as a once-weekly treatment for chronic weight management. The current study is the first Phase 2 trial testing LY3841136, aimed at evaluating safety and efficacy across a wide dose range in the target population. This study will inform the further clinical development of LY3841136.

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.

Study LAA1 includes the following LY3841136-specific features:

- Primary analysis endpoint occurs at Week 48
- Primary intervention is LY3841136
- Primary control is placebo

In addition to the objectives and endpoints stated in the CWMM master protocol, objectives, and their respective endpoints specific for Study LAA1 are listed in this table. Exploratory objectives are listed in the main body of Study LAA1.

Objectives	Endpoints
Secondary (in addition to secondary objectives listed in the CWMM master protocol)	
To characterize the pharmacokinetics (PK) of LY3841136	PK parameters AUC and C_{max}

Abbreviations: AUC = area under the curve; Cmax = maximum serum concentration.

Overall Design:

Study LAA1 is a Phase 2, parallel-group, double-blind study to investigate weight management with LY3841136 subcutaneously administered once weekly compared with placebo.

The study consists of a 6-week screening period (V401 to V0), a 48-week treatment period, and a posttreatment follow-up period of approximately 10 weeks after the last visit in the treatment period. Dose escalation will occur in 2 treatment groups by increasing the volume of administered study intervention (or placebo) at Week 20.

The primary endpoint will be at Week 48.

Brief Summary:

The purpose of this study is to measure weight loss with LY3841136 administered subcutaneously once weekly compared with placebo in participants with obesity or overweight.

Study details include:

- The total study duration will be up to approximately 64 weeks including the screening/lead-in, treatment, and posttreatment follow-up periods.
- The treatment duration will be approximately 48 weeks.
- Dose escalation arm up to Week 8
- The visit frequency will be
  - weekly - Visit 0 to Visit 2 (Visit 2 may be a telephone visit)
  - every 4 weeks - Visit 4 to Visit 24, and
  - every 12 weeks - Visit 24 to Visit 48.

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 any form of diabetes mellitus except for a prior diagnosis of gestational diabetes mellitus.

Number of Participants:

The study sample size approximately of 250 participants will be randomly assigned to placebo (approximately 50 participants), 1 mg LY3841136 (approximately 25 participants), 3 mg LY3841136 (approximately 25 participants), 6 mg LY3841136 (approximately 25 participants), 9 mg LY3841136 (approximately 50 participants), 6/9 mg LY3841136 (approximately 25 participants), or 3/6/9 mg LY3841136 (approximately 50 participants). To achieve this approximate allocation per arm, participants enrolling under protocol amendment (a) will be randomized in a ratio of 2:1:1:1:2:3:2 to placebo, 1 mg, 3mg, 6 mg, 9 mg, 6/9 mg, or 3/6/9 mg

Approximately 70% enrollment of females will be used to ensure a sufficiently large sample of males.

Sample size selection is guided by the objective of establishing superiority of each LY3841136 dose to placebo relative to the percent change from baseline in body weight at Week 48. Assuming a difference of 7.8% between the LY3841136 and placebo group means of percent change from baseline in body weight, and a standard deviation of 10%, a sample size of 50/arm

enrolled in the 3/6/9 mg and 9 mg LY3841136 arms provides over 90% power, and 25/arm enrolled in the 1 mg, 3 mg, 6 mg, and 6/9 mg LY3841136 arms will provide over 80% power using 2-sample t-test at a 2-sided significance level of 0.05

Intervention Groups and Duration:

This study includes a 6-week screening/lead-in period, a 48-week, double-blind treatment period, and a 10-week posttreatment follow-up period.

Participants will self-administer study intervention subcutaneously once weekly.

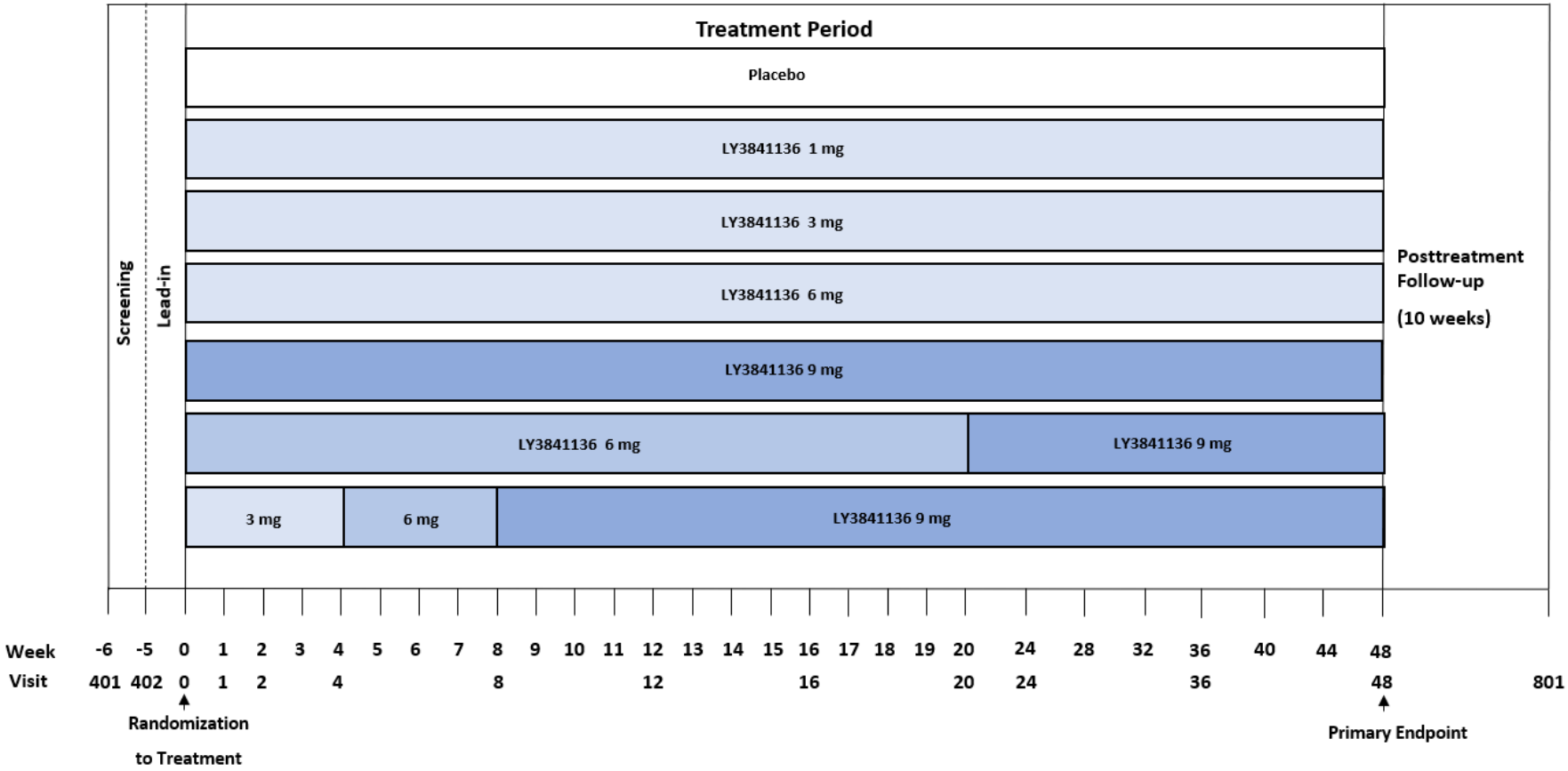
Intervention Name	**LY3841136**	**LY3841136 Placebo**
Dosage Level(s)	1 mg (0.1 mL) 3 mg (0.3mL) 6 mg (0.6mL) 9 mg (0.9 mL)	placebo (0.1 mL) placebo (0.3 mL) placebo (0.6 mL) placebo (0.9 mL)
Route of Administration	Subcutaneous using a syringe	Subcutaneous using a syringe
Frequency of Administration	Once weekly	Once weekly

Ethical Considerations of Benefit/Risk:

The potential benefits from participation in this study, which include frequent expert medical care for up to 48 weeks and the chance for achieving body weight reduction, are expected to outweigh the anticipated risks, which will be closely monitored and managed through the established procedures.

Data Monitoring Committee: Not applicable.

1.2. Schema


Treatment Period
Placebo
LY3841136 1 mg
LY3841136 3 mg
LY3841136 6 mg
LY3841136 9 mg
LY3841136 6 mg
LY3841136 9 mg
3 mg
6 mg
LY3841136 9 mg
Screening
Lead-in
Posttreatment Follow-up
(10 weeks)
Week -6 -5 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 24 28 32 36 40 44 48
Visit 401 402 0 1 2 4 8 12 16 20 24 36 48 801
Randomization to Treatment
Primary Endpoint

1.3. Schedule of Activities (SoA)

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-LAA1 (LAA1) for the primary intervention, LY3841136. Please refer to the CWMM master protocol SoA (Section 1.3) for information pertaining to screening (Visit 401).

Visit 402
Visit 402 may be used to accomplish Study LAA1-specific activities (such as dual-energy x-ray absorptiometry and qualitative interview activities) 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 the Study LAA1 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 10 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, the participant should return in a fasting state for sample collection within the visit interval tolerance specified in the SoA. A participant who attends Visits 8 or 16 in a non-fasting state does not need return in a fasted state.

Telephone/Telemedicine visits

Visit 2 may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit 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	

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X			X			X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3 of the CWMM master protocol. Additional data are collected for certain AEs.
Physical Evaluation																				
Weight		X	X	X	X	X	X	X	X	X			X			X		X	X	At Visit 1 and 2, weight will be measured in a non-fasting state. If the participant joins via telephone or

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																				telemedicine, weight is not required.
Waist circumference		X			X	X	X	X	X	X			X			X		X	X	Waist circumference should be obtained per guidance in the CWMM master protocol, Section 10.8.
Symptom-directed physical assessment			X		X	X	X	X	X	X			X			X	X	X	X	Symptom-directed physical assessment may be conducted during Visits 4-48, ED, and 801 at the discretion of the PI or qualified personnel as indicated per local regulations based on

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																				participant status and standard of care.
Vital signs (includes 3 measurements for blood pressure)		X	X		X	X	X	X	X	X			X			X		X	X	Includes pulse rate, (orthostatic - supine and standing) blood pressure measured in triplicate after participant has been sitting at least 5 minutes. See Section 10.8 of the CWMM master protocol.
ECG 12-lead (triplicate) (central)		X			X					X						X		X	X	Collect ECG within 30 minutes before blood samples for laboratory testing. ECG may be

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																				repeated at the investigator's discretion at any visit. See Section 8.2.3 of the CWMM master protocol.
Substudies																				
DXA informed consent	X																			DXA ICF must be signed before the DXA procedure is performed
DXA for body composition	X									X						X		X		Approximately 144 participants sub study. See Section 10.6.
Qualitative interview informed consent	X																			Qualitative Interview ICF must be signed before the

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																				interview is performed
Qualitative interview	X			X												X				Qualitative interview study of approximately 100 participants. See Section 10.7.
Actigraphy																				
Dispense actigraphy device (AX6)	X								X				X							See Section 4.1.1.
Remind participant to wear actigraphy device (AX6)	X								X				X							The AX6 is to be worn continuously for 2 weeks during study Visits 402 to 0, Weeks 22 to 24,

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																				and Weeks 46 to 48. See Section 4.1.1.
Participant returns actigraphy device (AX6)		X								X						X				See Section 4.1.1.
Participant Diary																				
Dispense diary	X																			Electronic
Diary review			X		X	X	X	X	X	X			X			X		X		
Diary return																X		X		
Clinician-administered																				

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Assessments (Paper)																				
C-SSRS Since Last Assessed (category version)		X	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.
Patient-reported Outcomes (Electronic)																				Complete prior to any clinician-administered assessments.
Patient Health Questionnaire-9 (PHQ-9)		X	X	X	X	X	X	X	X	X			X			X	X	X	X	
SF-36 v2 Acute Form		X								X						X		X		

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Control of Eating Questionnaire		X								X						X		X		
Fact GP5		X								X						X		X		
PGIS - Physical Function due to Weight		X								X						X		X		
PGIC - Physical Function due to Weight										X						X		X		
PGIS - Food Craving		X								X						X		X		
PGIC - Food Craving										X						X		X		

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Patient Assessment of GI Symptoms		X								X						X		X		
Participant Education																				
Review preparation of injection and injection technique		X	X		X	X	X	X	X	X			X				X			
Explain diet and physical activity plan	X	X																		
Explain symptoms of hypoglycemic events	X																			

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Review diet and physical activity goals					X	X	X	X	X	X			X			X				
Laboratory Tests and Sample Collections																				
Hematology		X			X		X			X			X			X		X	X	
Clinical chemistry		X			X		X		X	X			X			X		X	X	

Urine Pregnancy test (local)		X			X	X	X	X	X	X	X	X	X	X	X	X		X		The result must be available before the first dose of study intervention for WOCBP. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation. Monthly test information will be gathered through encounters conducted via telephone, telemedicine, or both platforms, and recorded in participant records. See Section 8.2.9.
Urinalysis		X					X			X			X			X		X		
Pancreatic amylase		X					X			X			X			X		X	X	
Lipase		X					X			X			X			X		X	X	
Hemoglobin A1c (HbA1c)		X					X			X			X			X		X	X	
Cystatin-C		X					X			X			X			X		X	X	
eGFR (CKD-EPI) calculated using cystatin-C		X					X			X			X			X		X	X	

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Urinary albumin/creatinine ratio (UACR)		X					X			X			X			X		X	X	
Pharmacokinetics (PK) Samples																				
Pharmacokinetic (PK) samples - random																X		X	X	At any time during visit.
Pharmacokinetic (PK) samples - predose		X			X	X	X			X			X							
Pharmacokinetic (PK) samples – postdose (2 to 6 hours)		X								X										At 2 to 6 hours postdose for V0 and V24.

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Pharmacokinetic (PK) samples – postdose (24 to 72 hours)							X													Participant will need to return 24 to 72 hours postdose for V12.
Immunogenicity		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 8.2.12.4. Immunogenicity samples and PK samples for immunogenicity

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
																				must be taken prior to drug administration.
Endpoint biomarkers		X								X			X			X		X	X	
Longitudinal biomarkers		X					X		X	X			X			X		X	X	
Stored Samples																				
Genetics sample		X																		Sample can be obtained at or after the specified visit.
Exploratory biomarker		X					X		X	X			X			X		X		
Epigenetic sample		X														X				

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Randomization and Dosing																				
Register visit with IWRS	X	X	X		X	X	X	X	X	X			X			X		X	X	
Randomization via IWRS		X																		
Dispense study intervention via IWRS		X	X		X	X	X	X	X	X			X							
Observe participant administer study intervention		X	X		X	X	X	X	X	X			X							
Dispense ancillary supplies to participant		X	X		X	X	X	X	X	X			X							

		Treatment Period																	Post Tx Follow-up	Comments
CRF Visit Number	**402**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**UnSch 997**	**ED**	**801**	
Weeks	**-5 to 0**	**0**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**			**58**	
Visit Interval Tolerance (+/- days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**		**T**	**F**	**F**	**F**	**F**	**F**	**F**	**T**	**T**	**F**	**T**	**T**	**F**		**F**	**F**	F = Fasting visit T = The specified visits may occur remotely via telephone and/or telemedicine. An onsite visit is also acceptable.
Participant returns unused study intervention and ancillary supplies					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		

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; DXA = dual-energy x-ray absorptiometry; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; FACT GP5 = Functional assessment of Chronic Illness Therapy - Item GP5; GI = gastrointestinal; IWRS = interactive web-response system; LAARA= long-acting amylin receptor agonist; NRS = numeric rating scale; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of Severity; PI = principal investigator; SF-36v2 = short-form 36 version 2; Tx = treatment; UnSch = unscheduled visit; V = visit; WOCBP = women of childbearing potential.

2. Introduction

2.1. Study Rationale

LY3841136 is a potent, selective, LAARA being evaluated as a once-weekly treatment for chronic weight management. The current study is the first Phase 2 trial testing LY3841136, aimed at evaluating safety and efficacy across a wide dose range in the target population. This study will inform the further clinical development of LY3841136.

2.2. Background

Amylin is a 37-residue peptide hormone that is co-secreted with insulin from pancreatic β-cells in the ratio of approximately 100:1 (insulin:amylin). Amylin is involved in the regulation of both energy and glucose metabolism. It slows gastric emptying and promotes satiety (mediated by the area postrema in the brainstem, a central effect), but also complements insulin by suppressing postprandial glucagon secretion (in hyperglycemic state). Amylin thereby reduces food intake and lowers body weight, as well as prevents postprandial spikes in blood glucose.

Clinical validation for targeting the amylin receptor for obesity is demonstrated by pramlintide (Symlin®, AC0137), a short-acting amylin agonist dosed twice daily (360 µg BID dose in participants with type 2 diabetes), that elicited placebo-corrected weight loss of 3.3 kg and 7.2 kg at 4 and 12 months, respectively (Smith et al. 2008).

LY3841136 is a potent and selective long-acting amylin receptor agonist that maintains the pharmacology of pramlintide while overcoming shortcomings such as short plasma half-life and instability at neutral pH formulation. LY3841136 has been evaluated in the ongoing Study YDAA in single ascending and multiple ascending dose cohorts. Preliminary observations motivate further evaluation of LY3841136 to better understand the balance of tolerability and efficacy as a potential treatment for chronic weight management.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3841136 may be found in the IB.

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.

Study LAA1 includes the following LY3841136-specific features:

- Primary analysis endpoint occurs at Week 48
- Primary Intervention is LY3841136
- Primary Control is placebo

As specified in the CWMM master protocol, the Study LAA1 treatment period is 48 weeks in duration, and the primary endpoint will be 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 Study LAA1 are listed in this table.

Objectives	Endpoints
Secondary (in addition to secondary objectives listed in the CWMM master protocol)	
To characterize the pharmacokinetics (PK) of LY3841136	PK parameters AUC and C_{max}
Exploratory (in addition to exploratory objectives listed in the CWMM master protocol)	
To evaluate the development of treatment-emergent antidrug antibodies to LY3841136	Treatment-emergent antidrug antibodies
To compare the effect of LY3841136 versus placebo on change in physical activity from baseline to Weeks 24 and 48	Change from baseline in physical activity measured by: • Daily step 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 LY3841136 versus placebo on health-related quality of life, function, and appetite	Change from baseline in: • SF-36 v2 acute form domain and summary scores • CoEQ scores • Fact GP5 score • PGIS - Physical Function due to Weight • PGIC - Physical Function due to Weight

	• PGIS - Food Craving • PGIC - Food Craving • Patient assessment of GI symptoms
To compare the effect of LY3841136 versus placebo on blood glucose regulation from baseline to Week 48	Change from baseline in: • Fasting insulin • Fasting glucose • HbA1c • HOMA2-IR • HOMA2-B
To compare the effect of LY3841136 versus placebo on mechanistic biomarkers at longitudinal time points from baseline to Week 48	Change from baseline in longitudinal and endpoint biomarkers
To assess the relationships between LY3841136 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

Abbreviations: AUC = area under the curve; C_{max} = maximum serum concentration; CoEQ = The Control of Eating Questionnaire; FACT GP5 = Functional assessment of Chronic Illness Therapy - Item GP5; HbA1c = hemoglobin A1c; HOMA2-B = homeostasis model of beta-cell function; HOMA2-IR = homeostasis model assessment of insulin resistance; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of Severity; SF-36 v2 = Short-form 36 version 2.

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 LY3841136 and placebo.

4. Study Design

4.1. Overall Design

Study LAA1 is a Phase 2, parallel-group, double-blind study to investigate weight management with LY3841136 subcutaneously administered once weekly compared with placebo. Dose escalation to improve GI tolerability will occur in 2 treatment groups by increasing the dose of study intervention. The first escalation treatment group will begin with 6 mg. The second dose escalation group will begin with 3 mg and escalate every 4 weeks to reach 9 mg LY3841136 (or placebo) at Week 8. At Week 20, participants may escalate to 9mg in the 6/9 mg arm and in the 3/6/9 mg arm based on the results of safety data reviews in advance of the first participant reaching Week 20. If it is decided to not escalate participants to 9mg, the participants will not escalate beyond 3 mg and 6 mg, respectively.

For convenience, the functional combination of the CWMM master protocol plus the Study LAA1 ISA will be simply described as “the study”.

The study consists of a 6-week screening period (V401 to V0), a 48-week treatment period, and a posttreatment follow-up period of approximately 10 weeks after the last visit in the treatment period.

The primary endpoint will be at Week 48.

The study schema is presented in Section 1.2.

4.1.1. Overview of Study Periods

Screening period

The screening period consists of Visit 401 (screening) and Visit 402 and is split across the CWMM master protocol and Study LAA1; Visit 401 occurs as part of the CWMM master protocol and Visit 402 occurs as part of Study LAA1. Signing ICFs, completing screening procedures, and randomization to the ISA all take place during Visit 401.

Visit 402 will be used to complete any Study LAA1-specific baseline procedures including baseline procedures for Study LAA1 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 Study LAA1 occurs during the CWMM master protocol Visit 401 and is described in the CWMM master protocol Sections 1.3 (SoA) and 4.1.

Participants who successfully pass screening procedures and are assigned to participate in Study LAA1 will proceed with Visit 402 as detailed below.

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

Visit 402 (Start of Study LAA1 procedures)

Prior to Visit 402, all screening results, including laboratory results, will be reviewed to confirm participant eligibility for the CWMM master protocol and Study LAA1.

Participants will sign the Qualitative Interview and DXA ICFs and 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 the CWMM master protocol).

Participants will be registered in IWRS.

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 additional information on actigraphy.

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 Study LAA1, will perform all required study procedures prior to randomization to a treatment arm (see SoA).

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

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

- SF-36 v2 acute form
- Control of Eating Questionnaire - NRS
- Fact GP5
- PGIS - Physical Function due to Weight
- PGIC - Physical Function due to Weight
- PGIS - Food Craving
- PGIC - Food Craving
- Patient assessment of GI symptoms

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 randomly assigned treatment group for the duration of the 48-week treatment period (primary endpoint at 48 weeks) as per the SoA (Section 1.3).

Following randomization, study site personnel will discuss the treatment volume with the participant. Site personnel should 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 LY3841136 (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 LY3841136 or matching placebo.

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

Study intervention dosing

Injections of the study intervention on study visit days should only occur after all other site procedures have been completed.

After the initial study visits to acquaint participants with dilution and self-administration of LY3841136, visits are every week from Visits 0 to 2 and 2 weeks until Visit 4. After Visit 4, visits are every 4 weeks.

Site personnel should observe the participant to check that the participant is correctly injecting LY3841136 (or matching placebo). Sites may have participants return to the site for unscheduled visits to assist participants with study intervention injections as needed.

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

Actigraphy

At Visits 20 and 36, the AX6 device will be dispensed to participants. Participants will wear the device continuously for at least 2 weeks (Weeks 22 to 24 and Weeks 46 to 48). The device will be returned to site at the next visit (Weeks 24 and 48).

See Section 8.1.2 for addition information on actigraphy.

Patient-reported outcomes

The mental health questionnaires (PHQ-9 and C-SSRS) should be completed after the assessment for AEs. Patient-reported outcomes questionnaires should be administered according to the SoA.

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 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 at the time of a scheduled visit, perform that visit 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 or Visit 801.

Posttreatment follow-up period

Visit 801

Visit 801, a posttreatment follow-up visit, will occur approximately 10 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

Study LAA1 is a Phase 2 study designed to examine the body weight-lowering efficacy and safety of LY3841136 QW (planned dose range: 1 mg to 9 mg) compared with placebo during the 48-week treatment period (with the primary endpoint at Week 48), 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 demonstrated that LY3841136 has potential to produce clinically meaningful weight loss with an acceptable safety and tolerability profile.

In Study LAA1, a placebo arm is included to determine if any LY3841136 safety or efficacy effects are different from no treatment.

A primary study endpoint at Week 48 is considered sufficient duration for an adequate understanding of drug effect on body weight.

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 the CWMM master protocol, Section 10.9.

In the 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 the 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 LY3841136 on safety, BP, lipids, PK and PD parameters, and patient-reported outcomes. Further, safety and tolerability over a wide dose range of LY3841136 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

The LY3841136 doses of 1 mg, 3 mg, 6 mg, and 9 mg are selected to be administered subcutaneously QW for Study LAA1 based on the following:

- Safety and tolerability of LY3841136 in healthy and overweight participants in the Phase 1 SAD and MAD Study YDAA. The SAD range tested was 0.04 to 12 mg. The MAD study tested 1.2 mg and up to 12 mg QW for 12 weekly doses.
- Preliminary safety, tolerability, and weight loss data from the MAD study provided the necessary safety, tolerability, and efficacy clinical data to support dosing up to the highest selected Phase 2 dose of 9 mg QW.
- While some AEs were observed at the 12 mg QW dose in Phase 1, this dose was generally tolerated without utilizing a dose-escalation approach. The 6/9 mg and 3/6/9 mg arms are included in this study to evaluate if more gradual dose-escalation can further improve tolerability to the 9 mg QW dose
- At Week 20, participants may escalate to 9 mg in the 6/9 mg arm and in the 3/6/9 mg arm based on the results of safety data reviews in advance of the first participant reaching week 20.
- PK/PD modeling of dose-exposure-response data from Study YDAA.
- Acceptable exposure margin for the 9 mg QW maximum dose in this study and up to 12 mg QW in previous studies, relative to the no observed adverse-effect level in monkeys in the 6-month toxicology studies.
- The lowest maintenance dose of 1 mg QW is anticipated to provide modest weight loss benefit but will be necessary for robust characterization of the LY3841136 dose-exposure-response relationship for weight change.
- Doses of 3 mg, 6 mg, and 9 mg QW are expected to provide clinically meaningful weight loss relative to placebo in a dose-related manner.
- 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 LY3841136 in chronic weight management.

4.4. End of Study Definition

A participant is considered to have completed Study LAA1 if the participant has completed all periods of the study including the last scheduled procedure shown in the SoA.

The end of Study LAA1 is defined as the date of the last visit of the last participant in Study LAA1 or last scheduled procedure shown in the SoA for the last participant in Study LAA1 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 Study LAA1 as detailed below. Participants must first meet all criteria for the CWMM master protocol, and then must meet all criteria for Study LAA1 to be eligible to participate in Study LAA1.

5.1. Inclusion Criteria

Sex and contraceptive/barrier requirements

200. Are males and females who agree to abide by the reproductive and contraceptive requirements provided in Study LAA1, Section 10.3.

5.2. Exclusion Criteria

In addition to meeting the exclusion criteria specified in the CWMM master protocol Visit 401, Study LAA1 participants will be excluded if any of the following apply at the time of screening:

Medical conditions

Diabetes-related

201. Have been diagnosed with any form of diabetes mellitus except for a prior diagnosis of gestational diabetes mellitus.
202. 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).

Cardiovascular

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

    Note: This supersedes the CWMM master protocol Section 5.2, exclusion criterion 16.

Other medical

205. Have renal impairment measured as estimated glomerular filtration rate <45 mL/min/1.73 m^2, calculated per Chronic Kidney Disease Epidemiology Collaboration as determined by the central laboratory during screening.
206. 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.
207. 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.
208. Have fasting triglycerides >500 mg/dL (5.7 mmol/L).

Prior/concomitant therapy

209. 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

210. Have participated within the last 6 months, whether on active drug or placebo, in a clinical study that contained a LAARA, GIP/GLP-1 RA, GLP-1/GCG RAs, or GIP/GLP-1/GCG RAs or combination of any those.
211. Have known or suspected hypersensitivity to trial product(s), LAARA.

Cardiovascular, additional criteria

213. Have an on-going or history of bradyarrhythmia and/or sinus bradycardia at screening and baseline.

    Note: This supersedes the CWMM master protocol Section 5.1, exclusion criterion 18.

214. Have an elevated resting pulse rate (PR) (mean >100 bpm) or reduced resting pulse rate (mean <60 bpm) at screening and baseline.

    Note: This supersedes the CWMM master protocol Section 5.1, exclusion criterion 15.

Prior/concomitant therapy, additional criteria

215. All concomitant medications should be at a stable dose for at least 3 months prior to randomization except for highly effective contraceptive pills such as combination oral contraceptive pill, progestin-only contraceptive pill (mini-pill), implanted contraceptives, or injectable contraceptives should be at a stable dose for 1 month prior to randomization.

    Note: This supersedes the CWMM master protocol Section 5.1, exclusion criterion 37.

5.3. Lifestyle Considerations

Refer to the CWMM master protocol, Section 5.3.

5.4. Screen Failures

Refer to the 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 medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Study 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 6.6.

This table lists the interventions used in this clinical study.

Intervention Name	**LY3841136**	**LY3841136 Placebo**
Dosage Level(s)	1 mg (0.1 mL) 3 mg (0.3 mL) 6 mg (0.6 mL) 9 mg (0.9 mL)	placebo (0.1 mL) placebo (0.3 mL) placebo (0.6 mL) placebo (0.9 mL)
Route of Administration	Subcutaneous using a syringe	Subcutaneous using a syringe
Frequency of Administration	Once weekly	Once weekly

The first injections of study intervention should occur at Visit 0 after the participant has undergone all other study procedures and assessments. Injections (LY3841136/matching placebo) should be administered on the same day and close to the same time. 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.

As stated in Section 4.1.1, after the initial visits to acquaint participants with self-injection of LY3841136, in-person visits will then occur every 4 weeks. Participants should inject study intervention in different quadrants of the abdomen and should rotate abdomen injection sites throughout the study.

A caregiver may administer the injection after appropriate training. A new syringe will be used for each injection of LY3841136 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 interventions 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.

6.1.1. Medical Devices, Investigational Devices, or Device Constituents

Instructions for device use and risks will be provided.

Any medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (refer to the CWMM master protocol, Section 10.3.3).

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 in the Pharmacy Manual.

6.3. Assignment to Study Intervention

Participants who meet all criteria for enrollment will be randomly assigned to 1 of the study intervention groups. Assignment to treatment groups will be determined by a computer-generated, random sequence using an IWRS. The study sample size approximately of 250 participants will be randomly assigned to placebo (approximately 50 participants), 1 mg LY3841136 (approximately 25 participants), 3 mg LY3841136 (approximately 25 participants), 6 mg LY3841136 (approximately 25 participants), 9 mg LY3841136 (approximately 50 participants), 6/9 mg LY3841136 (approximately 25 participants), or 3/6/9 mg LY3841136 (approximately 50 participants). To achieve this approximate allocation per arm of 2:1:1:1:2:1:2 as described previously for the overall study, participants enrolling under protocol amendment (a) or later will be randomized in a ratio of 2:1:1:1:2:3:2 to placebo, 1 mg, 3mg, 6 mg, 9 mg, 6/9 mg, or 3/6/9 mg.

Participants randomized to placebo will be randomly assigned to a dose volume group to maintain the blind.

The randomization will be stratified by

- BMI (<35, ≥35 kg/m^2 at screening)
- sex (female, male), and
- DXA substudy participation (Y/N)

6.4. Blinding

This is a double-blind study. Investigators, site staff, clinical monitors, participants, and parents or legal guardians will remain blinded to the treatment assignments until the ISA is complete.

To maintain the blind, 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.

6.5. 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.

6.6. Dose Modification

6.6.1. Temporary Interruption and Restarting of Study Intervention

In certain situations, participants may need to temporarily interrupt study intervention for example due to AEs deemed by the investigator severe enough to warrant dosing interruption.

If the reason for temporary dosing interruption is related to safety, for example an SAE, or poor participant tolerability of study intervention, 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, up to 2 weekly doses of study intervention can be omitted as deemed necessary by the investigator. A longer interruption must be approved by Lilly study physician upon review of the case with the primary investigator or designee. 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 safety of the participant, dosing interruption will be considered a protocol deviation.

Every effort should be made by the investigator to maintain participants on study intervention and restart dosing as soon as it is safe 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. Any other situation of study intervention interruption that is not described in this section (for example, interruption of treatment for more than 3-4 weeks) will be discussed between the primary investigator or designee and Lilly study physician to decide on an appropriate dosing plan for any participants with such events.

The following table provides detailed guidance on procedures related to temporary interruption of study intervention.

Reason for interruption	Number of doses missed	Actions at dosing reinitiation
Tolerability TEAEs related to study intervention and other TEAEs	1 or more consecutive doses	Restart dosing with the same dose that was last administered prior to interruption and then follow the planned dosing schedule. • If the rechallenge is not tolerated, reduce the dose to the next lower dose at the following dosing week and keep the participant on that dose until the end of the treatment period. • If the lower dose is not tolerated, participant will discontinue study intervention. • In the 6 mg/9 mg arm: 1. If the rechallenge is not tolerated at 9 mg, reduce the dose to 6 mg level at the next scheduled dosing week and keep the participant at this level until the end of treatment period 2. If the rechallenge is not tolerated at 6 mg dose level, participant will discontinue study intervention. • In the 3 mg/6 mg/9 mg arm: 1. If the rechallenge is not tolerated at 9 mg, reduce the dose to 6 mg level at the next scheduled dosing week and keep the participant at this level until the end of treatment period. 2. If the rechallenge is not tolerated at 6 mg dose level,

Reason for interruption	Number of doses missed	Actions at dosing reinitiation
		reduce the dose to 3 mg level at the next scheduled dosing week and keep the participant at this level until the end of treatment period. 3. If the rechallenge is not tolerated at 3 mg dose level, participant will discontinue study intervention.

Not related to TEAEs (that is, due to a protocol deviation)	1 or more consecutive doses	Restart at prior dose and if applicable continue the prior dose arm or dose escalation arm from that point. If new TEAEs emerge manage as above. • If the rechallenge is not tolerated, reduce the dose to the next lower dose at the following dosing week and keep the participant on that dose until the end of the treatment period. • If the lower dose is not tolerated, participant will discontinue study intervention. • In the dose escalation arm (6 mg/9 mg): 1. If the rechallenge is not tolerated at 9 mg, reduce the dose to 6 mg level at the next scheduled dosing week and keep the participant at this level until the end of treatment period. 2. If the rechallenge is not tolerated at 6 mg dose level, participant will discontinue study intervention. • In the dose escalation arm (3 mg/6 mg/9 mg): 1. If the rechallenge is not tolerated at 9 mg dose level, reduce the dose to 6 mg level at the next scheduled dosing week and keep the participant at this level until the end of treatment period. 2. If the rechallenge is not tolerated at 6 mg dose level, reduce the dose to 3 mg level at the next scheduled dosing week

Reason for interruption	Number of doses missed	Actions at dosing reinitiation
		and keep the participant at this level until the end of treatment period. 3. If the rechallenge is not tolerated at 3 mg dose level, participant will discontinue study intervention.

Abbreviation: TEAE = treatment-emergent adverse event.

Investigators should inform the sponsor that study intervention has been temporarily interrupted. The data related to temporary interruption of study treatment will be documented in source documents and entered on the CRF.

6.6.2. Dose Reductions Indicated to Ensure Participant Safety

In addition to the dose modifications described in Section 6.6.1, there may be situations where only a dose reduction (without interrupting dosing) would be appropriate.

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 (for a given treatment arm) in the following circumstances:

- any clinically significant changes as deemed necessary by the investigator, and
- if BMI decreases to ≤ 22 kg/m^2.

Participants should be permanently discontinued from study intervention if BMI decreases to $\leq$19 kg/m^2. Refer to Section 7.1 for guidance on discontinuation of study intervention.

Clinically significant adverse events

If a participant has intolerable AEs associated with a dose level of study intervention and the investigator does not believe that the participant will tolerate the dose with further exposure, then the investigator may reduce the dose or consider discontinuation of study intervention in consult with sponsor.

6.6.3. Management of Participants with Gastrointestinal Symptoms

To mitigate GI symptoms and manage participants with intolerable GI AEs, the investigator should

- advise participants to eat smaller meals, for example, splitting 3 daily meals into 4, or more smaller meals, and to stop eating when they feel full. Also, participants may be informed that lower-fat meals could be better tolerated
- prescribe symptomatic medication (for example, antiemetic or antidiarrheal medication) per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the CRF, and
- temporarily interrupt study intervention (omit 2 dose). Refer to Section 6.6.1 for further guidance on restarting study intervention after temporary discontinuation of study intervention. The data related to temporary interruption of study treatment should be documented in source documents and entered on the CRF.

If intolerable GI symptoms or events persist despite the above measures, see Section 6.6.

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

LY3841136 will not be made available after conclusion of the study.

6.8. Treatment of Overdose

For this study, any dose of study drug greater than the highest possible dose (9 mg) within a 72-hour time period, will be considered an overdose and should be reported as an AE.

In the event of an overdose, the investigator should:

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the 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 until, for example, study intervention no longer has a clinical effect or can no longer be detected systemically after approximately 10 weeks.

6.9. 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 LAA1 should be permanently discontinued from study intervention if

- the participant is diagnosed with pancreatitis
- BMI ≤19 kg/m^2 is reached at any time during the treatment period
- if participants answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
- answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS.

In addition, study drug may be permanently discontinued at the discretion of the investigator if participants at any study visit demonstrate symptoms of depression as assessed using the PHQ-9 questionnaire.

7.1.1. Liver Chemistry Stopping Criteria

Refer to the CWMM master protocol Section 7.1.1.

7.1.2. QTc Stopping Criteria

Refer to the 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, 2 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.

See Section 6.6.1 for guidance on restarting study intervention following temporary interruption.

7.2. Participant Discontinuation/Withdrawal from the Study

Refer to the CWMM master protocol Section 7.2.

7.3. Lost to Follow up

Refer to the CWMM master protocol Section 7.3.

8. Study Assessments and Procedures

See the CWMM master protocol (Section 8).

8.1. Efficacy Assessments

Primary

The primary efficacy measure is to compare the effect of the primary intervention (LY3841136) versus the primary control (placebo) for weight reduction at the primary analysis time point (48wks). 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

Secondary efficacy measures will characterize PK of LY3841136.

Exploratory

See Section 3 of the CWMM master protocol and Section 3 of LAA1 for specific efficacy endpoints. The following exploratory efficacy measures will be collected or calculated at the times shown in the SoA:

- TEAE
- SBP, DBP
- Actigraphy -Change in Physical activity (daily steps, M10 and MVPA)
- Mechanistic biomarkers (see Section 10.4) related to
    - insulin sensitivity
    - glucose metabolism
    - lipid metabolism
    - regulation of BP and fluid metabolism
    - regulation of calcium and bone metabolism, and
    - inflammation.
- Change in body composition—as measured by DXA (see Section 10.6)
- Patient-reported outcomes
    - SF-36 v2 Acute Form
    - Control of Eating Questionnaire-NRS
    - Fact GP5
    - PGIS Physical Function Weight
    - PGIC Physical Function Weight
    - PGIS Food Craving
    - PGIC Food Craving
    - Patient Assessment of GI Symptoms

8.1.1. Patient-reported Outcomes

8.1.1.1. Short-Form 36 Version 2 Health Survey, Acute Form (1-Week Recall Version)

The SF-36v2 assesses health-related quality of life. The SF-36v2 acute form, 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. It does not have a recall period, whereas the remaining domains assess functioning "in the past week." Each domain is scored individually and information from these 8 domains is 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).

8.1.1.2. Control of Eating Questionnaire

The Control of Eating Questionnaire (CoEQ) (Dalton et al. 2015) is a 19-item participant-completed questionnaire that assesses the intensity of food cravings, food types craved, appetite, and mood over the past 7 days. The 11-point numeric rating scale (NRS) ranges from 0 (not at all) to 10 (extremely) for each of the 19 items.

Seventeen of the 19 items are grouped into the 4 domains of

- craving control
- positive mood
- craving for savory foods, and
- craving for sweet foods.

The remaining 2 items, which assess the degree of hunger and fullness, are scored individually.

Higher scores represent higher levels of the concept measured in each domain or individual item (for the 2 standalone items).

8.1.1.3. Functional Assessment of Chronic Illness Therapy - Item GP5 (FACT-GP5)

This is a single, participant-completed item from the Functional Assessment of Chronic Illness Therapy (FACT) general scale that assesses the degree to which side-effects of treatment are bothersome. Response options are on a 5-point Likert scale ranging from "not at all" to "very much".

8.1.1.4. Patient Global Impression of Severity - Physical Function due to Weight

The 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."

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

The PGIC - Physical Function Weight questionnaire assesses participants' 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".

8.1.1.6. Patient Global Impression of Severity - Food Craving

The PGIS Food Craving item is a participant-completed, single-item measure that assesses overall perception of food craving in the past 7 days on a 5-point scale:

- Much higher than usual
- Somewhat higher than usual
- Same as usual
- Somewhat lower than usual, and
- Much lower than usual.

8.1.1.7. Patient's Global Impression of Change – Food Craving

The Patient Global Impression of Change (PGIC) Food Craving item is a patient-reported, single-item measure that assesses participants' change in their food craving since they started taking the study medication. The item is rated on a 5-point scale

- Increased a lot
- Increased a little
- No change
- Decreased a little, and
- Decreased a lot.

8.1.1.8. Patient Assessment of Gastrointestinal Symptoms

Three questions will be used to assess the GI symptoms of nausea, vomiting, and diarrhea. These single-item, participant-completed measures how often nausea, vomiting, and diarrhea occurred in the past 7 days. Response options are on a 5-point scale ranging from "0 days" to "everyday".

8.1.2. Actigraphy

The Axivity AX6 (actigraphy data capture tool) will be utilized to objectively assess various physical activity parameters including but not limited to change in daytime physical activity from baseline. The AX6 is 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 duration of

use in this study, thus is ideal for collecting longitudinal movement data in real-world health research and well-defined clinical trials.

The AX6 device meets Conformité Européenne mark requirements, Federal Communications Commission certified, and IP68 rated. Participants should wear the AX6 for 2 weeks, 3 times during the study, per the SoA.

8.2. Safety Assessments

Planned time points for safety assessments are provided in the LAA1 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 LAA1 must be followed in addition to those described in the CWMM master protocol.

Planned time points for all safety assessments are provided in the SoA.

8.2.1. Vital Signs

Refer to the CWMM master protocol, Section 8.2.1.

8.2.2. Physical Examinations

Refer to the CWMM master protocol, Section 8.2.2.

8.2.3. Electrocardiograms

Refer to the CWMM master protocol, Section 8.2.3.

Triplicate 12-lead ECGs will be collected at visits specified in the relevant ISA and at additional visits or time points when deemed clinically necessary.

8.2.4. Clinical Safety Laboratory Tests

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

See LAA1 ISA, Section 10.2 and the CWMM master protocol, Section 10.2 for the list of clinical laboratory tests.

8.2.5. Major Adverse Cardiovascular Events

Refer to the CWMM master protocol, Section 8.2.5.

8.2.6. Deaths

Refer to the CWMM master protocol, Section 8.2.6.

8.2.7. Hepatobiliary Disorders

Refer to the CWMM master protocol, Section 8.2.7.

8.2.8. Acute Renal Events

Refer to the CWMM master protocol, Section 8.2.8.

8.2.9. Pregnancy Testing

Refer to the CWMM master protocol, Section 8.2.9.

Participants in this ISA who are women of childbearing potential (WOCBP) will undergo routine pregnancy testing, beginning at study entry (Week 0) and occurring every 4 weeks as indicated in the SoA (Section 1.3) via urine pregnancy test. Participants will be provided with at-home urine pregnancy kits with instructions to perform the test with first morning void. Site personnel will contact participants via telephone and/or telemedicine encounters at Weeks 28, 32, 40, and 44. Information from these test results will be recorded in participant records. **Hepatic Monitoring**

Refer to the CWMM master protocol, Section 8.2.10.

8.2.11. Suicidal Ideation and Behavior Risk Monitoring

Refer to the CWMM master protocol, Section 8.2.11.

Participants in this ISA will be referred to a Mental Health Professional if in the opinion of the investigator it is necessary for the safety of the participant or if at any time the participant shows any suicidal behavior.

8.2.11.1. Columbia-Suicide Severity Rating Scale

Refer to the CWMM master protocol, Section 8.2.11.1.

Participants in this ISA will be referred to a Mental Health Professional if in the opinion of the investigator it is necessary for the safety of the participant or if at any time the participant shows any suicidal ideation of type 4 or 5 on the C-SSRS.

8.2.11.2. Patient Health Questionnaire-9

Refer to the CWMM master protocol, Section 8.2.11.1.

Participants in this ISA will be referred to a Mental Health Professional if in the opinion of the investigator it is necessary for the safety of the participant or if at any time the participant has a PHQ-9 score ≥10.

8.2.12. Additional Safety Data and Sample Collections

8.2.12.1. 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 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) in the hypoglycemia diary.

Participants who develop incident diabetes during the study may be started on allowed glucose-lowering medications (Section 6.8). If 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).

8.2.12.2. Pancreatitis

Diagnosis of acute pancreatitis

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 6.6.1.

Case adjudication and data entry

An independent 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.

8.2.12.3. 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 the CWMM master protocol, Section 10.3 must be reported as SAEs.

8.2.12.4. 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. Laboratory results are provided to the sponsor via the central laboratory.

8.2.12.5. 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 LY3841136 ADAs and LY3841136 concentration.

8.2.12.6. Antidrug Antibodies

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

8.2.12.7. Severe Gastrointestinal Adverse Events

LY3841136 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 the CWMM master protocol, Section 8.3.1.

8.3.2. Pregnancy

See the CWMM master protocol, Section 8.3.2.

8.3.3. Adverse Events of Special Interest

AEs of special interest include:

- hypotension and related neurological signs and symptoms
- acute renal failure
- suicidal ideation and behavior, and
- depression.

Refer to the CWMM master protocol, Section 8.2.11. for information on suicidal ideation and behavior risk monitoring.

8.3.3.1. Hypotension and Related Neurological Signs and Symptoms

Hypotension events may be identified by spontaneous reporting of symptoms (for example dizziness, blurred vision, fainting) and BP levels. If SBP persisted below 90 mmHg or DBP persisted below 60 mmHg or recurrent symptomatic hypotension has occurred, principal investigator should reduce antihypertensive medication dose level or inform participants to consult with their physician. Changes of antihypertensive medication will be recorded in CRF.

8.3.3.2. Acute Renal Failure

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.

LY3841136 may cause nausea, vomiting, and diarrhea, consistent with other GLP-1 RAs (Aroda and Ratner 2011). These events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure.

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

8.3.4. Incident Diabetes

Participants may be diagnosed with T2D 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 LAA1:

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 (LY3841136), 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.

- 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
- Major depressive disorder/suicidal ideation or behavior
- Abuse/liability potential
- Hypersensitivity reactions
- 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 SAP.

8.4. Pharmacokinetics

See the LAA1 (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 LY3841136 as specified in the SoA.

A maximum of 2 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 LY3841136. Samples collected for analyses of LY3841136 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 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 LY3841136 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 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 LY3841136 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 LY3841136 or after LY3841136 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 the CWMM master protocol, Section 10.5 for information regarding genetic research, 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, exploratory 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 LY3841136, pathways associated with obesity, diabetes mellitus, related clinical traits or complications including nonalcoholic steatohepatitis, mechanism of action of LY3841136, 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 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 LY3841136 or after LY3841136 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 to determine antibody production against LY3841136. Antibodies may be further characterized for cross-reactive binding to amylin and/or their ability to neutralize the activity of the LY3841136.

To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the serum concentrations of LY3841136. 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 treatment-emergent antidrug antibodies (TE ADA), additional samples may be taken for up to 1 year after last dose, or until the signal returns to baseline, whichever is shorter.

Immunogenicity will be assessed by a validated assay designed to detect ADAs in the presence of LY3841136 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.

TE ADA are defined in Section 9.3.4.2. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples may be collected as described in Section 10.2.3.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP will be finalized prior to first unblinding, and it 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.

9.1. Statistical Hypotheses

The primary hypothesis that is being tested in this study is that 1 mg, 3 mg, 6 mg, and 9 mg administered SC QW is superior to placebo with regard to percent change in body weight from baseline to Week 48, in participants without T2D who have obesity or are overweight with weight-related comorbidities.

9.1.1. Multiplicity Adjustment

No adjustment for multiplicity will be performed.

9.2. Analysis Sets

In addition to the analysis sets and data point sets defined in the CWMM, the following analysis sets are defined:

Population	Description
Entered	All participants who sign the ICF.
Randomized	All participants assigned to treatment, regardless of whether they took any dose of study treatment, or whether they took the correct treatment.
Pharmacokinetic Analyses	All randomly assigned participants who received at least 1 dose of LY3841136 and have at least 1 evaluable PK sample.
Pharmacodynamic Analyses	All randomly assigned participants who received at least 1 dose of LY3841136 or placebo and have at least 1 post baseline PD measurement.

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of sponsor or its designee.

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all confidence intervals will be given at a 2-sided 95% level. In statistical summaries and analyses, participants will be analyzed as randomized.

The primary estimand of interest in comparing efficacy of LY3841136 doses with placebo for this study is the “efficacy” estimand, which represents the efficacy prior to discontinuation of study intervention. The primary efficacy assessment, guided by the “efficacy” estimand, will be

conducted using the efficacy analysis set. The "treatment-regimen" estimand, which represents the efficacy irrespective of adherence to study intervention, may also be used to compare the primary efficacy of LY3841136 doses with placebo. The analysis guided by the "treatment-regimen" estimand will use the full analysis set. Additional exploratory analyses for participants who can comply with treatment of LY3841136 based on principal stratification may be performed. Details will be provided in the SAP.

The summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time (in addition to the baseline and end of treatment measurements) will be a mixed model for repeated measures (MMRM). Further specification of the model will be included in the SAP, including selection of covariance structure. Analysis of covariance (ANCOVA) may be used to make comparisons among treatment groups for continuous measurements with only 1 post-baseline assessment.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Fisher's exact test will be used to examine the treatment difference in categorical outcomes. Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. The negative binomial regression model may be used for the treatment comparison of discrete count measures if deemed appropriate. Participant-specific random effects may be added to the logistic and the negative binomial regression models if longitudinal measurements are available.

Other statistical methods may be used, as appropriate, and details will be documented in the SAP.

9.3.2. Treatment Group Comparability

9.3.2.1. Participant Disposition

See the CWMM master protocol, Section 9.3.6.1.

9.3.2.2. Participant Characteristics

See the CWMM master protocol, Section 9.3.6.2.

9.3.2.3. Concomitant Therapy

See the CWMM master protocol, Section 9.3.6.3.

9.3.2.4. Treatment Compliance

Treatment compliance is defined as taking at least 75% of required injections of study intervention during the treatment period while on study intervention. Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment group using the full analysis set.

9.3.3. Primary Endpoint Analysis

See the CWMM master protocol, Section 9.3.2.

The efficacy analyses for the primary endpoint will be conducted to establish superiority over placebo of 1 mg, 3 mg, 6 mg, 9 mg without dose escalation, 6/9 mg dose escalation, and 3/6/9mg dose escalation, with regard to mean percent change of body weight from randomization (Week 0) to Week 48.

The primary efficacy analysis will be guided by the "efficacy" estimand and conducted using the efficacy analysis set. The primary analyses model will be a MMRM with treatment, visit, and treatment-by-visit interaction as fixed effects, baseline body weight at randomization (Week 0) and sex as covariates, and participant as a random effect. Additional covariates may be added and will be detailed in the SAP.

9.3.4. Safety Analyses

See the CWMM master protocol, Section 9.3.5.

9.3.4.1. Central Laboratory Measures, Vital Signs, and Electrocardiograms

See the CWMM master protocol, Section 9.3.5.1.

9.3.4.2. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with TE ADA to LY3841136 may be tabulated. Treatment-emergent ADA 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 to baseline if ADAs were detected at baseline (treatment-boosted ADA).

For the TE ADA+ participants, the distribution of maximum titers may be described.

The frequency of cross-reactive ADA neutralizing antibodies against LY3841136, if performed, may be tabulated in TE ADA+ participants. If cross-reactivity to native amylin or neutralizing antibodies against native amylin assays are performed, the frequency of each may be reported.

The relationship between the presence of antibodies and the PK parameters and PD response including safety and efficacy to LY3841136 may be assessed.

9.3.5. Exploratory Endpoints

Details will be provided in the SAP.

9.3.6. Other Safety Analyses

Other safety analyses may be conducted, if deemed necessary. Details will be provided in the SAP.

9.3.6.1. Analysis of PHQ-9 Data

Specific diagnostic symptoms that determine the presence of a clinical depressive disorder per the Diagnosis and Statistical Manual for Mental Disorders will be summarized based on responses to the PHQ-9 questionnaire (Kroenke et al. 2001, Moriarty et al. 2015). Details will be provided in the SAP.

9.3.6.2. Analysis of C-SSRS Data

Suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS. Details will be provided in the SAP.

9.3.7. Other Analyses

9.3.7.1. Pharmacokinetic/Pharmacodynamic Analyses

LY3841136 concentration data will be analyzed using a population PK approach via nonlinear mixed-effects modeling with the NONMEM software. The relationships between LY3841136 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 LY3841136 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.

9.4. Interim Analysis

An interim efficacy assessment may occur approximately when all participants have the opportunity to complete Visit 24 (Week 24) of the treatment period to support planning activities associated with the clinical development program. An additional interim analysis may be performed approximately when all participants have the opportunity to complete Visit 36 (Week 36). An IAC will be formed to review the interim analyses for the safety and efficacy reports in an unblinded manner.

Additionally, safety reviews may be conducted to monitor safety of study participants. Details on the exact timing of the safety reviews, operational support, and unblinding will be specified in the IAC charter and in the study unblinding plan.

Early access to the PK and PD data for LAA1 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.

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 SAP will describe the planned interim analyses in greater detail. Only the Assessment Committee (AC) is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

9.5. Sample Size Determination

The study sample size approximately of 250 participants will be randomly assigned to placebo (approximately 50 participants), 1 mg LY3841136 (approximately 25 participants), 3 mg LY3841136 (approximately 25 participants), 6 mg LY3841136 (approximately 25 participants), 9 mg LY3841136 (approximately 50 participants), 6/9 mg LY3841136 (approximately 25 participants), or 3/6/9 mg LY3841136 (approximately 50 participants). To achieve this approximate allocation per arm of 2:1:1:1:2:1:2 as described previously for the overall study, participants enrolling under protocol amendment (a) or later will be randomized in a ratio of 2:1:1:1:2:3:2 to placebo, 1 mg, 3mg, 6 mg, 9 mg, 6/9 mg, or 3/6/9 mg**.**

Approximately 70% enrollment of females will be used to ensure a sufficiently large sample of males.

Sample size selection is guided by the objective of establishing superiority of each LY3841136 dose to placebo relative to the percent change from baseline in body weight at Week 48. Assuming a difference of 7.8% between the LY3841136 and placebo group means of percent change from baseline in body weight, and a standard deviation of 10%, a sample size of 50/arm enrolled in the 3/6/9 mg and 9 mg LY3841136 arms provides over 90% power, and 25/arm enrolled in the 1 mg, 3 mg, 6 mg, and 6/9 mg LY3841136 arms will provide over 80% power using 2-sample t-test at a 2-sided significance level of 0.05.

10. Supporting Documentation and Operational Considerations

This section provides information specific to the LAA1 ISA. For supporting documentation and operational considerations applicable to all ISAs, see Section 10 of the Master Protocol CWMM.

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

10.1.1. Regulatory and Ethical Considerations

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

See Section 9.4 of LAA1 ISA for information on efficacy interim analyses and the IAC.

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 may be performed at additional times noted in the LAA1 SoA (Section 1.3).

This table describes tests unique to LAA1 ISA.

10.2.1. Secondary Endpoints and Analysis

10.2.1.1. Efficacy Analyses

See the CWMM master protocol, Section 9.3.3.

10.2.2. Clinical Laboratory Tests Performed Starting at Visit 0

Clinical Laboratory Tests	Comments
Hormones	
Insulin	Results will not be provided to the investigative sites
Hormones (female)	
Urine pregnancy	See Section 8.2.9 (Pregnancy Testing)
Calculations	Generated by Lilly-designated laboratory
eGFR (CKD-EPI) calculated using cystatin-C	
Pharmacokinetics	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
PK samples –LY3841136 concentration	
Biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Longitudinal biomarkers	See Section 10.4 (Mechanistic Biomarkers) for specific laboratory tests.
Endpoint biomarkers	See Section 10.4 (Mechanistic Biomarkers) for specific laboratory tests.
C-Reactive protein, high-sensitivity	
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
Serum	

Plasma (EDTA)	
LTS P800	
Whole-blood epigenetics	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Anti-LY3841136 antibodies (ADA)	

Abbreviations: ADA = anti-drug antibodies; EDTA = ethylenediaminetetraacetic acid; HbA1c = hemoglobin A1c.

10.2.3. 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.	LY3841136 antidrug antibodies (ADA)
	LY3841136 concentration

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 and Guidance

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 resulting in confirmed infertility. • are infertile due to surgical sterilization, or • are postmenopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone ≥40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women **should not** be taking medications during amenorrhea such as oral contraceptives, hormonal replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea. Females on HRT and those whose menopausal status cannot be confirmed will be required to comply with protocol contraception requirements if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.3.2. Contraception Guidance

10.3.2.1. Guidance for Females

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 methods of effective contraception, where at least 1 method must be highly effective. These methods of contraception must be used during the study and for at least 5 half-lives plus 30 days which is equal to approximately 3.5 months after the last dose of the study intervention.

10.3.2.2. Guidance for Males

The table below describes contraception guidance for all men.

Participant Population	Contraception Guidance
All men...	should refrain from sperm donation for the duration of the study and for at least 5 half-lives plus 90 days which is equal to approximately 5.5 months after the 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 and at least 1 additional effective method of contraception for the duration of the study and for at least 5 half-lives plus 90 days which is equal to approximately 5.5 months after the 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 for the duration of the study and for at least 5 half-lives plus 90 days which is equal to approximately 5.5 months after the last dose of the study intervention.
Men in exclusively same-sex relationships, as their preferred and usual lifestyle...	are not required to use contraception.

10.3.3. Examples of Different Methods of Contraception

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the WNOCBP definition above. • 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 (for men in clinical trials and for female partner 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 methods 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

10.4. Appendix 4: Mechanistic Biomarkers

Mechanistic biomarkers will be measured at longitudinal intervals (longitudinal biomarkers) or less frequently to correspond with primary and/or interim analysis endpoints (endpoint biomarkers). To explore potential mechanisms of action related to changes in glucose, lipid or nutrient metabolism, or target receptor-related functions 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), IGF-1, total adiponectin, and leptin
- Biomarkers related to glucose metabolism: HbA1c, fasting glucose
- Biomarkers related to lipid metabolism: fasting cholesterol, triglycerides, LDL cholesterol, HDL cholesterol, VLDL cholesterol, non-HDL cholesterol
- Biomarkers related to regulation of BP and fluid balance: sodium, potassium, plasma renin activity, aldosterone
- Biomarkers related to regulation of calcium and bone metabolism: calcium, phosphate, 25-OH vitamin D, PTH, P1NP, CTX-1, calcitonin
- Biomarker related to inflammation: hsCRP

Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Insulin sensitivity	• Fasting glucose • Fasting insulin[a] • Fasting C-peptide[a] **Calculation:** HOMA2-IR[a] (computed with fasting glucose and fasting insulin or fasting C-peptide)	Total adiponectin[a] IGF-1[a] Leptin[a]
Glucose metabolism	• Fasting glucose • HbA1c **Calculations:** • HOMA2-B[a] (computed with fasting glucose and fasting insulin or fasting C-peptide)	
Regulation of blood pressure and fluid balance	• Plasma renin activity[a] • Aldosterone[a] • Sodium • Potassium	
Lipid metabolism	• Fasting lipid panel: o total cholesterol o LDL cholesterol (LDL-c) – LDL direct measure if triglycerides >400 mg/dL o HDL cholesterol (HDL-c)	

Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
	○ non-HDL cholesterol (non HDL-c) ○ triglycerides ○ VLDL cholesterol (VLDL-c)	
Bone and calcium metabolism	Calcium Phosphate Calcitonin[a]	PTH[a] 25-OH vitamin D[a] CTX-1[a] P1NP[a]
Inflammation	hsCRP[a]	

Abbreviations: CTX-1 = collagen cross-linked C-telopeptide; HbA1c= hemoglobin A1c; 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; IGF-1= insulin-like growth factor 1; LDL = low-density lipoprotein; P1NP= procollagen 1 Intact N-terminal propeptide; PTH = parathyroid hormone; VLDL = very low-density lipoprotein.

Note: Calcium, phosphate, sodium, and potassium will be measured within the clinical chemistry panel.

a Results will not be reported to investigators.

10.5. Appendix 5: Definition and Management of Incident Diabetes

Definition of incident diabetes

Incident diabetes is defined when any 1 of the following occurs after randomization (ADA 2023):

- In a participant with classic symptoms of hyperglycemia or hyperglycemic crisis, a random serum glucose ≥200 mg/dL (11.1 mmol/L)
- Within a 4-week period, any 2 of the following criteria are observed or 1 abnormal value is observed and confirmed
    - HbA1c ≥6.5% (48 mmol/mol)
    - Fasting serum glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours, and
    - Initiation of any medication for the treatment of diabetes.

Management of incident type 2 diabetes

Participants who develop T2D during the study will be

- provided and trained to use a glucometer (the frequency of self-monitoring of BG will be at the discretion of the investigator)
- educated on the signs and symptoms of hypoglycemia and its treatment, and
- provided a diary to record hypoglycemic episodes per Section 8.2.12.1.

Participants will be referred to their usual care provider and provided with a letter showing the study results indicative of diabetes. The decision to initiate glucose-lowering medication and the choice of glucose-lowering medication will be at the discretion of the participant's usual care provider, except for the following medications that are not allowed in the study:

- GLP-1 RA
- GIP/GLP1 RAs

GLP-1RA and GIP/GLP1 RAs should not be used in combination with LY3841136 due to overlapping pharmacology and the potential for increased GI AEs. Although metformin is not allowed upon study entry, it is allowed for treatment of incident T2D and is recommended for initial glucose-lowering therapy in this circumstance. Metformin should not be initiated during the study for the treatment of other metabolic conditions (for example, polycystic ovary syndrome and diabetes prevention). If additional glucose-lowering therapy beyond metformin is needed to treat incident T2D, DPP4i, SGLT-2 inhibitors, sulfonylureas, or long-acting basal insulin may be considered.

Monitoring for hypoglycemia includes capture of events as defined in Section 8.2.12.1. Date of diagnosis of diabetes will be captured in the CRF. If participants are diagnosed with incident T1D, discontinuation of study intervention should be considered as noted in Section 7.1 of the CWMM master protocol.

10.6. Appendix 6: Dual-energy x-ray Absorptiometry

A substudy using DEXA to assess body composition will be performed in a subset of LAA1 participants. This sub study is only applicable for sites that have access to either Hologic® or Lunar™ whole-body DXA scanners with body composition capability.

10.6.1. Introduction

Although 5% to 10% body weight reduction has been shown to reduce complications related to obesity and improve quality of life (Knowler et al. 2002; Jensen et al. 2014; Li et al. 2014; Warkentin et al. 2014), both fat and lean body mass are lost (Wadstrom et al. 2000; Jendle et al. 2009; Cava et al. 2017).

Weight-loss-associated loss of lean body mass (including muscle) could then increase the risk of sarcopenia (defined as low muscle mass and impaired muscle function), affecting individuals' mobility, increasing the risk of falls, and reducing the ability to perform daily living activities (Cava et al. 2017; Barazzoni et al. 2018).

Therefore, decreasing fat body mass while preserving sufficient lean body mass is important in any population where large decreases in body weight occur in a short period of time (Kulovitz et al. 2014).

Regulatory guidance

The Food and Drug Administration Draft Guidance for Industry, Developing Products for Weight Management (2007) and the European Medicines Agency (EMA) Guideline on clinical evaluation of medicinal products used in weight management (2016) recommend that a representative sample of study participants should have an assessment of body composition by dual-energy x-ray absorptiometry, or a suitable alternative, to ensure that weight loss, drug or biologic induced, is caused primarily by a reduction in fat content.

DXA total body composition

Dual-energy x-ray absorptiometry total body composition with regional analysis provides a measure of physiological response to obesity interventions superior to simple anthropometrics, such as BMI. It is safe and widely available in clinical practice (Kendler et al. 2013), making it a useful method to detect changes in fat and lean body mass in weight management studies (Dordevic et al. 2018).

The risk associated with DXA scan is low, with a radiation exposure (effective dose) of about 5 µSv or 0.005 mSv (millisievert). The typical level of background radiation to which the general population is exposed, not including radiation due to medical procedures, has been estimated to be about 2.5 mSv/year (Lewiecki et al. 2016).

Total body composition assessments for this study

In this study, a subset of approximately 160 study participants will undergo a body composition assessment via DXA scans, measured at baseline, Week 24 (Visit 24) and Week 48 (Visit 48) or at the time of ED (if at least 1 month after the baseline scan was performed), with the intent of evaluating changes in body composition associated with weight reduction, including both fat and lean mass compartments.

10.6.2. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Exploratory Objectives	
• To compare the effect of LY3841136 versus placebo on change in body composition from baseline to Week 48	• Percent change from baseline to Week 48 in total fat mass, as measured by DXA • Percent change from baseline to Week 48 in body weight • Percent change from baseline to Week 48 in total lean mass, as measured by DXA • Ratio between total fat mass and total lean mass at Week 48 • Percent change from baseline to Week 48 in visceral fat mass, as measured by DXA

Abbreviation: DXA = dual-energy x-ray absorptiometry.

10.6.3. Study Population

Inclusion criteria

212. All participants meeting all the inclusion and exclusion criteria in Section 5 will have the option to consent to the DXA procedure until the required number of participants is met.

Exclusion criteria

213. Have had a procedure within 10 days of screening (Visit 402) where oral contrast or radionuclides were administered, for example, CT with contrast or nuclear medicine.
214. Have a body weight, height, or width that prohibits the ability to obtain accurate measurements according to the DXA manufacturer's specification.
215. Have implants, hardware, devices, or other foreign materials in the measurement area that may interfere with the scan, according to the DXA manufacturer's specification.

10.6.4. Dual-energy x-ray Absorptiometry Scan

Participants who give consent and meet all eligibility requirements should have a DXA scan performed at the visits described in the SoA Section 1.3.

DXA instrument

Investigative sites will perform the body composition DXA scans on either Hologic® or Lunar™ DXA scanners with total body composition capabilities according to the imaging guidelines.

A DXA scan should be performed within 2 weeks of ED visit, at least 1 month after the baseline scan. Participants who stop study treatment but agree to return for Visit 48 will have an additional scan performed within ±7 days of Visit 48.

Guidance for conducting DXA scans

To obtain consistent and acceptable quality data, investigators will receive detailed instructions on the DXA scan protocol to be used.

The scans will be read and evaluated by a central reader.

Recommendations

Perform all scans for a given participant using the same DXA scanner and software.

Perform all scans for a given participant under similar circumstances, for example, using consistent scan status and performing the scan at the same time of day.

10.6.5. Randomization

Participants will be randomly assigned to treatment in the main study as described in Section 6.3. To be considered eligible for inclusion in the DXA substudy, participants from the main study must consent to the DXA substudy and must meet inclusion criteria but not meet any of the exclusion criteria for this substudy. Eligible participants may enroll in the substudy until the desired sample size has been met. Participants enrolled in the substudy will perform the procedures as outlined in the SoA for DXA.

10.6.6. Statistical Analyses

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2 sided.

Unless otherwise specified, all analyses for the variables measured or derived from DXA will be conducted on all participants who are enrolled in this substudy, randomly assigned, and have at least 1 dose of study intervention, with baseline measurement, excluding data after discontinuation of study intervention or initiation of rescue medication. There will be no multiplicity adjustment for secondary objectives.

The analysis model for continuous endpoints to make comparisons among treatment arms will be an analysis of covariance model (ANCOVA) with terms of treatment and baseline measurement as a covariate. Baseline is defined as the last non-missing data collected at randomization (prior to first dosing of study intervention). A Bayesian approach may be used as the dose–response model for selected endpoints. Further details and other statistical methods that may be used as appropriate will be described in the SAP.

10.6.7. Sample Size

The DXA substudy will enroll approximately 160 eligible participants from the main study to placebo (32 participants), 1 mg LY3841136 (16 participants), 3 mg LY3841136 (16 participants), 6 mg LY3841136 (16 participants), 9 mg LY3841136 (32 participants), 6/9 mg LY3841136 (16 participants), or 3/6/9 mg LY3841136 (32 participants).To achieve this approximate allocation per arm, participants enrolling under protocol amendment (a) will be randomized in a ratio of 2:1:1:1:2:3:2 to placebo, 1 mg, 3mg, 6 mg, 9 mg, 6/9 mg, or 3/6/9 mg**.**

Sample size selection is guided by the objective of establishing superiority of each LY3841136 dose to placebo relative to the percent change from baseline in total body fat mass at Week 48. Assuming a difference of 17% between the LY3841136 and placebo group means of percent change from baseline in total body fat mass, and a standard deviation of 19.5%, the chosen sample size of 32/arm enrolled in the 9 mg LY3841136 and 3/6/9 mg arms provide over 90% power, and 16/arm enrolled in the 1 mg, 3 mg, and 6 mg, and 6/9 mg LY3841136 arms will provide approximately 80% power using 2-sample t-test at a 2-sided significance level of 0.05.

10.6.8. Data Capture

Any diagnostic data collected from a contracted vendor will be stored electronically in that central vendor's database system. Data will subsequently be transferred from the central vendor according to the contract.

10.7. Appendix 7: Qualitative Interviews

A substudy using qualitative interviews to assess participants' treatment experiences will be performed in a subset of LAA1 participants. The qualitative interview sub-study will enroll approximately the first 100 participants at selected sites who meet eligibility criteria for the main study and who consent to the qualitative interview substudy.

While every effort will be made to complete this substudy as described, participant refusal to complete an interview, or interviews collected outside the targeted interview window after the selected study visit will not be recorded as protocol deviations. These events have no impact on the overall conduct nor the objectives of the Study LAA1. Given the qualitative nature of this sub-study above events will still allow to achieve the objective of describing study intervention experience of a subset of trial participants.

Clinical site staff will be responsible for consenting participants and transferring patient contact information forms to an independent healthcare research company, who will be responsible for scheduling and conducting the interviews. Details will be provided in a separate interview process study manual, which will be available to the participating sites.

Introduction

Qualitative interviews with participants from a clinical trial can provide insight into the participants' treatment experience, such as impacts on their lives in terms of physical, emotional and functional outcomes as well as on specific topics like how participants experience potential weight loss, and how eating behaviors, enjoyments and habits change throughout the study (FDA 2019a). In addition, data allow to reveal outcomes that are most important to participants, help discover unknown treatment impacts, provide information to supplement quantitative data obtained via clinical outcome assessments. Qualitative interviews satisfy FDA's recommendation to document meaningful change and responder thresholds in the context of use.

Regulatory guidance

Qualitative interviews have been recommended as a method for determining whether treatment-related changes are truly meaningful to participants (FDA 2018) and have been used for this purpose across numerous medical conditions (Gelhorn et al. 2016; Anthony et al. 2017; Ervin et al. 2017, 2019; Lewis et al. 2019). Qualitative interview data provide supportive information to conceptualize treatment response and characterize a meaningful change from participants' perspectives, which can help to interpret trial findings, for example, to confirm the meaningfulness of changes observed in the clinical outcome assessments included in the trial and help to understand and explain differences in outcomes between groups (Staunton et al. 2019). These interviews can be particularly helpful in providing insight into newer medications when less is known about participants' subjective treatment experience.

Qualitative interview design

In this study, participants will be interviewed during a pre-arranged phone call within approximately 4 weeks of Visit 402, Visit 2, and Visit 48 respectively, or after the time of ED, with the intent of capturing changes participants may experience during their participation in the clinical trial.

- **Interview Study Objectives**

  The goal of the qualitative interview study is to conduct participant interviews at up to 3 interview timepoints (baseline, interim, and exit) to gather qualitative data on participants' experience taking LY3841136 or placebo as part of Study LAA1**.** Interviewing participants prior to commencing study intervention (baseline interview V402) allows to establish a functional, physical, and emotional background prior to study intervention as well as describing goals and expectations. The interim interview (V2) will capture time-sensitive changes participants may experience early in their study intervention journey. The interview at study end (V48) will allow to evaluate changes participants may experience throughout the trial as well as to check if baseline goals and expectations were met.

- **Study Population**
  Approximately 100 participants at selected sites who meet all the inclusion and exclusion criteria in Section 5 will have the option to consent to participate in the interview study until the required number of participants is met.

- **Qualitative Interviews**

  Participants who give consent and meet all eligibility requirements would be interviewed approximately (giving some scheduling flexibility) within 4 weeks after the visits described in the SoA Section 1.3. Interviews will take place over the phone and are expected to last approximately 60 to 90 minutes. They will be scheduled at a time convenient to the participants to fit approximately within the appropriate interview window. Interviews will be conducted in English or Spanish by the interviewers specifically trained in qualitative data collection. All interviews will follow a semi-structured interview guide which will cover topics such as

    - History with overweight/obesity and previous weight-management experiences
    - Motivators and goals when joining the trial and how their expectations were met throughout the trial
    - Day-to-day routines and habits in terms of eating, sleep, and alcohol and tobacco use
    - Experience with the study intervention during the trial with respect to changes meaningful to the participant, in weight, appetite/eating behaviors, emotions, physical functioning and lifestyle as well as day-to-day routines and habits
    - Unmet treatment needs

  All interviews will be audio-recorded with each trial participant's permission and subsequently transcribed and coded following a coding framework prior to qualitative analysis.

- **Statistical Analysis**

  Qualitative data from the interviews will be extracted from interview transcripts. These data will be analyzed using a qualitative data analysis program that allows for qualitative

data (participant's quotes) to be systematically organized, coded, and compared. Analysis of coded interview data results will be detailed in a separate analysis plan.

10.8. Appendix 8: 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 Study LAA1.

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 include, but are not limited to,

- concomitant medications
- AEs
- review diet and exercise goals
- injection training
- 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 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. However, central laboratory testing must be retained for Visits 0, 12, 24, 48, ED, and 801.

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 Schedule of Activities. 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.

Visit Number	Tolerance
Visit 402	No adjustment to the visit window described SoA
Visit 0 to Visit 24	Within 7 days before the intended date, or up to 7 days after the intended date
Visit 24 to 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.

10.9. Appendix 9: 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
BG	blood glucose
BID	two times a day
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
BP	blood pressure
CEC	Clinical Events Committee
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.
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CV	cardiovascular
Device deficiencies	Equivalent to product complaint
DBP	diastolic blood pressure
DPP4i	dipeptidyl peptidase 4 inhibitor

DXA	dual-energy x-ray absorptiometry
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.
FACT-GP5	Functional Assessment of Chronic Illness Therapy - Item GP5
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
HbA1c	Hemoglobin A1c
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
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."
ISA	intervention-specific appendix
IWRS	interactive web-response system
LAARA	long-acting amylin receptor agonist
LDL	low-density lipoprotein
MACE3	3-point major adverse cardiovascular events: cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke
MAD	multiple ascending dose
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 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MI	myocardial infarction
MRI	magnetic resonance imaging
MVPA	moderate-to-vigorous physical activity
NRS	Numeric rating scale

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.
PGIC	Patient’s Global Impression of Change
PGIS	Patient’s Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
QW	once weekly
Q4W	once every 4 weeks
SAD	single-ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
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.
SD	standard deviation
SF-36 v2	Short-Form-36 version 2
SGLT-2	sodium-glucose cotransporter-2
SoA	schedule of activities
T1D	type 1 diabetes
T2D	type 2 diabetes
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
VLDL	very low-density lipoprotein
V	Visit

10.10. Appendix 10: Protocol Amendment History

Amendment [a]

Overall rationale for the amendment

The main purpose of this ISA amendment is to add a 6/12 mg escalation arm and increase the existing 3/6/9 mg escalation arm to a maximum dose of 12 mg (3/6/9/12 mg).

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	Number of Participants: • Randomization ratio updated to 2:1:1:1:2:3:2 for participants enrolling under amendment (a) • 6/12 mg arm added (25 participants) • Escalated 3/6/9 mg arm to 12 mg (3/6/9/12 mg)	Alignment with updated dosing arms
	Overall design: dose escalation will occur in ~~1~~2 treatment group<u>s</u> by increasing the volume of administered study intervention (or placebo) <u>at</u> ~~up to~~ Week 20~~8~~	Alignment with updated dosing arms
	Number of participants: • Increased sample size to 250 participants	Alignment with updated dosing arms
	Number of participants: • Revised percentage of female participants to "Approximately an upper limit of 70% enrollment of females…"	Allow flexibility in gender ratio
	Intervention Groups and Duration: 12 mg and placebo doses added to intervention table	Alignment with updated dosing arms
1.2. Schema	6/12 mg arm added	Alignment with updated dosing arms
	Escalated 3/6/9 mg arm to 12 mg at Week 20 (3/6/9/12 mg)	Alignment with updated dosing arms
1.3. Schedule of Activities	ED visits: removed the wording "study intervention"	Correction

Section # and Name	Description of Change	Brief Rationale
	Removed prespecified medical history from V402	Relevant medical history is taken at V401
	Fasting visits: a participant must be fasting for V20	Updated sample collections at V20
	Review diet and physical activity goals added to V8, V16, V20, V36, and V48	Closely monitor participant diet and physical activity goals
	Clinical chemistry added to V20	Safety labs collection prior to first 12 mg dose
	Longitudinal and exploratory biomarker sample collection added to V20	Biomarker collection prior to first 12 mg dose
4.1. Overall Design	Dose escalation details added for 6/12 mg and 3/6/9/12 mg arms	Assess dose escalation to 12 mg for tolerability
	Escalation to 12 mg dose for both 6/12 mg and 3/6/9/12 mg arms will be based on the results of safety data reviews in advance of the first participant reaching week 20	Assess safety before escalating to 12 mg
4.1.1. Overview of Study Periods	Added signing of Qualitative Interview and DXA ICFs	Clarification
4.2. Scientific Rationale for Study Design	Increased dose range from 9 mg to 12 mg	Alignment with updated dosing arms
4.3. Justification for Dose	Justification for 6/12 mg and 3/6/9/12 mg dosing arm escalations added	Alignment with updated dosing arms
	Escalation to 12 mg dose for both 6/12 mg and 3/6/9/12 mg arms will be based on the results of safety data reviews in advance of the first participant reaching week 20	Assess safety before escalating to 12 mg
5.2. Exclusion Criteria	Removed EC #204	Correction; redundancy as this is in the CWMM master protocol
	Added EC #213: current or history of bradyarrhythmia and/or sinus bradycardia at screening and baseline	Clarify sinus bradycardia is included in bradyarrhythmia

Section # and Name	Description of Change	Brief Rationale
	Added EC #214: have an elevated resting pulse rate (mean >100 bpm) or reduced pulse rate mean (<60 bpm) at screening and baseline	Clarify upper and lower limits of pulse rate permitted in the study
	Added EC #215: all concomitant medications should be at a stable dose for at least 3 months prior to randomization except for specified contraceptives may be stable for 1 month prior to randomization	To align with highly effective contraceptive guidance for female participants with childbearing potential
6.1. Study Intervention(s) Administered	12 mg and placebo doses added to intervention table	Alignment with updated dosing arms
6.3. Assignment to Study Intervention	• Randomization ratio updated to 2:1:1:1:2:3:2 for participants enrolling under amendment (a) • 6/12 mg arm added (25 participants) • Escalated 3/6/9 mg arm to 12 mg at week 20 (3/6/9/12 mg)	Alignment with updated dosing arms
6.6.1. Temporary Interruption and Restarting of Study Intervention	Added dose reduction and rechallenge instructions for "TEAEs related to study intervention and other TEAEs" for 6/12 mg and 3/6/9/12 mg arms	Alignment with updated dosing arms
	Added dose reduction and rechallenge instructions for "not related to TEAEs (that is, due to a protocol deviation)" for 6/12 mg and 3/6/9/12 mg arms	Alignment with updated dosing arms
7.1. Discontinuation of Study Intervention	Added that participant should be permanently discontinued if answered "yes" to question 4 or 5 of the suicidal ideation of the C-SSRS	Per regulatory request
	Added that participant should be permanently discontinued if answered "yes" to any suicidal-related behaviors	Per regulatory request
	Added that study drug may be permanently discontinued at investigator discretion if participants demonstrate symptoms of depression	Per regulatory request

Section # and Name	Description of Change	Brief Rationale
	at study visits as assessed by the PHQ-9	
8.2.11. Suicidal Ideation and Behavior Risk Monitoring	Added referral to mental health professional at investigator discretion if necessary for the safety of the participant or if at any time the participant shows any suicidal behavior	Per regulatory request
8.2.11.1. Columbia-Suicide Severity Rating Scale	Added referral to mental health professional at investigator discretion if necessary for the safety of the participant or if the participant shows any suicidal ideation of type 4 or 5 on the C-SSRS	Per regulatory request
8.2.11.2. Patient Health Questionnaire-9	Added referral to mental health professional at investigator discretion if necessary for the safety of the participant or if the participant has a PHQ-9 score ≥10	Per regulatory request
8.3.3. Adverse Events of Special Interest	Added AESI • hypotension and related neurological signs and symptoms • acute renal failure • suicidal ideation and behavior, and • depression.	Per regulatory request
	Added reference to the CWMM master protocol for information on suicidal ideation and behavior risk monitoring and on depression monitoring	Clarification
9.3.3. Primary Endpoint Analysis	Added 6/12 mg and escalated 3/6/9 mg arm to 12 mg at Week 20 (3/6/9/12 mg)	Collect additional safety and efficacy data for 12 mg dose
9.5. Sample Size Determination	Increased sample size to 250 participants	Alignment with updated dosing arms
	• Randomization ratio updated to 2:1:1:1:2:3:2 • 6/12 mg arm added (25 participants)	Alignment with updated dosing arms

Section # and Name	Description of Change	Brief Rationale
	• Escalated 3/6/9 mg arm to 12 mg at Week 20 (3/6/9/12 mg)	
	Number of participants revised to "Approximately ~~an upper limit of~~ 70% enrollment of females…"	Allow flexibility in gender ratio
10.3.2.1. Guidance for Females	For WOCBP, updated required contraception use duration to approximately 3.5 months after the last dose of study intervention	Alignment with current half-life in the IB
10.3.2.2. Guidance for Males	Updated requirement for men to not donate sperm to approximately 5.5 months after the last dose of study intervention	Alignment with current half-life in the IB
	Updated required contraception use duration for men with partners who are WOCBP or pregnant to approximately 5.5 months after the last dose of study intervention	Alignment with current half-life in the IB
10.4. Appendix 4: Mechanistic Biomarkers	Indicated which results will not be reported to investigators in the biomarker table	Provide clinically relevant study information to the investigators while maintaining appropriate blinding
10.6. Appendix 6: Dual-energy x-ray Absorptiometry	Increased substudy sample size to 160 participants	To accommodate the extra 25 pts in the 6/12 arm
	• Substudy randomization ratio updated to 2:1:1:1:2:3:2 for participants enrolling under amendment (a) • Substudy 6/12 mg arm added (16 participants)	Alignment with updated dosing arms
Throughout	Minor editorial corrections and clarifications	Clarification

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