Title Page

Master Protocol Title:

A Master Protocol for Phase 3 Randomized, Double-Blind, Placebo-Controlled Studies to Investigate the Efficacy and Safety of Once Weekly Eloralintide in Adult Participants with Moderate to Severe Obstructive Sleep Apnea, and Obesity or Overweight (ENLIGHTEN-3)

Master Protocol Number: J3R-MC-YDAO

Amendment Number: This is the initial protocol.

List of Intervention-Specific Appendices (ISAs):

J3R-MC-YSA1: Participants unable or unwilling to use positive airway pressure therapy

J3R-MC-YSA2: Participants treated with positive airway pressure therapy

Compound: Eloralintide (LY3841136)

Master Protocol Brief Title:

Efficacy and Safety of Eloralintide in Participants with Obstructive Sleep Apnea and Obesity or Overweight

Study Phase: 3
Acronym: ENLIGHTEN-3

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

IND: 177359

EU trial number: 2025-523769-11-00

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-199850

Medical Monitor Name and Contact Information will be provided separately.

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1. Protocol Summary

1.1. Synopsis

Master Protocol Title:

A Master Protocol for Phase 3 Randomized, Double-Blind, Placebo-Controlled Studies to Investigate the Efficacy and Safety of Once Weekly Eloralintide in Adult Participants with Moderate to Severe Obstructive Sleep Apnea, and Obesity or Overweight (ENLIGHTEN-3)

Master Protocol Brief Title:

Efficacy and Safety of Eloralintide in Participants with Obstructive Sleep Apnea and Obesity or Overweight

Regulatory Agency Identifier Number(s):

IND: 177359

EU trial number: 2025-523769-11-00

Rationale:

This Phase 3 multicenter, randomized, double-blind, master protocol is designed to assess the safety and efficacy of weekly eloralintide treatment compared with placebo in participants with moderate-to-severe obstructive sleep apnea and obesity or overweight, without type 2 diabetes.

Objectives, Endpoints, and Estimands:

This YDAO Phase 3 master protocol creates a framework to evaluate the safety and efficacy of weekly eloralintide for the treatment of participants with moderate-to-severe obstructive sleep apnea and obesity or overweight without type 2 diabetes.

The primary and secondary objectives stated in the table below are applicable to all Indication Specific Appendices (ISAs) under this YDAO master protocol.

Objectives	Endpoints
Primary	
To demonstrate that eloralintide MTD QW is superior to placebo for change in:	From baseline to Week 64:
body weight	percent change in body weight
AHI	absolute change in AHI (events per hour)
Key Secondary	
To demonstrate that eloralintide MTD QW is superior to placebo in change from baseline for:	From baseline to Week 64:
body weight	the achievement (Y/N) of body weight reduction of ○ ≥5% ○ h) (○ h) - ○ h * (

Objectives	Endpoints
blood pressure	change in SBP (mmHg)
lipid parameters	percent change in o triglycerides o non-HDL cholesterol
biomarkers of inflammation	percent change in hsCRP
AHI	percent change in AHI
sleep-related impairment	change in PROMIS Short Form sleep-related impairment 8a T-score
achieving OSA remission or mild asymptomatic OSA	the achievement (Y/N) of o AHI <5 or o AHI 5-) , b T _ S : F F g)
hypoxic burden	percent change in SASHB (% min/hour)
clinically meaningful change in AHI	the achievement (Y/N) of h50% decrease in AHI
Secondary	
To assess the effect of eloralintide MTD QW relative to placebo for:	From baseline to Week 64:
body weight	change in body weight (kg)
BMI	change in BMI (kg/m^2)
glycemic parameters	change in fasting glucose change in HbA1c (%)
sleep disturbance	change in PROMIS Short Form Sleep Disturbance 8b T-score
excessive daytime sleepiness	change in ESS score
health-related quality of life	change in SF-36 v2 Acute Form domain and summary scores
health status	change in EQ-5D-5L health state utility and VAS
insulin sensitivity	percent change in fasting insulin
central adiposity measurements	change in waist circumference (cm) change in neck circumference (cm)
medication use	change in use of antihypertensive medications lipid-lowering medications
lipid parameters	percent change in o HDL cholesterol

Objectives	Endpoints
blood pressure patient-reported symptoms	○ VLDL-cholesterol ○ total cholesterol ○ LDL-cholesterol change in DBP (mmHg) the achievement (Y/N) of improved categorical shift in: ○ PGIS-OSA Fatigue ○ PGIS-OSA Sleepiness ○ PGIS-OSA Snoring ○ PGIS-OSA Sleep Quality
To assess the effect of eloralintide MTD QW relative to placebo for: patient-reported symptoms	At Week 64 the achievement (Y/N) of improvement in: ○ PGIC-OSA Fatigue ○ PGIC-OSA Sleepiness ○ PGIC-OSA Snoring ○ PGIC-OSA Sleep Quality ○ PGIC most bothersome OSA symptom
To characterize eloralintide PK and exposure-response relationships between eloralintide and key efficacy, safety and tolerability measures	PK and PD parameters
To describe the safety of eloralintide MTD QW as compared with placebo	Summary of safety data, including number and incidence of: treatment-emergent adverse events nausea, vomiting and diarrhea events adjudicated events (CV events, neurologic events, pancreatic events; new diagnosis of T2D; see Section 8.3.4)

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; DBP = diastolic blood pressure; EQ-5D-5L = 5-level version of EQ-5D; ESS = Epworth sleepiness scale; FOSQ = functional outcomes of sleep questionnaire; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MTD = maximum tolerated dose; PD = pharmacodynamic; PGIC-OSA=Patient Global Impression of Change-Obstructive Sleep Apnea; PGIS-OSA =Patient Global Impression of Severity-Obstructive Sleep Apnea; PK = pharmacokinetic; PROMIS = patient-reported outcomes measurement information; QW = once weekly; SAHB= sleep apnea specific hypoxic burden; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; SBP = systolic blood pressure; TBD = to be determined; VAS =Visual Analog Scale; VLDL = very low-density lipoprotein; Y/N = yes/no.

Estimands

The study will use 2 estimands to address ICEs for the primary and key secondary objectives: a treatment-regimen estimand for the treatment policy strategy, and an efficacy estimand for the hypothetical strategy. These estimands have distinct interpretations and serve different purposes.

Estimands for OSA-related parameters

Treatment-regimen estimand

GSP %BPWL_PO NWTYTNLW \`P^_TZY ZQ TY_P]P^_ T^2

D*What is the treatment difference in the change of AHI from baseline to Week 64 between eloralintide MTD QW and placebo, as an adjunct to healthy diet and physical activity, in participants with YDAO study condition/disease regardless of adherence to study intervention?* E

%% ' " ! " - $ + , ' (!) #

D,4-? 5> ?41 ?=1-?91:? 05221=1:/1 5: ?41 /4 &8;=-85%*?,5 0:10 <8-/1.; -> :@?=50?6@<4C>5;-81- -/?5A5?C 5: *participants with YDAO study condition/disease* 52 ?41C B;@80 =19- =-:0;98C ->>53:10 ?=1-?91:? 2;= "! B117> - ?=1-?91:?> #E

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Estimands for weight-related parameters

Treatment regimen estimand

The clinical question of interest is:

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Efficacy estimand

GSP NWTYTNLW \`P^_TZY ZQ TY_P]P^_ T^

D,4-? 5> ?41 ?=1-?91:? 05221=1:/1 5: ?41 <1 "! B117> .1?B)1+1%::&8<8-85:?501> -: -06@:/? <4C>5/-8 *participants with YDAO study condition/disease* 52 ?41C B;@80 = ;: ?415= =-:0;98C ->>53:10 ?=1-?91:? 2;= " B1534? 9-:-31E91:? ?=1-?91:?>#

Overall Design:

Study J3R-MC-YDAO (YDAO) is a multicenter, randomized, parallel-arm, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of eloralintide maximum

tolerated dose (MTD) (1.5, 3, 6, or 9 mg) QW versus placebo in participants with obesity or overweight, without type 2 diabetes, who have been diagnosed with moderate-to-severe obstructive sleep apnea (OSA).

Brief Summary:

Study YDAO is a master protocol designed to investigate 2 participant populations, described in 2 Indication Specific Appendices (ISAs):

YSA1 will include participants who are unable or unwilling to use Positive Airway Pressure therapy (PAP).
YSA2 will include participants who are on PAP therapy and plan to continue PAP therapy during the study.

Participants will be assigned to the ISA that reflects their current PAP usage.

Master protocol eligible participants will be assigned to either Study YSA1 or YSA2.

Within each ISA eligible participants will be randomly assigned in a 1:1 ratio to treatment (eloralintide MTD QW) or placebo.

The study consists of

Screening: up to 6 weeks
Treatment: 64 weeks
- dose-escalation period (to MTD): 12 weeks, and
- treatment maintenance period: 52 weeks.

Posttreatment follow-up: 6 weeks

The visit frequency will be every 4 to 6 weeks.

Study Population:

In general, an individual may participate in this study if they

are at least 18 years of age and of the legal age of consent in the jurisdiction in which the study is taking place at the time of signing the informed consent
hLaP L 7@3 h*/ VR'X
have a confirmed history of moderate-to-severe obstructive sleep apnea, and
have an apnea-hypopnea index h) - polysomnography.

Number of Participants:

Approximately 800 participants, 400 participants in each corresponding ISA, will be randomly assigned to associated ISAs based on baseline PAP use.

Participants will be randomized in a 1:1 ratio to eloralintide maximum tolerated dose or placebo.

Intervention Groups and Duration:

Intervention Name	**Eloralintide**	**Eloralintide Placebo**
Dosage Level(s)	1.5 mg 3 mg 6 mg 9 mg	Placebo
Route of Administration	Subcutaneous using a PFS	Subcutaneous using a PFS
Frequency of Administration	Once weekly	Once weekly
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized

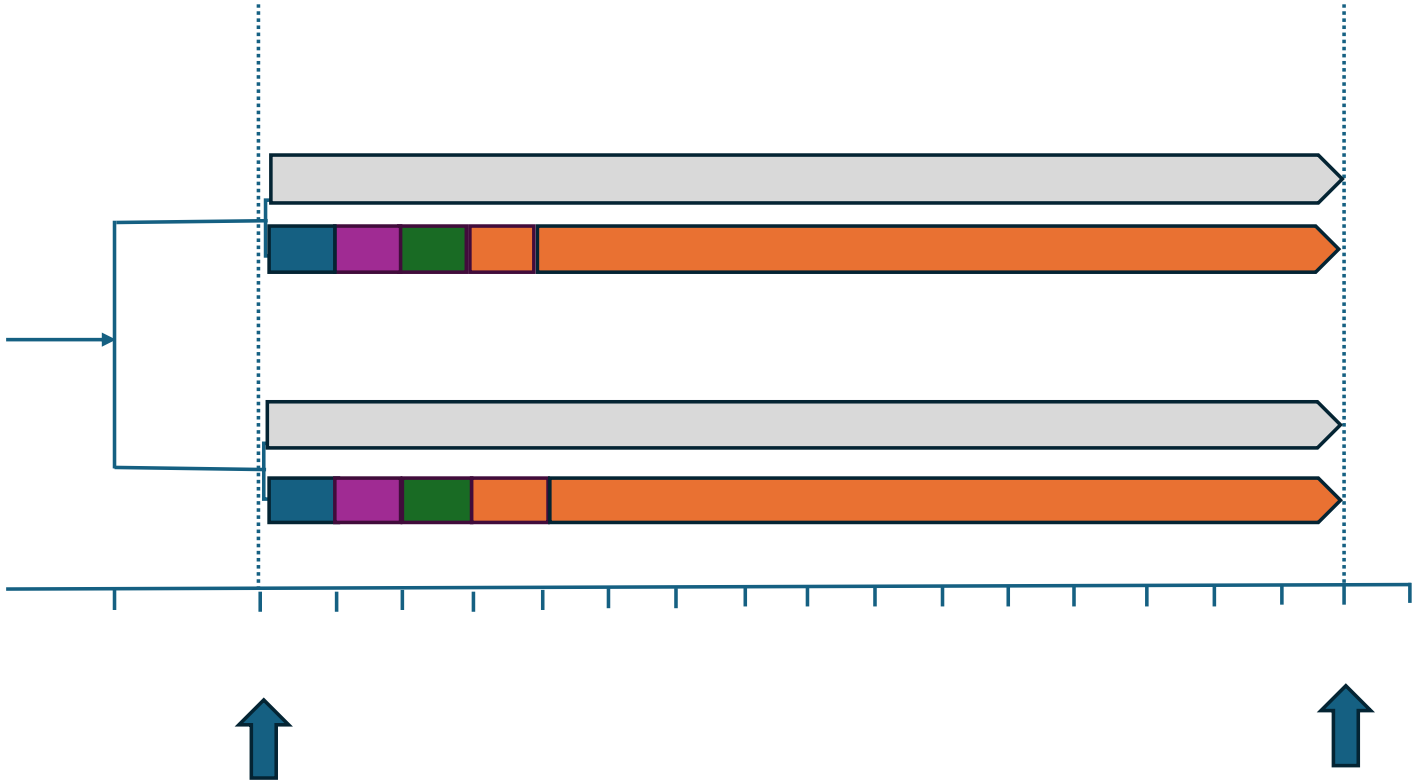
Abbreviations: EU=European Union; PFS= prefilled syringe

Ethical Considerations of Benefit/Risk:

The safety and efficacy profile seen to date for eloralintide supports the overall benefit-risk profile for participants in this study. Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with eloralintide are outweighed by the anticipated benefits that may be afforded to participants living with obesity or overweight and obstructive sleep apnea.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: ISA= intervention-specific appendix; MTD= maximum tolerated dose; PAP=positive airway pressure; QW= once weekly.

1.3. Schedule of Activities (SoA)

The SoA described in this section should be followed for all participants enrolled in Study YDAO.

Visit information

Visit procedures may be conducted over more than 1 day if all activities are completed within the allowed visit tolerance period of each visit. Participants should not initiate first dose of study intervention or escalate study intervention until all required activities for that visit are complete.

Fasting visits

On all clinic visits, except PK only visits, remind participants to report to the site in a fasting [illegible] except water, or performing any significant physical activity. Participants should not take their study intervention prior to the fasting visit. If a participant is adversely affected by the fasting condition, they are allowed to eat; however, specific study procedures need to be completed while fasting.

If a participant attends a fasting visit in the non-fasting state, reschedule a visit to complete the required fasting activities within the allowable visit interval.

Screening

All screening activities must take place within the defined screening window, including both MP and ISA screening activities [illegible] conducted under this MP. Additional screening procedures and laboratory testing will be listed in an ISA when applicable.

Randomization should not occur until all screening results are received, and initial assessments of eligibility are completed at the MP and then the ISA level (when applicable). At randomization, all screening results will be reviewed to confirm eligibility at the MP and then at the respective ISA level.

Visit 2 (randomization to treatment)

Visit 2 should be scheduled as soon as all screening activities have been performed, and results are available to assess eligibility. Participants will be randomly assigned to the treatment arms at Visit 2 and will receive their first dose of study intervention after completing all baseline assessments including labs.

Telehealth or remote visits

Telehealth visits may be by telephone or other technology.

PK only

The only procedure performed for these visits is PK sample collection.

Early discontinuation visits

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

If the participant is discontinuing the study at the time of a scheduled visit, perform that visit as an ED Visit. Participants who withdraw from the study after signing the informed consent but who have not taken a dose of study intervention do not need to complete ED Visit.

Unscheduled visits

An ` Y ^ N S P O ` W P O a T ^ T _ X L d Z N N `] L N N Z] O T Y R _ Z _ S F
The study site will determine if fasting status is needed prior to the visit. Concomitant medications, AEs, and endpoint events reviews are required and should be recorded on the CRF.

Visit 801

A posttreatment safety follow-up visit will occur approximately 6 weeks following the last treatment period visit or final treatment visit. All participants are required to complete the safety follow-up visit. The SoA reflects the procedures that may occur during these visits.

1.3.1. Period I Screening and Period II Dose Escalation Treatment

Study YDAO	Period I Screening	Period II Dose-Escalation Treatment				Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-6	0	4	8	12	
Visit Interval Tolerance (+/-days)		-	3	3	3	
Visit Detail	F	F	F	F	F	F=fasting
Consent and Demographics						
Informed consent	X					ICF must be signed before any protocol-specific tests/procedures are performed.
Inclusion/ exclusion criteria; confirmation of eligibility	X	X				Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.
Demographics	X					Includes year of birth, sex, ethnicity (where permissible) and race.
Preexisting conditions and family history, medical history, including relevant surgical history	X					Collect all ongoing conditions and relevant past surgical and medical history, including menopausal status female.
Prespecified medical history (indication and history of interest)	X					Should include, but not be limited to, collecting diagnosis of OSA and obesity or overweight-related health problems.
Prior treatments for indication	X					Includes treatments for OSA and obesity or overweight.
Substance use (alcohol, tobacco, recreational drug use)	X					
Education level	X					
Treatment goal assessments		X				Participants will be asked to provide a personal goal, which could include BMI, weight, and other weight-related comorbidities.
Concomitant medications	X	X	X	X	X	Include doses required for antihypertensive and lipid-lowering medications. Refer to Section 6.9 for additional details.
Adverse events (AEs)	X	X	X	X	X	Collect additional data for AESIs and other safety topics. See Section 8.3.
Investigation of the most bothersome symptom of OSA	X					Refer to Section 8.1.6.
Physical Evaluation						
Height	X					Height should be obtained per the instructions in Section 10.7.
Weight	X	X	X	X	X	Must be measured in the fasting state. See Sections 10.7.

Study YDAO	Period I Screening	Period II Dose-Escalation Treatment				Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-6	0	4	8	12	
Visit Interval Tolerance (+/-days)		-	3	3	3	
Visit Detail	F	F	F	F	F	F=fasting
Waist circumference		X				See instructions in Section 10.7.
Neck circumference		X				See instructions in Section 10.7.
Vital signs	X	X	X	X	X	Collect 3 measures of sitting vital signs (BP and pulse rate) before obtaining ECG and before collecting blood samples for laboratory testing. See Section 8.2.2.
Physical examination	X					Visit 1 requires a complete physical examination. At all other visits, additional Symptom-directed physical assessment can be conducted at the discretion of the investigator. See Section 8.2.1.
12-lead ECG (central)	X	X				Collect ECG before blood sample collection for laboratory testing if these procedures occur at the same visit. See Section 8.2.3 for details.
Polysomnography Assessments						
Schedule PSG at sleep center	X			X		
Polysomnography	X					PSG results must be reviewed to confirm eligibility prior to randomization.
PAP adherence questionnaire		X				
Participant Diary (electronic)						
Provide diary device, instruct on use	X					An electronic diary device will be provided and training conducted. Participants will use this device to record weekly study medication injections (Section 6.1), and other data as applicable. All training should be repeated as needed to encourage participant compliance.
Assist in the study medication injection diary		X				Site personnel should assist the participant in completing the first entry of the dosing diary.
Review diaries		X	X	X	X	Includes weekly study medication injection diary (Section 6.1), and other data as applicable. Site personnel should review study medication injection diary for completeness at every visit. Provide retraining to participant and help participants catch up during visit if data entry is behind
Participant Education and Supplies						
Lifestyle counseling		X	X	X	X	? T Q P ^ _ d W P N Z ` Y ^ P W T Y R X L d Z N N `] Z ` study procedures. Counseling may be delivered by telehealth. See Section 5.3.

Study YDAO	Period I Screening	Period II Dose-Escalation Treatment				Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-6	0	4	8	12	
Visit Interval Tolerance (+/-days)		-	3	3	3	
Visit Detail	F	F	F	F	F	F=fasting
Injection training		X				Repeat as needed.
Participant Log (Paper)						
Nutrition and physical activity log		X	X	X	X	Includes dispensing, collection, and review as applicable. Monitor for and encourage adequate nutritional intake and hydration throughout the study. See Sections 5.3.1 and 5.3.2.
Patient-reported Outcomes (Electronic)						For participants on PAP (YSA2) at visits with PSG, PROs will be completed after PAP wash-out, on the day of PSG, before start of PSG study. Completing the PRO assessments on the next day after PSG is not considered a protocol deviation. For participants not on PAP (YSA1), PROs will be completed within the visit interval or within ±7 days of the PSG study.
PROMIS SRI 8a	X					
PROMIS SD 8b	X					
Epworth Sleepiness Scale	X					
SF-36v2	X					
EQ-5D-5L	X					
PGIS jFatigue, Sleepiness, Snoring, Sleep Quality	X					
Mental Health Assessments (Paper)						
Patient Health Questionnaire-9 (PHQ-9)	X	X		X		Collect AEs before the PHQ-9 collection. See Sections 8.2.7 and 8.2.7.1.
C-SSRS Screening/ Baseline (Category Version)	X					Collect AEs before the C-SSRS collection.
C-SSRS Since Last Assessed (Clinical Categories Version)		X	X	X	X	Collect AEs before the collection of the C-SSRS.
Laboratory Tests and Sample Collection						
Hematology	X	X	X		X	
Hemoglobin A1c (HbA1c)	X	X			X	
Clinical chemistry	X	X	X	X	X	

Study YDAO	Period I Screening	Period II Dose-Escalation Treatment				Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-6	0	4	8	12	
Visit Interval Tolerance (+/-days)		-	3	3	3	
Visit Detail	F	F	F	F	F	F=fasting
Lipid panel	X	X		X		
Urinalysis	X	X			X	
Serum pregnancy	X					For IOCBP only. Definition in Section 10.4.1. If the initial serum pregnancy test at Visit 1 is performed more than 30 days before the first dose (Visit 2), a second negative serum test by the central lab, confirmed by the investigator, must be completed before Visit 2 and dosing. See Section 8.2.5 for details.
Urine pregnancy test (local)		X	X	X	X	For IOCBP only. Definition in Section 10.4.1. Week 0 (Visit 2): Results must be available before the first administration of study intervention. Perform additional pregnancy tests at any time during the study if needed. See Section 8.2.5.
Follicle-stimulating hormone (FSH)	X					Collect FSH only as required to confirm postmenopausal state. Refer to Section 10.4.
Thyroid-stimulating hormone (TSH)	X					Refer to Section 5.
Insulin		X		X		
C-peptide		X		X		
Free Fatty Acids		X		X		
Apolipoprotein B (ApoB)		X		X		
Apolipoprotein C-3 (ApoC3)		X		X		
Intact Proinsulin		X		X		
C-reactive protein, high-sensitivity (hsCRP)		X		X		
Urinary albumin/creatinine ratio (UACR)		X				
Estimated glomerular filtration rate (eGFR)	X	X		X		Calculated using CKD-EPIcreat-cyst C (2021 version).
Cystatin-C	X	X		X		
Pancreatic Amylase		X		X		
Lipase		X		X		
Renin		X				
Aldosterone		X				

Study YDAO	Period I Screening	Period II Dose-Escalation Treatment				Comments
Visit Number	1	2	3	4	5	
Weeks from Randomization	-6	0	4	8	12	
Visit Interval Tolerance (+/-days)		-	3	3	3	
Visit Detail	F	F	F	F	F	F=fasting
Micronutrient panel		X				Micronutrient deficiencies identified via laboratory tests should be repleted as clinically appropriate. See Section 5.3.2.
Immunogenicity (ADA) samples (predose)		X	X			Collect additional unscheduled samples if systemic drug hypersensitivity reactions occur (see Section 8.3.5.9 and 10.2.1) Collect immunogenicity and PK samples for immunogenicity before dosing.
PK sample (predose)		X	X			PK sample to be taken prior to study intervention administration. Site should confirm that participant has accurately entered the dose date and time in their Diary.
PK (2 to 6 h post dose)		X				This sample should be taken post dose on the same day after dosing of study intervention.
PK Random (at any time during visit)					X	PK sample can be taken at any time during the visit.
Stored Samples						
Genetics sample		X				Collect sample at or after the specified visit.
Exploratory biomarkers		X				
Randomization and Dosing						
Register visit with IWRS	X	X	X	X	X	
Assignment to ISA via IWRS	X					
Randomization to treatment via IWRS		X				
Dispense study intervention via IWRS		X	X	X	X	
Observe participant administer study intervention		X				
Dispense supplies to participant		X	X	X	X	Ancillary supplies: dispense as needed.
Participant returns study interventions supplies			X	X	X	See Section 6.5
Assess study intervention(s) compliance			X	X	X	See Section 6.5

Abbreviations: ADA = anti-drug antibodies; AESI = adverse events of special interest; BG = blood glucose; BMI= body mass index; BP = blood pressure; CKD-EPI = CKD Epidemiology Collaboration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FAS = full analysis set; ICF= informed consent form; IOCBP = individuals of childbearing potential; ISA = intervention-specific appendix; IWRS = interactive web response system; OSA= obstructive sleep apnea; PAP= positive airway pressure; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics, PRO = patient-reported-outcome; PROMIS SD 8b= PROMIS Short Form v1.0 Sleep Disturbance 8b; PROMIS SRI 8a =PROMIS Short Form v1.0 Sleep Related Impairment 8b; PSG= polysomnography; SF-36v2 = Short Form 36 Version 2 Health Survey, Acute Form; SMBG = self-monitoring blood glucose; T2D = type 2 diabetes; V = visit; Wks = weeks.

1.3.2. Period III Maintenance Treatment

Study YDAO	Period III ⊢Maintenance Treatment																	Comments
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Consent and Demographics																		
Substance use (alcohol, tobacco, recreational drug use)	X							X							X	X		
Treatment goal assessments															X			Participants will be asked to provide a personal goal which could include BMI, weight, and other weight-related comorbidities.
Concomitant medications	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	Include doses required for antihypertensive and lipid-lowering medications. Refer to Section, 6.9 for additional details.
Assess medication intensity (dyslipidemia, hypertension)				X											X	X		As applicable for participants receiving these medications. Evaluate the changes in treatment intensity, within each therapeutic area, from randomization until the time of evaluation.

Study YDAO	Period III ⊢Maintenance Treatment																	Comments
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Additional data are collected for certain AEs. Collect additional data for AESIs and other safety topics. See Section 8.3.
Investigation of change in most bothersome symptoms of OSA	X														X	X		Refer to Sections 8.1.6 and 8.1.7.
Physical Evaluation																		
Weight	X			X				X				X			X	X	X	Must be measured in the fasting state. See Section 10.7.
Waist circumference	X			X				X				X			X	X	X	See instructions in Section 10.7.
Neck circumference	X			X				X				X			X	X	X	See instructions in Section 10.7.
Vital signs	X			X				X				X			X	X	X	Collect 3 measures of sitting vital signs (BP and pulse rate) before obtaining ECG and before collecting blood samples for laboratory testing. See Section 8.2.2.

Study YDAO	**Period III ⊢Maintenance Treatment**																	**Comments**
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Physical examination															X	X		Visit 18 (or ED if applicable) requires a complete physical examination. At all other visits symptom-directed physical assessment can be conducted at the discretion of the investigator. See Section 8.2.1.
12-lead ECG (central)	X							X							X	X		Collect ECG before blood sample collection for laboratory testing if these procedures occur at the same visit. See Section 8.2.3.
Polysomnography																		
Schedule PSG at sleep center													X					
Polysomnography (PSG)	X														X			PSG at Visit 6 and Visit 18 may be scheduled for any day ±7 days
PAP adherence questionnaire						X								X				
Participant E-diary																		

Study YDAO	**Period III ⊢Maintenance Treatment**																	**Comments**
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Review diaries	X	X	X	X		X	X	X		X	X	X	X	X	X	X		Includes study medications injections diary (Section 6.1), and other data as applicable. Site personnel should review study medication injection diary for completeness at every visit, provide retraining to participant, and help them catch up during visit if data entry is behind
Diary return																X	X	Participants will return their device during their last visit.
Participant Education and Supplies as Appropriate																		
Lifestyle counseling	X	X		X		X		X		X		X	X		X	X		Lifestyle counseling may occur on a separate day Q] Z X _ S P] P study procedures. Counseling may be delivered by telehealth. See Section 5.3

Study YDAO	Period III – Maintenance Treatment																	Comments
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Participant Log (Paper)																		
Nutrition and physical activity log	X							X				X			X	X		Includes dispensing, collection, and review as applicable. Monitor for and encourage adequate nutritional intake and hydration throughout the study. See Section 5.3
Patient-Reported Outcomes (Electronic)																		For participants on PAP (YSA2) at visits with PSG, PROs will be completed after PAP wash-out, on the day of PSG, before start of PSG study. Completing the PRO assessments on the next day after PSG is not considered a protocol deviation. For participants not on PAP (YSA1), PROs will be completed within the visit interval or within ±7 days of the PSG study.
PROMIS SRI 8a	X														X	X		
PROMIS SD 8b	X														X	X		
Epworth sleepiness scale	X														X	X		

Study YDAO	**Period III – Maintenance Treatment**																	**Comments**
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
SF-36v2 acute form	X														X	X		
EQ-5D-5L	X														X	X		
PGIS j fatigue, sleepiness, snoring, sleep quality	X														X	X		
PGIC j fatigue, sleepiness, snoring, sleep quality	X														X	X		
Mental Health Assessments																		Mental health assessments should be completed during the visits.
Patient health questionnaire-9 (PHQ-9)	X		X			X		X			X	X		X	X	X	X	Collect AEs before the PHQ-9 collection. See Sections 8.2.7 and 8.2.7.1.
C-SSRS since last assessed (clinical categories version)	X	X	X	X		X	X	X		X	X	X	X	X	X	X	X	Collect AEs before the collection of the C-SSRS.
Laboratory Test and Sample Collection																		
Hematology				X				X				X			X	X	X	
Hemoglobin A1c (HbA1c)				X				X				X			X	X	X	
Clinical chemistry	X			X				X				X			X	X	X	
Lipid panel	X			X				X							X	X	X	
Urinalysis	X			X				X				X			X	X	X	

Study YDAO	**Period III – Maintenance Treatment**																	**Comments**
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Urine pregnancy (local)	X	X	X	X				X				X			X	X	X	For IOCBP only. Definition in Section 10.4.1. Perform additional pregnancy tests at any time during the study if there is clinical suspicion of pregnancy, or as required by local law or regulation. See Section 8.2.5.
Remind urine pregnancy (at-home test)						X	X			X	X		X	X			X	For IOCBP only. Definition in Section 10.4. Recommend participants take additional home UPT 4 weeks after V801. See Section 8.2.5.
Insulin	X			X				X							X	X	X	
C-peptide	X			X				X							X	X	X	
Free fatty acids	X			X				X							X	X	X	
Apolipoprotein B (ApoB)	X														X	X	X	
Apolipoprotein C-3 (ApoC3)	X														X	X	X	
Intact proinsulin	X														X	X	X	
C-reactive protein, high-sensitivity (hsCRP)	X							X							X	X	X	

Study YDAO	**Period III ⊢Maintenance Treatment**																	**Comments**
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Urinary albumin/creatinine ratio (UACR)	X			X				X				X			X	X	X	
Estimated glomerular filtration rate (eGFR)	X			X				X				X			X	X	X	Calculated using CKD-EPIcreat-cystC (2021 version).
Cystatin-C	X			X				X				X			X	X	X	
Pancreatic amylase	X			X				X				X			X	X	X	
Renin	X			X				X							X	X		
Aldosterone	X			X				X							X	X		
Lipase	X			X				X				X			X	X	X	
Micronutrient panel	X							X							X	X		Micronutrient deficiencies identified via laboratory tests should be repleted as clinically appropriate. See Section 5.3.2.
Immunogenicity (ADA) samples (predose)	X			X								X				X	X	Collect additional unscheduled samples if systemic drug hypersensitivity reactions occur. Collect immunogenicity and PK samples for immunogenicity before dosing. (See Sections 8.3.5.9 and 10.2.1)

Study YDAO	**Period III – Maintenance Treatment**																	**Comments**
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
PK sample (predose)	X			X				X				X						PK sample to be taken predose, followed by study intervention administration. Site should confirm that participant has accurately entered the dose date and time in their diary.
PK (2 to 6h post dose)	X																	This sample should be taken on the same day after the W16 dose.
PK (12 to 48 h postdose)					X													This would be an additional PK sampling only visit at 12 to 48 h after the Week 28 dose.
PK (48 to 120 h postdose)									X									This would be an additional PK sampling only visit at 48 to 120 h after the Week 40 dose.
PK Random (at any time during visit)															X	X	X	PK sample can be taken at any time during the visit.
Stored Samples																		
Exploratory biomarker samples	X			X				X				X			X	X		

Study YDAO	Period III – Maintenance Treatment																	Comments
Visit Number	6	7	8	9	-	10	11	12	-	13	14	15	16	17	18	ED	V801	
Weeks From Randomization	16	20	24	28	28	32	36	40	40	44	48	52	56	60	64		6 wks after last tx dose	
Visit Interval Tolerance (+/- Days)	3	3	3	3	-	3	3	3	-	3	3	3	3	3	3		5	
Visit Detail	F			F	PK	T	T	F	PK	T	T	F	T	T	F	F	F	F = fasting T = telehealth
Randomization and Dosing																		
Register visit with IWRS	X	X	X	X				X				X			X	X		For Unscheduled Visits: Only needed when dispensing study intervention.
Dispense study intervention via IWRS	X	X	X	X				X				X						For Unscheduled Visits: Only needed when dispensing study intervention.
Dispense supplies to participant	X			X				X				X						Ancillary supplies dispense as needed.
Participant returns study intervention supplies	X	X	X	X				X				X			X	X		See Section 6.5.
Assess study intervention(s) compliance	X	X	X	X		X	X	X		X	X	X	X	X	X	X		See Section 6.5.

Abbreviations: ADA = anti-drug antibodies; AESI = adverse events of special interest; BG = blood glucose; BMI= body mass index; BP = blood pressure; CKD-EPI = CKD Epidemiology Collaboration; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; FAS = full analysis set; ICF= informed consent form; IOCBP = individuals of childbearing potential; ISA = intervention-specific appendix; IWRS = interactive web response system; OSA= obstructive sleep apnea; PAP= positive airway pressure; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetics, PRO = patient-reported-outcome; PROMIS SD 8b= PROMIS Short Form v1.0 Sleep Disturbance 8b; PROMIS SRI 8a =PROMIS Short Form v1.0 Sleep Related Impairment 8b; PSG= polysomnography; SF-36v2 = Short Form 36 Version 2 Health Survey, Acute Form; SMBG = self-monitoring blood glucose; T2D = type 2 diabetes; V = visit; wks = week.

2. Introduction

2.1. Study Rationale

This Phase 3 multicenter, randomized, double-blind, master protocol is designed to assess the safety and efficacy of weekly eloralintide treatment compared with placebo in participants with moderate-to-severe obstructive sleep apnea and obesity or overweight, without type 2 diabetes.

2.2. Background

Obesity or overweight

The ongoing global obesity epidemic is associated with multiple comorbidities, including

rising incidence of type 2 diabetes (T2D)
increased risk for premature death, and
increased risk for some cancers (AMA 2013; CSAPH 2013; Lauby-Secretan et al. 2016).

Although lifestyle intervention is a cornerstone of treatment of obesity and overweight, efforts focused on reduced-calorie diets and increased physical activity have been shown to prompt physiological counterregulatory mechanisms that make it difficult to achieve and maintain weight reduction (Leibel et al. 1995; Sumithran et al. 2011). Lifestyle interventions alone are typically insufficient to achieve sustainable weight reduction in a majority of patients with obesity (Dombrowski et al. 2014).

Bariatric surgery has been considered the most potent clinical intervention for durable weight reduction. However, only about 1% of eligible patients with obesity are treated with surgical intervention (ASMBS 2018; Campos et al. 2020). Barriers to bariatric surgery include limited access, limited reversibility, and the potential risk of periprocedural complications.

For many individuals with obesity or overweight, pharmacological management may be a preferred or medically indicated option. With the advent of injectable incretin-based therapies, efficacious medications with an acceptable safety profile, are increasingly available for people with obesity or overweight (with at least 1 weight-related medical condition). These include the GLP-1 receptor agonists liraglutide 3.0 mg (Saxenda® package insert 2025) and semaglutide 2.4 mg (Wegovy® package insert 2025) and the GIP/GLP-1 receptor agonist tirzepatide (Zepbound® package insert 2025).

To expand treatment options for individuals living with obesity or overweight, Eli Lilly and Company (Lilly) is developing eloralintide.

Obstructive sleep apnea

Obstructive sleep apnea is a breathing disorder characterized by recurrent episodes of upper airway collapse during sleep, causing reductions or cessations of airflow and contributing to cardiovascular and metabolic morbidity and mortality (Gottlieb and Punjabi 2020). OSA affects approximately 25% of US adults (Gottlieb and Punjabi 2020), with 40% experiencing moderate-to-severe disease (Benjafield et al. 2019). Prevalence increases with age, is twice as common in

males (Peppard et al. 2013) and spans all racial and ethnic groups (Chen et al. 2015). Obesity is a major risk factor (Peppard 2000).

OSA treatment

Positive airway pressure is the first-line therapy for moderate-to-severe OSA, but adherence is variable, and many patients are unable or unwilling to use PAP long-term (Cowen et al. 2023; Gottlieb and Punjabi 2020). Weight reduction via anti-obesity medications and lifestyle interventions improves AHI and cardiometabolic outcomes (Hudgel et al. 2018). Bariatric surgery can improve OSA in patients with severe obesity but is associated with risk for perioperative and postoperative complications (Al Oweidat et al. 2023; Katasani et al. 2023).

Tirzepatide (Zepbound®) is the only FDA-approved pharmacotherapy for the treatment of OSA (Zepbound package insert, 2022).

Eloralintide treatment and unmet need

Eloralintide is a selective, long-acting amylin receptor agonist being developed as a once-weekly subcutaneous injection for the treatment of obesity and overweight in individuals with and without type 2 diabetes.

Weight reduction is associated with reduction of AHI (Malhotra et al. 2024), and available data suggest eloralintide n effect on weight may significantly improve OSA severity.

Eloralintide may serve as monotherapy or an adjunct to PAP with the potential to provide clinically meaningful improvements in sleep-disordered breathing, patient-reported outcomes, and cardiometabolic parameters.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of eloralintide may be found in the > Y a P ^ _ T R L _. Z] n ^ 7] Z N S `] P

2.3.1. Risk Assessment

To date, the described potential risks associated with eloralintide have been similar to those of newly approved obesity management medications. The most commonly reported TEAEs observed in eloralintide clinical studies were

decreased appetite
headache
fatigue
diarrhea, and
nausea.

2.3.2. Benefit Assessment

The potential benefits from participation in this study include body weight reduction and continued expert medical care for the study duration.

Participants may benefit by receiving personal health information, routine safety assessments, healthy nutrition and physical activity counseling, and frequent engagement with healthcare professionals during the study, including opportunities for lifestyle counseling and support.

Assessment of potential benefits can be found in Section 2 (Introduction) of the IB.

2.3.3. Overall Benefit-Risk Conclusion

The safety and efficacy profile seen to date for eloralintide (LY3841136) supports the overall benefit risk for participants in this study.

Given the measures taken to minimize participant risk in this study, the potential risks associated with eloralintide are justified by the anticipated benefits for individuals living with obstructive sleep apnea and obesity or overweight.

3. Objectives, Endpoints, and Estimands

This YDAO Phase 3 master protocol creates a framework to evaluate the safety and efficacy of weekly eloralintide for the treatment of participants with moderate-to-severe obstructive sleep apnea and obesity or overweight without type 2 diabetes.

The primary and secondary objectives stated in the table below are applicable to all ISAs under this YDAO master protocol.

Objectives	Endpoints
Primary	
To demonstrate that eloralintide MTD QW is superior to placebo for change in:	From baseline to Week 64:
body weight	percent change in body weight
AHI	absolute change in AHI (events per hour)
Key Secondary	
To demonstrate that eloralintide MTD QW is superior to placebo in change from baseline for:	From baseline to Week 64:
body weight	the achievement (Y/N) of body weight reduction of o ≥5% o h) (o h) - o h * (
blood pressure	change in SBP (mmHg)
lipid parameters	percent change in o triglycerides o non-HDL cholesterol
biomarkers of inflammation	percent change in hsCRP
AHI	percent change in AHI
sleep-related impairment	change in PROMIS Short Form sleep-related impairment 8a T-score
achieving OSA remission or mild asymptomatic OSA	the achievement (Y/N) of o AHI <5 or o AHI 5-) , b T _ S : F F g)
hypoxic burden	percent change in SASHB (% min/hour)
clinically meaningful change in AHI	the achievement (Y/N) of h50% decrease in AHI
Secondary	
To assess the effect of eloralintide MTD QW relative to placebo for:	From baseline to Week 64:
body weight	change in body weight (kg)

Objectives	Endpoints
BMI	change in BMI (kg/m^2)
glycemic parameters	change in fasting glucose change in HbA1c (%)
sleep disturbance	change in PROMIS Short Form Sleep Disturbance 8b T-score
excessive daytime sleepiness	change in ESS score
health-related quality of life	change in SF-36 v2 Acute Form domain and summary scores
health status	change in EQ-5D-5L health state utility and VAS
insulin sensitivity	percent change in fasting insulin
central adiposity measurements	change in waist circumference (cm) change in neck circumference (cm)
medication use	change in use of antihypertensive medications lipid-lowering medications
lipid parameters	percent change in o HDL cholesterol o VLDL-cholesterol o total cholesterol o LDL-cholesterol
blood pressure	change in DBP (mmHg)
patient-reported symptoms	the achievement (Y/N) of improved categorical shift in: o PGIS-OSA Fatigue o PGIS-OSA Sleepiness o PGIS-OSA Snoring o PGIS-OSA Sleep Quality
To assess the effect of eloralintide MTD QW relative to placebo for:	At Week 64
patient-reported symptoms	the achievement (Y/N) of improvement in: o PGIC-OSA Fatigue o PGIC-OSA Sleepiness o PGIC-OSA Snoring o PGIC-OSA Sleep Quality o PGIC most bothersome OSA symptom

Objectives	Endpoints
To characterize eloralintide PK and exposure-response relationships between eloralintide and key efficacy, safety and tolerability measures	PK and PD parameters
To describe the safety of eloralintide MTD QW as compared with placebo	Summary of safety data, including number and incidence of: treatment-emergent adverse events nausea, vomiting and diarrhea events adjudicated events (CV events, neurologic events, pancreatic events; new diagnosis of T2D; see Section 8.3.4)

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; DBP = diastolic blood pressure; EQ-5D-5L = 5-level version of EQ-5D; ESS = Epworth sleepiness scale; FOSQ = functional outcomes of sleep questionnaire; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MTD = maximum tolerated dose; PD = pharmacodynamic; PGIC-OSA=Patient Global Impression of Change-Obstructive Sleep Apnea; PGIS-OSA =Patient Global Impression of Severity-Obstructive Sleep Apnea; PK = pharmacokinetic; PROMIS = patient-reported outcomes measurement information; QW = once weekly; SAHB= sleep apnea specific hypoxic burden; SF-36 = Medical Outcomes Study 36-Item Short Form Health Survey; SBP = systolic blood pressure; TBD = to be determined; VAS =Visual Analog Scale; VLDL = very low-density lipoprotein; Y/N = yes/no.

Estimands

The study will use 2 estimands to address ICEs for the primary and key secondary objectives: a treatment-regimen estimand for the treatment policy strategy, and an efficacy estimand for the hypothetical strategy. These estimands have distinct interpretations and serve different purposes.

Treatment policy strategy

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

Hypothetical strategy

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

Estimands for OSA-related parameters

Treatment-regimen estimand

G S P %3 P W L _ P O NWTYTNLW \ ` P ^ _ T Z Y ZQ TY _ P] P ^ _ T ^ 2

What is the treatment difference in the change of AHI from baseline to Week 64 between eloralintide MTD QW and placebo, as an adjunct to healthy diet and physical activity, in participants with YDAO study condition/disease regardless of adherence to study intervention?

Treatment-regimen estimand attributes:

Population: participants with YDAO study condition/disease.
Endpoint: change of AHI from baseline to Week 64.

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

Intercurrent event:

Intercurrent Event	Handling Strategy
Permanent discontinuation of study intervention	Treatment policy
Initiation of prohibited OSA medication or procedure	No treatment hypothetical
Initiation of prohibited weight management medication or procedure that is highly effective in weight loss or for treatment of OSA condition	No treatment hypothetical
Initiation of PAP therapy (YSA1 only)	No treatment hypothetical

Population-level summary and treatment effect of interest: difference in mean change in AHI from baseline to Week 64 between eloralintide MTD and placebo.

Rationale for the estimand*:* This estimand aims to evaluate the efficacy of eloralintide that reflects the real-life behavior of the target population.

%% ' " ! " - $ + , ' (!) #

GSP %8 PW L_PO NWTYTNLW \`P^_TZY ZQ TY_P]P^_ T^2

D, 4 - ? 5 > ? 4 1 ? = 1 - ? 9 1 : ? 0 5 2 2 1 = 1 : / 1 5 : ? 4 1 / 4
&8 ; = - 8 5 %?,5 0 1 < 8 - / 1 . ; - > : @ ? = 5 ? 6 @ < 4 C > 3 / - 8 1 -
- / ? 5 A 5 ? C 5 *participants with YDAO study condition/disease* 5 2 ? 4 1 C B ; @ 8 0 = 1 9 -
= - : 0 ; 9 8 C - > > 5 3 : B 1 1 0 1 7 ? >= 1 - - : ? 0 5 1 B 5 ; ? @ 5 8 2 0 ? = 1 : ; <? != ; 4 5 . 5 ? 1 0
? = 1 - ? 9 1 : ? > # E

C] Z S T M T _ P O _] P L _ X P Y _ ^ T Y N W ` O P 2 [ ] Z S T M T _ P O
_ 8 S T R S W d bPPQTQRPSN__ TWaZP^ ^ Z] Q Z] _] P L _ X P Y _ ZQ B F 6
Z Y W & d "

Efficacy estimand attributes:

Population: in participants with YDAO study condition/disease
Endpoint: absolute change of AHI from baseline to 64 weeks
Treatment condition: the randomized treatment with allowance for potential dose interruptions and modifications
Intercurrent events:

Intercurrent event	Handling strategy
permanent discontinuation of study intervention	hypothetical strategy

initiation of prohibited OSA treatment	hypothetical strategy
initiation of prohibited weight management treatments related to highly effective weight loss or for treatment of OSA condition	hypothetical strategy
Initiation of PAP therapy (YSA1 only)	hypothetical strategy

Population-level summary and treatment effect of interest: difference in mean change in AHI from baseline to Week 64 between eloralintide MTD and placebo.

Rationale for the estimand: This estimand aims to evaluate the efficacy of eloralintide under the ideal condition that all participants would adhere to the randomly assigned study intervention without being confounded by the initiation of prohibited treatments.

Estimands for weight-related parameters

Treatment-regimen estimand

The clinical question of interest is:

D, 4 - ? 5 > ? 4 1 ? = 1 - ? 9 1 : ? 0 5 2 2 1 = 1 : / 1 5 : ? 4 1 < 1
- ? 1 1"7! . 1 1 B; 1 - 8) 5 + : % ? 5 0 1 < 8 - / 1 . ; - > - : - 0 6 @ : / ?
< 4 C > 5 / - 8 *participants with YDAO study condition/disease* = 1 3 - = 0 8 1 > > ; 2
- 0 4 1 = 1 : / 1 ? ; > ? @ 0 C 5 : ? 1 = A 1 : ? 5 ; : ; = 5 : 5 ? 5 - ?
? = 1 - ? E 9 1 : ? > #

Treatment-regimen estimand attributes:

Population: in participants with YDAO study condition/disease.
Endpoint: percent change in body weight from baseline to Week 64.
Treatment condition: the randomized treatment with allowance for potential dose interruptions and modifications regardless of adherence to study intervention or initiation of prohibited weight management treatments.
Intercurrent event: there will be no ICEs since treatment adherence, and the initiation of prohibited weight management treatments are part of the treatment condition.
Population-level summary and treatment effect of interest: difference in mean percent change in body weight from baseline to Week 64 between eloralintide MTD and placebo.

Rationale for the estimand

G S T ^ P ^ _ T X L Y O L T X ^ P W Z] P W L S W L _ T O] P P Q W S P H Q _ P ^ Q] Q R Q S P L a N] d Z L Z W
_ S P _ L] R P _ [Z [` W L _ T Z Y &

Efficacy estimand

G S P N W T Y T N L W \ ` P ^ _ T Z Y Z Q T Y _ P] P ^ _ T ^

D, 4 - ? 5 > ? 4 1 ? = 1 - ? 9 1 : ? 0 5 2 2 1 = 1 : / 1 5 : ? 4 1 < 1
" ! B 1 1 7 > . 1 ? B) 1 + 1 % : 0 & 8 < 8 - 8 1 : ? 5 0 1 > - : - 0 6 @ : / ?

< 4 C > 5 / - B *participants with YDAO study condition/disease* 5 2 ? 4 1 C B ; @ 8 0 =
; : ? 4 1 5 = = - : 0 ; 9 8 C - > > 5 3 : 1 0 ? = 1 - ? 9 1 : ? 2 ; = "
B 1 5 3 4 ? 9 - : - 3 1 1 : ? ? = 1 - ? 9 1 : ? > #

Efficacy estimand attributes:

Population: in participants with YDAO study condition/disease.
Endpoint: percent change in body weight from baseline to 64 weeks.
Treatment condition: the random treatment with allowance for potential dose interruptions and modifications.
Intercurrent events:

Intercurrent event	**Handling strategy**
permanent discontinuation of study intervention	hypothetical strategy
initiation of weight management treatments	hypothetical strategy

Population-level summary and treatment effect of interest: difference in mean percent change in body weight from baseline to Week 64 between eloralintide MTD and placebo.

Rationale for the estimand

G S T ^ P ^ _ T X L Y O L T X ^ P W Z] P W I Y O _ P T] O P _ S P S P T O P P Q L Q W T N N L Z N Y d O T Z _
[L] _ T N T [L L O Y S _ P ^] P b Z _ ` Z W O _ S P ] L Y O Z X W d L ^ ^ T R Y P O ^ _ ` O d
M d _ S P T Y T _ T L _ T Z Y Z Q [ ] Z S T M T _ P O b P T R S _ X L Y L R P

4. Study Design

4.1. Overall Design

Study J3R-MC-YDAO (YDAO) is a multicenter, randomized, parallel-arm, double-blind, placebo-controlled Phase 3 study to evaluate the efficacy and safety of eloralintide maximum tolerated dose (1.5, 3, 6, or 9 mg) QW versus placebo in participants with obesity or overweight, without type 2 diabetes, who have been diagnosed with moderate-to-severe OSA.

This basket-type master protocol will investigate 2 participant populations, described in 2 ISAs:

YSA1 will include participants who are unable or unwilling to use PAP therapy.
YSA2 will include participants who are on PAP therapy for at least 3 consecutive months prior to Visit 1, and plan to continue PAP therapy during the study.

Participants will be assigned to the ISA that reflects their current PAP usage.

At Visit 1, master protocol eligible participants will be assigned to either Study YSA1 or YSA2.

At Visit 2, within each ISA, eligible participants will be randomly assigned in a 1:1 ratio to treatment (eloralintide MTD QW) or placebo. See Section 6.3.

The study consists of

Screening: up to 6 weeks
Treatment: 64 weeks
- dose-escalation period (to MTD): 12 weeks, and
- treatment maintenance period: 52 weeks

Posttreatment follow-up: 6 weeks

The visit frequency will be every 4 to 6 weeks.

The maximum duration of treatment is 64 weeks.

The study schema is presented in Section 1.2. Procedures and assessments for each visit are presented in the SoA, Section 1.3.

Number of participants

YSA1: Approximately 400 participants will be randomized in a 1:1 ratio to eloralintide MTD or placebo.

YSA2: Approximately 400 participants will be randomized in a 1:1 ratio to eloralintide MTD or placebo.

An upper limit of approximately 70% enrollment of AMAB participants will be used to ensure a sufficient number of AFAB participants. To ensure adequate representation of individuals with higher BMI, no more than 10% of participants will have a BMI between 27 kg/m² and less than 30 kg/m². This approach is intended to address the significant unmet needs within this population.

4.2. Scientific Rationale for Study Design

Two studies conducted as independent ISAs under a master protocol will evaluate the efficacy of weekly eloralintide compared to placebo in participants with overweight or obesity who have a diagnosis of moderate-to-severe OSA without T2D.

Choice of primary endpoint

The 2 independent primary objectives are

to demonstrate that eloralintide MTD QW is superior to placebo for the percent change in body weight at Week 64 compared to baseline, and
to demonstrate that eloralintide MTD QW is superior to placebo for absolute change in apnea-hypopnea index (AHI) at Week 64 compared to baseline.

Study YDAO will be considered positive if either or both independent primary objectives are met.

Key secondary objectives will include changes from baseline at Week 64 in selected parameters, including weight-related, systolic blood pressure, lipid, biomarkers of inflammation, AHI-related, hypoxic burden, and sleep-related impairment parameters.

Choice of comparator

A placebo comparator was selected for this study in accordance with regulatory guidance (EMA 2016; FDA 2025) and to evaluate weight maintenance and dynamic changes in body composition during weight regain. Unfortunately, obesity management medication discontinuation remains common after achieving initial BW reduction, and thus the placebo arm serves as data to represent this real-world scenario (Gleason et al. 2024). In addition, all participants, regardless of treatment assignment, will continue to receive lifestyle-modification counseling consistent with current guidelines and local standards for weight management (AACE-ACE 2016; Jensen et al. 2014; Apovian et al. 2015). Specifically, participants will consult with a dietitian or equivalent qualified delegate throughout the study to focus on a healthy diet and physical activity. Participants who develop T2D will also receive diabetes education consistent with guidelines for T2D management (American Diabetes Association-EASD 2022).

Study duration

The planned duration of treatment for the primary endpoint at 64 weeks allows for at least a 52-week treatment period at the maximum tolerated dose (MTD or 9 mg). This duration is considered appropriate to assess the effects and benefit-risk of eloralintide compared with placebo on body weight and is consistent with regulatory guidelines (EMA 2016; FDA 2025).

The effects of study intervention cessation will be assessed in the 6-week posttreatment follow-up period.

Concomitant medications

To minimize the potential confounding effect of changes to concomitant medications, participants will be permitted to use concomitant medications that do not interfere with the assessment of efficacy or safety characteristics of the study intervention.

Refer to Section 6.9 for the concomitant medications relevant to participants with OSA, overweight, and obesity without T2D.

Collection of race and ethnicity data

In this study, collection of demographic information includes race and ethnic origin. The scientific rationale is based on the need to assess variable response in safety or efficacy based on race or ethnic origin. This question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

The justification for eloralintide Phase 3 doses in OSA and the dose-escalation scheme is based on the totality of evidence from the Phase 1 single and multiple ascending dose Study J3R-MD-YDAA and Phase 2 dose-finding Study W8M-MC-LAA1, including safety, tolerability, PK, PD, and efficacy data.

For the Phase 3 OSA studies (Master Protocol YDAO and all studies evaluated under this protocol [YSA1 and YSA2]), an MTD approach will be employed.

Participants randomly assigned to receive eloralintide will start with a subcutaneous 1.5 mg dose QW and undergo dose escalation every 4 weeks until the 9 mg dose or the MTD is reached. Investigators will be instructed to make all efforts to dose-escalate all participants to the intended 9 mg subcutaneous weekly target dose. To maintain blinding, participants randomly assigned to the placebo treatment group will also receive study intervention every 4 weeks during the dose-escalation period, following a sham dose-escalation schedule to match the eloralintide group.

In addition to the target 9 mg dose, other permitted maintenance doses in this study are 1.5 mg, 3 mg, or 6 mg for participants unable to attain the target dose.

Dose adjustment will be allowed for participants experiencing tolerability issues.

In the J3R-MC-YDAG (ENLIGHTEN-1) and J3R-MC-YDAF (ENLIGHTEN-2) studies, all 4 doses will be included as separate arms. The safety data for each dose will be collected from the weight management population and used as supplemental information for the safety assessment of the permitted doses in this OSA study.

> In Part B (multiple ascending dose) of Study YDAA, a dose range of eloralintide from 1.2 to 12mg SC QW treatment (without dose-escalation) in participants with obesity or overweight, showed a weight reduction trend that was dose- and time-dependent. At the highest dose of 12 mg QW, the maximal LS mean percent change from baseline in weight and 90% CI weight reduction observed on Day 85, were -11.3% (-12.5, -10.0). The placebo-adjusted LS mean percent change and 90% CI were -11.5% (-13.3, -9.6).
> In Study YDAA, eloralintide was well-tolerated in participants with obesity or overweight without adopting a gradual dose-escalation approach, even for the highest dose of 12 mg QW.
> In Study LAA1, a Phase 2 parallel-group, double-blind study to investigate weight management with eloralintide SC administered QW compared with placebo in participants with obesity or overweight and without diabetes mellitus, eloralintide

showed a dose-related weight reduction relationship covering the doses 1 mg, 3 mg, 6 mg, 9 mg, 6/9 mg or 3/6/9 mg compared with placebo.
While a non-dose-escalated dosing approach to 9 mg showed acceptable tolerability, data from Study LAA1, which utilized a dose-escalation approach to reach 9 mg, suggested that tolerability, in particular GI AEs, can be further improved with a 3/6/9 mg dose-escalation approach.
In general, small reductions in heart/pulse rate, systolic and diastolic BPs have been observed. There are no other AEs noted across studies that would preclude evaluation of eloralintide in a Phase 3 clinical program.

Considering OSA outcomes in participants with obesity or overweight are closely related to meaningful weight reduction, the current eloralintide single arm versus placebo study design encourages participants to reach their maximal tolerated dose for body weight reduction.

4.4. End of Study Definition

The end of the Master Protocol will occur when all ISAs are complete. For each ISA, the end of the study is defined as the date of the final visit or the last scheduled procedure of the last active participant assigned to treatment in that ISA.

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

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

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria before receiving a dose of study intervention as part of an ISA. Participant eligibility under the master protocol must be met to be eligible for randomization to an ISA. Additional eligibility criterion may apply for each particular ISA.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Age

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

Type of participant and disease characteristics

2. Investigator confirms that participant has a confirmed history of moderate-to-severe OSA. The moderate-to-severe OSA history should be confirmed by a source other than the participant.
3. Have an AHI h) - Z Y C F < study at screening. Z Q _ S P

Weight

4. = L a P L 7 @ >at Visit 1. V R ' X *
   Note: In participants with limb amputation or limb loss, the investigator should reach out to the Lilly medical monitor for information regarding calculation of BMI.
5. Have a stable body weight (<5% body weight change) for 90 days prior to screening at Visit 1.
6. Have a history of at least 1 self-reported unsuccessful dietary effort to reduce body weight

Sex assigned at birth and contraceptive/barrier requirements

7. IOCBP, INOCBP, and individuals AMAB who agree to abide by the reproductive and contraceptive requirements provided in Section 10.4. may participate in this study. See Section 10.4 for definitions and additional requirements related to contraception.

Note: Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

Informed consent

8. Are capable of giving signed informed consent as described in Appendix 1, Section 10.1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Other inclusion criteria

9. Are reliable and willing to make themselves available for the duration of the study and attend required study visits, and are willing and able to follow study procedures as] P \ ` T ] P O $ ^ ` N S L ^ q
   self-inject study intervention
   Note: Persons who are not able to perform the injections must have the assistance of an individual trained to inject the study intervention
   store and take the provided study intervention as directed
   maintain electronic study diary and paper log, and
   complete the required questionnaires.

5.2. Exclusion Criteria

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

Medical conditions

Obesity-related

10. Have a prior or planned surgical treatment for obesity

Exception: The following are allowed if performed > 1 year before screening (Visit 1):

   liposuction
   cryolipolysis, or
   abdominoplasty.

11. Have a prior or planned endoscopic procedure and/or device-based therapy for obesity, such as, but not limited to
   mucosal ablation
   gastric artery embolization
   laparoscopic adjustable gastric banding
   intragastric balloon, or
   duodenal-jejunal endoluminal liner.

Exception: Prior device-based therapy is acceptable if device removal was more tha Y . q X Z Y _ S ^ prior to screening (Visit 1)

12. Have obesity induced by other endocrinologic disorders, for example, Cushing Syndrome, or are diagnosed with monogenetic or syndromic forms of obesity, for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome.

Sleep-disordered breathing related

13. Any previous or planned surgery for sleep apnea or major ear, nose or throat surgery, including tonsillectomy and adenoidectomy, that still may affect breathing at time of Visit 1. Inclusion of a participant with more minor ear, nose or throat surgery (for P c L X [W P $ O P a T L _ P O ^ P [_ ` X " b T W W M P L _ _ S P T
14. Diagnosis of Central or Mixed Sleep Apnea with % of mixed or central L [Y P L ^ ' S d [Z [Y P L ^ h - ($ Z] O T L R Y Z ^ T ^ Z Q 8 S P
15. Diagnosis of Obesity Hypoventilation Syndrome or daytime hypercapnia.
16. Active device treatment of OSA other than PAP therapy (for example, dental appliance), or other treatment, that in the opinion of the investigator, may interfere with study outcomes, unless willing to stop treatment at Visit 1 and throughout the study.
17. Respiratory and neuromuscular diseases that could interfere with the results of the study in the opinion of the investigator.
18. Significant craniofacial abnormalities that may affect breathing.

Diabetes-related

19. Have T1D, T2D, or any other types of diabetes, history of ketoacidosis, or hyperosmolar state/coma.

Note: Participants with a history of gestational diabetes are eligible to participate in this study.

20. Have central laboratory evidence diagnostic of diabetes at screening (Visit 1), indicated by 1 or more of the following criteria:
    = M 6) N h . &mmol/mol) h , 0
    Q L ^ _ T Y R ^ P] ` X R W ` N Z ^ P or h) * . X R ' O ? ! h / & (
    ] L Y O Z X R W ` N Z ^ P h * ((X R ' O ? ! h)) &) X X Z W ' ?

Renal

21. Have renal impairment measured as eGFR <30 mL/min/1.73 m2, calculated by eGFRcr-cys (CKD-EPIcreat-cyst) formula as per Chronic Kidney Disease Epidemiology Collaboration as determined by central laboratory during screening (Visit 1).

Autoimmune

22. Have evidence of significant, active autoimmune abnormality, for example, lupus or rheumatoid arthritis, that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids during the course of the study.

Cardiovascular

23. Have had within 90 days prior to screening (Visit 1):
    acute myocardial infarction
    cerebrovascular accident (stroke)
    coronary artery revascularization
    unstable angina, or
    hospitalization due to congestive heart failure.

24. Have a history or diagnosis of New York Heart Association Functional Classification Class IV congestive heart failure.

25. Have either

    ongoing asymptomatic bradycardia defined as < 50 beats per minute at Visit 1, or
    ECG findings at Visit 1 of second degree AV block or higher, or
    history of symptomatic bradycardia with uncorrected etiology, including diagnosis of sick sinus syndrome.

    Note: historical symptomatic bradycardia or AV nodal block due to a corrected transient etiology will not be considered exclusionary (for example, previous beta-blocker, calcium channel blocker, or other medication that can lead to AV block; or conduction disorder corrected with a cardiac device).

Hepatic

26. Have acute or chronic hepatitis, including a history of autoimmune hepatitis, signs, or symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of these laboratory values confirmed by central labs at screening (Visit 1)

    6?G Z] 6FG WPaPW h+&(c _SP H?A

    Note: Participants with nonalcoholic fatty liver disease may participate in the study if their ALT level is <3.0x the ULN (Visit 1).

    6?C WPaPW h)&-c _SP H?A

    G7? WPaPW h)&-c _SP H?A$ST^P_cXNPd[_ZQQZ<]TW[MH]

    Syndrome.

Endocrine

27. Have evidence of a significant, uncontrolled endocrine abnormality, in the opinion of the investigator, for example, thyrotoxicosis or adrenal crisis.
28. Have thyroid-stimulating hormone levels outside the normal reference range for the central laboratory at Visit 1.

    Exception: Participants with hypothyroidism who are clinically euthyroid and on stable thyroid replacement therapy for at least 60 days prior to Visit 1 are acceptable exceptions to this criterion.

Malignancy

29. Have a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.
30. Have a history of an active or untreated malignancy or are in remission from a malignancy for less than 5 years (Visit 1).

    Exceptions:

    basal or squamous cell skin cancer
    in situ carcinomas of the cervix
    Grade 1 (for example, Gleason 6 or lower) prostate cancer

Hematology

31. Have any hematological condition that may interfere with HbA1c measurement, for example, hemolytic anemias or sickle cell disease.

Psychobehavioral

32. Have a history of significant active or unstable major depressive disorder or other severe psychiatric disorder, such as schizophrenia, bipolar disorder, or other serious mood or anxiety disorder, within the last 2 years
    OR
    > Y _ S P T Y a P ^ _ T R L _ Z] n ^ Z [T Y T Z Y $ S L a P L Y d ^ T
    individual at higher risk of study participation.
33. Have a PHQ-9 score of 15 or more at screening visit (Visit 1), or at randomization (Visit 2).
34. Are, in the judgment of the investigator, deemed to be at significant risk for suicide
35. H L a P L Y ^ b P] P O l d P ^ m _ Z P T _ S P `] T N D T O P L ^ W _ T > Z O Y P L , _ T Z
    portion of the C-SSRS and the ideation occurred within the past 3 months
    OR
    S L a P L Y ^ b P] P O l d P - r e l a t e d b e h a v i o r s (a c t u a l a t t e m p t , i n t e r r u p t e d
    attempt, aborted attempt, preparatory act or behavior) Z Y _ S P l ^ ` T N T O L W M P S
    of the C-SSRS and the behavior occurred within the past 5 years.
    Note: Non-suicidal self-injurious behavior is not considered suicide-related behavior.

Gastrointestinal

36. Have a known clinically significant gastric emptying abnormality, such as severe diabetic gastroparesis or gastric outlet obstruction, or chronically take drugs that directly affect GI motility.
37. Have had a transplanted organ or are awaiting an organ transplant.
    Exception: corneal transplants or keratoplasty are allowed.
38. At the time of screening, have a planned surgery, except for minor surgical procedures, to occur during the study.

Prior/concomitant therapy

39. Are receiving metformin or any other glucose-lowering medication, regardless of the indication for use, within 90 days prior to screening (Visit 1), or between Visit 1 and Visit 2
    Note: The use of SGLT-2 inhibitors is only permitted if the participant has been on a stable dose for at least 90 days prior to screening and if it is used for nondiabetic indications.
40. Are receiving or have received within 90 days prior to screening chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, single intraarticular injections, single localized injections of skin lesions or tendon, or inhaled preparations).

41. Have known or suspected hypersensitivity to amylin or, study product.
42. Have taken within 90 days prior to screening (Visit 1) prescribed or over-the-counter medications, or alternative remedies, including herbal or nutritional supplements, intended to promote body weight reduction. Examples include, but are not limited to
    GLP-1 RA
    GIP/GLP-1 RA
    orlistat
    sibutramine
    phenylpropanolamine
    mazindol
    phentermine
    lorcaserin
    phendimetrazine
    phentermine/topiramate
    naltrexone/bupropion, and
    ingested material that transiently occupies space in the stomach, for example, hydrogel capsules made of cellulose and citric acid.
43. Are receiving or have received within 90 days of screening, medications that may cause significant weight gain, including but not limited to tricyclic antidepressants, atypical antipsychotics, and mood stabilizers, unless at a stable dose for more than 6 months with no planned dose changes, and documented weight stability (see Appendix 8: Section 10.8)
44. Have started subcutaneous/intramuscular or implantable/injectable contraceptives such as Depo-Provera® and Nexplanon, within 18 months prior to screening (Visit 1).
    Note: Intrauterine devices are acceptable.
45. Unwillingness to discontinue over the counter (herbal or supplemental) medication that, in the opinion of the investigator, can interfere with the study.
46. Use of stimulants less than 90 days prior to Visit 1. For example,
    modafinil
    armodafinil
    solriamfetol
    pitolisant
    amphetamine
    dextroamphetamine
    dexmethylphenidate
    methylphenidate, or
    lisdexamfetamine.
47. Use of other medications less than 90 days prior to Visit 1. For example,
    hypnotics
    mirtazapine
    opioids, or
    trazodone.

Other medical

48. Use of any over the counter or prescription medications that could affect the evaluation of excessive sleepiness, per investigator discretion.
49. Requires the use of supplemental oxygen.
50. Has a history of clinically relevant medical, behavioral, or psychiatric disorder, other than OSA, that is associated with insomnia or excessive sleepiness.

Prior/concurrent clinical study experience

51. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
52. Within the last 90 days before screening (Visit 1), have participated in a clinical study and received active treatment, or unknown if they received active treatment.
53. Have previously completed or withdrawn from this study or any other study investigating eloralintide after receiving at least 1 dose of intervention.

Other exclusion criteria

54. Are pregnant, intending to breastfeed or intending to conceive.
55. Are investigator site personnel directly affiliated with this study and/or their immediate family. Immediate family is defined as a spouse, legal partner, parent, child, or sibling, whether biological or legally adopted.
56. Have any condition, unwillingness, or inability, not covered by any of the other exclusion N] T _ P] T L $ b S T N S T Y _ S P T Y a P ^ _ T R L _ Z] n ^ Z [T Y example, hypersensitivity or contraindication.
57. Have any medical condition that, in the opinion of the investigator, would be a contraindication to participation in the study.
58. Are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), participants will meet a dietitian, or equivalent qualified delegate, according to local standards, to receive lifestyle counseling.

Healthy nutrition patterns and physical activity goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the study will be reinforced at each visit by site staff. Ensuring participants have optimal nutritional intake is highly recommended. In addition to Section 5.3.1, nutrition support and lifestyle resources are available in the investigator resources.

To encourage adherence, it is recommended that the participant complete their 3-day nutrition and physical activity log before visits per SoA & 9 `] T Y R P L N S a l o g i s T _ $ _ S P [L reviewed, and advice may be provided as needed to maximize adherence, nutrition, and hydration.

5.3.1. Meals and Nutrition

At the randomization visit and subsequent visits, study participants will receive individualized counseling regarding a healthy nutrition pattern with the goal of optimizing nutritional status. The counseling will be performed by a dietitian or nutritionist, or equivalent qualified designee, according to the local standard.

Counseling considerations

The focus of the counseling should facilitate balanced and sufficient food and beverage choices for adequate nutritional intake and hydration. Counseling should include instruction on customized nutrient-dense food and beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations.

The 3-day nutrition and physical activity log should be reviewed at lifestyle consultations per SoA (Section 1.3). It is recommended that the dietitian or equivalent qualified delegate communicate with the investigator regarding participant intake and/or physical activity. Any concerns should be discussed with the investigator. At the discretion of the investigator, to provide additional support of nutrition and physical activity goals, the 3-day nutrition and physical activity log can be completed more frequently than what is indicated in the SoA.

The table below summarizes the recommendations for both general dietary and fluid intake (Almandoz et al. 2024; US Dietary Guidelines 2020-2025) and minimum dietary and fluid intake. Adequate nutritional intake and hydration recommendations, in the setting of weight XLYLRPXPY_$ XLd MP TYOTaTO`LWTePO ML^PO ZY _S comorbidities, appetite levels, and GI tolerability. Recommendations should focus on prioritizing intake of healthy carbohydrate, protein, and fluid.

	General intake recommendations	Minimum intake recommendations
Fluids (that is, water or decaffeinated and non-sugary beverages)	2000-3000 ml/day	2000 ml/day
Energy	1200-1500 kcal/day (women) 1500-1800 kcal/day (men)	800-1000 kcal/day
Protein	0.8-1.2 g/kg/day (in some cases, calculation may be based on ideal body weight)	60 g/day
Carbohydrates	45%-65% of energy intake	50 g/day
Fat	20%-35% of energy intake	15 g/day (<10% saturated fat/day)

Consider the following principles to guide participant education in counseling sessions:

the importance of meeting nutritional and hydration recommendations ^STQ_TYR _SP QZN`^ ZQ ZMP^T_d _]PL_XPY_ Q] for optimal health

decreased appetite and increased fullness after eating typically drive a reduction in food intake. Additional voluntary food restriction, when appetite is reduced, is unnecessary and may be harmful

avoid skipping meals

eating smaller and more frequent (every 3 to 4 hours) meals or snacks

focus on nutrient-rich, minimally processed foods. Limit foods high in solid fats, added sugar, and salt
include fiber-rich foods, and
for each meal (on an 8- to 10-inch [20-25 cm] plate), consider including approximately half plate of fruits or vegetables, quarter plate of whole grains, and quarter plate of protein-rich foods. Incorporate 1 to 2 servings of healthy, unsaturated fats on most days (for example, nuts, avocado, olive oil, and salmon).

In addition, the following strategies are encouraged to facilitate adequate nutritional intake and hydration:

multivitamin and/or micronutrient supplementation
meal replacements (for example, protein- and micronutrient-rich shakes or bars) that can be sipped or eaten slowly over several hours, particularly for participants with markedly reduced appetite and poor intake, and
more frequent nutritional counseling if needed.

5.3.2. Monitoring Nutritional Needs

As with other obesity management medications, there is potential that a small number of participants on study intervention will experience a significantly reduced caloric intake.

Individual risk factors for inadequate nutrition or dehydration should be taken into consideration, including, but not limited to, age, medical history/comorbidities, concomitant medications, clinical conditions (for example, infection), and GI symptoms (for example, nausea, vomiting, diarrhea). Clinically monitor the nutritional and hydration status of participants and assess for any signs or symptoms of inadequate nutrition or dehydration, including

vital signs
targeted physical examination
recent central laboratory data, and
nutrition and physical activity log (per SoA).

Obtain additional laboratory tests as clinically appropriate via the central laboratory. Use local laboratory tests as needed, for example for acute management, or if lab tests are not available centrally. See Sections 8.3.5.13, 10.2, and 10.2.2 for more information on clinical laboratory tests.

By recognizing early signs of inadequate nutrition and dehydration, preventive actions can be taken to reduce the risk of potential complications.

Monitor for the following, which could be risk factors/signs for inadequate nutrition or dehydration.

Potential concern	Early signs include, but are not limited to
Inadequate nutrition	carbohydrate intake <50 g/day protein intake <60 g/day fat intake <15 g/day caloric intake <800-1000 kcal/day, and skipping multiple meals
Dehydration	low fluid intake (<2000 ml/day) volume loss (for example, diuretic or laxative use, diarrhea, and vomiting) elevated pulse rate decreased or low blood pressure, and high blood urea nitrogen to creatinine (BUN:Cr) ratio

If there are concerns of inadequate nutrition or dehydration, mitigation strategies should be R`TOPO Md LY L^^P^^XPY_ ZQ _SP ^PaP]T_d ZQ _S etiologies, and GI symptoms. See Sections 6.6.2 and 10.2.2 for the recommended steps to follow.

5.3.3. Healthy Physical Activity

At the randomization visit and subsequent visits, participants will receive guidance on achieving and maintaining a healthy physical activity level. A minimum of 150 minutes per week of moderate intensity aerobic exercise, along with a minimum of 3 muscle strengthening (resistance) workouts per week, is recommended.

Lifestyle-modification counseling should be completed according to the SoA and must be OZN`XPY_PO TY _SP [L]_TNT[LY_n^ XPOTNLW]PNZ]

5.3.4. Other Restrictions

Activity before blood collections

Participants will abstain from significant exercise 24 hours before each blood collection for clinical laboratory tests.

Blood donation

Study participants should not donate blood or blood products during the study or for 10 weeks after their last dose of study intervention.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

5.5. Criteria for Temporarily Delaying Randomization of a Participant

Participants may have their randomization temporarily delayed if additional clinical information, including laboratory testing, is needed to be repeated.

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.

This table lists the interventions used in this clinical study.

Intervention Name	Eloralintide	Eloralintide Placebo
Dosage Level(s)	1.5 mg 3 mg 6 mg 9 mg	Placebo
Route of Administration	Subcutaneous using a prefilled syringe	Subcutaneous using a prefilled syringe
Frequency of Administration	Once weekly	Once weekly
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized

Abbreviation: EU= European Union.

Eloralintide dose escalation

Participants randomly assigned to eloralintide will start with a 1.5 mg QW dose. Increase dose every 4 weeks until 9 mg or MTD is reached, as outlined in Section 4.1. During the dose-escalation period, the investigator should make every effort to proceed through each dose-escalation step per the study schedule in order for participants to achieve their MTD dose.

Allowed MTD doses

Allowed doses are 1.5 mg, 3 mg, 6 mg, or 9 mg.

Participants randomly assigned to placebo

To maintain blinding, participants randomly assigned to the placebo treatment group will also receive study intervention every 4 weeks during the dose-escalation period, following a sham dose-escalation schedule to match the eloralintide treatment group.

Timing of dose administration

Participants should try to administer the SC injections on the same day of the week and similar time of day, but there are no restrictions on the time of day for each weekly dose.

The participant will record the actual date and time of all dose administrations in the diary.

Missed doses

If a dose is missed, the participant should take it as soon as possible unless it is within 72 hours of the next dose, in which case that dose should be skipped. If a dose is skipped, the next dose should be taken at the appropriate time, and the skipped dose should be recorded in diary.

Site staff should document the planned treatment date for the dose and record a reason the dose was missed in the eCoA portal.

The day of weekly administration can be changed, if necessary, if the last dose was administered 72 or more hours before.

Anatomical location of injections

Acceptable locations for injection by the participant include the abdomen or thigh, or upper arm if another person gives the injection.

Participants should rotate injection sites from 1 injection to the next, even when injecting within the same region.

A new prefilled single-dose syringe will be used for each injection.

The participant will record the injection-site location of all dose administrations in the diary.

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.

6.2. 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 interventions 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.

Participant responsibilities

Study participants will be trained on the proper storage and handling of the study intervention and should follow in-use storage conditions according to the instructions for use provided by the Sponsor.

6.3. Assignment to Study Intervention

Participants will be assigned to 1 of 2 ISAs according to baseline PAP at Visit 1.

Participants with OSA who are unable or unwilling to use PAP therapy will be assigned to YSA1.

Participants who are on PAP therapy for at least 3 months at time of screening and plan to continue PAP therapy during the study will be assigned to YSA2.

At Visit 2, for each ISA, approximately 400 participants will be randomly assigned in a 1:1 ratio to receive weekly doses of placebo or eloralintide MTD.

Stratification will occur independently in each study. Participants will be stratified by:

sex (AMAB/AFAB), and

baseline AHI (X Z O P] L _ P 2 6 = > h) - L Y O 4 + (' ^ P a P] P 2 6 =

6.4. Blinding

This is a double-blind study. Study participants and study personnel are blinded to study intervention. Blinding will be maintained throughout the conduct of the study, as described in the separate Blinding and Unblinding Plan.

Method of treatment assignment

Randomization to the ISAs and to the treatment groups within the ISAs will be determined by a computer-generated random sequence using an IWRS. Participants will be aware of which ISA they are assigned to but will be blinded to the treatment group to which they are assigned.

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

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from a Sponsor medical monitor for the participant to continue in the study.

Emergency unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding Z Q L [L] _ T N T [L Y _ n ^ _] P L _ X P Y _ L ^ ^ T R Y X P Y _ T ^ b L participant n safety must always be the first consideration in making such a determination. If a [L] _ T N T [L Y _ n ^ _] P L _ X P Y _ L ^ ^ T R Y X P Y _ T ^ ` Y M W T Y O

If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Emergency unblinding may be performed through the IWRS. This option may be used ONLY if [illegible] requires knowledge of the [illegible] treatment assignment. All unblinding events are recorded and reported by the IWRS.

Discontinuation after unblinding

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

6.5. Study Intervention Compliance

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

Participant compliance with ISA study interventions will be assessed at each visit summarized in the SoA (Section 1.3). Compliance will be assessed by direct questioning and counting of unused study intervention returned and documented in the source documents. Study intervention compliance will be determined by the following:

- Study intervention administration data will be recorded by the participant in the diary and reviewed for completeness and accuracy at each study visit.
- The participants will be instructed to return any unused study intervention at the next visit to the study site for the purpose of performing study intervention accountability.
- Treatment compliance is defined as taking at least 75% of the required SC doses of study intervention. Similarly, a participant will be considered significantly noncompliant if the investigator determines that they have intentionally or repeatedly taken more than the prescribed amount of medication (125% or more of the required SC doses of the study intervention).

[illegible] the visit schedule, study diaries, and any other parameters the investigator considers necessary.

Participants considered poorly compliant will receive additional training and instruction as required. Additional unscheduled visits may be scheduled if study site staff determine that a participant requires additional training.

Site staff will capture all dose modifications in the CRF.

6.6. Dose Modification

All participants will undergo each dose-escalation step regardless of randomized treatment assignment. These dose-escalation steps will be handled in a blinded fashion using the IWRS. During the dose-escalation period, the investigator should make every effort to proceed through each dose-escalation step per the study schedule in order for participants to achieve their maximum tolerated dose. Participants should continue this dose for the duration of the treatment period.

Allowed dose modifications

Dose modification is only allowed for the management of

intolerable GI symptoms (Sections 6.6.1)
inadequate nutrition or dehydration (Sections 6.6.2), and
[L] _ T N T [L Y _ ^] P L (Sections 6.6.3) L 7 @ > g * * V R ' X

6.6.1. Management of Participants with GI Symptoms

All efforts should be made to prevent permanent discontinuation of study intervention. For participants who report intolerable GI symptoms during the study, the investigator should implement the following steps:

STEP 1	The initial step is based on the T Y a P ^ _ assessment of predominant gastrointestinal symptoms with an approach that includes dietary adjustments, lifestyle modifications, with or without symptomatic medications. Counsel participant on dietary behaviors that may help mitigate gastrointestinal symptoms, such as for nausea, eating smaller meals splitting 3 daily meals into 4 or more smaller ones, and stopping eating before feeling full. 6 W ^ Z $ L _ _ S P T Y a P ^ _ T R L _ Z] n ^ O T ^ N] P _ T Z n Y $ ^ d X diarrheal medication can be prescribed.
STEP 2	If Step 1 does not alleviate intolerable gastrointestinal symptoms, a temporary interruption of study intervention **for 1 weekly dose is permitted within each dose-escalation level**. Study intervention should be resumed immediately after temporary interruption, either alone or in combination with symptomatic medication, which can also be utilized to manage symptoms.
STEP 3	If significant GI symptoms persist despite the above measures (Step 1 and Step 2), the investigator should contact the Lilly medical monitor to consider a temporary dose de-escalation.

Abbreviation: GI = gastrointestinal.

Temporary dose de-escalation

If intolerable GI symptoms persist despite the measures outlined in Steps 1 to 2 above, the investigator should contact the Lilly medical monitor to consider de-escalating the dose to the next lower dose for 4 weeks.

All dose modifications will be handled by IWRS in a blinded fashion.

The table below provides guidance for de-escalating the dose.

' 4 / = / > @ 7 1 7 = / ; @ 7 '	**then de-** 3 ? 1 / 9 / @ 3 @ 6 3 2 < ? 3 @ < G
1.5 mg	discontinue the study intervention and continue in the study
3 mg	1.5 mg
6 mg	3 mg
9 mg	6 mg

Dose re-escalation

After temporary dose de-escalation, if intolerable GI symptoms do not stop and dose re-escalation is not deemed appropriate, the investigator should contact the Lilly medical monitor to discuss next steps.

If GI symptoms become tolerable or resolve with dose de-escalation, the investigator should initiate re-escalation after 4 weeks have passed.

If the re-escalation attempt is tolerated, then the participant should continue to complete the remaining dose-escalation steps.

If the re-escalation attempt is not tolerated or if intolerable GI symptoms recur at any subsequent time point following the re-escalation, then, depending on which dose level is achieved, the participant should undergo a permanent dose reduction to the next lower dose level.

The table below provides guidance if the re-escalation attempt was not tolerated.

If the re-escalation attempt is not tolerated with @6 7 ? 2 < ? 3 G	**then the dose will be reduced for the remainder of the** ?@A 2 E @< G
blinded 3 mg	blinded 1.5 mg
blinded 6 mg	blinded 3 mg
blinded 9 mg	blinded 6 mg

Note: If a participant does not tolerate blinded 1.5 mg, then the participant will discontinue the study intervention and continue in the study.

Please note the following

A maximum of 1 dose re-escalation is allowed per participant for the duration of the study.
Following a de-escalation/re-escalation cycle, any additional dose modification to a lower dose will be considered a permanent dose reduction.

If intolerable GI symptoms persist despite symptomatic treatment, temporary drug interruption, temporary dose de-escalation, dose re-escalation, and permanent dose reduction, the participant should be permanently discontinued from the study intervention. All participants who permanently discontinue study intervention should be encouraged to continue to attend all scheduled study visits.

All dose adjustments, for example, de-escalation or re-escalation, are to be recorded in the CRF.

6.6.2. Management of Participants with Inadequate Nutrition or Dehydration

Follow these steps (and refer to Section 10.2.2) if a participant is at risk of inadequate nutrition or dehydration based on clinical judgment and criteria described in Sections 5.3.1 and 5.3.2,

1. Assess if there is an intercurrent illness (for example, systemic infection, cholecystitis, etc.) that could be causing or contributing to the inadequate oral intake.
    a. If yes, consider temporary interruption of study intervention per Section 7.1.2.
    b. If no, go to Step 2.
2. Assess if increased oral intake is likely to trigger GI symptoms.

a. If no
   i. Provide nutritional counseling and consider strategies to increase oral intake. Refer to Sections 5.3.1 and 5.3.2.
   ii. Review concomitant medications and adjust as appropriate; consider relevant laboratory tests (see Sections 6.9 and 10.2).
b. If yes
   i. Temporarily interrupt study intervention for 1 to 2 doses per Section 7.1.2
   ii. Provide nutritional counseling and consider strategies to increase oral intake. Refer to Sections 5.3.1 and 5.3.2.
   iii. Review concomitant medications and adjust as appropriate; consider relevant laboratory tests (see Sections 6.9 and 10.2).
   iv. Reassess if nutritional and hydration concerns persist
      1. If no, restart study intervention per Section 7.1.2.
      2. If yes, contact the Lilly medical monitor to request a permanent dose reduction to the next lower dose level or discontinue study intervention. However, the participant should remain in the study.
      Note: Dose re-escalation is not permitted
   v. Assess if nutritional and hydration concerns persist despite dose reduction
      1. If no, continue study intervention at the reduced dose
      2. If yes, despite dose reduction, contact the Sponsor for further guidance.

6.6.3. Management of Participants with BMI ≤ 22 k

' 4 G	**then** G
L [L] _ T N T [L Y _ [illegible] at any time during the study	**Step 1:** the investigator should adjust nutritional intake to avoid ongoing weight reduction and contact the Lilly medical monitor. **Step 2:** the participant should be assessed at least every 2 to 4 weeks for weight stabilization with either an in-office weight check or self-report via telehealth. **Step 3:** if body weight reduction continues despite nutritional intake guidance, contact the Lilly medical monitor to consider a permanent dose reduction to the next lower dose level.
body weight reduction continues to decline despite a permanent dose reduction and the investigator or participant wants to consider discontinuing study intervention	contact the Lilly medical monitor for further discussion.
a participant has a BMI ≤18.5 kg/m^2 at any time during the study	dose interrupt and contact Lilly medical monitor.

Abbreviation: BMI = body mass index.

All participants who discontinue study intervention are encouraged to continue to attend the remaining scheduled study visits (see Section 7.1).

6.6.4. Management of Participants with Perceived Excessive Weight Reduction

If there are concerns that the degree of body weight reduction may lead to a participant's decision to discontinue from study intervention, the investigator should contact the Lilly medical monitor.

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

Eloralintide will not be available to participants after completion of the study.

6.8. Treatment of Overdose

For this study, any total dose of study intervention within a 72-hour period greater than the dose assigned by IWRS for that participant will be considered an overdose and should be assessed for AE reporting as per criteria described in Section 10.3.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
if indicated, T Y T _ T L _ P ^ ` [[Z] _ T a P _] P L _ X P Y _ L N N Z] O T and symptoms, and
on a case-by-case basis, it may be recommended to obtain a plasma sample for PK analysis within 5 days from the date of the last dose of study intervention if requested by the medical monitor.

6.9. Prior and Concomitant Therapy

Participants are permitted to use concomitant medications that they require during the study except medications that may interfere with the assessment of efficacy and safety characteristics of the study interventions.

Participants must consult with the investigator or a designated site staff member if they are prescribed any new medications during the study. If this is not possible due to treatment of medical emergencies, the participant will inform the investigator or a designated site staff member as soon as possible.

The initiation of weight gain-promoting medications is discouraged, and alternate therapies not associated with weight gain should be considered whenever possible (refer to Section 5.2, exclusion criterion [43] and Section 10.8).

In this study population, many study participants will be taking medications to treat weight-related comorbidities, such as antihypertensive, diuretic, and lipid-lowering agents; or medications to mitigate GI intolerability, including laxatives, and anti-emetics; or medications with weight-based dosing such as thyroid hormone.

Investigators are responsible for closely monitoring the need to adjust these medications throughout the study. Discuss medication adjustment as soon as possible with primary care physician or specialist, as applicable.

The initiation of SGLT-2 inhibitors is only permitted if the participant:

- develops diabetes during the study (See Section 10.10), and
- develops a new non-glycemic indication during the study (for example, heart failure, chronic kidney disease).

The use of metformin is only permitted if the participant:

- develops diabetes during the study (See Section 10.10). Metformin should not be initiated during the study for non-diabetes uses.

Recording concomitant medications

Site staff will record changes in intensity of medications of special interest on the level of medication intensity CRF at intervals specified in the SoA. These changes should also be recorded in the concomitant medication CRF. Medications of special interest that should be recorded in both CRFs include

- antihypertensive, and
- lipid-lowering medications.

Any medication or vaccine, continuous positive airway pressure, over the counter, or prescription medicine (including hormonal contraceptives), vitamins or herbal supplements, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded in the CRF along with

- reason for use
- dates of administration, including start and end dates, and
- dosage information, including dose and frequency only for concomitant medications of special interest, for example, antihypertensive, and lipid-lowering medications.

Non-study medications taken by participants who are screened but not randomly assigned to treatment will not be reported to the Sponsor unless an SAE or AE occurs that the investigator believes may have been caused by a study procedure.

Permitted treatments

Short-term use of medication, for example, stimulants, hypnotics, opioids, anti-epileptics, and other over the counter or prescription medications that could affect the evaluation of excessive sleepiness, is permitted to treat medical conditions other than sleepiness or obstructive sleep apnea (for example, injury, outpatient procedure) for no more than a total of 14 days during the treatment phase. Participants should be instructed to avoid use of these medications for at least 7 days prior to sleep efficacy assessments (for example, PSG, sleep PROs). For these situations, contact the medical monitor.

Participants should be instructed to avoid scheduling non-emergent elective procedures that require stimulant, hypnotic, or other medications that could affect the evaluation of sleep 7 days prior to in-clinic sleep efficacy assessments.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

6.9.1. Prohibited Medications

Regardless of indication of use, these medications are prohibited during the study, including after permanent discontinuation of study intervention, as rescue therapy, or during the posttreatment safety follow-up period

amylin analogs/agonists
GLP-1R agonists
GIP/GLP-1R agonist
insulin, or
Note: Insulin, if necessary, may be used as rescue therapy. If so, it should be in accordance with the most recent ADA/EASD 2022 or ADA 2025 or local guidelines, and as short a duration as possible.
medications intended to promote weight reduction, including prescribed, OTC, or herbal remedies and medications and therapies as listed in Exclusion Criterion 42. (see also Section 5.2).

Any use of the following therapies to treat sleepiness or obstructive sleep apnea is prohibited during the study. Short-term (14 days) use of these therapies for other non-OSA-related medical conditions, as described in Permitted treatments, should be discussed with the medical monitor before use:

Stimulants (for example, modafinil, armodafinil, solriamfetol, pitolisant, amphetamine, dextroamphetamine, dexmethylphenidate, methylphenidate, and lisdexamfetamine).
Hypnotics, mirtazapine, opioids, trazodone, and zonisamide.
Use of any over the counter or prescription medications that could affect the evaluation of excessive sleepiness, per investigator discretion (for example, but not limited to, cannabidiol oil, tetrahydrocannabinol).
Active device treatment of OSA other than PAP therapy (for example, dental appliance), or other treatment that, in the opinion of the investigator, may interfere with study outcomes.

6.9.2. Prohibited Surgical Treatments, Procedures, or Medications for Weight Management

Any planned elective major surgery during the study should be discussed with the Sponsor.

Bariatric surgical treatments are prohibited during the study. This includes, but is not limited to, gastric bypass, sleeve gastrectomy, etc.

Procedures for weight management are prohibited during the study. This includes, but is not limited to, liposuction, abdominoplasty, cryolipolysis, etc.

Endoscopic or device-based therapy for obesity is prohibited. Examples include

mucosal ablation
laparoscopic adjustable gastric banding

gastric artery embolization
intragastric balloon, or
duodenal-jejunal endoluminal liner.

Prohibited medications include those intended to promote weight reduction, including prescribed, over the counter, or alternative remedies (see also Section 5.2).

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

This section outlines

permanent discontinuation of study intervention
temporary interruption of study intervention
discontinuation of participants from the study, and
participants lost to follow-up.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant should discontinue the study intervention (treatment) and will remain in the study and follow procedures for all remaining study visits, as shown in the SoA. Participants who discontinue from the study intervention will not be replaced by new participants.

A participant must be permanently discontinued from study intervention if

the participant requests to discontinue study intervention
the participant becomes pregnant during the study
the participant is diagnosed with
- T1D
- medullary thyroid cancer or multiple endocrine neoplasia type 2 syndrome, or
- an active or untreated malignancy.

Exception:

- basal cell or squamous cell skin cancer
- in situ prostate cancer, for example, Gleason 6 or lower, or
- Stage 0 noninvasive cervical cancer.

the participant develops any other TEAE, SAE, or clinically significant laboratory value, or other safety reasons for which the investigator believes that permanent study intervention discontinuation is appropriate
the participant receives or needs prohibited medications during the study described in Section 6.9.1. If the participant will not or cannot discontinue them, or
if an investigator, site staff performing assessments, or participant is unblinded.

Other possible reasons that may lead to permanent discontinuation of study intervention are as follows:

if the participant has intolerable GI symptoms despite management as described in Sections 6.6.1
if the participant is unable to maintain adequate nutrition or hydration despite management as described in Section 6.6.2
if the participant is pregnant at any time during the treatment period &

Note: The investigator should contact the Lilly medical monitor to discuss whether it is medically appropriate for the participant to continue study intervention.

the participant has bariatric surgery, body weight reduction procedures, or medications for weight management described in Section 6.9.2 and if the participant will not or cannot discontinue them.
the participant has a systemic hypersensitivity reaction (Section 8.3.5.9)

Note: If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the Sponsor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the Sponsor.

PHQ-1 ^ N Z] P h) -
L Y ^ b P] P O l d P ^ m _ Z D ` P ^ _ T Z Y , Z ] D ` P ^ _ T Z Y -
C-SSRS, **or**
L Y ^ b P] P O l d P ^ m -related behaviors on the Suicidal Behavior portion
of the C-SSRS.

Note: In the 3 situations above related to PHQ-9 and C-SSRS, it is recommended that the participant be assessed by a psychiatrist or appropriately trained professional to assist in deciding whether the participant can resume the study intervention.
If it is determined that a participant will permanently discontinue the study intervention due to increased suicidal risk, the participant will be followed within the study until the event leading to discontinuation resolves, stabilizes, or the participant is referred to a mental health professional for further evaluation and care.

If a participant permanently discontinues study intervention for any reason, the participant will complete procedures for an ED of Treatment visit.

The participant should be encouraged to remain in the study and adhere to the study schedule, except in the case of pregnancy.

If the participant is unwilling or unable to return for all applicable study visits, the site should attempt to collect as much follow-up information as possible, especially data collection pertaining to primary and key secondary efficacy endpoints at Week 64 of the treatment period.

7.1.1. Liver Chemistry Stopping Criteria

See Section 8.2.9 for Hepatic Criteria for Study Intervention Interruption or Discontinuation.

7.1.2. Temporary Study Intervention Interruption

All efforts should be made to keep participants on study intervention at the MTD dose level and with minimal dose interruptions throughout the study.

In certain situations, other than GI events, after randomization, the investigator may need to temporarily interrupt study intervention. When there is temporary interruption of study intervention, it is expected that the investigator reassesses the participant regularly (in an effort

to restart study intervention as soon as medically appropriate). The investigator should make every attempt to restart as soon as possible.

Clinical decision making should consider the approximate 14-day half-life of eloralintide. If 2 consecutive weekly doses are missed and restarting intervention remains medically inappropriate, the investigator must contact the Lilly medical monitor before the next scheduled dose to discuss continued interruption or dose de-escalation. Temporary interruption longer than 3 months should be discussed with the Lilly medical monitor.

Distribution of study intervention at the correct dose will be implemented by the IWRS.

' 4 ?@A2E 7;@3>B3;	@63;G
2 consecutive doses or fewer	participant resumes the study intervention at the last administered dose level. If the dose interruption occurred within 1-2 weeks from a dose-escalation visit the participant should proceed with the next escalation.
3 consecutive doses or more	Participant restarts study intervention at 1.5 mg and repeats dose-escalation scheme as appropriate.
due to an AE	the event is to be documented and followed according to the procedures in Section 8 of this protocol.
due to intolerable persistent GI AE	participant should be treated as suggested in Section 6.6.1.
due to inadequate nutrition or dehydration	participant should be treated as suggested in Section 6.6.2.
due to perceived excessive weight]PO`N_TZY Z] 7@>	participant should be treated as suggested in Section 6.6.3 and 6.6.4.

Abbreviations: AE = adverse event; BMI = body mass index; GI = gastrointestinal; IWRS = interactive web-response system.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon. To minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep participants in the study regardless of study intervention use.

AFAB participants will be discontinued from the study if the participant becomes pregnant.

A participant may withdraw from the study

- at any time at the [L]_TNT[Y_n^ own request or for any reason or without providing any reason
- at the request of _SP [L]designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

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

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

Participants who agree to provide information relevant to any study endpoint at the end of the study are not considered to have discontinued from the study.

7.3. Lost to Follow up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

The primary efficacy measures are to compare the effect eloralintide versus placebo for percent change in body weight and absolute change in AHI at 64 weeks. Body weight measurements and polysomnography assessments will be collected at specific clinic visits in a fasted state, and as summarized in the SoA (Section 1.3). Methods for measuring body weight are described in Appendix 7(Section 10.7).

8.1.2. Key Secondary Efficacy Assessments

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

body weight
blood pressure
lipid parameters
biomarkers of inflammation
AHI
sleep impairment
hypoxic burden, and
OSA remission or mild asymptomatic OSA.

8.1.3. Other Secondary Efficacy Assessments

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

body weight
BMI
glycemic parameters
sleep disturbance, including excessive daytime sleepiness
health-related quality of life
health status

medication use
PK/PD parameters
insulin sensitivity
lipid parameters
central adiposity measurements
blood pressure, and
patient-reported symptoms.

8.1.4. Polysomnography

Polysomnography assessments (including AHI, blood oxygen saturation parameters, heart rate, sleep parameters) will be performed during 1-night, overnight sleep center stays, per the SoA. Participants on PAP will suspend their PAP use for 7 to 9 days prior to the scheduled PSGs. The wash-out period is to allow for measurement of drug treatment effect unobscured by PAP and is based on literature citing 14 days as a safe discontinuation period (Rossi et al. 2012; Stradling et al. 2015; Schwarz et al. 2016a, 2016b, 2016c, 2018).

Data from the PSGs will be read and scored centrally using the American Academy of Sleep @P O T N T Y P) 7 S d [Z [Y P L ^ N Z] T Y R X P _ S Z O ! b S P Y _ S P baseline) (Hamilton et al. 2021). Given that PAP needs may evolve with weight reduction, [L] _ T N T [L Y _ ^ Z Y C 6 C X L d ` Y O P] R Z C 6 C _ T _] L _ T Z Y

Investigators should confirm whether PAP suspension was conducted appropriately. Participants who have not suspended PAP for the 7 consecutive days prior to the PSG should be managed as follows:

Participants who tolerated PAP suspension but inadvertently suspended PAP for 4 or fewer days prior to PSG should reschedule the PSG assessment, if possible. Screening PSG must be rescheduled prior to randomization.
In case of uninterrupted suspension of PAP for at least 5 days immediately preceding the PSG, the PSG assessment should be completed.
In case a participant does not tolerate 7-day PAP suspension, the investigator should contact Lilly to discuss options.

8.1.5. Patient-Reported Outcomes

The self-reported questionnaires will be administered at times noted in the SoA in the translated version for the native language of the region.

Preferred administration order is:

1. PROMIS SRI
2. PROMIS SD
3. ESS
4. SF-36v2 Acute Form
5. EQ-5D-5L
6. PGIS-OSA Fatigue, Sleepiness, Snoring, Sleep Quality
7. PGIC-OSA Fatigue, Sleepiness, Snoring, Sleep Quality

8.1.5.1. PROMIS Short Form v1.0 Sleep-Related Impairment 8a

The PROMIS Short Form v1.0 Sleep-related Impairment 8a assesses self-reported perceptions of alertness, sleepiness, and tiredness during usual waking hours, and the perceived functional impairments associated with sleep problems or impaired alertness. The PROMIS Short Form v1.0 Sleep-related Impairment 8a consists of 8 items each rated on a 5-point scale ranging from not at all to very much. Items have a recall period of the past 7 days. Individual item scores are totaled to obtain a raw score, with higher scores indicating more sleep-related impairment. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a SD of 10. (Northwestern, 2016a)

8.1.5.2. PROMIS Short Form v1.0 Sleep Disturbance 8b

The PROMIS Short Form v1.0 Sleep Disturbance 8b assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep, including perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. The PROMIS Short Form v1.0 Sleep Disturbance 8b consists of 8 items each rated on a 5-point scale ranging from not at all to very much. Items have a recall period of the past 7 days. Individual item scores are totaled to obtain a raw score, with higher scores indicating more sleep disturbance. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a SD of 10. (Northwestern, 2016b)

8.1.5.1. Epworth Sleepiness Scale

The ESS will be included to assess improvements in excessive daytime sleepiness from baseline to Week 64. The ESS is an 8-item, participant-completed measure that asks the participant to rate on a scale of 0 (no chance of dozing) to 3 (high chance of dozing), their usual chances of dozing in 8 [illegible] the sum of the 8-item scores and ranges from 0 to 24, with higher scores indicating greater daytime sleepiness (Johns 1991).

8.1.5.2. SF-36 v2 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 is a 36-item generic, patient-completed measure designed to assess the following 8 health domains:

- physical functioning
- role-physical
- bodily pain
- general health
- vitality
- social functioning
- role-emotional, and
- mental health

[illegible]

information from these 8 domains are further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales). Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and SD of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

8.1.5.3. EQ-5D-5L

The EQ-5D-5L (EuroQol Research Foundation 2019) is a standardized, self-administered instrument for use as a measure of health outcome. It consists of the EQ-5D-5L descriptive system and the EuroQol visual analog scale (EQ-VAS). It provides a simple EQ-5D-5L descriptive profile and a single EQ-5D-5L index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L descriptive system includes 5 items that assess 5 dimensions of health:

- mobility
- self-care
- usual activities
- pain/discomfort, and
- anxiety/depression.

Each dimension has 5 response levels:

- no problems
- slight problems
- moderate problems
- severe problems, and
- extreme problems.

The EQ-VAS ^ N Z] P] P N Z] O ^ -rated health on a vertical visual analog scale P W Q b S P] P _ S P P Y O [Z T Y _ ^ L] P W L M P W P O L ^ I G S P M P ^ _ S P L W _ S d Z `(0).N L Y T X L R T Y P m

8.1.5.4. Patient Global Impression of Severity Obstructive Sleep Apnea (PGIS-OSA) Symptoms Scales

Four patient global impression of severity scales will be included to assess categorical shift in participant self-rated assessment of their OSA symptom severity from baseline to Week 64.

PGIS-OSA fatigue

This is a single-item, participant self-rated assessment of their overall level of fatigue due to B F 6 over the past 7 days & m G S P T _ P4X [Z T T Y _] L ^ _ N P L O W P X Q L L Y R R R Y R m Q] Z X Severe Q L _ T R ` P & m

PGIS-OSA sleepiness

This is a single-item, participant self-rated assessment of their overall level of sleepiness due to OSA during waking hours over the past 7 days & m G S P T _ P4X point scale ranging P O Z Y L Q] Z X I A Z _ L _ Very L ^ W W P P ^ [W d P & P m [d m _ Z I

PGIS-OSA snoring

The PGIS-OSA Snoring scale consists of 2 items. The first item is a participant self-rated assessment [illegible] over the past 7 days [illegible] how much their snoring has affected their sleep. The item is rated on a 4-[illegible] for the second item, participants will be asked on a 3-point scale ([illegible]) if they have ever been told by someone else that they snore in their sleep.

PGIS-OSA sleep quality

This is a single-item, participant self-rated assessment of how refreshing their sleep felt in the past 7 days. The item is rated on a 5-[illegible]

8.1.5.5. Patient Global Impression of Change Obstructive Sleep Apnea (PGIC-OSA) Symptoms Scales

Four patient global impression of change scales will be included to assess categorical shift in participant self-rated assessment of change in their OSA symptom severity from baseline to Week 64.

PGIC-OSA fatigue

This is a single-item, participant self-rated assessment of the change in their overall level of [illegible] since you started taking the study medication & [illegible]

PGIC-OSA sleepiness

This is a single-item, participant self-rated assessment of the change in their overall level of sleepiness due to OSA during waking hours [illegible] since you started taking the study medication & [illegible] The item is rated on a 5-[illegible]

PGIC-OSA snoring

This is a single-item, participant self-rated assessment of the overall change in how their snoring has affected their sleep [illegible] since you started taking the study medication & [illegible]

PGIC-OSA sleep quality

This is a single-item, participant self-rated assessment of the change in their overall sleep quality [illegible] since you started taking the study medication & [illegible] point scale [illegible]

8.1.6. Most Bothersome Symptom of OSA

This is a single-item, site staff-administered question about participants experience with various symptoms of OSA, highlighting the different levels of discomfort these symptoms cause. The item includes 9 common symptoms associated with OSA. The participant must choose which symptom was the most bothersome to them in the past 7 days. Site staff will record their selection in the CRF.

8.1.7. Change in Most Bothersome Symptom of OSA

This is a single-item, site staff-L O X T Y T ^ _ P] P O \ ` P ^ _ T Z Y L MZr` _ [L] _ T most bothersome OSA symptom since starting study treatment. The item is rated on a 5=point ^ N L W P] L Y R T Y R Q] Z X I XSite staff will record their selection in the N S M P _ _ CRF.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

Complete physical examination

A complete physical examination will include, at a minimum, assessments of these systems:

- heart
- lungs
- thyroid
- abdomen
- neurological, and
- extremities.

A complete physical examination excludes pelvic, rectal, and breast examinations unless clinically indicated.

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

Symptom-directed physical assessment may be conducted at the discretion of the investigator or qualified personnel, as indicated per local regulations based on participant status and standard of care.

Additional assessments

Height, weight, waist circumference, neck circumference and vital signs will also be measured and recorded. Refer to Section 10.7 for further details.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3). See Section 10.7.

8.2.3. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (Section 1.3). ECGs must be recorded before collecting any blood samples. Participants must be supine for at least 5 to 10 minutes before ECG collection, and remain supine and awake, during ECG collection. ECGs will be interpreted by the investigator (a physician or qualified designee) at the site after the time of ECG collection, as practical, and ideally while the participant is still present for immediate participant management, should any clinically relevant findings be identified. The investigator or qualified designee must document their review of the ECG printed at the time of evaluation. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the

participant receives the first dose of the study intervention should be reported to the ECGs may be obtained at additional times when deemed clinically necessary (for example, to assess [illegible] digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements. The machine-read ECG intervals and heart rate may be used for data analysis and report-writing purposes, unless a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2, Section 10.2 for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. [illegible]

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 6 weeks after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

All protocol-required laboratory assessments, as defined in Appendix 2, Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.5. Pregnancy Testing

Collection of serum pregnancy samples during screening (Visit 1) should be performed within 30 days prior to the first study intervention administration (Visit 2).

If the initial serum test during screening is performed more than 30 days prior to administration of the first dose, a second negative serum pregnancy test performed by the central lab with results confirmed by the investigator is required prior to Visit 2 and administration of the first dose.

Participants who are IOCBP will undergo routine urine pregnancy testing, beginning at study entry (Week 0) and occurring every 4 weeks as indicated in the Schedule of Activities (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, telemedicine visits, or both at Weeks 32, 36, 44, 48, 56, 60 Information from these test results will be recorded in participant records.

If the urine pregnancy test is inconclusive at any visit, collect an additional serum pregnancy test and hold study intervention dosing until negative serum pregnancy test is confirmed by site via central laboratory test.

Participants should notify the investigator as soon as possible if they test positive for pregnancy and to hold the next dose of study intervention until additional testing. A positive test should be confirmed with onsite clinical serum testing.

Study intervention should not be administered after positive home urine test unless that test is confirmed (at least 2 serum tests separated by 14 days) to be a false positive. Participants who become pregnant during the study should be permanently discontinued from the study (Section 7.2). Participants who become pregnant will complete procedures for an ED Visit and safety follow-up, as shown in the SoA.

Participants should be advised to conduct final at-home urine pregnancy test 4 weeks after V801 and to call the study site for any positive test. Contraception guidance continues 4 weeks after V801.

Details of all pregnancies in AFAB participants and, if indicated, AFAB partners of AMAB participants will be collected as outlined in Sections 8.3.2.1 and 8.3.2.2.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Participants being treated with eloralintide should be monitored appropriately and observed closely for suicidal ideation and behavior or any other unusual changes in behavior, especially at the beginning and end of the course of intervention, or at the time of dose changes, either increases or decreases. Participants who experience signs of suicidal ideation and behavior should undergo a risk assessment. All factors contributing to suicidal ideation and behavior should be evaluated and consideration should be given to discontinuation of the study intervention.

Baseline assessment of suicidal ideation and behavior will be monitored during YDAO using C-SSRS.

Participants will be monitored for suicidal ideation through AE collection and by using the C-SSRS.

8.2.6.1. Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS is a scale that captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period using a semi-structured interview by a trained rater.

For this study, the Categories Version of the C-SSRS will be used.

The C-SSRS Categories Version is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

The trained site personnel may administer the C-SSRS and will report the emergence of suicidal TOPL_TZY$ ^[PNTQTNLWWd LYd [L]_TNT [tdLthe _ LY^bP] study investigator.

It is important to document a description of any suicidal ideation or behavior, or non-suicidal self-injurious behavior captured on the C-SSRS during the participant interview.

For this study, a free text description of the ideation or behavior is documented via the eCOA system.

Timing of collection and AE monitoring

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

Follow standard procedures for reporting SAEs.

8.2.7. Depression Monitoring

When informed consent or assent is given, study site personnel should instruct caregivers/of study participants about the need to monitor participants for the emergence of depression or unusual changes in behavior, and to report such symptoms immediately to the study investigator.

Study site personnel should monitor participants receiving study intervention for depression or any other unusual changes in behavior, especially at the beginning and end of the course of treatment, or at the time of dose changes, either increases or decreases.

8.2.7.1. Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a validated, participant-reported instrument that assesses the specific diagnostic symptoms that determine the presence and severity of a clinical depressive disorder per the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (APA, WWW) (Spitzer, et.al. 1999; Kroenke, et al. 2001; Moriarty, et.al. 2015). This scale is validated for use in individuals 18 years of age and older.

The questionnaire assesses the previous 2 weeks.

The PHQ-9 assesses 9 diagnostic symptoms:

- mood
- anhedonia
- sleep disturbance
- loss of energy
- appetite change
- feelings of worthlessness or guilt
- diminished concentration
- psychomotor agitation or retardation, and
- suicidal thoughts or attempts.

Each question has 4 response options, with scores ranging from 0 to 3, corresponding to NL_PRZ]TP^ ZQ lYZ_ L_ LWWm _Z lYPL]Wd PaP]d O

This table describes the interpretation of results. The total score is the sum of scores for the 9 items.

Interpretation of Depression	Total Score
Minimal to none	0-4
Mild	5-9
Moderate	10-14
Moderately severe	15-19
Severe	20-27

8.2.8. Fatigue Assessment Scale

The FAS is a validated 10-item respondent-reported questionnaire that self-assesses both the mental and physical aspects of fatigue (Michielsen et al. 2003, Shahid et al. 2011).

Each item of the FAS is answered using a five-point, Likert- _ d [P ^ N L W P] L Y R T Y R Q] _ Z - ! l L W b L d ^ m " &

8.2.9. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Intervention Interruption or Discontinuation

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

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

' 4 @6 7 ? 9 / 0 < > / @ < > E B / 9 A 3	- 6 3 ; G		
	Initiate or continue close hepatic monitoring	**Initiate comprehensive evaluation**	**Interrupt or discontinue study intervention**
6 ? G Z] 6 F G h + c H ? A	X		
6 ? C h * c H ? A	X		
G 7 ? h * c H ? A	X		
ALT or 6 F G h - c H ? A	X	X	
6 ? C h * & - c H ? A	X	X	
6 ? G Z] 6 F G h + c H ? A b T _ S	X	X	X
6 ? G Z] 6 F G h - c H ? A Q Z] X	X	X	X
6 ? G Z] 6 F G h 0 c H ? A	X	X	X
6 ? G Z] 6 F G h + c H ? A Z] L Y O A	X	X	X
6 ? C h + c H ? A	X	X	X
ALP h * & - c H ? A L Y O G 7 ? h * c	X	X	X
6 ? C h * & - c H ? A b T _ S S P [L _	X	X	X

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

[a] > Y [L] _ T N T [L Y _ ^ b T _ S < T W M P] _ n ^ ^ d Y O] Z X P $ _ S P _ S] P ^ S Z W L Y O G 7 ? h * c M L ^ P W T Y P $ T Q M L ^ P W T Y P T ^ h) & - c H ? A &

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

Participants with elevated baseline % (- ! % , - ! < > % (+ F # " $ D . (*

' 4 @ 6 7 ? 9 / 0 < > / @ < > E B / 9 A 3 7	- 6 3 ; G		
	Initiate or continue close hepatic monitoring	**Initiate comprehensive evaluation**	**Interrupt or discontinue study intervention**
6 ? G Z] 6 F G h * c M L ^ P W T Y P	X		
6 ? C h * c M L ^ P W T Y P	X		
G 7 ? h * [a] c H ? A	X		
6 ? G Z] 6 F G h + c M L ^ P W T Y P Z] (whichever occurs first)	X	X	
6 ? C h * & - c M L ^ P W T Y P	X	X	
6 ? G Z] 6 F G h * c M L ^ P W T Y P Z] (whichever occurs first) with hepatic signs or symptoms[b]	X	X	X
6 ? G Z] 6 F G h + c M L ^ P W T Y P Z] (whichever occurs first) for more than 2 weeks	X	X	X
6 ? G Z] 6 F G h , c M L ^ P W T Y P Z] first)	X	X	X
6 ? G Z] 6 F G h * c M L ^ P W T Y P Z] ! b S T N S P a P] Z N N `] ^ [a] Q T] > A E h l)	X	X	X
6 ? C h + c M L ^ P W T Y P	X	X	X
6 ? C h * & - c M L ^ P W T [a] Y P L Y O G 7 ?	X	X	X
6 ? C h * & - c M L ^ P W T Y P b T [b] _ S S P	X	X	X

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

[a] > Y [L] _ T N T [L Y _ ^ b T _ S S] P < T W Z M P] _ Q Z ^] ^ G 7 ? O] Z T W P $ M P S P G 7 ? h + c H ? L Y O G 7 ? h * c M L ^ P W T Y P $ T Q M L ^ P W T Y P T ^ h) & - c H ? A &

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

8.2.9.1. Close Hepatic Monitoring

> Q L [L] _ T N T) [Z L Q Y _ _ S O P P ^ a P P W W Z S [L ^ Y R L P Y ^ d $ T Y T _ T L _ P N W Z ^ P

Participants with normal or near normal baseline (ALT, AST, or ALP<1.5x ULN)	Participants with elevated baseline (ALT, AST, or % (+ F # " $ D . (*
6 ? G Z] 6 F G **or** h + c H ? A	6 ? G Z] 6 F G h * c M L ^ P W T Y P
6 ? C h * **or** H ? A	6 ? C h * c M L ^ P W T Y P
G 7 ? h * [a] c H ? A	G 7 ? h * [a] c H ? A

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

[a] > Y [L] _ T N T [L Y _ ^ b T _ S < T W M R [illegible] T B L h^+dcY O H] ? Z A X $ P $ T Q _ S M P L ^ _ P S W] T P Y ^ P S Z T W and TBL h * c M L ^ P W T Y P $ T Q M L ^ P W T Y P T ^ h) & - c H ? A &

Close hepatic monitoring should include these actions:

Laboratory tests (Section 10.6) including ALT, AST, ALP, TBL, D. Bil, GGT, CK, and CBC with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.

If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2-3 times weekly until levels start normalizing or return to approximate baseline values. Subsequently, the frequency of monitoring may be lowered to once every) _ Z * b P P V ^ $ T Q _ S P [L] _ T N T [L Y _ n ^ N W T Y T N L

In addition to lab tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over the counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

8.2.9.2. Comprehensive Hepatic Evaluation

> Q L [L] _ T N T) [Z L Q Y _ _ S O P P a Q P Z W W Z W [Z ^ b T L Y Y R d W L M Z] L _ Z] d Z] N W N Z X [ ] P S P Y ^ T a P S P [L _ T N P a L W ` L _ T Z Y 2

Participants with normal or near normal baseline (ALT, AST, or ALP<1.5x ULN)	+ / > @ 7 1 7 = / ; @ ? C 7 @ 6 3 9 3 B / @ 3 1.5x ULN)
6 ? G Z] 6 F G **or** h - c H ? A	6 ? G Z] 6 F G h + c M L ^ P W T Y P Z (whichever occurs first) **or**
6 ? C h * & **or** c H ? A	6 ? C h * & - **or** M L ^ P W T Y P
ALT or AST h + c H ? A b T _ S S P symptoms[a] **or**	6 ? G Z] 6 F G h * c M L ^ P W T Y P Z (whichever occurs first) with hepatic signs or symptoms[a] **or**
6 ? G Z] 6 F G h + c H ? A or L Y > A E h) & -	6 ? G Z] 6 F G h * c M L ^ P W T Y P Z (whichever occurs first) and G 7 ? h * [b] c Z] H ? > A A E h

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

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

b >Y [L]_TNT[LY_^ bT_S <TWMP]_n^ h^+dcY CH]?ZAX PT$Q _MSLP^ P_WST]YPP^ STZ^W and TBL h*c ML^PWTYP TQ ML^PWTYP T^ h)&-c H?A&

8ZX[]PSPY^TaP SP[L_TN PaLW`L_TZY ^SZ`WO TYNW`

Clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels start normalizing or return to approximate baseline values.

6_ L XTYTX`X$ NZX[]PSPY^TaP SP[L_TN PaLW`L LYO L _SZ]Z`RS XPOTNLW ST^_Z]d$ %>$A EL3^ _ZP`^_W^TYQPZ aT]LW SP[L_T_T^ 6$ 7$ 8$ LYO :3 _PLR_TYRQZ] ^_`Od !QZ] PcLX[WP$ `W_]L^Z`YO Z] 8G ^NLY" PaLW`L_TZY XLd MP ^_Z]PO G^SPLY Pc ZWWPOL^ZXd MP `^PO QZ] _SP WTXT_PO [`][Z^P ZQ &LOOT_TZ 7L^PO ZY _SP [L]_TNT[LY_n^ ST^_Z]d LYO TYT TY NZY^`W_L_TZY RT_S _SP OTWWW XZYT_Z]$ TY aT]`^ !=9I"$ Nd_ZXPRLWZaT]`^ !8@SPY$ W:P[LR_P_T LNP_LXTYZ[SPY []Z_PTY LOO`N_^$ `]TYP _ZcTN WPaPW^$ `]TYL]d P_SdW RW`N`]ZYTOP$ LYO MWZ ;Z] [L]_TNT[LY_^ bT_S -T^_Z]d ZQ _SZ]_ PWP6LPW NZY^TOP] _P^_TYR QZ] 6?C T^ZPYedXP^ LYO Pa OT^PL^P !P&R&$ Q]LN_`]P^$ ^MZYTP^ PXLP^_PL"^$_ LZ^]P^[$] 7L^PO ZY _SP NT]N`X^_LYNP^ LYO _SP TYaP^_T NZYOT_TZY$ _SP TYaP^_TRL_Z] ^SZ`WO NZY^TOP RL^_]ZPY_P]ZWZRT^_ NZY^`W_L_TZY^$ZLYONPLOOT_ NSZWLYRTZ[LYN]PL_ZR]L[Sd !@E8C"$ PYOZ^NZ[T !:E8C"$ NL]OTLN PNSZNL]OTZR]LX$ Z] L WTaP] 6WW _SP XPOTNLW TYQZ]XL_TZY LYO _P^_^]P^` NZX[]PSPY^TaP SP[L_TN PaLW`L_TZY should be collected and recorded in CRFs, including the hepatic safety CRF.

8.2.9.3. Study Intervention Interruption or Discontinuation

>Q L [L]_TNT)[ZLQY __ SOPP aQPZWZW[Z^b TLYYRd WLMZ]L_Z]d Z] NW
^_%O]d`R LYO NZY_TY`P NWZ^P XZYT_Z]TYR LYO NZX
FPN_0T&Z*Y& 1 (&) * & 1 & *

Participants with normal or near normal baseline (ALT, AST, or ALP<1.5x ULN)	+/>@717=/;@? C7@6 393B/@32 1.5x ULN)
6?G Z] 6FG h+c H?A b symptoms[a] **or**	6?G Z] 6FG h*c ML^PWTYP Z] (whichever occurs first) with hepatic signs or symptoms[a] **or**
6?G Z] 6FG h-c H?A Q **or**	6?G Z] 6FG h+c ML^PWTYP Z] (whichever occurs first) for more than 2 weeks **or**
6?G Z] 6FG **or** h0c H?A	6?G Z] 6FG h,c ML^PWTYP Z] first) **or**
6?G Z] 6FG h+c H?A[b] **or** L >AEh **or**)&-	6?G Z] 6FG h*c ML^PWTYP Z] !bSTNSPaP] ZNN`]^ [b]ZT]] >A **or** hL
6?C h+ **or** H?A	6?C h+c **or** ML^PWTYP
6?C h*&-c H?A L[b]Y **or** O G7	6?C h*&-c ML^PWT[b]Y **or** P LYO G7?
6?C h*&-c H?A bT_S S symptoms[a]	6?C h*&-c ML^PWTYP bT[a]_S SF

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

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

[b] >Y [L]_TNT[LY_^ bT_S <TWMP]_n^ h^+dcY CH]ZXK PT$Q baseline TBL<1.5x ULN, _S]P^SZW and TBL h*c ML^PWTYP TQ ML^PWTYP T^ h)&-c H?A&

>Y_P]]`[_TZY Z] OTY^R Z Y BZ YWOY TZ NWZQP^_SOd P LN_

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

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

The definitions of the following events can be found in Appendix 3 Section 10.3:

- AEs
- SAEs, and
- PCs.

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). All AEs of fatigue should be evaluated using the FAS (Section 8.3.5.11).

For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in Appendix 3, Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Events					
AEs including SAEs	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Additional Reporting for Serious Adverse Events					
SAE and SAE updates jprior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of study intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates jafter start of study intervention	Start of study intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE f jafter [L] _ T N T study participation has ended **and** the investigator becomes aware	After [L] _ T N study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in participants and partners of participants	After the start of study intervention	70 days after last dose of study intervention	Within 24 hours (see Section 8.3.2)	Pregnancy CRF	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	k	k	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

fSerious adverse events should not be reported unless the investigator deems them to be possibly related to study intervention or study participation.

8.3.2. Collection of Pregnancy Information

8.3.2.1. Participants Who Become Pregnant

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

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

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

A spontaneous abortion (occurring at <20 weeks gestational age) or stillbirth ! Z N N `]] T Y R L _ weeks gestational age) is always considered to be an SAE and will be reported as such.

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

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

8.3.2.2. Participants With Partners Who Become Pregnant

When to collect pregnancy information

In most circumstances, the investigator will attempt to collect pregnancy information from a [L] _ T N T [L Y _ n ^ [L] _ Y P] b S Z M P N Z X P ^ [ ] P R Y L Y _ b S

After learning about a pregnancy in the partner of a study participant, the investigator

> will obtain permission to release information from the pregnant partner directly, and within 24 hours after obtaining this permission, will record pregnancy information on the appropriate form and submit it to the Sponsor.

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

When not to collect pregnancy information

It is not necessary to collect information about a pregnancy in the partner of a study participant in these circumstances

> the partner of the study participant was not exposed to the study intervention via semen during conception or pregnancy, or
> the participant did not contribute the spermatozoid or ova that resulted in the pregnancy.

8.3.3. Adverse Events of Special Interest

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 persists below 90 mmHg, DBP persists below 60 mmHg, or recurrent symptomatic hypotension has occurred, the investigator should

reduce the antihypertensive medication dose level or inform participants to consult with their physician. Changes of antihypertensive medication will be recorded in the CRF.

8.3.3.2. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute renal events or worsening of preexisting chronic kidney disease.

Eloralintide may cause nausea, vomiting, and diarrhea. 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

8.3.3.3. Suicidal Ideation and Behavior

[illegible] Refer to Section 7.1 for discontinuation criteria related to suicidal ideation and behavior. At the discretion of the investigator, a participant may be referred to a mental health professional at any time during the study regardless of C-SSRS score.

8.3.3.4. Depression

Participants will be screened at study entry and monitored during the study for depression using PHQ-9 (Section 8.2.7.1). It is recommended that participants who develop moderate depressive symptoms (increase in PHQ-9 total score to 10-14) be assessed for risk of depression. The [illegible] the study intervention, and the participant can be referred to a mental health professional for further evaluation at the discretion of the investigator. Refer to Section 7.1 for discontinuation criteria related to depression monitoring.

8.3.4. Adjudicated Events

The Phase 3 eloralintide program will include an independent adjudication committee to adjudicate suspected cases of the events described in this table in a blinded manner. Any completed adjudications will be utilized in safety analyses.

CV events Death (CV and non-CV) Myocardial infarction Hospitalization for unstable angina Hospitalization or urgent visit for heart failure
Neurologic events Stroke Transient ischemic attack
Pancreatic events Pancreatitis (acute or chronic) Pancreatic hyperenzymemia with symptoms Pancreatic hyperenzymemia that undergoes further diagnostic follow-up Severe or serious abdominal pain of unknown etiology
New diagnosis of Type 2 diabetes

8.3.5. Safety Topics for Monitoring

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 (eloralintide), 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, `YWP^^ QT__TYR ZYP ZQ _SP YZ_LMWP N]T_P]TL L^ 8ZY_PY_ ZQ 8WTYTns, SAEs, and AEs leading to permanent discontinuation of the investigational drug.

8.3.5.1. Hypoglycemia

Distribution of glucometers

All participants who develop T2D during the study will be provided with glucometers.

CL]_TNT[LY_^ bT_SZ`_ OTLMP_P^ XLd$ L_ _SP TYa in the evaluation of reported symptoms consistent with hypoglycemia.

Participants receiving glucometers will be instructed to provide glucose readings to site personnel that meet the definition of hypoglycemia.

Participants will also be trained about the signs and symptoms of hypoglycemia and its treatment. Participants will be asked to contact site personnel if they experience any of these symptoms with or without accompanying glucose readings.

Responding to recurrent hypoglycemia in participants taking concomitant antihyperglycemic medication

If a participant develops recurrent, unexplained hypoglycemia during the treatment period, the investigator should consider reducing the dose of or discontinuing any concomitant antihyperglycemic medication commonly associated with hypoglycemia, for example, sulfonylureas. Study intervention discontinuation for recurrent hypoglycemia should be considered only if these events continue despite complete discontinuation of concomitant

medications, and at the discretion of the investigator, other potential causes of hypoglycemia have been addressed.

Recording hypoglycemic episodes

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

All hypoglycemic episodes will be recorded as AEs. 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 Sponsor as an SAE.

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

Hypoglycemia definitions and categories

Investigators should use the following classification of hypoglycemia. The plasma glucose values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips.

Level 1 hypoglycemia:
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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 blood glucose 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.

8.3.5.2. Severe/Serious Gastrointestinal Adverse Reactions

Severe GI AEs, like nausea, vomiting, and diarrhea, may occur. Information on severe GI AEs and antiemetic/antidiarrheal use will be recorded in the AE and concomitant medication CRFs. For details on managing GI AEs, refer to Section 6.6.1.

8.3.5.3. Pancreatitis Events

The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks 2006, Kouzumi 2017)

- abdominal pain, characteristic of acute pancreatitis (that is, epigastric pain radiating to the back, often associated with nausea and vomiting)
- ^ P] ` X L X d W L ^ P ! _ Z _ L W $ [L V N] a d L _ T N $ Z] M Z _ S "
  characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, the investigator should

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

When it is deemed clinically safe and the Sponsor has been notified, study participants may resume study intervention at the discretion of the investigator. Resumption of study intervention is not dependent on adjudication outcome.

Case adjudication and data entry

An independent CEC will adjudicate all suspected cases of acute pancreatitis.

Asymptomatic elevation of serum amylase and/or lipase

Currently there is not sufficient data to determine if there is an association of eloralintide with pancreatitis. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck et al. 2016; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or p- L X d W L × U P N) is not mandated but may be performed M L ^ P O Z Y _ S P T Y a R P Y T R L Y Q] h ^ ^ R W T X P M L W Z Q ` O S P [L condition.

8.3.5.4. Hepatobiliary Disorders

In cases of elevated liver laboratory tests, initiate hepatic monitoring as outlined in Section 8.2.9.

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All events of TE biliary colic, cholecystitis, cholelithiasis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed.

8.3.5.5. Adjudicated Cardiovascular Events

Nonfatal CV AEs and all deaths will be adjudicated by a committee of physicians external to Lilly. This committee will be blinded to treatment assignment. The nonfatal CV AEs to be adjudicated include

myocardial infarction
hospitalization for unstable angina
hospitalization or urgent visit for heart failure, and
cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

Case adjudication and data entry

An independent CEC will adjudicate all suspected cases of major adverse cardiovascular events. The investigator must first report these events as an AE as described in Section 8.3 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (Section 8.3.4). Clinical event reporting begins after randomization.

8.3.5.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

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.

Record the specific diagnosis as an AE.

Record events that meet criteria for serious conditions, as described in Section 10.3.2 as SAEs.

8.3.5.7. Malignancies

Evaluate all events of malignancy or other suspected events related to malignancy and perform additional diagnostic tests as needed.

8.3.5.8. Abuse/Liability Potential

All events of abuse potential should be evaluated, and additional investigations performed as needed.

8.3.5.9. 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 10.2.1. Laboratory results are provided to the Sponsor n ^ medical monitor via the central laboratory.

8.3.5.10. Injection-Site Reactions

Symptoms and signs of a local injection-site reaction may include erythema, induration, pain, pruritus, and edema (see also Section 8.3.5.9).

If an ISR is reported by a participant or site staff, it will be reported as an AE and a specific ISR CRF will be used to capture additional information about this reaction for example, injection-site pain, degree and area of erythema, induration, pruritus, and edema.

8.3.5.11. Fatigue

The investigator should evaluate for contributors to fatigue, including clinical, lifestyle, and concomitant medication-related.

During the maintenance phase, if fatigue is persistent, lasting longer than 4 weeks, the investigator should evaluate the participant's tolerability to fatigue and, if needed, consider a temporary dose interruption of 1 to 2 weeks. After a 1 to 2-week dose interruption, the participant should be clinically re-evaluated and, if medically appropriate, restart the previous dose. In cases of persistent or recurrent intolerable fatigue, the investigator should contact the Lilly medical monitor.

If AEs related to fatigue, including the AEs lethargy, asthenia, and malaise, are reported by the participant, the site should trigger the FAS (Section 8.2.8) in the eCOA system for participant completion.

8.3.5.12. Bradycardia

: W Z] L W T Y _ T O P X L d O P N] P L ^ P S P L] _] L _ P & G : 6 : n ^ should be evaluated. Development of symptomatic bradycardia should be managed at the discretion of the investigator.

8.3.5.13. Inadequate Nutrition or Dehydration

Investigators should monitor participants for signs and symptoms of inadequate nutrition and provide nutritional guidance. By recognizing early signs of inadequate oral intake, preventative actions can be implemented to reduce the risk of potential complications. Supplementation and treatment of deficiencies should be provided as clinically indicated.

See Section 10.3 for any additional samples and data collections when certain AEs occur.

8.3.5.14. Incident Diabetes During the Treatment Period

Participants will be monitored throughout the study for incident diabetes. For the definition of incident diabetes, confirmation of diabetes diagnosis, recording of incident diabetes events, and management of incident diabetes, refer to Section 10.10. All reported or suspected cases of incident diabetes will be adjudicated by an independent CEC (adjudication committee) with endocrinology expertise that will be blinded to treatment assignment. The investigator must first report these events as an AE as described in Section 8.3 and then report them as an endpoint on

the CRF with all required source documents provided to the CEC for adjudication (see Section 8.3.4). Decisions of the CEC regarding diabetes diagnosis and the onset date will be recorded in a dedicated adjudication CRF. Participants with incident diabetes during the study will continue participation in the study with study intervention unless discontinuation criteria are met (Section 7).

8.4. Pharmacokinetics

Pharmacokinetic samples will be collected from all randomized participants.

Whole blood samples will be collected for measurement of plasma concentrations of eloralintide as specified in the SoA (Section 1.3). Blood samples collected from participants in the placebo arms will not be included in the bioanalyses of drug concentrations.

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

Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of every dose and each sample collected will be recorded on the appropriate forms.

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

Refer to Section 9.3.5 for population PK and PK/PD analysis.

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

Pharmacokinetic sampling times

Week from Randomization	PK Sample Relative to Last Study Intervention Dose
Week 0	Predose[a] and 2 to 6 hour postdose
Week 4	Predose[a]
Week 12	Random (at anytime during visit)
Week 16	Predose[a] and 2 to 6 hour postdose
Week 28	Predose[a] and 12 to 48 hour postdose
Week 40	Predose[a] and 48 to 120 hour postdose
Week 52	Predose[a]
Week 64	Random (at anytime during visit)
Early discontinuation[b]	Random (at anytime during visit)
6 weeks after last treatment dose	Random (at anytime during visit)

[a] Participants should take study intervention only after PK samples are taken on the predose PK sample visits.

[b] Early discontinuation PK samples should be collected regardless of study week at which the discontinuation occurs (even if after Week 48).

8.4.1. Bioanalysis

Plasma samples will be analyzed at laboratories approved by the Sponsor and stored at facilities designated by the Sponsor.

Concentrations of eloralintide will be analyzed using validated liquid chromatography mass spectrometry (LC/MS) methods. Analyses of samples collected during placebo treatment are not planned.

Bioanalytical samples collected to measure eloralintide 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, and/or bioanalytical method cross-validation.

8.5. Pharmacodynamics

Samples to assess the PD properties of eloralintide are included under efficacy or other laboratory measures.

8.6. Genetics

A whole blood sample will be collected from participants to enable DNA isolation for exploratory pharmacogenetics analysis as specified in the SoA, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future.

Samples may be used to investigate variable exposure or response to eloralintide and to investigate genetic variants thought to play a role in obesity, diabetes mellitus, and related clinical traits or complications. Assessment of variable response may include evaluation of AEs or differences in PD, mechanistic, safety, or efficacy measures.

See Appendix 5 (Section 10.5) for Information regarding genetic research and Appendix 1 (Section 10.1.12) for details about sample retention and custody.

8.7. Biomarkers

Serum and plasma samples for exploratory biomarker research will be collected at times specified in the SoA, where local regulations allow.

All samples will be used but not limited to develop or validate new assays, research methods or diagnostic tools, or conduct research on the drug targets, disease process, variable response to eloralintide, pathways associated with Obesity or overweight , obstructive sleep apnea, and related clinical traits or complications, mechanism of action of eloralintide and/or other amylin agonists, or other relevant disease states.

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 staff. The cadence of collection is described in the Schedule of Activities (Section 1.3).

See Section 10.1.12 for details about sample retention.

8.8. Immunogenicity Assessments

At visits and time specified in the SoA, venous blood samples will be collected to determine antibody production against eloralintide. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity sample. All samples for immunogenicity should be taken predose where applicable and possible. In the event of drug hypersensitivity events, additional samples will be taken as specified in Section 10.2.1.

The detection and characterization of antibodies to eloralintide will be performed using a validated assay under supervision of the Sponsor. ADA may be further characterized for cross-reactivity to native amylin, their ability to neutralize eloralintide, and/or their ability to neutralize native amylin. Immunogenicity samples may be used for control or validation of the ADA assay.

TE ADA are defined in Section 9.3.7.2.

See Section 10.1.12 for details on sample retention.

8.9. Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The statistical analysis plan will be finalized prior to 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.

Unblinding details are specified in the Blinding and Unblinding Plan.

9.1. Statistical Hypotheses

The null hypotheses corresponding to the primary objectives are as follows:

$H_{1,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in body weight from baseline at Week 64.
$H_{2,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean change in AHI from baseline at Week 64.

The null hypotheses corresponding to the key secondary objectives are as follows:

$H_{3,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 5% from baseline at Week 64.
$H_{4,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 10% from baseline at Week 64.
$H_{5,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 15% from baseline at Week 64.
$H_{6,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 20% from baseline at Week 64.
$H_{7,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean change in SBP from baseline at Week 64.
$H_{8,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in triglyceride from baseline at Week 64.
$H_{9,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in non-HDL cholesterol from baseline at Week 64.
$H_{10,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in AHI from baseline at Week 64.
$H_{11,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean change in PROMIS Short Form Sleep-related Impairment 8a T-score from baseline at Week 64.
$H_{12,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving AHI<5 or AHI 5 to 14 with ESS $\leq$ 10 at Week 64.

$H_{13,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in SASHB from baseline at Week 64.
$H_{14,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving AHI reduction of at least 50% from baseline at Week 64.
$H_{15,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in hsCRP from baseline at Week 64.

9.1.1. Multiplicity Adjustment

Multiplicity-adjusted analyses will be performed on the primary and key secondary objectives in study to control the overall family-wise type I error rate at a 2-sided alpha level of 0.05 for each ISA study independently. The graphical multiple testing procedure described by Bretz et al. (2011) will be used. The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all hypotheses tested (Alosh et al. 2014).

The study will be considered positive if either or both of the independent primary objectives is/ are met.

H Y W P ^ ^ Z _ S P] b T ^ P ^ [P N T Q T P O $ _ S P I _] P L _ X P Y _] P [ ] Z O ` N _] P R T ^ _] L _ T Z Y L Y O _ S P I P Q Q T N L N d P ^ _ T X L disclosures and other purposes. Since these 2 types of estimands are intended for distinct purposes, no multiplicity adjustment will be made for conducting separate analyses on the same objectives.

The detailed graphical testing procedure will be included in the statistical analysis plan prior to the unblinding.

9.2. Analyses Sets

The following participant analysis sets are defined:

Participant Analysis Set	Description
Entered participants	All participants who sign informed consent.
Randomized participants	All participants who are randomly assigned a study intervention.
Safety participants	All participants who are randomly assigned a study intervention and who take at least 1 dose of study intervention.

The following data points sets are defined:

Data Points Sets	Description
Treatment regimen estimand data points set for AHI-related parameters	All data points obtained during the treatment period defined as at or after baseline and up to the last visit within the planned treatment period, regardless of study intervention discontinuation or initiation of prohibited OSA, excluding data collected after initiation of prohibited OSA treatment data collected after initiation of prohibited weight management treatments related to highly effective weight loss or for treatment of OSA condition data collected after initiation of PAP therapy (YSA1 only) Definition of prohibited treatments will be provided in SAP.
Treatment regimen estimand data points set for all other efficacy endpoints	All data points obtained during the treatment period defined as at or after baseline and up to the last visit within the planned treatment period, regardless of study intervention discontinuation or initiation of prohibited OSA or weight management treatments.
Efficacy estimand data points set for AHI-related parameters	Data points obtained during the treatment period at or after randomization up to the earliest date of discontinuation of study intervention or initiation of prohibited OSA or weight management treatments related to highly effective weight loss or for treatment of OSA condition or initiation of PAP therapy (YSA1 only). Details for list of prohibited treatments will be provided in SAP.
Efficacy estimand data points set for all other efficacy endpoints	All data points obtained during the treatment period defined as at or after baseline and up to the earliest date of study intervention discontinuation or initiation of prohibited weight management treatments.
Safety data points set	All data points obtained during the intervention period and the follow-up period defined as at or after baseline and up to the date of study withdrawal, including the follow-up period and regardless of occurrences of intercurrent events.

Additional data points sets for other parameters may be provided in the SAP.

9.3. Statistical Analyses

9.3.1. General Considerations

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

Unless otherwise noted, all tests for superiority will be conducted at the 2-sided alpha level of 0.05, and CIs will be calculated at 95%, 2-sided. For objectives controlled for type 1 error, the alpha will be allocated by the graphical testing scheme.

Baseline is defined as the last available non-missing measurement prior to the first dosing of study intervention, unless otherwise specified. If there are no doses of study intervention, baseline will be defined as the last available non-missing measure on or prior to randomization.

General descriptions of analyses

For continuous measures, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum for both the actual and the change from baseline measurements, model-based estimates (MBE) and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference model-based estimates and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons.

Strata variable defined for statistical modeling consists of joint levels of all stratification factors.

The analysis model to make comparisons between treatment groups relative to continuous efficacy measurements with only 1 postbaseline assessment or under treatment regimen estimand will be an ANCOVA using robust inference (Ye et al. 2022, FDA 2023). The model will include treatment group, strata variable, the continuous covariate of baseline values and their interactions with treatment group.

For continuous measures evaluated at multiple postbaseline visits and analysis guided by efficacy estimand, a maximum likelihood based-MMRM analysis (Wang and Du 2022) will be used. The analysis model to make comparisons between treatment groups relative to continuous measurements assessed over time will include fixed effects of visit, and treatment, strata variable, and baseline measurement all nested within treatment and visits. The variance-covariance matrix will be estimated using sandwich variance estimators (Tsiatis 2007).

For categorical measures, summary statistics will include sample size, frequency, and percentages. For safety categorical measures, risk difference and its 95% CI will be provided. ; T ^ S P] n ^ P c L N Chi-square test will be used for treatment comparisons without covariate adjustment, if applicable.

For binary measures, a logistic regression model with treatment group and strata variable as fixed effects and the continuous baseline value and their interactions with treatment group as a covariate will be used to examine the treatment difference with missing endpoints imputed. The unconditional treatment group effect will be assessed by risk difference and relative risk using the marginal standardization method, where the treatment group-specific risk will be derived from the counterfactual risks for each participant that are predicted with the fitted logistic model (FDA 2023; Ye et al. 2023). The estimated treatment group-specific risk, risk difference, relative risk, p-value, and 95% CI will be presented.

For time-to-event measures, Kaplan jMeier method will be used for estimation of cumulative event-free survival rates over time and Cox proportional hazards regression analysis will be used to compare hazard rates among treatments.

Unless specified otherwise, safety and tolerability assessments will be guided by an estimand comparing safety of eloralintide doses with placebo in safety participants using safety data point set.

Missing data should be minimized as the best precaution. Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses will be described in the final clinical study report.

Participants will be analyzed according to the treatment group to which they were randomly assigned.

In case of mis-stratification, actual strata variable value collected at baseline, instead of as-randomized value will be used for covariate adjustment.

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

9.3.2. Treatment Group Comparability

9.3.2.1. Participant Disposition

A detailed description of participant disposition will be provided.

Frequency counts and percentages of all randomly assigned participants will be presented by treatment groups. A listing of randomly assigned participants not receiving study intervention will be provided. All participants who discontinue the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment groups. Kaplan jMeier analyses of time from randomization to premature discontinuation from study and premature discontinuation from study intervention by treatment group will be provided.

9.3.2.2. Participant Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for all randomly assigned participants.

9.3.2.3. Concomitant Therapy

Concomitant medications and previous therapy, will be summarized descriptively by treatment group for the randomly assigned participants during treatment period.

9.3.2.4. Treatment Compliance

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

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

There will be 2 estimands of interest in comparing efficacy of Eloralintide doses with placebo. No multiplicity adjustment is planned between these 2 estimands.

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Primary analysis aligned to treatment regimen estimand will be conducted using the randomly assigned participants with treatment regimen estimand data points set. The primary analysis model will be ANCOVA characterizing change in AHI and percent change in body weight from baseline at the 64-week visit. The model includes the following as covariates:

treatment as a factor variable,

strata variable as factor variables,
baseline value (of the dependent variable),
interaction between strata variable and treatment group, and
interaction between baseline value and treatment group.

The estimated treatment group effect and comparison between eloralintide MTD and placebo will be reported together with the variability estimated using the robust inference (Ye et al. 2022). The associated 2-sided 95% CI and corresponding p-values will also be reported.

Missing data at Week 64 will be imputed in a fashion consistent with what the values would likely have been had they been collected, namely using multiple imputation based on data retrieved from participants who permanently discontinued study intervention but continued in the study with non-missing measurements (i.e. retrieved dropouts). The statistical inference over multiple imputed datasets will be guided by the method proposed by Rubin (1987). The details of the imputation strategy will be specified in the statistical analysis plan.

A multiple imputation-based tipping-point analysis is planned as a sensitivity analysis to assess the robustness of primary efficacy results. Additional details on sensitivity analyses will be provided in the SAP.

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Primary analysis aligned to efficacy estimand will be conducted using the randomly assigned participants with efficacy data points set, i.e., data collected before the occurrence of any ICEs (Section 9.2). All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The primary analysis model will be a mixed model for repeated measures model characterizing percent change in body weight over time.

The MMRM model will include the following terms:

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

The estimated treatment group effect and comparison between eloralintide MTD and placebo at the scheduled visits will be reported together with the variability estimated using the robust inference (Wang and Du 2022). The addition of 3-way interaction terms is not intended to estimate the heterogeneity effect but to provide robustness and efficiency for the estimate of treatment comparisons on the unconditional effect. The associated 2-sided 95% CI and corresponding p-values will also be reported. An unstructured covariance matrix by each treatment group will be used to model the within-participant errors, assuming heteroscedasticity and the measurements for different participants are independent.

Through the MMRM, the efficacy measures (after the ICEs) will be implicitly imputed as if participants did not have ICEs.

Additional details of the statistical modeling will be provided in the SAP.

9.3.4. Secondary Endpoint(s)/Estimand(s) Analysis

All these key secondary analyses will be addressed using 2 estimands as mentioned in Section 9.3.3. Additional details, including the strategy for controlling overall Type 1 error rate at a 2-sided alpha of 0.05 of primary and key secondary endpoint evaluation for each of the estimand and analysis details for all secondary endpoints and exploratory endpoints, will be provided in the SAP.

Analyses for key secondary endpoints will be controlled for type 1 error through the graphical approach.

Continuous endpoints for secondary endpoints will be analyzed using similar methods as primary endpoint outlined in Section 9.3.3, aligning with respective estimand of interest.

The binary outcomes will be analyzed using the following procedure:

Impute missing underlying continuous data that determines the binary value at visit of interest

- . * $!-;* ($ &) (stim)nd - using the same imputation strategy on the underlying continuous endpoint that determines the binary value.
- . %% ' " ! " -- Imputing the missing continuous-valued measurements at the scheduled visits using the randomized participants with efficacy estimand data points

^ P _ L ^ ^ ` X T Y R I X T ^ ^ T Y R L _ ] L Y O Z X m b T _ S X ` W

Transforming the observed and imputed continuous value to the binary value (Ma et al. 2022).

Fitting a logistic regression model to the data with the following terms

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

Providing for the visit of interest estimates and inferences of unconditional treatment effects defined by the risk difference and/or risk ratio based on the delta method using the formula provided (Ye et al. 2023).

9 P] T a T Y R _ S P Q T Y L W T Y Q P] Pooling estimates from multiply E ` M T Y n ^ imputed datasets.

Details for additional secondary analyses will be provided in the SAP.

9.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Eloralintide concentration data will be analyzed using a population PK approach using nonlinear mixed-effects modeling techniques implemented in the NONMEM® or equivalent software.

The relationships between eloralintide doses and/or concentration and selected efficacy, tolerability, and safety endpoints may be characterized. Additionally, the impact of intrinsic and extrinsic participant factors such as age, weight, gender, and renal function on eloralintide PK and/or PD parameters may be evaluated.

If ADA titers are detected from immunogenicity testing, then the impact of immunogenicity on eloralintide 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 will be provided in the PK/PD analysis plan.

9.3.6. Safety Analyses

Safety analyses will be conducted using the safety participants and the safety data points set, unless otherwise specified.

AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported by preferred terms within system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized Medical Dictionary for Regulatory Activities Queries. Summary statistics will be provided for incidence of

TEAEs
SAEs
study discontinuation due to AEs
study intervention discontinuation due to AEs
deaths, and
other CV endpoints.

Counts and percentages of participants experiencing AEs will be reported for each treatment group. Details regarding safety analysis will be provided in the SAP and program safety analysis plan (PSAP).

9.3.6.1. Adverse Events of Special Interest and Other Safety Topics

The analysis details for the AEs of special interest and other safety topics (as defined in Sections 8.3.3 and 8.3.5) will be provided in the SAP.

9.3.6.2. Gastrointestinal Events

Summaries and analyses for incidence, prevalence, and severity of the GI events of nausea, vomiting, constipation, and diarrhea will be provided by treatment group.

9.3.6.3. Depression, Suicidal Ideation, and Behavior

In addition to the summary of TEAEs, suicide-related thoughts and behaviors occurring during treatment will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide [C-SSRS]. Depression-related symptoms will be summarized based on responses to the PHQ-9.

The analysis details will be provided in the SAP.

9.3.6.4. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Actual and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. Continuous variables, as well as the change from baseline for these variables, will be analyzed by MMRM models, as described in Section 9.3.1 The percentages of participants with treatment-emergent

abnormal, high, or low measures (including laboratory, vital, and ECG parameters) will be
^ ` X X L] T e P O L Y O N Z X [L] P O M P _ b P P Y _] P L _ X P Y _ R] Z
square test.

9.3.7. Other Analyses

9.3.7.1. Subgroup Analyses for Primary Objective

Subgroup analyses to assess consistency of the effect of eloralintide across subgroups for the primary endpoints will be detailed in the SAP. The following subgroups will be considered (but not limited to):

L R P R] Z ` [! 4 . - $ h . - d P L] ^ "
sex (AMAB, AFAB)
M L ^ P W T Y P 7 @ > 2 L!YgO+ (4$+ -5$+ L(hY+6Y+R 4VXkg(m$2X h , (
race
prediabetes status (yes, no)
ethnicity
M L ^ P W T Y P B F 6 ^ P a P] T _ d ! X Z O P] L _ P 2 6 = > h) - L
M L ^ P W T Y (P, >10), and ! g
country/region.

If the number of participants is too small (less than 10%) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. Additional subgroup analyses on the key secondary endpoints, may also be performed. Further details on the statistical analysis will be provided in the SAP.

9.3.7.2. Immunogenicity

The frequency and percentage of participants with preexisting ADA, and TE ADA to eloralintide 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 ADA were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADA were detected at baseline (treatment-boosted ADA).

For TE ADA+ participants, the distribution of maximum titers may be reported. The frequency of TE ADA+ participants with cross-reactive antibodies against native amylin and/or neutralizing antibodies against eloralintide and/or native amylin may also be tabulated if available.

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

9.4. Interim Analysis

No efficacy interim analyses are planned for this study. If an unplanned efficacy interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

An independent DMC will be established for interim safety monitoring and have the responsibility to review unblinded interim safety analysis results. A statistical analysis center

independent from the Sponsor will perform the data analysis for the DMC. The first interim analysis will be performed approximately 6 months after the first participant enters treatment of the first study in the program. These interim safety analyses will occur every 6 months to monitor the safety of the participants in the study.

The study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded interim safety analyses. Study sites will receive information about interim safety results only if they need to know for the safety of their participants. Details of the DMC are described in Section 10.1.5.2 and the DMC charter.

The database lock will occur after all randomized participants complete the 64-week treatment period and the posttreatment safety follow-up period of the study or discontinue the study early. The primary objective of the study will be assessed following this database lock.

Details regarding maintaining the blind during the conduct of this study will be specified in the Blinding and Unblinding Plan document.

9.5. Sample Size Determination

The master protocol will allow participants to be randomized into associated ISAs based on baseline PAP use until each study has approximately 400 participants randomized. The sample size determination assumes that evaluation of superiority of eloralintide MTD to placebo for the percent change in body weight and the absolute change in AHI at Week 64 will be conducted in parallel in each ISA at a 2-sided significance level of 0.025. In addition, a difference of at least 11% reduction in mean body weight change from baseline at Week 64 for eloralintide MTD compared with placebo, a common SD of 11%, and a difference of at least 15 events/hour improvement in AHI change from baseline at Week 64 for eloralintide MTD compared with placebo, with a common SD of 25 events/hour will be assumed. Under the assumptions above, randomizing 400 participants in a 1:1 ratio to eloralintide MTD or placebo provides more than 95% power to demonstrate superiority of eloralintide MTD to placebo in both primary endpoints.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

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

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
Applicable ICH Good Clinical Practice (GCP) Guidelines

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

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

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

The investigator will be responsible for the following

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

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

10.1.2. Financial Disclosure

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

10.1.3. Informed Consent Process

The investigator or _ S P T Y a P^ T R L Z] ^ will explain the nature of the study, including the risks and benefits, to the potential participant or their legally authorized representative and answer all questions regarding the study.

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

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with Sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant Z] _ S P [L] _ T N T [L Y _ n ^ W representative and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the Sponsor _ Z [ ] Z _ P N _ _ S P [L] _ T personal data. Any participant information, such as records, datasets or tissue samples that are transferred to the Sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that _ S P [L] T N T [L Y _ h ^ personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

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

The Sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The Sponsor n ^ [ ] Z N P ^ ^ P ^ L] P N Z X [W T L Y _ b T _ S W Z legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

10.1.5.1. Clinical Endpoint Committee

An independent CEC with membership external to the Sponsor will be responsible for event adjudication in a blinded fashion.

The independent CEC will adjudicate events listed in Section 8.3.4. The CEC charter will contain the final detailed event definitions used for adjudication.

10.1.5.2. Data Monitoring Committee

An independent, external DMC will be responsible for reviewing unblinded data during the study.

The committee will include, at a minimum, a physician with appropriate expertise and a statistician.

Access to the unblinded data will be limited to the DMC and the external statistical analysis center statisticians who are providing the analysis of the data. These statisticians will be independent from the study team. The study team will not have access to the unblinded data. Only the DMC is authorized to evaluate unblinded interim safety analyses.

Details about the membership, purpose, responsibilities, and operation will be included in the DMC charter.

10.1.6. Dissemination of Clinical Study Data

Reports

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

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

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

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

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

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

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

10.1.7. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

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

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

Quality tolerance limits (QTLs) will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the QTLs and remedial actions taken will be summarized in the clinical study report.

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

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

The Sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

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

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

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

Data capture system

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

Electronic data capture system

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

Clinical Outcome assessments

Additionally, electronic Clinical Outcome Assessment (eCOA) data (participant-focused outcome instrument) will be directly recorded by the participant or investigator site personnel, into an instrument (for example, handheld smart phone or tablet). The eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in _ S P N P Y _] L W a P Y O Z reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Sponsor data warehouse.

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the T Y _ P R] T _ d Z Q _ S P O L _ L N Z W W P N _ P O & F Z ` ] N P O Z N ` X

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

Definition of what constitutes source data can be found in the site confirmation of source data.

10.1.9. Study and Site Start and Closure

Study start

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

First act of recruitment

The first act of recruitment is the opening of the first site.

Study or site termination

The Sponsor or Sponsor n designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

for study termination due to discontinuation of further study intervention development
for site termination due to

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

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the Sponsor n ^ [` MW T N, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

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

10.1.12. Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of eloralintide or after eloralintide become(s) commercially available.

Sample Type	Custodian	Maximum Retention Period after the Last Participant Visit[a]
Exploratory biomarkers	Sponsor or designee	Up to 7 years
Pharmacokinetic	Sponsor or designee	1 year
Genetics	Sponsor or designee	Up to 7 years
Immunogenicity	Sponsor or designee	Up to 15 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory.

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

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

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

Laboratory or analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

Clinical Laboratory Tests	**Comments**
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs jred blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs jwhite blood cells)	
Differential jabsolute	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Clinical Chemistry Panel	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Magnesium	
Chloride	
Bicarbonate	

Clinical Laboratory Tests	Comments
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Uric acid	
Lipid Panel	Assayed by Lilly-designated laboratory unless stated otherwise
High-density lipoprotein cholesterol (HDL-C)	
Low-density lipoprotein cholesterol (LDL-C) (Direct measure)	Direct measurement will be performed if triglycerides exceed maximum value for calculation
Very low-density lipoprotein cholesterol (VLDL-C)	Calculated by Lilly-designated laboratory
Total cholesterol	
Triglycerides	
Non-high-density lipoprotein cholesterol (Non-HDL-C)	Calculated by Lilly-designated laboratory
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment	Only if abnormalities are detected
Hormones	Assayed by Lilly-designated laboratory unless stated otherwise
Serum pregnancy	
Urine pregnancy	Evaluated locally

Clinical Laboratory Tests	Comments
Follicle-stimulating hormone (FSH)	
Urine Chemistry	Assayed by Lilly-designated laboratory
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory
eGFR (CKD-EPIcreat-cystC)	
Urinary albumin/creatinine ratio (UACR)	
Renin/aldosterone ratio	Results will not be provided to the investigative sites
Pharmacokinetic Samples jeloralintide concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Eloralintide PK	
Other Testing	Assayed by Lilly-designated laboratory
Free fatty Acids	Results will not be provided to the investigative sites
Aldosterone	Results will not be provided to the investigative sites
Apolipoprotein C3	Results will not be provided to the investigative sites
Apolipoprotein B	Results will not be provided to the investigative sites
C-peptide	Results will not be provided to the investigative sites
C-reactive protein, high-sensitivity (hsCRP)	Results will not be provided to the investigative sites
Cystatin-C	
HbA1c	
Insulin	Results will not be provided to the investigative sites
Intact proinsulin	Results will not be provided to the investigative sites
Lipase	
Pancreatic amylase	
Renin	Results will not be provided to the investigative sites
Thyroid-stimulating hormone (TSH)	
Micronutrient Panels	**Assayed by Lilly-designated laboratory**
Vitamin B1 (Thiamine)	
Vitamin B9 (Folate)	
Vitamin B12	
Vitamin D (25-hydroxy vitamin D)	
Iron Panel (iron, ferritin, TIBC, transferrin saturation)	
Zinc	

Clinical Laboratory Tests	Comments
Genetic Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Whole blood	
Exploratory Biomarker Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Serum	
Plasma (EDTA)	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Anti-eloralintide antibodies	
Anti-eloralintide antibodies neutralization	

Abbreviations: CKD-EPIcreat-cyst C = chronic kidney disease epidemiology collaboration using creatinine and cystatin-C; eGFR = estimated glomerular filtration rate; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; PK = pharmacokinetic.

10.2.1. Laboratory Samples to be Obtained at the Time of a 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. p 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. p Note: If collecting, collect up to 12 hours after the start of the event.	eloralintide anti-drug antibodies (ADA)
	eloralintide 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.

10.2.2. Nutritional Monitoring Panel to be Obtained in Case of Suspected Malnutrition

Purpose of collecting samples in case of suspected malnutrition

Investigators should monitor participants for signs and symptoms of malnutrition. Refer to Sections 5.3.1, 5.3.2 and 6.6.2.

When to collect samples in case of suspected malnutrition

Collect the samples listed below if malnutrition is suspected.

Category	Laboratory Test
Special tests	Vitamin A
	Vitamin B1 (Thiamine)
	Vitamin B9 (Folate)
	Vitamin B12
	Vitamin D (25-hydroxy vitamin D)
	Vitamin K_1[a]
Hematology	Complete blood count[b]
Clinical chemistry	Clinical chemistry panel[c]
	Zinc
	Intact parathyroid hormone (iPTH)
Iron panel	Serum iron
	Total iron binding capacity (TIBC)
	Transferrin saturation (%)
	Ferritin

[a] Results of vitamin K1 may not be available in all countries.
[b] Refer to Section 10.2 for contents of complete blood count panel.
[c] Refer to Section 10.2 for contents of clinical chemistry panel.

Note: Tests will be assayed by a Lilly-designated laboratory and results will be provided to the investigative sites where allowed (or appropriate).

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, or
a test is not available centrally.

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

10.3.1. Definition of AE

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product, whether or not related to the medicinal (investigational) product or investigational combination product.

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

In line with clinical practice for this disease state, and based on the defined criteria for adverse events and related clarifications (ICH 1994, FDA 2012, EMA 2017, CFR 2024), the following are not considered adverse events:

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the T Y a P ^ _ T R L _ Z] _ Z M P X Z] P ^ P a P] P _ S L Y P c [P N _
The disease or disorder being studied or expected progression, signs, or symptoms of the disease or O T ^ Z] O P] M P T Y R ^ _ ` O T P O $ ` Y W P ^ ^ X Z] P ^ P condition.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

Results in death
Is life-threatening
- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

Requires inpatient hospitalization or prolongation of existing hospitalization
- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the [S d ^ T N T L Y n^ Z Q Q T N P Z] Z` occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity
- G S P _ P] X O T ^ L M T W T _ d X P L Y ^ L ^ ` M ^ _ L Y _ T L W normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

Is a congenital anomaly/birth defect
- Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.

Other situations:
- Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:

deficiencies in labeling information, and
use errors for device or drug-device combination products due to ergonomic design elements of the product.

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

If the participant identifies a product complaint or a problem with the study intervention, investigators will instruct participants to contact the site as soon as possible so that the situation can be assessed.

An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

Device deficiencies are product complaints.

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

AE, SAE, and product complaint **recording**

When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/product complaint information in the [illegible] AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

It is **not** [illegible] to the Sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint form for product complaints.

There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

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

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

Assessment of causality

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

‘6 reasonable possibility’ means there is evidence and arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the Sponsor by telephone.

Contacts for SAE reporting can be found in study training materials.

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the Sponsor.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in the SAE paper form.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

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

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

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

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Individuals assigned female at birth (AFAB)	Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus, and thus are capable of exposing an egg, embryo, or fetus to study intervention or drug effects.
Individuals assigned male at birth (AMAB)	Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus but are capable of exposing a fetus to study intervention or drug effects via their semen. Individuals AMAB are considered to be not of reproductive potential if they have had bilateral orchiectomy (orchidectomy) with or without penectomy.
Individuals of childbearing potential (IOCBP)[a]	Adult individuals AFAB are considered IOCBP unless they are INOCBP. **Note:** Adult individuals AFAB who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP.
Individuals not of childbearing potential (INOCBP)[b]	Individuals AFAB are considered INOCBP if they are not capable of producing ova or embryo, and/or are not capable of potentially gestating a fetus. Such individuals include those who 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[c]	The postmenopausal state is defined as an individual: at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[c], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone h , (X > H ' X ? 3 Z] 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] IOCBP is inclusive of the concept of women of childbearing potential (WOCBP or WCBP), a term often used in literature and regulatory guidance documents.

[b] INOCBP is inclusive of the concept of women not of childbearing potential (WNOCBP).

[c] The individual **should not** be taking medications during amenorrhea such as oral contraceptives, hormone replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Individuals on HRT and those whose postmenopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

10.4.2.1. Guidance for Individuals Assigned Female at Birth

IOCBP who are completely abstinent as their preferred and usual lifestyle or exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle must follow the rules in this table.

) A ? @ G	) A ? @ ; < @ G
agree to either remain abstinent or exclusively engage in sexual relations with other individual(s) who are AFAB, 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 study, or use the withdrawal method

IOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or who do NOT exclusively engage in sexual relations with other individual(s) who are AFAB as their preferred and usual lifestyle, must follow the rules in this table.

) A ? @ G
Agree to use 1 **highly** effective method of contraception together with a barrier method of contraception. These methods of contraception must be used during the study and for at least 70 days after the last dose of the study intervention.

10.4.2.2. Guidance for Individuals Assigned Male at Birth

The table below describes contraception guidance for individuals AMAB.

Participant Population	Contraception Guidance
6WW TYOTaTO`LW^ 6@6	should refrain from sperm donation for the duration of the study and for 70 days after the last dose of the study intervention.
Individuals AMAB with partner(s) who are IOCBP[a] ¡	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 70 days after the last dose of the study intervention.
Individuals AMAB with partner(s) who are pregnant[a] ¡	must remain abstinent (if this is their preferred and usual lifestyle), or use condoms for the duration of the study and for 70 days after the last dose of the study intervention.
Individuals AMAB who exclusively engage in sexual relations with other individual(s) who are AMAB, as their preferred and usual WTQP^_dWP i	are not required to use contraception.

[a] Individuals AMAB who have undergone orchiectomy but not penectomy must use condoms during sex, but the partner who is IOCBP is not required to use an additional form of contraception. Individuals AMAB who have undergone orchiectomy and penectomy are not required to use condoms.

10.4.2.3. Examples of Different Methods of Contraception[a]:

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 INOCBP definition above. combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation: o oral o intravaginal (vaginal ring) o transdermal (for example, contraceptive patch) (only for individuals <198 pounds or 90 kg) progestogen-only hormonal contraception associated with inhibition of ovulation o oral o injectable o implantable total abstinence sexual relationships exclusively between individuals who are assigned the same sex at birth vasectomy j for individuals AMAB in clinical trials and for the partner of an individual AFAB (if only sexual partner) fallopian tube implants (if confirmed by hysterosalpingogram), or intrauterine devices (IUD) with or without hormone-releasing system
Effective contraception	progestogen-only hormonal contraception, where inhibition of ovulation is not the primary mode of action penile condom with or without spermicide vaginal condom with or without spermicide diaphragm with spermicide cervical sponge with spermicide cervical cap with spermicide Note: Penile and vaginal 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

a Ablation (endometrial or uterine) is not considered a form of contraception.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic a L] T L _ T Z Y X L d T X [L N _ L [L] _ T N T [L Y _ n ^] P ^ [Z severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated.

Therefore, where local regulations and IRB/IEC allow, a whole blood sample will be collected for DNA analysis from consenting participants.

DNA samples will be used for research related to eloralintide, obesity or overweight or obstructive sleep apnea and related diseases. They may also be used to develop tests/assays including diagnostic tests related to eloralintide and/or other amylin agonists and obesity or overweight and OSA. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to eloralintide or study interventions of this class to understand study disease or related conditions.

The results of genetic analyses may be reported in the clinical study report or in a separate study summary.

The Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on eloralintide continues but no longer than 7 years or other period as per local requirements.

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

Hepatic evaluation testing

Note that testing for some analytes may not be available from the central lab or local lab in certain regions due to local availability of assay or regulatory requirements. If testing is not available, this will not be considered a protocol deviation.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management. If local testing is performed in lieu of central testing, the results should be recorded in the appropriate local lab CRF. For example, if immediate participant management circumstances preclude collection of central lab samples je.g., emergency room visit or hospitalization. The local laboratory must be qualified in accordance with applicable local regulations.

TESTS AVAILABLE FROM LILLY-DESIGNATED CENTRAL LABORATORY	
Hepatic Clinical Chemistry Panel	**Hepatitis A virus (HAV) testing:**
Total bilirubin	HAV total antibody
Direct bilirubin	HAV IgM antibody
Alkaline phosphatase (ALP)	**Hepatitis B virus (HBV) testing:**
Alanine aminotransferase (ALT)	Hepatitis B surface antigen (HBsAg)
Aspartate aminotransferase (AST)	Hepatitis B surface antibody (anti-HBs)
Gamma-glutamyl transferase (GGT)	Hepatitis B core total antibody (anti-HBc)
Creatine kinase (CK)	Hepatitis B core IgM antibody
Hepatic Coagulation Panel	HBV DNA
Prothrombin time, INR (PT-INR)	**Hepatitis C virus (HCV) testing:**
Hepatic Hematology Panel	HCV antibody (total or IgG)
Hemoglobin	HCV RNA
Hematocrit	**Hepatitis E virus (HEV) testing:**
Erythrocytes (RBCs - red blood cells)	HEV IgG antibody
Leukocytes (WBCs - white blood cells)	HEV IgM antibody
Differential:	HEV RNA
Neutrophils	**Anti-nuclear antibody (ANA)**
Lymphocytes	**Anti-smooth muscle antibody (ASMA) or anti-actin antibody**
Monocytes	**Haptoglobin**
Basophils	**Immunoglobulin IgA, IgG, IgM (quantitative)**
Eosinophils	**Urine Chemistry**
Platelets	Drug Screen
Cell morphology (RBC and WBC)	

TESTS TO BE PERFORMED BY INVESTIGATOR-DESIGNATED LABORATORY, AS NEEDED	
Acetaminophen	**Hepatitis D virus (HDV) testing:**
Acetaminophen protein adducts	HDV total antibody
Alkaline phosphatase isoenzymes	HDV IgM antibody
Ceruloplasmin	HDV RNA
Copper	**Herpes simplex virus (HSV) testing:**
Cytomegalovirus (CMV) testing:	HSV (Type 1 and 2) antibody
CMV antibody	HSV (Type 1 and 2) DNA
CMV DNA	**Iron**
Ethyl alcohol (ethanol, EtOH)	**Liver kidney microsomal type 1 (LKM-1) antibody**
Ethyl glucuronide (EtG)	**Phosphatidylethanol (PEth)**
Epstein-Barr virus (EBV) testing:	**Microbiology Culture:**
EBV antibody	Blood
EBV DNA	Urine
Ferritin	**Total Iron Binding Capacity or Transferrin Saturation**

10.7. Appendix 7: Measurement of Height, Weight, Waist and Neck Circumference, Vital Signs, and Calculation of BMI

The following information has been adapted from standardized physical measurement protocols Q Z] _ S P J Z] W O = P L W _ S B] R L Y T e L _ T Z Y n ^ F G : C b T ^ P

Height

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

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

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

Step 4. 6 ^ V _ S P [L] _ T N T [L Y _ _ Z M] P L _ S P T Y L Y O ^ _ L Y height in **centimeters to 1 decimal place**.

Weight

Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in **kilograms to 1 decimal place**.
All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
Body weight will be measured in fasting state at all visits. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

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

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

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

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

Waist circumference

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

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

Step 1. Ask the participant to wear light clothing (if available, patient gowns could also be used).

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

Step 3. Ask _ S P [L] _ T N T [L Y _ _ Z] P W L c L Y O X P L ^ `] P _ S P

Measuring neck circumference

Participants should look straight ahead during the measurement, with shoulders down (not hunched).
Measure the neck N T] N ` X Q P ] P Y N P L _ L [ Z T Y _ U ` ^ _ M P W Z b perpendicular to the long axis of the neck.
9 Z Y Z _ [W L N P _ S P _ L [P X P L ^ `] P Z a P] _ S P 6 O L
The tape will be as close to horizontal as anatomically feasible (the tape line in the front of the neck should be at the same height as the tape line in the back of the neck).
Care should be taken so as not to involve the shoulder/neck muscles (trapezius) in the measurement.
Measurements should be taken using a non-stretchable measuring tape.

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

Guidance for vital sign measurements of blood pressure and heart rate

measure vital signs before obtaining an ECG tracing and before collection of blood samples for laboratory testing
have the participant sit quietly for about 15 minutes before vital signs measurements are taken
for each parameter, take 3 measurements from the same arm, preferably the nondominant arm
measure the recordings at least 3 minutes apart
blood pressure must be taken with an automated BP instrument with the appropriate size cuff on the upper arm; Each measurement of sitting pulse and BP needs to be recorded in the CRF
heart rate is measured by pulse, and

Note: In the event pulse measurement cannot be taken via an automated BP instrument, the preferred location for measurement of pulse is the radial artery, and if BP and pulse measurements are taken separately, pulse should be taken prior to BP.

any clinically significant findings from vital signs measurement that result in a diagnosis and occur during the study should be reported to the Sponsor as an AE via CRF.

Calculating BMI

Round to 1 decimal place. For example, a BMI of 26.6 kg/m^2 should **not** be rounded to 27.0 kg/m^2.

10.8. Appendix 8: Select Medications Associated with Weight Gain

Antidepressants	***Antihistamines***
Nortriptyline	Diphenhydramine
Doxepin	Cetirizine
Amitriptyline	Hydroxyzine
Imipramine	Fexofenadine
Phenelzine	Meclizine
Paroxetine	Cyproheptadine
Escitalopram	***Antipsychotics***
Citalopram	Clozapine
Fluoxetine (>1 year)	Olanzapine
Sertraline (>1 year)	Risperidone
Mirtazapine	Quetiapine
Antihypertensives	Perphenazine
Prazosin	Aripiprazole
Doxazosin	***Mood Stabilizers***
Terazosin	Lithium
Metoprolol tartrate	***Steroids***
Propranolol	Glucocorticoids
Atenolol	Progestins
Antidiabetics	Corticosteroids (such as prednisone)
Insulin	***Contraceptives and hormones***
Sulfonylureas	Depo-medroxyprogesterone acetate
Thiazolidinediones	Megestrol acetate
Anti-epileptics	
Gabapentin	
Pregabalin	
Valproic acid	
Vigabatrin	
Carbamazepine	

Note: Adapted from Apovian et al. 2025.

10.9. Appendix 9: Definitions of Normoglycemia, Prediabetes, and Diabetes

Definitions of normoglycemia, prediabetes and T2D (participants with T2D are excluded in YDAO) are below, as defined by 2025 American Diabetes Association Standards of Medical Care in Diabetes (ADAb 2025).

	Normoglycemia	Prediabetes	Diabetes
HbA1c	<5.7% ! 4 + 1 q X X Z	5.7%-6.4% (39- , / q X X Z V	h . & - ! h , 0 q X X Z V
Fasting serum glucose (FSG)	4) ((q X R ! 4 - & . q X X	100-) * - q X R (5.6- . & 1 q X X	h) * . q X R ! h / & (q X X

Abbreviations: H = hour; HbA1c = hemoglobin A1c.

Note: Adapted from American Diabetes Association b 2025

10.10. Appendix 10. Management of Incident Diabetes

10.10.1. Definition and Confirmation of Incident Diabetes.

Incident diabetes is defined when any 1 of the following occurs after randomization (ADA 2025).

- ` Y P \ ` T a Z N L W S d [P] R W d N P X T mg/dL [11].1 mmol/L) Y O Z] X with ^ P] ` X R W signs or symptoms of hyperglycemia, or
  any 2 of the following criteria are observed at the same visit, or 1 value indicative of diabetes is observed and subsequently confirmed, with repeat of the abnormal test within 4 weeks, to ensure that diabetes management is initiated without delay:
  - = M 6) N h .mmol/mol) ! , 0
  - fasting serum R W ` N Z ^ mg/dL (7.0 mmol/L); fasting is defined as no caloric intake for at least 8 hours
    - ; F < a L W ` P h) * . X R ' O ? ! h / & (X X Z W ' ? " ^ **consecutive** FSG measurement (either at a scheduled or an unscheduled visit)

      Note: If diabetes diagnosis has not been confirmed at the consecutive FSG measurement, another FSG observed during the study will be considered as a new finding requiring confirmation.
  - initiation of any medication for the treatment of diabetes.

Note: Once diabetes has been confirmed, repeating any future abnormal test within 4 weeks is no longer required.

10.10.2. Recording of Diabetes Events

Diabetes diagnosis and the onset date as assessed by investigator will be recorded in the AE CRF and the dedicated endpoint CRF.

If the diagnosis of diabetes is based on laboratory results, the date of the first abnormal HbA1c or glucose value above the defined glycemic thresholds should be indicated as the date of O T L R Y Z ^ T ^ $ ` Y W P ^ ^ $ T Y _ S P T Y a P ^ _ T R L _ Z] n appropriate.
If the diagnosis is based on initiation of any medication for the treatment of diabetes, the investigator should indicate the most probable date of diagnosis in the CRFs.

All reported or suspected cases of diabetes will be adjudicated by an independent CEC (adjudication committee), see Section 10.1.5. Decisions of the adjudication committee regarding diabetes diagnosis will be recorded in the adjudication system.

10.10.3. Management of Incident Diabetes

Participants who develop diabetes during the study will be

provided and trained to use a glucometer.

Note 2 C L] _ T N T [L Y _ ^ b T _ S Z ` _ O T L M P _ P ^ X L d $ L _
glucometers to assist in the evaluation of reported symptoms consistent with hypoglycemia.
educated by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMBG, and diabetes management according to American Diabetes Association Standards of Medical Care in Diabetes and/or a Consensus Report by the American Diabetes Association and the European Association for the Study of Diabetes (ADA 2025, Davies et al. 2022) or local standards, and
instructed to report hypoglycemic episodes to the PI, and
followed up with local standard of care (ADA 2025, Davies et al. 2022) or local standards and perform retinal assessment as appropriate based on medical judgment.

Participants will be referred to their usual care provider and provided with a letter showing the study results indicative of diabetes. The decision to further evaluate, to initiate antihyperglycemic therapy, and the choice of antihyperglycemic medication will be at the O T ^ N] P _ T Z Y Z Q _ S P [L] _ T N T [L Y _ ^ ` ^ ` L W N L] P [ ] Additionally, standards of care guidelines for T2D management (eg. ADA/EASD 2022 or ADA 2025) should be followed in accordance with local standards. Initiation of metformin or SGLT-2i for the treatment of diabetes is permitted. The following medications are prohibited during the study, including after permanent discontinuation of study intervention, as rescue therapy, or during the posttreatment safety follow-up period

amylin analogs/agonists
GLP-1R agonists, or
GIP/GLP-1R agonist.

10.10.4. Therapy for Participants who Discontinue Study Intervention and Continue Participation in the Study or During the Posttreatment Safety Follow-Up Period

> Y a P ^ _ T R L _ Z] ^ Z] _ S P [L] _ T N T [L Y _ n ^ ` ^ ` L W N L] P antihyperglycemic medications or may initiate new antihyperglycemic medications for participants who permanently discontinue study intervention and continue participation in the study, or during the posttreatment safety follow-up period. However, prohibited anti-hyperglycemic medicines should not be used (Section 6.9.1).

This is not considered rescue therapy, and it must be differentiated from rescue therapy when reported in the CRF.

10.10.5. Management of Hypoglycemia Risk

Participants will be trained in the signs and symptoms of hypoglycemia and its treatment and instructed to report events to the investigator. Participants who develop persistent or recurrent unexplained hypoglycemia during the treatment period will be asked to reduce the dose of or discontinue any concomitant antihyperglycemic medications, starting preferably with the ones commonly associated with hypoglycemia. Monitoring for hypoglycemia includes capture of events as described in Sections 8.3.4 and 10.10.2.

10.10.6. Diabetes Education

Diabetes education, as well as a glucometer, will be provided to study participants who develop T2D (Refer to Section 8.3.5.1) during the study. Education will be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMBG, and diabetes management according to American Diabetes Association Standards of Medical Care in Diabetes and/or a Consensus Report by the American Diabetes Association and the European Association for the Study of Diabetes (ADA 2025, Davies et al. 2018) or local guidelines

Refer to previous section for management of hypoglycemia risk.

10.10.7. Rescue Therapy for Severe, Persistent Hyperglycemia

Criteria for initiation of glycemic rescue therapy for severe, persistent hyperglycemia

Investigators will be trained on how to apply decision criteria for the timing and method of intervention in participants who do not reach glycemic targets during the treatment period. Glycemic rescue criteria will be primarily determined from fasting SMBG values recorded in the [L] _ T N T [L Y _ n ^ RW ` N Z X P _ P] Z]SG NrPIYA1c.] L W W L M Z] L _ Z]

Participants should continue administering assigned study intervention.

Glycemic rescue therapy should be considered in participants who meet the following criteria in this table.

If a participant has G	
≥2 confirmed fasting SMBG/fasting glucose values Z a P] L _ WP L ^ _ * N Z Y ^ P N	
>270 mg/dL (15.0 mmol/L)	at any time from Week 0 and prior to Week 4
>240 mg/dL (13.3 mmol/L)	at any time from Week 4 to Week 8
>200 mg/dL (11.1 mmol/L)	at any time after Week 12
h) =M 6) N h 0 & - ! . 1 X X Z	on and after Week 16
Note: Investigators should first confirm that the study participant is fully compliant with the assigned study intervention and that he or she does not have an acute condition causing severe hyperglycemia.	

Recommended glycemic rescue therapy

Participants who develop severe persistent hyperglycemia during the treatment period may be candidates for glycemic rescue and should be considered for addition of or dose increase in antihyperglycemic therapies.

The choice of new antihyperglycemic therapy or amount of dose increase will be at the O T ^ N] P _ T Z Y Z Q _ S P T Y a P ^ _ T R L _ Z] Z Additionally, [L] _ T N T national standards of care or guidelines for T2D management (for example, ADA Standards of Care 2025 or ADA/EASD Consensus Report 2022) should be followed, and avoid the prohibited medications listed in Section 6.9.1.

Insulin rescue therapy can be initiated as rescue therapy based on the discretion of the investigator. Insulin therapy should be administered according to ADA 2025, ADA/EASD 2022 or local standards or guidelines and for as short of a duration as possible.

The use of rescue therapy should be recorded on a specific CRF page.

Short-term treatment with insulin not as rescue therapy

Short-term treatment with insulin, for less than 14 days, is allowed for certain clinical situations, such as, elective surgery, during hospitalization, hyperosmolar states, or acute illness.

This is not considered as rescue therapy, and it must be differentiated from rescue therapy when reported in the CRF with the name and dosage regimen.

10.11. Appendix 11: Region- or Country-Specific Requirements

10.11.1. European Union

The study will be conducted in accordance with the Regulation (EU) No 536/2014.

Regulatory reporting requirements

The Sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to EU regulatory requirements. The Sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority, per European Union Clinical Trial Regulation 536/2014 submission of SUSARs to the Eudra Vigilance database.

10.11.2. Germany

This section describes protocol changes applicable for adult participants in study sites in Germany.

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

Protocol Section Number and Name	Description of the Change	Brief Rationale
7.2. Participant Discontinuation/Withdraw from the Study 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.1.3. Informed Consent Process	Deleted references to l W P R L ` _ S Z ] T e P O ] P l W P R L W R ` L] O T	The German Drug Law (Arzneimittelgesetz j AMG) with reference to EU Regulation 536/2014 requires that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.

The revised text in the following sections show the changes applicable for adult participants at study sites in Germany. Deletions are identified by strikethrough format.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

L _ L Y d _ T X P L _ _ S P [L] _ T N T [L Y _ n ^ Z b Y] P \ ` P
reason
~~at _ S P] P \ ` P ^ _ Z Q _ S P [L] _ T N T [L Y _ n ^~ O P ^ T R Y P P
at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
if enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

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

The definitions of the following events can be found in Appendix 3 Section 10.3:

AEs
SAEs, and
PCs.

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

10.1.3. Informed Consent Process

G S P T Y a P ^ _ T R L _ Z] Z] _ S P T Y a P ^ _ T R L _ Z] n ^] P [ ] P ^ including the risks and benefits, to the potential participant ~~or the potential participant or their legally authorized representative,~~ and answer all questions regarding the study.

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

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with Sponsor and ERB consenting guidance.

A copy of the ICF(s) must be provided to the participant ~~Z] _ S P [L] _ T N T [~~ L Y _ n ^ W ~~representative~~ and is kept on file.

10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances

> Y < P] X L Y d $ _ S P _ P X [Z] L] d X P L ^ ` ] P ^ O P ^ N ] T M P O 9 `] T Y R : c N P [_ T Z Y L W 10813T"] NL`]XP^ _LL[Y[NWPT^NmL M!WHP9P NZ_YTWZdY _ Z pandemicm

10.12. Appendix 12: Abbreviations and Definitions

enter	Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~

10.11.3. India

This section describes protocol changes applicable for participants in study sites in India.

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

Protocol Section Number and Name	Description of the Change	Brief Rationale
8.3.1. Timing and Mechanism for Collecting Events	Revised footnote in timing and mechanism for collecting events table	ALL SAEs irrespective of the cause or causality, need to be reported to Indian Ministry of Health within 14 calendar days by the Sponsor.

The revised text in the following section shows the changes applicable only to participants in India.

All additions have been identified by the use of underscore, and all deletions have been identified by strikethroughs.

8.3.1 Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Events					
AEs including SAEs	Signing of the ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Additional Reporting for Serious Adverse Events					
SAE and SAE updates jprior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of study intervention	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE and SAE updates jafter start of study intervention	Start of study intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE f jafter [L] _ T N T study participation has ended **and** the investigator becomes aware	After [L] _ T N study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in participants and partners of participants	After the start of study intervention	70 days after last dose of study intervention	Within 24 hours (see Section 8.3.2)	Pregnancy CRF	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	k	k	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

f Serious adverse events should ~~not~~ be reported ~~unless the investigator deems them to be possibly related to study intervention or study participation~~.

10.11.4. Brazil

This section describes protocol changes applicable for participants at study sites in Brazil. This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
10.1.12. Sample Retention	Biological samples will be stored for up to 10 years.	Compliance with Brazilian regulation applicable to sample storage, resolution CNS 441 (Brazil 2011).
10.5. Appendix 5: Genetics	Biological samples obtained to evaluate genetic material (DNA/RNA).	Compliance with Brazilian laws and regulations (CNS 340/2004 and CNS 441/2011).
Patient Access to the Project Benefits	New section specific to Brazil.	Clarifies the Sponsor responsibilities to comply with Resolution CNS 466 (Brazil 2012) and RDC 38 (Brazil 2013) and Clinical Research Law 14.874 (Brazil 2024).
Section 11. References	Addition of Brazil-specific references	The references are specific to the Brazil-specific requirements.

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

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10.1.12. Sample Retention

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

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10.5. Appendix 5: Genetics

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

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Patient Access to the Project Benefits

In Brazil, at the end of each individual participation in the study, investigators may request post-trial access to the experimental drug to participants. The free provision of the experimental drug after the clinical trial could be carried out when it is considered the best therapy or treatment for the clinical condition of the participant and presents a more favorable risk-benefit ratio compared to other available treatments. The investigator is responsible for the assessment of risk-benefit, requesting post-trial access, abiding to local regulations, and in accordance with the country post-trial access plan.

11. References

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

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

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

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

BRASIL, LEI Nº 14.874, DE 28 DE MAIO DE 2024: Dispõe sobre a pesquisa com seres humanos e institui o Sistema Nacional de Ética em Pesquisa com Seres Humanos.

10.12. Appendix 12: Objectives, Endpoints, and Statistical Considerations for Japan

10.12.1. Objectives and Endpoints

All additions have been identified by the use of underscore and all deletions have been identified by ~~strikethroughs~~.

Objectives	Endpoints
Primary	
To demonstrate that eloralintide MTD QW is superior to placebo for change in: ~~body weight~~ AHI	From baseline to Week 64: ~~percent change in body weight~~ absolute change in AHI (events per hour)
~~Key~~ Secondary	
To demonstrate that eloralintide MTD QW is superior to placebo in change from baseline for: body weight	From baseline to Week 64: percent change in body weight

10.12.2. Statistical Hypotheses

The null hypotheses corresponding to the primary objective~~s are~~ is as follows:

- ~~$H_{1,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in body weight from baseline at Week 64.~~
  $H_{2,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean change in AHI from baseline at Week 64.

~~The null hypotheses corresponding to the key secondary objectives are as follows:~~

- ~~$H_{3,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 5% from baseline at Week 64.~~
- ~~$H_{4,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 10% from baseline at Week 64.~~
- ~~$H_{5,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 15% from baseline at Week 64.~~
- ~~$H_{6,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving body weight reduction of at least 20% from baseline at Week 64.~~
- ~~$H_{7,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean change in SBP from baseline at Week 64.~~

- ~~$H_{8,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in triglyceride from baseline at Week 64.~~
- ~~$H_{9,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in non-HDL from baseline at Week 64.~~
- ~~$H_{10,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in AHI from baseline at Week 64.~~
- ~~$H_{11,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean change in PROMIS Short Form Sleep-related Impairment 8a T-score from baseline at Week 64.~~
- ~~$H_{12,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants achieving AHI<5 or AHI 5 to 14 with ESS $\leq$ 10 from baseline at Week 64.~~
- ~~$H_{13,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the geometric mean percent change in SASHB from baseline at Week 64.~~
- ~~$H_{14,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the percentage of participants AHI reduction of at least 50% from baseline at Week 64.~~
- ~~$H_{15,0}$: No difference in eloralintide MTD QW compared to placebo with respect to the mean percent change in hsCRP from baseline at Week 64.~~

10.12.3. Multiplicity Adjustment

~~Multiplicity-adjusted analyses will be performed on the primary and key secondary objectives in study to control the overall family-wise type I error rate at a 2-sided alpha level of 0.05 for each ISA study independently. The graphical multiple testing procedure described by Bretz et al. (2011) will be used. The graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all hypotheses tested (Alosh et al. 2014).~~

~~The study will be considered positive if either or both of the independent primary objectives is/ are met.~~

H Y W P ^ ^ Z _ S P] b T ^ P ^ [P N T Q T P O $ _ S P l _] P L _ X P Y _] P
[ ] Z O ` N _] P R T ^ _] L _ T Z Y L Y O _ S P l P Q Q T N L N d P ^ _ T X L
disclosures and other purposes. Since these 2 types of estimands are intended for distinct purposes, no multiplicity adjustment will be made for conducting separate analyses on the same objectives.

~~The detailed graphical testing procedure will be included in the statistical analysis plan prior to the unblinding.~~

10.13. Appendix 13: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

In an exceptional circumstance, the Sponsor n ^ [ ] Z N P O ` ] P ^ P Y ^ `] P _ S L _] I informed of changes to the design and conduct of the study.

Exceptional circumstances

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

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the Sponsor n ^ b] T _ _ P Y L [[ ] Z a L W $ implement changes if permitted by local regulations.

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

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

Considerations for making a change

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

Informed consent

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

a change in the method of study intervention administration
dispensation of additional study intervention during an extended treatment period
alternate delivery of study intervention and ancillary supplies, and
provision of their personal or medical information required prior to implementation of these activities.

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

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, C-SSRS since last assessed, lifestyle counseling, and diary review.

Other alternative locations - Local laboratories may be used to collect laboratory samples only for safety assessments

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: Visits 1, 2, 9, 12, 18, ED, 801 and PK visits. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
asking the participant n designee to go to the site and receive study supplies on a
[L] _ T N T [L Y _ n ^ M P S L W Q
arranging delivery of study supplies, and

These requirements must be met before action is taken:

alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of
[L] _ T N T [L Y _ n ^] P N P T [_ Z Q ^ _ ` O d ^ ` [[W T P ^ &

When delivering supplies to a location other than the study site (for example, [L] _ T N T [ ), the investigator, Sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).

Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at[screening Visit 1 are valid for a maximum of 60 days. Except for serum pregnancy tests which are only valid for a maximum of 30 days.

The following rules will apply to active, nonrandomized participants whose participation in the study must be interrupted due to exceptional circumstances.

If screening is interrupted for less than 60 days from screening visit to Visit 2], the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 60 days from screening visit (Visit 1).

The site should conduct the next a T ^ T _ T Q _ S P [L] _ T N T [L Y _ n ^ confirmed, and the site should document the reason for delay.

The site ^ S Z ` W O L W ^ Z] P N Z Y Q T] X _ S P T X [L N _ P O [L confirmation in the source documentation.

If screening is interrupted for more than 60 days from screening visit to Visit 2, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can reconsent and be rescreened as a new participant. The screening procedures per the usual Schedule of Activities should be followed, starting at Visit 1 to ensure participant eligibility by Visit 2.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by _ S P T Y a P ^ _ T P 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 2 (Randomization)	Within 60 days after Visit 1
Visits 4 to 19	Within 7 days before or after the intended date
Week 28 PK only visit	No adjustment to the visit window described in SoA
Week 40 PK only visit	No adjustment to the visit window described in SoA
Visit 801	Within 14 days before or after the intended date

Abbreviations: PK = pharmacokinetics; SoA = schedule of activities

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

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.14. Appendix 14: Abbreviations and Definitions

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
ADA	anti-drug antibodies
AE	adverse event
AFAB	assigned female at birth
AHM	antihyperglycemic medication
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMAB	assigned male at birth
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or _ S P T Y a R aff are T R 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/ _ S P T Y a R aff and T R L _ Z] n participant are not. A double-blind study is one in which neither the participant nor any of the investigator or Sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BP	blood pressure
CEC	clinical endpoint committee
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CI	confidence interval
C-SSRS	Columbia-suicide severity rating scale
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.

CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, clinical pharmacologist, global safety physician or other medical officer.
CT	computed tomography
CV	cardiovascular
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the Sponsor regarding the stopping of a study for efficacy, or for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DPP-4i	dipeptidyl peptidase-4 inhibitor
DXA	dual-energy X-ray absorptiometry
EASD	European Association for the Study of Diabetes
ECG	electrocardiogram
eCOA	electronic clinical outcomes and assessments
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.
EQ-5D-5L	European quality of life-5 dimensions-5 level
FAS	fatigue Assessment Scale
GCP	Good Clinical Practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GIP/GLP RA	glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonist
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
hsCRP	high-sensitivity C-reactive protein
IB	i Y a P ^ _ T b r c h u r e Z] n ^

ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonization
IMP	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 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.
IP	investigational product
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.
INOCBP	individual not of childbearing potential
IOCBP	individual of childbearing potential
IRB	institutional review board
IWRS	interactive web-response system
LDL	low density lipoprotein
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more 1. the right participant 2. the right drug 3. the right dose 4. the right route, 5. at the right time.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MMRM	mixed models for repeated measures
participant	either as recipient of an investigational medicinal product or as a control

PC	product complaint
PK/PD	pharmacokinetics/pharmacodynamics
QTc	corrected QT interval
QW	once-weekly
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SGLT-2	Sodium-glucose co-transporter 2
SMBG	self-monitoring of blood glucose
SoA	schedule of activities
SU	Sulfonylurea
SUSAR	suspected unexpected serious adverse reactions Refers to an adverse event that occurs in a clinical trial participant, which is assessed by the Sponsor and or study investigator as being unexpected, serious and as having a reasonable possibility of a causal relationship with the study intervention.
T2D	type 2 diabetes
TE ADA	treatment-emergent anti-drug antibody
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

11. References

[AACE-ACE] Garvey WT, Mechanick JI, Brett EM, et al; Reviewers of the AACE/ACE Obesity Clinical Practice Guidelines. American Association of Clinical Endocrinologists and American College of Endocrinology comprehensive clinical practice guidelines for medical care of patients with obesity. *Endocr Pract*. 2016;22 Suppl 3:1-203. https://doi.org/10.4158/ep161365.gl

[ADA-EASD] American Diabetes Association. Management of Hyperglycemia in Type 2 Diabetes: ADA-EASD Consensus Report 2022. Presented at the 58th EASD Annual Meeting on September 23, 2022. Accessed January 18, 2023. https://professional.diabetes.org/content-page/management-hyperglycemia-type-2-diabetes-ada-easd-consensus-report-2022

[ADA] American Diabetes Association Professional Practice Committee. 9. Pharmacologic Approaches to Glycemic Treatment: Standards of Care in Diabetes-2025. *Diabetes Care*. 2025a;48(Supplement_1):S181-S206. https://doi.org/10.2337/dc25-S009

[ADA] American Diabetes Association Professional Practice Committee. 2. Diagnosis and Cladssification of Diabetes : Stndards of Care in Diabetes-2025. *Diabetes Care* 2025; 48(Suppl.1):S27-S49. https://doi.org//10.2337/dc25-S002

Almandoz JP, Wadden TA, Tewksbury C, et al. Nutritional considerations with antiobesity medications. *Obesity* 2024;32(9):1613-1631. https://doi.org/10.1002/oby.24067.

Al Oweidat, K., Toubasi, A.A., Tawileh, R.B.A. et al. Bariatric surgery and obstructive sleep apnea: a systematic review and meta-analysis. *Sleep Breath* **27**, 2283 2294 (2023). https://doi.org/10.1007/s11325-023-02840-1

Alosh, M, Bretz, F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med.* 2014;33(4):693-713. https://doi.org/10.1002/sim.5974

[AMA] American Medical Association House of Delegates: Recognition of obesity as a disease. Resolution: 420 (A-13). 2013. Accessed February 03, 2023. https://media.npr.org/documents/2013/jun/ama-resolution-obesity.pdf.

[AACE-ACE] American Association of Clinical Endocrinologists and American College of Endocrinology Comprehensive Clinical Practice Guidelines For Medical Care of Patients with Obesity. *Endocrine Practice.* 2016;22(Supplement 3):1-203. https://doi.org/10.4158/EP161365.GL

Apovian CM, Aronne LJ, Bessesen DH, et al. Pharmacological management of obesity: an endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2015;100(2):342-362. https://doi:10.1210/jc.2014-3415

Aroda VR, Ratner R. The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes: a review. *Diabetes Metab Res Rev.* 2011;27(6):528-542. https://doi.org/10.1002/dmrr.1202

[ASMBS] American Society for Metabolic and Bariatric Surgery (ASMBS). New study finds most bariatric surgeries performed in Northeast, and fewest in South where obesity rates are highest, and economies are weakest. Published 15 November, 2018. Accessed October 1, 2023. https://asmbs.org/app/uploads/2018/11/Bariatric-Surgery-by-State.pdf

Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400. https://doi.org/10.1111/j.1572-0241.2006.00856.x

Barazzoni R, Bischoff S, Boirie Y, et al. Sarcopenic obesity: time to meet the challenge. *Obes Facts*. 2018;11(4):294-305. https://doi.org/10.1159/000490361

Benjafield AV, Ayas NT, Eastwood PR, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respir Med*. 2019;7(8):687-698. https://doi.org/10.1016/S2213-2600(19)30198-5

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

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

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

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

BRASIL, LEI Nº 14.874, DE 28 DE MAIO DE 2024: Dispõe sobre a pesquisa com seres humanos e institui o Sistema Nacional de Ética em Pesquisa com Seres Humanos.

Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. *Stat Med*. 2009;28(4):586-604. https://doi.org/10.1002/sim.3495

Bretz F, Posch M, Glimm E, et al. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894-913. https://doi.org/10.1002/bimj.2010002

Campos GM, Khoraki J, Browning MG, et al. Changes in utilization of bariatric surgery in the United States from 1993 to 2016. *Ann Surg.* 2020;271(2):201-209. https://doi.org/10.1097/SLA.0000000000003554

Cava E, Yeat, NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Adv Nutr*. 2017;8(3):511-519. https://doi.org/10.3945/an.116.014506

Chen X, Wang R, Zee P, et al. Racial/ethnic differences in sleep disturbances: the Multi-Ethnic Study of Atherosclerosis (MESA). *Sleep*. 2015;38(6):877-888. https://doi.org/10.5665/sleep.4732

[CFR] Code of Federal Regulations. Title 21 jFood and Drugs. Part 312 jInvestigational New Drug Application. 21CFR312. April 1, 2024. Accessed July 18, 2025.

[CSAPH] Council on Science and Public Health. Report of the Council on Science and Public Health: is obesity a disease? (Resolution 115-A-12). Report number: 3-A-13. 2013. Council on Science and Public Health. Accessed February 03, 2023. https://www.ama-assn.org/sites/ama-

assn.org/files/corp/media-browser/public/aboutama/councils/Council%20Reports/council-on-science-public-health/a13csaph3.pdf.

Cowen J, Harrison S, Thom L, et al. Use of historical remote monitoring data to determine predictors of CPAP non-compliance in patients with OSA. *Sleep Breath*. 2023;27(5):1899-1908. https://doi.org/10.1007/s11325-023-02806-3

Craig CL, Marshall AL, Sjöström M, et al. International physical activity questionnaire: 12-country reliability and validity. *Med Sci Sports Exerc*. 2003;35(8):1381-1395. https://doi.org/10.1249/01.MSS.0000078924.61453.FB.

Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10278):971-984. https://doi.org/10.1016/S0140-6736(21)00213-0

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701. https://doi.org/10.2337/dci18-0033

Dombrowski SU, Knittle K, Avenell A, et al. Long term maintenance of weight loss with non-surgical interventions in obese adults: systematic review and meta-analyses of randomised controlled trials. *BMJ*. 2014 May 14;348:g2646. https://doi.org/1010.1136/bmj.g2646.

Dordevic AL, Bonham M, Ghasem-Zadeh A, et al. Reliability of compartmental body composition measures in weight-stable adults using GE DXA: implications for research and practice. *Nutrients*. 2018;10(10):1484. https://doi.org/10.3390/nu10101484

[EMA] European Medicines Agency. Committee for Medicinal Products for Human Use Guideline on clinical evaluation of medicinal products used in weight management. EMA/CHMP/311805/2014. Adopted June 23, 2016. Accessed August 28, 2025. https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-evaluation-medicinal-products-used-weight-management-revision-1_en.pdf(CHMP).

[EMA] European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). EMA/873138/2011 Rev. 2. Published July 28, 2017. Accessed July 18, 2025. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vi-collection-management-and-submission-reports-suspected-adverse-reactions-medicinal-products-rev-2_en.pdf.

EuroQol Research Foundation. EQ-5D-5L user guide, version 3.0. Updated September 2019. https://euroqol.org/publications/user-guides. Accessed January 28, 2025.

[FDA] Food and Drug Administration. Obesity and Overweight: developing drugs and biological products for weight reduction j Guidance for industry. Published January 2025. Accessed August 5, 2025. https://www.fda.gov/media/71252/download[FDA]

[FDA] Food and Drug Administration. Adjusting for covariates in randomized clinical trials for drugs and biological products: guidance document: guidance for industry. May 2023. Accessed Dec 20, 2024. https://www.fda.gov/regulatory-information/search-fda- guidance-documents/adjusting-covariates-randomized-clinical-trials-drugs-and-biological- products

[FDA] United States Food and Drug Administration. Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies. December 2012. Accessed September 3, 2025.

Frias JP, Hsia S, Eyde S, et al. Efficacy and safety of oral orforglipron in patients with type 2 diabetes: a multicentre, randomised, dose-response, phase 2 study. *Lancet*. 2023;402(10400):472-483. https://doi.org/10.1016/S0140-6736(23)01302-8.

Giugliano D, Scappaticcio L, Longo M, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol*. 2021;20(1):189. https://doi.org/10.1186/s12933-021-01366-8

Gleason P, Marshall L, Urick B, et al. Year-two real world analysis of glucagon-like peptide-1 agonist (GLP-1) obesity treatment adherence and persistency. *Prime Therapeutics.* 2024. Accessed 9/10/2024. prime-mrx-glp-1-year-two-study-abstract-final-7-10 (primetherapeutics.com)

Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. *JAMA*. 2020;323(14):1389-1400. https://doi.org/10.1001/jama.2020.3514

Hamilton GS, Gupta R, Vizcarra D, et al; Guidelines Committee Members and Governing 8 Z ` Y N T W Z Q _ S P J Z ] W O F W P P [ F Z N T P _ d & : Y O Z ] ^ P X diagnostic testing for adult obstructive sleep apnea: an American academy of sleep medicine N W T Y T N L W [ ] L N _ T N P R ` T O P S W T M P 2021;79:152-154. P J Z] W O F W https://doi.org/10.1016/j.sleep.2020.12.044.

Hedrington MS, Davis SN. Oral semaglutide for the treatment of type 2 diabetes. Expert Opin *Pharmacother*. 2019;20(2):133-141. https://doi.org/10.1080/14656566.2018.1552258

Hudgel DW, Patel SR, Ahasic AM, et al.; American Thoracic Society Assembly on Sleep and Respiratory Neurobiology. The role of weight management in the treatment of adult obstructive sleep apnea. An official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2018;198(6):e70-e87.

[ICH] International Conference on Harmonisation. Clinical Safety Data Management: Definitions and Standards for Expedited Reporting E2A. Step 4 version published October 27, 1994. Accessed July 18, 2025.

Jendle J, Nauck MA, Matthews DR, et al. LEAD-2 and LEAD-3 Study Groups. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. *Diabetes Obes Metab*. 2009;11(12):1163-1172. https://doi.org/10.1111/j.1463-1326.2009.01158.x

Jensen MD, Ryan DH, Donato KA, et al.; Expert Panel Members. Executive summary: guidelines (2013) for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Obesity Society published by the Obesity Society and American College of Cardiology/American Heart Association Task Force Currie et al. 2021on Practice Guidelines. Based on a systematic review from the Obesity Expert Panel, 2013. *Obesity (Silver Spring)*. 2014;22:(suppl 2):S5-S39. https://doi.org/10.1002/oby.20821

Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep*. 1991;14(6):540-545. https://doi.org/10.1093/sleep/14.6.540

Katasani, T, Holt G, Al-Khyatt W, et al. Peri- and Postoperative Outcomes for Obstructive Sleep Apnoea Patients after Bariatric Surgery-a Systematic Review and Meta-analysis. *Obes Surg.* 2023 Jul;33(7):2016-2024.: https://doi.org/10.1007/s11695-023-06557-8.

Kendler DL, Borges JL, Fielding RA, Itabashi A, Krueger D, Mulligan K, Camargos BM, Sabowitz B, Wu CH, Yu EW, Shepherd J. The Official Positions of the International Society for Clinical Densitometry: Indications of Use and Reporting of DXA for Body Composition. *J Clin Densitom*. 2013 Oct-Dec;16(4):496-507. https://doi.org/10.1016/j.jocd.2013.08.020.

Knowler WC, Barrett-Connor E, Fowler, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med.* 2002;346(6):393-403. https://doi.org/10.1056/NEJMoa012512

Koizumi M, Takada T, Kawarada Y, et al. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32. https://doi.org/10.1007/s00534-005-1048-2.

Kolotkin RL, Ervin CM, Meincke HH, et al. Development of a clinical trials version of the impact of weight on quality of life-lite questionnaire (IWQOL-Lite clinical trials version): results from two qualitative studies. *Clin Obes.* 2017;7(5):290-299. https://doi.org/10.1111/cob.12197

Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: impact of weight on quality of life-lite clinical trials version. *Clin Obes.* 2019;9(3):e12310. https://doi.org/10.1111/cob.12310

Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: impact of weight on quality of life-lite clinical trials version. *Clin Obes.* 2019;9(3):e12310. https://doi.org/10.1111/cob.12310

Kulovitz MG, Kolkmeyer D, Conn CA, et al. Medical weight loss versus bariatric surgery: does method affect body composition and weight maintenance after 15% reduction in body weight?. *Nutrition*. 2014;30(1):49-54. https://doi.org/10.1016/j.nut.2013.06.008

Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer -viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794-798. https://doi.org/10.1056/NEJMsr1606602

Leibel RL, Rosenbaum M, Hirsch J. Changes in energy expenditure resulting from altered body weight. *N Engl J Med*.) 1 1 - 3 + + * !) (" 2 . *) r . * 0 & https://doi.org/10.1056/NEJM199503093321001

Lewiecki EM, Binkley N, Morgan SL, et al. International Society for Clinical Densitometry. Best practices for dual-energy x-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance. *J Clin Densitom.* 2016;19(2):127-140. https://doi.org/10.1016/j.jocd.2016.03.003

Li G, Zhang P, Wang J, An Y, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing

Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol*. 2014;2(6):474-480. https://doi.org/10.1016/S2213-8587(14)70057-9

Lincoff MA, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *NEJM*. 2023;389(24):2221-2232. Malhotra A, et al. Weight reduction and the impact on apnea-hypopnea index: A systematic meta-analysis. *Sleep Med.* 2024 Sep;121:26-31. https://doi.org/10.1016/j.sleep.2024.06.014

Ma C, Shen X, Qu Y, Du Y. Analysis of an incomplete binary outcome dichotomized from an underlying continuous variable in clinical trials. *Pharm Stat*. 2022;21(5):907-918. https://doi.org/10.1002/pst.2204

Malhotra A, Grunstein RR, Fietze I, SURMOUNT-OSA Investigators, et al. . Tirzepatide for the Treatment of Obstructive Sleep Apnea and Obesity. *N Engl J Med.* 2024 Oct 3;391(13):1193-1205. https://doi.org/10.1056/NEJMoa2404881.

@ L] ` T ^ S @ : $ P O T _ Z] &36v2 Health Survey. Lincoln, RI: QualityMetric Incorporated; 2011.

Mertens IL, Van Gaal LF. Promising new approaches to the management of obesity. *Drugs*. 2000 Jul;60(1):1-9. https://doi.org/10.2165/00003495-200060010-00001.

Michielsen HJ, De Vries J, Van Heck GL. Psychometric qualities of a brief self-rated fatigue measure: The Fatigue Assessment Scale. *J Psychosom Res*. 2003;54(4):345-352. doi:10.1016/s0022-3999(02)00392-6

Mounjaro [package insert]. Indianapolis, IN: Eli Lilly and Company; 2025.

Moriarty AS, Gilbody S, McMillan D, Manea L. Screening and case finding for major depressive disorder using the Patient Health Questionnaire. *Gen Hosp Psychiatry*. 2015;37(6):567-576. https://doi.org/10.1016/j.genhosppsych.2015.06.012

Nauck MA, Meier JJ, Schmidt WE. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and/or pancreatic cancer: reassuring data from cardio-vascular outcome trials. *Diabetes Obes Metab.* 2017;19(9):1327-1328. https://doi.org/10.1111/dom.12981

[Northwestern]. Northwestern University. PROMIS Short Form v1.0 jSleep-Related Impairment 8a. Published May 09, 2016a. Accessed December 01, 2021. https://www.healthmeasures.net/index.php?option=com_instruments&view=measure&id=185&Itemid=992

[Northwestern]. Northwestern University. PROMIS Short Form v1.0 jSleep Disturbance 8b. Published May 03, 2016b. Accessed December 01, 2021. https://www.healthmeasures.net/index.php?option=com_instruments&view=measure&id=184&Itemid=992

Ozempic [package insert]. Plainsboro, NJ: Novo Nordisk A/S; 2025.

Pastors JG, Warshaw H, Daly A, et al. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care.* 2002;25(3):608-613. https://doi.org/10.2337/diacare.25.3.608

Peppard PE, Young T, Palta M, et al. Longitudinal study of moderate weight change and sleep-disordered breathing. *JAMA*. 2000;284(23):3015-3021. https://doi.org/10.1001/jama.284.23.3015

Peppard PE, Young T, Barnet JH, et al. Increased prevalence of sleep-disordered breathing in adults. *Am J Epidemiol*. 2013;177(9):1006-1014. https://doi.org/10.1093/aje/kws342

Rossi VA, Stoewhas AC, Camen G, et al. The effects of continuous positive airway pressure therapy withdrawal on cardiac repolarization: data from a randomized controlled trial. *Eur Heart J.* 2012;33(17):2206-2212. https://doi.org/10.1093/eurheartj/ehs073

Rothberg AE, McEwen LN, Kraftson AT, et al. Impact of weight loss on waist circumference and the components of the metabolic syndrome. *BMJ Open Diabetes Res Care*. 2017;5(1):e000341. https://doi.org/10.1136/bmjdrc-2016-000341

Rubin, D.B. Multiple Imputation for Nonresponse in Surveys.John Wiley & Sons, Inc; 1987.

Rybelsus® [package insert]. Plainsboro, NJ: Novo Nordisk, Inc.; 2025.

Sattar N, Lee MMY, Kristensen, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol.*2021;9(10):653-662. https://doi.org/10.1016/S2213-8587(21)00203-5

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk, Inc.; 2025.

Schwarz EI, Schlatzer C, Rossi VA, et al. Effect of CPAP withdrawal on BP in OSA data from three randomized controlled trials. *Chest.* 2016a;150(6):1202 jl210. https://doi.org/10.1016/j.chest.2016.07.012

Schwarz EI, Schlatzer C, Stehli J, et al. Effect of CPAP withdrawal on myocardial perfusion in OSA: A randomized controlled trial. *Respirology*. 2016b;21(6):1126-1133. https://doi.org/10.1111/resp.12798

Schwarz EI, Stradling JR, Kohler M. Physiological consequences of CPAP therapy withdrawal in patients with obstructive sleep apnoea - an opportunity for an efficient experimental model. *J Thorac Dis.* 2018;10(Suppl 1):S24 jS32. https://doi.org/10.21037/jtd.2017.12.142

Schwarz EI, Sinues PML, Bregy L, et al. Effects of CPAP therapy withdrawal on exhaled breath pattern in obstructive sleep apnoea. *Thorax.* 2016c;71(2):110-117. https://doi.org/10.1136/thoraxjnl-2015-207597

Shahid A, Wilkinson K, Marcu S, et al. (eds.), STOP, THAT and One Hundred Other Sleep Scales, 161, 2012 Edition. (2011) Springer, New York, NY. https://doi.org/10.1007/978-1-4419-9893-4_33.

Spitzer RL, Kroeke K, Williams JB. Validation and utility of a self-report version of PRIME-MMD: The PHQ primary care stud. *JAMA*. 1999; 282(18):1737-1744. https://doi.org/10.1001/jama.282.18.1737

Steinberg WM, Buse JB, Ghorbani MLM, et al. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER randomized trial. *Diabetes Care.* 2017a;40(7):966-972. https://doi.org/10.2337/dc16-2747. Erratum in *Diabetes Care*. 2018;41(7):1538. https://doi.org/10.2337/dc18-er07

Steinberg WM, Rosenstock J, Wadden TA, et al. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the SCALE clinical development program. *Diabetes Care*. 2017b;40(7):839-848. https://doi.org/10.2337/dc16-2684

Stradling JR, Schwarz, EI, Schlatzer C, et al. Biomarkers of oxidative stress following continuous positive airway pressure withdrawal: data from two randomised trials. *Eur Respir J.* 2015;46(4):1065-1071. https://doi.org/10.1183/09031936.00023215

Sumithran P, Prendergast LA, Delbridge E, et al. Long-term persistence of hormonal adaptations to weight loss. *N Engl J Med* & * ( )) 3 + . - !) / " 2) - 1 / r) . (, & https://doi.org/10.1056/NEJMoa1105816

Tsiatis A. Semiparametric Theory and Missing Data. Springer Science & Business Media; 2007.

Trulicity® [package insert]. Indianapolis, IN: Eli Lilly and Company; 2022.

UKPDS Group. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. *Metabolism.* 1990;39(9):905-912. https://doi.org/10.1016/0026-0495(90)90299-R

US Department of Agriculture and US Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th edition. 2020.

Wadström C, Backman L, Forsberg AM, et al. Body composition and muscle constituents during weight loss: studies in obese patients following gastroplasty. *Obes Surg*. 2000;10(3):203-213. https://doi.org/10.1381/096089200321643313

Wang B, Du Y. Robustly leveraging post-randomization information to improve precision in randomized trials. 2022. https://doi.org/10.48550/arXiv.2110.09645

Warkentin LM, Das D, Majumdar SR, et al. The effect of weight loss on health-related quality of life: systematic review and meta-analysis of randomized trials. *Obes Rev*. 2014;15(3):169-182. https://doi.org/10.1111/obr.12113

Wharton S, Blevins T, Connery L, et al; GZGI Investigators. Daily Oral GLP-1 Receptor Agonist Orforglipron for Adults with Obesity. *N Engl J Med*. 2023;389(10):877-888. https://doi.org/10.1056/NEJMoa2302392.

Wegovy [package insert]. Plainsboro, NJ: Novo Nordisk, Inc.; 2025.

Wilding J PH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002. https://doi.org/ 10.1056/NEJMoa2032183

Wing RR, Lang W, Wadden TA, et al. Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care* & * ( )) 3 + , ! https://doi.org/10.2337/dc10-2415

[WHO] World Health Organization. WHO STEPS surveillance manual: the WHO STEPwise approach to noncommunicable disease risk factor surveillance. Updated January 26, 2017. Accessed January 05, 2022. https: //cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/steps/steps-manual.pdf?sfvrsn=c281673d_7

Ye T, Shao J, Yi Y, et al. Toward better practice of covariate adjustment in analyzing randomized clinical trials. *J Am Stat Assoc*. 2022;118(544):2370-2382. https://doi.org/10.1080/01621459.2022.2049278

Ye T, Bannick M, Yi Y, Shao J. Robust variance estimation for covariate-adjusted unconditional treatment effect in randomized clinical trials with binary outcomes. *Stat Theory Related Fields*. 2023;7(2):159-163. https://doi.org/10.1080/24754269.2023.2205802

Zepbound [package insert]. Indianapolis, IN: Eli Lilly and Company; 2025.

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