Protocol Amendment J2A-MC-GZGV (b)

A Phase 3, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Once Daily Oral Orforglipron Compared with Dapagliflozin in Adult Participants with Type 2 Diabetes and Inadequate Glycemic Control with Metformin (ACHIEVE-2)

NCT06192108

Approval Date: 14-Mar-2024

Title Page

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Protocol Title:

A Phase 3, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Once Daily Oral Orforglipron Compared with Dapagliflozin in Adult Participants with Type 2 Diabetes and Inadequate Glycemic Control with Metformin (ACHIEVE-2)

Protocol Number: J2A-MC-GZGV

Amendment number: b

Compound: Orforglipron (LY3502970)

Brief Title:

Effect of Orforglipron Compared with Dapagliflozin in Participants with Type 2 Diabetes Inadequately Controlled with Metformin (ACHIEVE-2)

Study Phase: 3

Acronym: ACHIEVE-2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

IND: 142842

EU trial number: 2023-507206-13-00

WHO: U1111-1296-1507

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

Document ID: VV-CLIN-148650

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	18-Jan-2024
Original Protocol	17-Aug-2023

Amendment (b)

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment

The primary rationale for this amendment is to address regulatory feedback.

<table>
<tr><th>Section # and Name</th><th>Description of Change</th><th>Brief Rationale</th></tr>
<tr><td>1.1 Synopsis and
3. Objectives, Endpoints, and Estimands</td><td>“[redacted] mg” strength has been removed from key secondary objectives to read “To demonstrate that orforglipron [redacted] and/or [redacted] mg are superior to dapagliflozin in weight management.”

The following objective and endpoint are added under Other Secondary Objectives, Endpoints, and Estimands:<table><tr><th>Objectives</th><th>Endpoints</th></tr><tr><td>To demonstrate that orforglipron [redacted] mg is superior to dapagliflozin in weight management</td><td>• Percentage change from baseline in body weight at Week 40
• Change from baseline in body weight at Week 40</td></tr></table></td><td>Clarification</td></tr>
<tr><td>9.1. Statistical Hypotheses</td><td>“$H_{5,3,0}$,” “$H_{6,3,0}$,” and “[redacted] mg” removed from the null hypotheses</td><td>To align with key secondary objectives</td></tr>
<tr><td>9.1.1. Multiplicity Adjustment</td><td>• Modified text for graphical approach to be used for multiplicity adjustment
• Added a figure to illustrate the current graphical testing procedure</td><td>Addition of the graphical testing procedure per regulatory feedback to supplement the pre-specified statistical analysis information</td></tr>
</table>

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Open-Label Study to Investigate the Efficacy and Safety of Once Daily Oral Orforglipron Compared with Dapagliflozin in Adult Participants with Type 2 Diabetes and Inadequate Glycemic Control with Metformin (ACHIEVE-2)

Brief Title: Effect of Orforglipron Compared with Dapagliflozin in Participants with Type 2 Diabetes Inadequately Controlled with Metformin (ACHIEVE-2)

Regulatory Agency Identifier Numbers:

IND: 142842

EU trial number: 2023-507206-13-00

WHO: U1111-1296-1507

Rationale:

ACHIEVE-2 (Study GZGV) is designed to determine the comparative benefits and risks of orforglipron versus dapagliflozin in participants with type 2 diabetes (T2D) who have inadequate glycemic control with metformin. This study will investigate the antihyperglycemic effect of [redacted] doses of orforglipron [redacted] with dapagliflozin [redacted]. Additionally, the study will compare the effects of orforglipron and dapagliflozin on body weight and overall safety profile.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To demonstrate that orforglipron [redacted] mg, [redacted] mg [redacted] mg are noninferior to dapagliflozin in glycemic control, [redacted]	• Change from baseline in HbA1c at Week 40
Key Secondary	
To demonstrate that orforglipron [redacted] mg, [redacted] mg [redacted] mg are superior to dapagliflozin in glycemic control	• Change from baseline in HbA1c at Week 40
To demonstrate that orforglipron [redacted] mg, [redacted] mg [redacted] mg are superior to dapagliflozin in additional measures of glycemic control	• Proportion of participants who achieved HbA1c <7.0% (53 mmol/mol) at Week 40 • Proportion of participants who achieved HbA1c ≤6.5% (48 mmol/mol) at Week 40
To demonstrate that orforglipron [redacted] mg [redacted] mg are superior to dapagliflozin in weight management	• Percentage change from baseline in body weight at Week 40 • Change from baseline in body weight at Week 40

Objectives	Endpoints
To demonstrate that orforglipron CCI mg is superior to dapagliflozin in lipid parameters	• Percentage change from baseline in non-HDL cholesterol at Week 40 • Percentage change from baseline in triglycerides at Week 40
To demonstrate that orforglipron CCI mg is superior to dapagliflozin in SBP	• Change from baseline in SBP at Week 40
Other Secondary	
To demonstrate that orforglipron CCI mg is superior to dapagliflozin in weight management	• Percentage change from baseline in body weight at Week 40 • Change from baseline in body weight at Week 40
To compare orforglipron CCI mg, CCI mg and CCI mg with dapagliflozin in additional measures of glycemic control	• Proportion of participants who achieved HbA1c CCI at Week 40 • Change from baseline in fasting serum glucose CCI at Week 40 CCI
To compare orforglipron CCI mg, CCI mg and CCI mg with dapagliflozin in additional measurements of weight management	• Proportion of participants who achieved weight loss of ≥5%, ≥10%, and ≥15% from baseline at Week 40 CCI
To compare orforglipron CCI mg and CCI mg with dapagliflozin in SBP	• Change from baseline in SBP at Week 40
To compare orforglipron CCI mg, CCI mg, and CCI mg with dapagliflozin in DBP	• Change from baseline in DBP at Week 40
To compare orforglipron CCI mg, CCI mg and CCI mg with dapagliflozin in lipid parameters	• Percentage change from baseline in lipid parameters at Week 40 ○ total cholesterol CCI
To compare orforglipron CCI mg and CCI mg with dapagliflozin in lipid parameters	• Percentage change from baseline in lipid parameters at Week 40 ○ non-HDL cholesterol ○ triglycerides
To compare orforglipron CCI mg, CCI mg CCI mg with dapagliflozin in patient-reported outcomes	• Change from baseline at Week 40 in: ○ SF-36v2 Acute Form domain and summary scores CCI

Objectives	Endpoints
	CCI • DTSQc scores at Week 40
CCI	

Abbreviations: CCI BMI = body mass index; DBP = diastolic blood pressure; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change; CCI HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; CCI SBP = systolic blood pressure; SF-36v2, Acute = Short Form-36 version 2 Health Survey acute form; CCI .

Primary estimands

There will be 2 estimands for the primary objective planned in the study. Details on the plan for use of each estimand can be found in Section 9.1. The 2 estimands, treatment regimen estimand and efficacy estimand, address intercurrent events using the treatment policy strategy and the hypothetical strategy, respectively.

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.

Treatment regimen estimand

The clinical question of interest is: *What is the treatment difference in the change in HbA1c from baseline at Week 40 between orforglipron CCI mg compared with dapagliflozin CCI mg, orforglipron CCI mg compared with dapagliflozin CCI mg and orforglipron CCI mg compared with dapagliflozin CCI mg in individuals who meet eligibility criteria regardless of adherence to study intervention or initiation of additional antihyperglycemic medications?*

Rationale for the treatment regimen estimand

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

Treatment regimen estimand attributes

- **Population -** individuals who meet the eligibility criteria.
- **Endpoints -** change from baseline in HbA1c at Week 40.
- **Treatment condition -** the randomized treatment with allowance for potential dose interruptions and dose modifications regardless of adherence to study intervention or initiation of additional antihyperglycemic medications.
- **Intercurrent events -** no ICEs are defined since treatment adherence and the initiation of additional antihyperglycemic medications are a part of the treatment condition.
- **Population-level summary and treatment effect of interest -** difference in mean changes in HbA1c from baseline at Week 40:
  - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg
  - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg, and
  - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg.

Efficacy estimand

The clinical question of interest is: *What is the treatment difference in the change in HbA1c from baseline at Week 40 between orforglipron [redacted] mg compared with dapagliflozin [redacted] mg, orforglipron [redacted] mg compared with dapagliflozin [redacted] mg and orforglipron [redacted] mg compared with dapagliflozin [redacted] mg in individuals who meet the eligibility criteria if they would remain on their randomly assigned study intervention for 40 weeks and would not initiate additional antihyperglycemic medications?*

Rationale for the efficacy estimand

This estimand aims to evaluate the efficacy of orforglipron under the ideal condition that all participants would adhere to the randomly assigned study intervention without being confounded by the initiation of antihyperglycemic medications.

Efficacy estimand attributes

- **Population -** individuals who meet the eligibility criteria.
- **Endpoints -** change from baseline in HbA1c at Week 40.
- **Treatment condition -** the randomized treatment with allowance for potential dose interruptions and dose modifications.
- **Intercurrent events -** ICEs include permanent discontinuation of study intervention and initiation of additional antihyperglycemic medications and will be handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned study intervention for 40 weeks and would not initiate additional antihyperglycemic medications. Dose modification and interruption will not be considered an ICE since they are part of the treatment condition.

- **Population-level summary and treatment effect of interest -** difference in mean changes in HbA1c from baseline at Week 40:
  - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg
  - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg, and
  - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg.

Overall Design:

ACHIEVE-2 (Study GZGV) is a Phase 3, multicenter, randomized, open-label (orforglipron dose blinded), active comparator-controlled, parallel-arm study designed to examine the efficacy and safety of orforglipron administered once daily compared with dapagliflozin, in participants with T2D with inadequate glycemic control using metformin (at least [redacted] mg/day).

Brief Summary:

The purpose of this study is to assess how different doses of orforglipron ([redacted] mg, [redacted] mg or [redacted] mg) compare with dapagliflozin [redacted] mg in improving blood sugar control in participants with T2D with inadequate glycemic control with metformin.

This study includes 3 periods:

- a screening and lead-in period: up to [redacted]
- a treatment period: 40 weeks, including [redacted] maintenance dose, and
- a safety follow-up period: [redacted].

The study duration will be approximately [redacted] weeks if a prescreening visit is performed, and approximately 46 weeks if it is not.

The treatment duration will be [redacted] weeks.

This is an open-label study with respect to assignment to orforglipron versus dapagliflozin. The orforglipron doses ([redacted] mg to [redacted] mg) will be double-blinded. [redacted]

During the treatment period, the visit frequency will be

- every [redacted] weeks for the first [redacted] weeks
- every [redacted] weeks from Week [redacted] to the end of the treatment period

Study Population:

In general, an individual may take part in this study if they

- are ≥18 years of age inclusive, or the legal age of consent in the jurisdiction in which the study is taking place at the time of signing the informed consent, whichever is older.
- have a clinical diagnosis of T2D based on the World Health Organization classification or other locally applicable diagnostic standards.
- have HbA1c ≥7.0% (53 mmol/mol) to ≤10.5% (91 mmol/mol) at screening.
- have been on stable diabetes treatment with metformin ≥[redacted] mg/day during the 90 days prior to Visit 1 and maintained through Visit 3 (randomization).

Number of Participants:

Approximately [redacted] participants will be randomly assigned in a [redacted] ratio to orforglipron [redacted] mg, orforglipron [redacted] mg, orforglipron [redacted] mg, dapagliflozin [redacted] mg, respectively.

Intervention Groups and Duration:

This table lists the interventions used in this clinical study.

Intervention Name	Orforglipron (LY3502970)	Dapagliflozin	Metformin[a]
Dosage Level(s)	[redacted]-mg, [redacted]-mg, [redacted]-mg, [redacted]-mg, [redacted]-mg, and [redacted]-mg capsules	[redacted]-mg [redacted]	≥[redacted] mg
Route of Administration	Oral QD	Oral QD	Oral[b]
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized in EU and used according to marketing authorization	Authorized in EU and used according to marketing authorization

[a] Metformin is a background therapy, and the daily dosing information will not be captured in the eDiary.

[b] The frequency of metformin dosing will vary based on formulation and dosage. The pre-study dose and formulation (short-acting or long- acting) should be maintained until completion of treatment period, except in specific situations.

Timing of Dose Administration

Orforglipron or dapagliflozin will be administered orally once daily. In general, there are no restrictions on the time of day each dose is taken, but it is recommended to take the dose at approximately the same time each day.

Participants Randomly Assigned to Orforglipron

All participants will initiate treatment with a [redacted] mg QD dose of orforglipron [redacted]



The maintenance dose CCI of orforglipron will be continued for the remainder of the treatment period.

Participants Randomized to Dapagliflozin

All participants will initiate treatment with a CCI mg QD dose of dapagliflozin and maintain the dose for the reminder of the treatment period.

Ethical Considerations of Benefit/Risk:

The safety and efficacy profile seen to date for orforglipron supports the overall benefit/risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of Glucagon-Like Peptide-1 receptor agonists (GLP-1 RAs), namely gastrointestinal tolerability, and increased heart rate. These risks can be monitored, are usually mild to moderate in severity, reversible, and readily manageable. To date there are no recognized adverse events from orforglipron other than those related to GLP-1 receptor agonism.

The potential risks based on the knowledge for the GLP-1 RA class are considered to be acceptable in the context of the potential benefits anticipated from treatment with orforglipron in adult participants with T2D.

Data Monitoring Committee: No


CCI

1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in ACHIEVE-2 (Study J2A-MC-GZGV [GZGV]). However, for those whose participation in this study is affected by exceptional circumstances such as pandemics or natural disasters, please refer to Section 10.11 for additional guidance.

Prescreening visit

The prescreening visit (Visit 601) is optional. Procedures may be conducted at a site or an alternate location under the oversight of an investigator to enable more access to potential participants, including underrepresented populations.

The purpose of this visit is to

- assess key eligibility factors associated with screen failures at the earliest time point
- improve the effectiveness of screening activities, and
- reduce burden for potential participants and investigators.

Fasting visits

The fasting state is defined as not having had anything to eat or drink but water for a minimum of 8 hours.

- Visit 1 (screening) and Visit 10: Fasting is not required.
- Visit 3 (randomization) and Visit 11: Participants must attend these visits in a fasting state. If a participant attends these visits in a non-fasting state, the participant should be asked to return to the site in a fasting state as soon as possible within the visit window. At Visit 3, all procedures, including patient-reported outcomes, laboratory procedures, and ECGs, should be completed prior to the participant taking study intervention at this visit.
- Visits 4 through 9: If a participant attends these visits in a non-fasting state, samples for laboratory testing should not be collected and the participant should be asked to return to the site in a fasting state as soon as possible within the visit window. All other procedures scheduled at the visit may be performed.

Early discontinuation (ED)

Participants who are unable or unwilling to continue the study treatment period for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit.

Safety follow-up visit

All participants are required to complete a safety follow-up visit (Visit 801), according to the SoA. Participants discontinuing the treatment period early and performing an ED visit will also be asked to perform the safety follow-up visit.

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
Prescreening (V601) assessments only															
Abbreviated informed consent for prescreening	X														
Demographics	X														
Abbreviated self-reported questionnaire on medical history and medications	X														
AEs	X														
Height	X														
Weight	X														
Hemoglobin A1c (HbA1c)	X														

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
Recommend whether participant may proceed to V1	X														
Screening and other study specific assessments															
Informed consent		X													
Inclusion/exclusion criteria; confirmation of eligibility		X	X	X											
Demographics		X													

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
Preexisting conditions and medical history, including relevant surgical history		X													
Prespecified medical history		X													
Prior treatments of interest		X													
Concomitant medications		X	X	X	X	X	X	X	X	X	X	X	X	X	
AEs		X	X	X	X	X	X	X	X	X	X	X	X	X	
	Any events that occur after signing the informed consent are considered AEs as defined in Section Additional data are collected for certain AEs. See Section 8.3.3														
Substance use (alcohol, caffeine, tobacco, nicotine replacement)				X											
Physical evaluation															
Height		X													
Weight		X		X	X	X	X	X	X	X	X	X	X	X	
CCI				X		X		X		X	X	X	X		

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
Physical examination		X													
Symptom-directed physical assessment			X												
	Symptom-directed physical assessment may be conducted at the discretion of the PI or qualified personnel as indicated per local regulations based on participant status and standard of care.														
Vital signs (triplicate)		X	X	X	X	X	X	X	X	X	X	X	X	X	
	Include pulse rate and blood pressure. Measured in triplicate after participant has been sitting at least 5 minutes. Vital signs should be taken before ECG tracing, if applicable. See Sections 8.2.2 and 10.9.														
ECG 12-lead (triplicate)				X								X	X	X	
	Collect triplicate ECGs before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. See Section 8.2.3.														

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
CCI			X							X		X	X		
	CCI														
Participant diary (electronic)															
Dispense or activate eDiary			X												CCI
eDiary review				X	X	X	X	X	X	X	X	X	X	X	

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
Remind participants about CCI			X						X		X				
Review CCI				X						X		X			
eDiary return or inactivation														X	
Patient-reported outcomes (electronic) *Note: At Visit 3, PROs should be administered before the administration of the first dose of study intervention*															
SF-36 v2, Acute				X								X	X		
CCI															

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
DTSQc												X	X		
Participant education															
Diabetes education (includes BG meter CCI)			X												
Dispense BG meter and supplies, as needed			X	X											
Laboratory tests and sample collections															
Hematology		X		X						X		X	X		
Clinical chemistry		X		X	X	X	X	X	X	X	X	X	X	X	
Glucose				X	X	X	X	X	X	X		X	X		
Hemoglobin A1c (HbA1c)	X	X		X	X	X	X	X	X	X		X	X		
Lipids				X			X			X		X	X		
Lipase				X			X			X		X	X	X	

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
Pancreatic amylase				X			X			X		X	X	X	
Calcitonin		X					X			X		X	X	X	
Serum pregnancy		X													
Urine pregnancy test (local)				X								X	X	X	
Urine pregnancy test (local)	The result must be available before the first dose of study intervention for WOCBP. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation.														
FSH		X													CCI
HCV screening tests		X													
HBV screening tests		X													

ACHIEVE-2 (Study J2A-MC-GZGV)	601	Screening/ Lead-In		Treatment Period										Safety Follow-Up Period	Comments
Visit Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**ED**	**801**	CCI
Weeks from Visit 3 (randomization)	CCI														
Visit Interval Tolerance (+/- days)															
Fasting Visit				**X**	**X**	**X**	**X**	**X**	**X**	**X**		**X**	**X**		
Cystatin-C		X		X	X		X			X		X	X		
eGFR		X		X	X		X			X		X	X		
UACR				X	X					X		X	X		
Stored samples															
Genetics sample				X											
Exploratory biomarker				X			X			X		X	X		
Randomization and dosing related activities for orforglipron or dapagliflozin															
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X		X	
Randomization via IWRS				X											
Dispense study intervention via IWRS				X	X	X	X	X	X	X	X				
Dispense study intervention to participant (for at home dosing)				X	X	X	X	X	X	X	X				
Participant returns unused study intervention					X	X	X	X	X	X	X	X	X		
Assess study intervention compliance					X	X	X	X	X	X	X	X	X		

Abbreviations: AE = adverse event; CCI [redacted] BG = blood glucose; CCI [redacted] DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change Version; CCI [redacted] ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; FSH = follicle-stimulating hormone; GLP-1 RA = Glucagon-Like Peptide-1 receptor agonist; HBcAb = hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; IWRS = interactive web response system; CCI [redacted] PI = principal investigator; SF-36v2, Acute = Short Form-36 version 2 Health Survey acute form; CCI [redacted] TxP = treatment period; UACR = urinary albumin/creatinine ratio; ULN = upper limit of normal; V = visit; WOCBP = women of childbearing potential.

Approved on 14 Mar 2024 GMT

2. Introduction

2.1. Study Rationale

GLP-1 receptor agonism is an established therapeutic mechanism for glycemic control in T2D, as well as weight management in individuals with obesity or overweight. Unlike injectable or orally available peptide GLP-1 RAs approved by regulatory authorities to date, orforglipron is an oral, non-peptide, small-molecule GLP-1 RA. Orforglipron is being developed for the treatment of T2D and for chronic weight management in individuals with overweight or obesity.

SGLT2 inhibitors are orally administered and approved for glycemic control in patients with T2D. They are widely used for glycemic control in patients who fail to reach target glycemic levels with metformin alone. Dapagliflozin is a selective and reversible SGLT2 inhibitor approved as an oral antihyperglycemic medication in patients with T2D. Highest approved dose of dapagliflozin for glycemic control is 10 mg once daily (Farxiga prescribing information, 2023; Forxiga SmPC).

ACHIEVE-2 (Study GZGV) is designed to determine the comparative benefits and risks of orforglipron versus dapagliflozin in participants with T2D who have inadequate glycemic control with metformin. This study will investigate the antihyperglycemic effect of 3 doses of orforglipron ([redacted] mg, [redacted] mg and [redacted] mg) with dapagliflozin [redacted] mg. Additionally, the study will compare the effects of orforglipron and dapagliflozin on body weight and overall safety profile.

The comparison of orforglipron with dapagliflozin will help regulators and healthcare providers to evaluate comparative efficacy and safety of an investigational oral GLP-1 RA against an oral antihyperglycemic medication that is used in clinical practice for the treatment of patients with T2D.

2.2. Background

Type 2 diabetes

T2D is a metabolic condition characterized by impaired glycemic control caused by increased insulin resistance and progressive beta-cell failure and consequently inadequate insulin secretion. T2D is frequently associated with comorbidities such as

- overweight or obesity
- hypertension
- increased blood lipoprotein concentrations, and
- a higher risk for macro- and microvascular complications.

Achieving HbA1c targets of <7% has been shown to reduce microvascular complications of T2D when instituted early in the course of disease (ADA 2023).

Unmet needs for diabetes treatment

With the prevalence of T2D increasing worldwide, new antihyperglycemic agents offering significant improvements in glycemic control as well as other potential health benefits, which would result in improved health outcomes, are highly desired.

Currently, there are GLP-1 RA therapies approved for glycemic control in patients with T2D and chronic weight management in patients with obesity or overweight with 1 or more weight-related comorbidity. The most commonly used GLP-1 RAs are administered once weekly through subcutaneous injection. Even with multiple marketed GLP-1 RAs available for use in adults, the injection may be a barrier for many patients to initiate and to adhere to a therapy long-term.

Among the multiple marketed GLP-1 RAs available for use in adults with T2D, all are injectables, except for one, semaglutide, which is available as an oral formulation. Oral semaglutide is a peptide combined with salcaprozate sodium (an absorption enhancer) that provides patients with a viable alternative to subcutaneous injection delivery. However, its administration requires the patient to adhere to certain restrictions of meal timing and amount of plain water consumed to ensure proper delivery of the medication through the gastric lining. Therefore, the challenge remains with either the mode of administration (injectables) or the complexity and adherence to multiple restrictions associated with the only orally available GLP-1 RA (Hedrington and Davis 2019; Rybelsus package insert, 2023; Rybelsus SmPC).

There is an unmet medical need for efficacious, safe, and well-tolerated oral formulations of GLP-1 RAs for the management of T2D. Oral GLP-1 RA formulations with fewer restrictions related to administration would allow for further tailoring of therapy to meet individual patient preferences and needs.

Clinical data for orforglipron

A detailed description of the chemistry, pharmacology, efficacy, and safety of orforglipron is provided in the IB.

The clinical pharmacology, PK, and PD of orforglipron were initially studied in 2 Phase 1 studies, J2A-MC-GZGA (GZGA) in healthy volunteers and J2A-MC-GZGC (GZGC) in patients with T2D. Results from these studies demonstrated CCI [redacted]

Study J2A-MC-GZGE (GZGE) was a Phase 2, randomized, double-blind, parallel, placebo- and active comparator (1.5 mg dulaglutide once weekly)-controlled 26-week study. The objective of the study was to investigate antihyperglycemic and body weight-lowering efficacy, as well as tolerability and safety of orforglipron (3 mg to 45 mg maintenance doses) in participants with T2D who failed to achieve adequate glycemic control on diet and exercise alone or when treated with metformin.

***Key efficacy and safety data at 26-weeks*:**

CCI [redacted]



- The overall safety profile of orforglipron was consistent with that established for the GLP-1 RA class, with most common TEAEs being GI related (nausea, vomiting, diarrhea, and constipation).
- The majority of the GI AEs were mild to moderate in severity and CCI

Data from Phase 2 studies supported further clinical development of orforglipron.

2.3. Benefit/Risk Assessment

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

In addition, detailed information about the known and expected benefits and risks of dapagliflozin may be found in the prescribing information and SmPC (Farxiga prescribing information, 2023; Forxiga SmPC).

2.3.1. Risk Assessment

Risks associated with orforglipron

The potential risks associated with orforglipron are similar to those of marketed GLP-1 RAs. The most commonly reported TEAEs observed across the orforglipron clinical studies in healthy participants or participants with T2D are GI effects including nausea, vomiting, diarrhea, and constipation. Most were mild to moderate in severity and tended to occur CCI

Other potential risks associated with orforglipron include

- acute pancreatitis
- increases in heart rate
- hypoglycemia when used with insulin or insulin secretagogues
- hypersensitivity reactions, and

- thyroid C-cell effects (only observed in rodents).

CCI

Sections 5.1, 5.2, and 8.2 address mitigation, management, and monitoring of the known potential risks associated with orforglipron.

Study procedures

Blood draws

Risks of blood draws for clinical laboratory assessments include the potential for some pain and a small risk of bruising or infection at the site.

ECG collection

Collection of ECGs may cause mild discomfort during placement and removal of leads from the skin. Some participants may experience local irritation or redness at the sites of lead attachment.

CCI

2.3.2. Benefit Assessment

The known pharmacology of GLP-1 receptor agonism and clinical data from Phase 2 studies supports the efficacy of orforglipron regarding glycemic control and weight loss in participants with T2D.

Improvements in some cardiometabolic risk factors, including BP and serum lipids, may also be expected. GLP-1 RAs have generally been associated with reduced risk of CV events in people with T2D (Giugliano et al. 2021).

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

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for orforglipron supports the overall benefit/risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 RAs, namely GI tolerability, and increased heart rate. These risks can be monitored, are usually mild to moderate in severity, reversible, and readily manageable. To date there are no recognized AEs from orforglipron other than those related to GLP-1 receptor agonism.

The potential risks based on the knowledge for the GLP-1 RA class are considered to be acceptable in the context of the potential benefits anticipated from treatment with orforglipron in adult participants with T2D.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that orforglipron [redacted] mg, [redacted] mg [redacted] mg are noninferior to dapagliflozin in glycemic control, [redacted]	• Change from baseline in HbA1c at Week 40
Key Secondary	
To demonstrate that orforglipron [redacted] mg, [redacted] mg [redacted] mg are superior to dapagliflozin in glycemic control	• Change from baseline in HbA1c at Week 40
To demonstrate that orforglipron [redacted] mg, [redacted] mg [redacted] mg are superior to dapagliflozin in additional measures of glycemic control	• Proportion of participants who achieved HbA1c <7.0% (53 mmol/mol) at Week 40 • Proportion of participants who achieved HbA1c ≤6.5% (48 mmol/mol) at Week 40
To demonstrate that orforglipron [redacted] mg [redacted] mg are superior to dapagliflozin in weight management	• Percentage change from baseline in body weight at Week 40 • Change from baseline in body weight at Week 40
To demonstrate that orforglipron [redacted] mg is superior to dapagliflozin in lipid parameters	• Percentage change from baseline in non-HDL cholesterol at Week 40 • Percentage change from baseline in triglycerides at Week 40
To demonstrate that orforglipron [redacted] mg is superior to dapagliflozin in SBP	• Change from baseline in SBP at Week 40
Other Secondary	
To demonstrate that orforglipron [redacted] mg is superior to dapagliflozin in weight management	• Percentage change from baseline in body weight at Week 40 • Change from baseline in body weight at Week 40
To compare orforglipron [redacted] mg, [redacted] mg and [redacted] mg with dapagliflozin in additional measures of glycemic control	• Proportion of participants who achieved HbA1c [redacted] at Week 40 • Change from baseline in fasting serum glucose [redacted] at Week 40 [redacted]
To compare orforglipron [redacted] mg, [redacted] mg and [redacted] mg with dapagliflozin in additional measurements of weight management	• Proportion of participants who achieved weight loss of ≥5%, ≥10%, and ≥15% from baseline at Week 40 [redacted]
To compare orforglipron [redacted] mg and [redacted] mg with dapagliflozin in SBP	• Change from baseline in SBP at Week 40

Objectives	Endpoints
To compare orforglipron [redacted] mg, [redacted] mg, and [redacted] mg with dapagliflozin in DBP	• Change from baseline in DBP at Week 40
To compare orforglipron [redacted] mg, [redacted] mg and [redacted] mg with dapagliflozin in lipid parameters	• Percentage change from baseline in lipid parameters at Week 40 ○ total cholesterol [redacted]
To compare orforglipron [redacted] mg and [redacted] mg with dapagliflozin in lipid parameters	• Percentage change from baseline in lipid parameters at Week 40 ○ non-HDL cholesterol ○ triglycerides
To compare orforglipron [redacted] mg, [redacted] mg [redacted] mg with dapagliflozin in patient-reported outcomes	• Change from baseline at Week 40 in: ○ SF-36v2 Acute Form domain and summary scores [redacted] • DTSQc scores at Week 40
[redacted]	

Abbreviations: [redacted] BMI = body mass index; DBP = diastolic blood pressure; DTSQc = Diabetes Treatment Satisfaction Questionnaire-Change; [redacted] HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; [redacted] SBP = systolic blood pressure; SF-36v2, Acute = Short Form-36 version 2 Health Survey acute form; [redacted]

Primary estimands

There will be 2 estimands for the primary objective planned in the study. Details on the plan for use of each estimand can be found in Section 9.1. The 2 estimands, treatment regimen estimand and efficacy estimand, address ICEs using the treatment policy strategy and the hypothetical strategy, respectively.

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.

Treatment regimen estimand

The clinical question of interest is: *What is the treatment difference in the change in HbA1c from baseline at Week 40 between orforglipron [redacted] mg compared with dapagliflozin [redacted] mg, orforglipron [redacted] mg compared with dapagliflozin [redacted] mg and orforglipron [redacted] mg compared with dapagliflozin [redacted] mg in individuals who meet eligibility criteria regardless of adherence to study intervention or initiation of additional antihyperglycemic medications?*

Rationale for the treatment regimen estimand

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

Treatment regimen estimand attributes

- **Population -** individuals who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- **Endpoints -** change from baseline in HbA1c at Week 40.
- **Treatment condition -** the randomized treatment with allowance for potential dose interruptions and dose modifications regardless of adherence to study intervention or initiation of additional antihyperglycemic medications.
- **Intercurrent events -** no ICEs are defined since treatment adherence and the initiation of additional antihyperglycemic medications are a part of the treatment condition.
- **Population-level summary and treatment effect of interest -** difference in mean changes in HbA1c from baseline at Week 40:
    - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg
    - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg, and
    - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg.

Efficacy estimand

The clinical question of interest is: *What is the treatment difference in the change in HbA1c from baseline at Week 40 between orforglipron [redacted] mg compared with dapagliflozin [redacted] mg, orforglipron [redacted] mg compared with dapagliflozin [redacted] mg and orforglipron [redacted] mg compared with dapagliflozin [redacted] mg in individuals who meet the eligibility criteria if they would remain on their randomly assigned study intervention for 40 weeks and would not initiate additional antihyperglycemic medications?*

Rationale for the efficacy estimand

This estimand aims to evaluate the efficacy of orforglipron under the ideal condition that all participants would adhere to the randomly assigned study intervention without being confounded by the initiation of antihyperglycemic medications

Efficacy estimand attributes

- **Population -** individuals who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- **Endpoints -** change from baseline in HbA1c at Week 40.
- **Treatment condition -** the randomized treatment with allowance for potential dose interruptions and dose modifications.
- **Intercurrent events -** ICEs include permanent discontinuation of study intervention and initiation of additional antihyperglycemic medications and will be handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned study intervention for 40 weeks and would not initiate additional antihyperglycemic medications. Dose modification and interruption will not be considered an ICE since they are part of the treatment condition.
- **Population-level summary and treatment effect of interest -** difference in mean changes in HbA1c from baseline at Week 40:
    - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg
    - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg, and
    - orforglipron [redacted] mg compared with dapagliflozin [redacted] mg.

4. Study Design

4.1. Overall Design

ACHIEVE-2 (Study GZGV) is a Phase 3, multicenter, randomized, open-label (orforglipron dose blinded), active comparator-controlled, parallel-arm study designed to examine the efficacy and safety of orforglipron administered QD compared with dapagliflozin, in participants with T2D with inadequate glycemic control using metformin (at least CCI mg/day).

This study will consist of 3 periods:

- a screening and lead-in period: up to CCI
- a treatment period: 40 weeks, including CCI maintenance dose, and
- a safety follow-up period: CCI .

For the randomization ratio and stratification factors, see Section 6.3.

4.2. Scientific Rationale for Study Design

Choice of primary endpoint

The primary endpoint of HbA1c is a commonly used endpoint in clinical trials evaluating the efficacy and safety of antihyperglycemic agents**.**

CCI

Choice of comparator

Dapagliflozin was chosen as the active comparator because it is an oral antihyperglycemic medication approved for participants with T2D that is commonly used in clinical practice for patients with inadequate glycemic control on metformin.

Open-label design

Treatment assignment to orforglipron doses (CCI mg, CCI mg or CCI mg) will be blinded to ensure unbiased assessment of safety and efficacy of all doses while the treatment assignment to dapagliflozin CCI mg will not be blinded due to difference in formulation.

Duration of the study treatment

The planned duration of the study treatment for 40 weeks is considered sufficient and appropriate for participants to optimize dosing of orforglipron to assess the full effects and benefit/risk of each maintenance dose of orforglipron compared to dapagliflozin on glycemic control.

Concomitant background medications

Metformin was chosen as a required concomitant antihyperglycemic medication because it is commonly used in clinical practice as first-line therapy and when used in combination, the risk of hypoglycemia is low. CCI

Collection of race and ethnicity data

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

4.3. Justification for Dose

4.3.1. Orforglipron

The orforglipron doses of [redacted] mg, [redacted] mg, and [redacted] mg QD were selected for assessment of efficacy and safety for glycemic control in participants with T2D in Phase 3 development program. These doses were selected for the T2D program primarily based on assessment of safety, efficacy (glycemic control and weight benefit), and GI tolerability data from Phase 2 studies. The Phase 2 data and exposure-response analysis have demonstrated a dose response in HbA1c lowering from baseline from 3 mg through 36-mg dose, with little additional effect of the 45-mg dose compared with 36 mg and no notable increase of GI events between the 12-mg and 36-mg doses.

In this study, the [redacted] doses of orforglipron, that is, [redacted] mg, [redacted] mg and [redacted] mg, will be evaluated as the target maintenance doses to compare efficacy and safety with the [redacted] maintenance dose of dapagliflozin, that is, [redacted] mg.

The dose escalation method for orforglipron was selected to optimize GI tolerability based on [redacted]

The selected doses [redacted] would enable further evaluation of the benefit/risk considerations for the [redacted] mg, [redacted] mg, and [redacted] mg doses of orforglipron.

4.3.2. Dapagliflozin

To allow the most robust comparison of orforglipron and dapagliflozin, the [redacted] dose of [redacted] mg QD for glycemic control in T2D was chosen to be studied.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit or last scheduled procedure shown in the SoA (Section 1.3) for the last participant.

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.

5.1. Inclusion Criteria

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

Age

1. Must be at least 18 years of age or the legal age of consent in the jurisdiction in which the study is taking place at the time of signing the informed consent, whichever is older.

Type of participant and disease characteristics

2. Have a clinical diagnosis of T2D based on the World Health Organization classification or other locally applicable diagnostic standards.
3. Have HbA1c ≥7.0% (53 mmol/mol) to ≤10.5% (91 mmol/mol), as determined by the central laboratory at Visit 1 (screening)
4. Have been on stable diabetes treatment with metformin ≥CCI mg/day during the 90 days prior to Visit 1 and maintained through Visit 3 (randomization)
5. Are motivated and willing to make themselves available for the duration of the study and are able to follow study procedures as required, including
    a. perform CCI per protocol
    b. maintain a study diary, and
    c. complete patient questionnaires.

Weight

6. Are of stable body weight (±5%) for at least 90 days prior to Visit 1 and agree to not initiate an intensive diet or exercise program during the study with the intent of reducing body weight, other than the lifestyle and/or dietary measures for diabetes treatment.
7. Have a BMI ≥23.0 kg/m^2 at Visit 1.

Sex and contraceptive/barrier requirements

8. Males, WOCBP, or WNOCBP may participate in this trial.

    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

9. Are capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical conditions

Diabetes related

10. Have T1D
11. Have a history of ketoacidosis or hyperosmolar state or coma within the last 6 months prior to Visit 1, or between Visit 1 and Visit 3.
12. Have a history of severe hypoglycemia or hypoglycemia unawareness within the last 6 months prior to Visit 1, or between Visit 1 and Visit 3.
13. Are currently receiving or planning to receive treatment for diabetic retinopathy and/or macular edema, for example, laser photocoagulation or intravitreal injections of anti-vascular endothelial growth factor inhibitors.

CCI [redacted]

Cardiovascular

14. Have New York Heart Association functional classification IV congestive heart failure.
15. Have had any of the following CV conditions within 60 days prior to Visit 1, or between Visit 1 and Visit 3.
    - acute myocardial infarction
    - cerebrovascular accident (stroke), or
    - hospitalization for congestive heart failure.

Gastrointestinal

16. Have a known clinically significant gastric emptying abnormality, for example, severe diabetic gastroparesis or gastric outlet obstruction, have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery, for example, Lap-Band®, or chronically take drugs that directly affect GI motility.

Hepatic

17. 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 the following as determined by the central laboratory during screening.

    - ALT or AST level >5.0x the ULN for the reference range
    - ALP level ≥1.5x the ULN for the reference range
    - TBL level ≥1.5x the ULN for the reference range, except for cases of known Gilbert's syndrome
    - Hepatitis B infection, defined as
        i. positive HBcAb and positive for HBV DNA or
        ii. positive hepatitis B surface antigen
    - Positive hepatitis C antibody and positive for HCV RNA

    Note: Participants with nonalcoholic fatty liver disease are eligible to participate only if their ALT level is ≤5.0x the ULN for the reference range.

Renal

18. Have an eGFR <45 mL/min/1.73 m^2 or lower than the country-specific threshold for discontinuing metformin therapy per local label as determined by the central laboratory at Visit 1 (calculated by Chronic Kidney Disease-Epidemiology cystatin-c equation).

Hematologic

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

Malignancy

20. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years.

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

Endocrine

21. Have family (first-degree relative) or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2.

22. Have a serum calcitonin level of ≥35 ng/L, as determined by the central laboratory at Visit 1.

General

23. Have had chronic or acute pancreatitis any time.

24. Have had a transplanted organ or awaiting an organ transplant.

Exception: corneal transplants (keratoplasty).

Prior/concomitant therapy

25. Have been treated with any antihyperglycemic medication (other than metformin) within the 90 days prior to Visit 1, or between Visit 1 and Visit 3.
26. Within 90 days prior to Visit 1, or between Visit 1 and Visit 3
    - are receiving or have received chronic (>14 days) systemic glucocorticoid therapy, excluding topical, intraocular, intranasal, interphalangeal, or inhaled preparations , or
    - have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that is likely to require, in the opinion of the investigator, such treatment during the study.
27. Have used any weight loss drugs or alternative remedies, including herbal or nutritional supplements, within 90 days prior to Visit 1 or between Visit 1 and Visit 3 (See Section 10.8 for examples).
28. Are receiving CCI [redacted]. See Sections 6.9.2 and 10.8 for further details.
    Note: Participants using these medications may be eligible for the study if the excluded drug can be washed out and replaced with an alternative medication for at least 2 weeks prior to Visit 3.

Prior/concurrent clinical study experience

29. 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.
30. Have previously completed or withdrawn from this study or any other study investigating orforglipron after receiving at least 1 dose of study intervention.
31. Have participated in a clinical study and received treatment, whether active or placebo, within the last 30 days or duration equal to 5 times the half-life of study intervention, whichever is longer.

Other exclusion criteria

32. Have any condition, unwillingness, or inability not covered by any of the other exclusion criteria, that, in the opinion of the investigator, might
    - jeopardize the safety of the participant, for example, hypersensitivity to trial product(s) or excipient or contraindication,
    - compromise compliance with the protocol, for example, recreational drug use or alcohol abuse, or
    - confound data interpretation.

33. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
34. Are Eli Lilly and Company employees or are employees of any third party involved in the study who requires exclusion of their employees.
35. Are pregnant or intend to become pregnant or to breastfeed during the study.

5.3. Lifestyle Considerations

Per the SoA (Section 1.3), participants will have access to qualified medical staff who will provide diabetes management counseling, which will include instructions on diet and exercise and education about the signs, symptoms, and treatment of hypoglycemia.

Participants should continue their usual exercise habits and generally follow a healthy meal plan, with consistent meal size and time of day, throughout the course of the study.

Dietary counseling may be reviewed throughout the study, as needed. Per Inclusion Criterion #6 (Section 5.1), participants should not initiate during the study an organized diet or exercise weight reduction program other than the lifestyle and/or dietary measures for diabetes treatment.

5.3.1. Diabetes Education

Diabetes education is to be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia and diabetes management. All trainings should be repeated as needed to ensure participant compliance.





5.3.2. Meals and Dietary Restrictions

For certain assessments, the participants will be required to come to the site in a fasting state, except for water, of at least 8 hours as specified in the SoA.



5.3.3. Blood Donation

Study participants should be instructed not to donate blood or blood products during the study, starting at Visit 1, and up to Visit 801 following the study.

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 CONSORT 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) will not be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable.

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

This table lists the interventions used in this clinical study.

Intervention Name	Orforglipron (LY3502970)	Dapagliflozin	Metformin[a]
Dosage Level(s)	CCI-mg, CCI-mg, CCI-mg, CCI-mg, CCI-mg, and CCI-mg capsules	CCI-mg CCI	≥CCI mg
Route of Administration	Oral QD	Oral QD	Oral[b]
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Authorized in EU and used according to marketing authorization	Authorized in EU and used according to marketing authorization

[a] Metformin is a background therapy, and the daily dosing information will not be captured in the eDiary.

[b] The frequency of metformin dosing will vary based on formulation and dosage. The pre-study dose and formulation (short-acting or long- acting) should be maintained until completion of treatment period, except as specified in Section 6.9.1.

Packaging and labeling

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

6.1.1. Background Therapy

Refer to Sections 6.1 and 6.9.1.

6.1.2. Timing of Dose Administration

Orforglipron or dapagliflozin will be administered orally once daily. In general, there are no restrictions on the time of day each dose is taken, but it is recommended to take the dose at approximately the same time each day.

Participants should administer their first dose of orforglipron or dapagliflozin at the end of Visit 3 prior to leaving the study site, after other study procedures and randomization are completed. The date and time of the first dose of orforglipron or dapagliflozin should be recorded on the CRF. Participants will record the actual date and time of all dose administrations in their eDiary.

6.1.2.1. Participants Randomly Assigned to Orforglipron

All participants will initiate treatment with a [redacted] mg QD dose of orforglipron [redacted]



The maintenance dose ([redacted] mg, [redacted] mg or [redacted] mg) of orforglipron will be continued for the remainder of the treatment period. For management of participants with intolerable GI symptoms, see Section 6.6.1.

Medications that may be affected [redacted] (Section 6.9).

Investigators, site staff, clinical monitors, and participants will remain blinded to the assigned maintenance dose of orforglipron, that is, [redacted] mg, [redacted] mg or [redacted] mg until the study is complete.

6.1.2.2. Participants Randomized to Dapagliflozin

All participants will initiate treatment with a [redacted] mg QD dose of dapagliflozin and maintain the dose for the reminder of the treatment period.

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 study intervention.

At the study sites where study intervention is stored, all study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel. For at-home administration, sponsor will provide storage instructions.

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 study training materials.

6.3. Assignment to Study Intervention

Method of treatment assignment

Participants who meet all criteria for enrollment will be randomly assigned to orforglipron or dapagliflozin using an IWRS.

Study intervention will be dispensed at the study visits summarized in the SoA. Returned study intervention should not be re-dispensed to the participants.

Randomization ratios and stratification factors

Participants will be randomly assigned in a [redacted] ratio to orforglipron [redacted] mg, orforglipron [redacted] mg, orforglipron [redacted] mg, or dapagliflozin [redacted] mg, respectively.

The randomization will be stratified by

- country, and
- [redacted]

6.4. Blinding, Masking

This is an open-label study with respect to assignment to orforglipron versus dapagliflozin.

The orforglipron doses ([redacted] mg to [redacted] mg) will be double-blinded. [redacted] Other details about blinding will be specified in the blinding and unblinding plan.

Emergency unblinding may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's orforglipron dose assignment. All unblinding events are recorded and reported by the IWRS.

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 on study drug, the investigator must obtain specific approval from a Lilly clinical research physician for the participant to continue in the study.

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's orforglipron dose assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's orforglipron dose assignment is unblinded, Lilly must be notified immediately. 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.

6.5. Study Intervention Compliance

Participant compliance with orforglipron or dapagliflozin will be assessed as indicated in the SoA (Section 1.3). Compliance will be

- assessed by
  - direct questioning
  - CCI
  - reviewing the eDiary, and
- documented in the source documents and CRF.

Participants will be instructed to return CCI at the times specified in the SoA.

Treatment compliance for each visit interval is defined as taking at least 75% of the required doses of orforglipron or dapagliflozin. Similarly, a participant will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication (more than 125%).

In addition to the assessment of a participant's compliance with orforglipron or dapagliflozin administration, other aspects of compliance with the study will be assessed at each visit based on the participant's adherence to the visit schedule, completion of study eDiaries, and any other parameters the investigator considers necessary.

Participants considered to be poorly compliant with their medication and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

A record CCI dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Orforglipron or dapagliflozin start and stop dates, including dates for orforglipron or dapagliflozin interruption, will also be recorded in the CRF.

6.6. Dose Modification

No dose modification will be allowed except as specified in Sections 6.6.1 and 6.6.2.

6.6.1. Management of Gastrointestinal Symptoms

Participants randomly assigned to orforglipron

For participants who report intolerable GI symptoms during the treatment period, the investigator should implement the following steps:

1. Advise participants to eat smaller meals; for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
2. Continue Step #1, and prescribe symptomatic medication, for example, antiemetic or antidiarrheal medication, per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the CRF.

3. Continue Steps #1 and #2 and consider temporarily interrupting study intervention: omit 1 dose or a maximum of 2 consecutive doses. After the interruption, the investigator should advise the participant to resume orforglipron at the same dose, with the participant taking medication to alleviate their GI symptoms. The data related to temporary interruption of study treatment should be documented in source documents.

If GI symptoms become tolerable or resolve with the above measures, the participant should continue study intervention at the same dose level CCI

If intolerable GI symptoms persist despite Steps #1 through #3, investigator may decide to permanently discontinue the study intervention. Dose de-escalation of orforglipron will not be allowed.

All participants who discontinue study intervention should continue to attend scheduled study visits. Initiation of another antihyperglycemic medication should be considered (see Section 7.1.1).

6.6.2. Temporary Dose Interruptions Unrelated to GI Tolerability

6.6.2.1. Orforglipron

All efforts should be made to keep participants on orforglipron at the assigned dose throughout the study. However, the investigator may need to temporarily interrupt orforglipron during the treatment period, for example, due to an AE unrelated to GI tolerability, a clinically significant laboratory value, or due to participant's personal circumstances (travel, hospitalizations, or planned or unplanned procedures).

Every effort should be made by the investigator to restart orforglipron after any temporary interruption as soon as it is safe to do so. Guidance on continuing or resuming orforglipron after temporary interruption is provided in the table below. Assignment of orforglipron at the correct dose will be per IWRS instructions in a blinded manner.

If participant misses…	…when...	then…
any number of doses	up to first 7 weeks of study treatment	continue assigned treatment per protocol
<3 consecutive doses	any time during the treatment period	continue assigned treatment per protocol
3 to 6 consecutive doses	after first 7 weeks of study treatment and prior to 24 weeks of study treatment	continue assigned treatment per protocol OR at investigator's discretion (based on tolerability of prior doses, GI AEs, etc.), restart treatment at [redacted] mg and CCI [redacted]
3 to 6 consecutive doses	after 24 weeks of study treatment	continue assigned treatment per protocol
≥7 consecutive doses	after first 7 weeks of study treatment	restart treatment at [redacted] mg and CCI [redacted]

If the interruption is due to an AE, the event is to be documented and followed according to the procedures in Section 8.3.

6.6.2.2. Dapagliflozin

All efforts should be made to keep participants on dapagliflozin treatment throughout the study. However, the investigator may need to temporarily interrupt dapagliflozin during the treatment period due to an AE, a clinically significant laboratory value, or due to participant's personal circumstances (travel, hospitalizations, or planned or unplanned procedures).

Every effort should be made by the investigator to restart dapagliflozin after any temporary interruption as soon as it is safe to do so.

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

Study intervention will not be made available to participants after conclusion of the study.

6.8. Treatment of Overdose

6.8.1. Orforglipron

Any dose of orforglipron greater than CCI mg within a 24-hour time period will be considered a potential overdose. Considering the maximum dose any participant may receive during the study treatment period is CCI mg, for this study with blinded dose of orforglipron, any dose of study intervention CCI within a 24-hour time period will be considered a potential overdose and should be reported per criteria described in Section 10.3.1.

In the event of an overdose, the investigator should

- initiate supportive treatment according to the participant's clinical signs and symptoms
- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether orforglipron should be interrupted, and
- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until, for example, orforglipron no longer has a clinical effect or is estimated to be cleared systemically based on half-life (at least 7 days).

6.8.2. Dapagliflozin

For this study, taking more than CCI mg dapagliflozin within the same day will be considered an overdose.

For additional information, refer to the product label for dapagliflozin, as applicable (Farxiga prescribing information, 2023; Forxiga SmPC, 2023).

6.9. Prior and Concomitant Therapy

Data on prior treatment with GLP-1 RA will be collected in CRF per the SoA (Section 1.3). Prior treatment refers to the treatment that was received by the participant before enrollment in the study and discontinued prior to Visit 1.

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/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 along with the

- reason for use
- dates of administration, including start and end dates, and
- dosage information, including dose and frequency for concomitant therapy of special interest.

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

Drugs that may be affected CCI . Examples (not exhaustive) relevant to the study population include

CCI

6.9.1. Antihyperglycemic Medications

Participants in this study must be treated with metformin for at least 90 days prior to Visit 1; the minimum required dose during this time will be CCI mg/day. The pre-study dose and formulation (short-acting or long-acting) should be maintained until completion of treatment period.

After randomization, discontinuation of metformin or change in dosage and formulation is not permitted, except in the following situations:

- In the event of a hypoglycemic episode(s) (clinical symptoms of hypoglycemia and/or BG-confirmed symptomatic BG hypoglycemia: glucose concentration <54 mg/dL [3.0 mmol/L]): Participants may reduce/discontinue the dose of metformin.
- In certain situations that require short-term discontinuation in line with the product(s) labeling for each respective country, for example, severe dehydration, elective surgery, or need for radiologic examination involving IV iodinated contrast dye. Once the situation that led to temporary discontinuation of metformin is resolved, treatment should be restarted within ≤14 days if it is safe to do so.
- If a participant develops contraindications or requires dose modification of metformin such that its use is contraindicated or requires dose modification according to the country-specific label.
- If participant meets the criteria for severe persistent hyperglycemia (Section 6.9.4) or discontinues orforglipron or dapagliflozin prematurely, then metformin dose may be increased according to country specific label as long as that is not the sole intervention.

A participant will be considered noncompliant with the protocol (protocol deviation) if he or she changes the dose or discontinues metformin for reasons other than those described here.

Dose modification/discontinuation of metformin during the trial should be properly documented and recorded on the appropriate CRF.

6.9.2. Prohibited or Restricted Use Medications

The following medications are prohibited throughout the study (up to Visit 801):

- Antihyperglycemic medications
    - Orforglipron arm: GLP-1 RA or tirzepatide, pramlintide (amylin analogs), or DPP-4 inhibitors (Section 10.8.1.1).
    - Dapagliflozin arm: other SGLT2 inhibitors (Section 10.8.1.1)

Use of other antihyperglycemic medications is prohibited except for the following:

- after permanent discontinuation of orforglipron or dapagliflozin (Section 7.1.1)
- as rescue therapy due to severe persistent hyperglycemia (Section 6.9.4)

  or
- during the safety follow-up period.

  Note: Short-term insulin use for up to 14 days is allowed for certain clinical situations, for example, elective surgery, during hospitalization, and hyperosmolar states, and must be differentiated from insulin use as rescue therapy when reported in the CRF.
- Medications intended to promote weight loss, including prescribed, over-the-counter, or alternative remedies. Examples are provided in Section 10.8.1.2.

- For participants randomized to orforglipron only:
  - CCI [redacted] Participants using these medications may be eligible for the study if the excluded drug can be washed out and replaced with an alternative medication for at least 2 weeks prior to Visit 3. Examples of these classifications of medications are provided in Section 10.8.1.3.
  - CCI [redacted] are strongly discouraged for initiation during the study, and alternative medications should be considered whenever possible. Examples are provided in Section 10.8.2.1.

6.9.3. Prohibited Surgical Treatments or Procedures for Weight Management

Surgical treatments, endoscopic therapy, and/or device-based therapy for weight management are not permitted during the study.

6.9.4. 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. An additional therapeutic intervention should be considered in participants who are fully compliant with the assigned therapeutic regimen in the absence of any acute condition that raises BG, **AND** who meet any of the following criteria:

Criteria for severe persistent hyperglycemia:

- Average BG from the CCI [redacted] profile is
  - >270 mg/dL (>15.0 mmol/L) over at least a consecutive 2-week period any time during the first 8 weeks post randomization

    OR
  - >240 mg/dL (>13.3 mmol/L) over at least a consecutive 2-week period at any time 9 to 16 weeks post randomization,

    OR
  - >200 mg/dL (>11.1 mmol/L) over at least a consecutive 2-week period at any time beyond the first 16 weeks post randomization

    OR
- HbA1c ≥8.5% (69 mmol/mol) at or after Week 24 with inadequate response to the existing regimen defined as improvement in HbA1c over the last 3 months that is <CCI [redacted]

During the weeks when CCI [redacted] profiles are collected, the CCI [redacted] values are included in the CCI [redacted] profiles.

Rescue medication

For participants who meet criteria for severe persistent hyperglycemia, the investigator will decide on an appropriate antihyperglycemic medication (rescue therapy) that is not a prohibited medication listed in Sections 6.9.2 and 10.8.

If a new antihyperglycemic medication is introduced during the treatment period, the participant should be treated with a locally approved antihyperglycemic agent according to the following order of preference based on the recommendations in the 2022 ADA EASD consensus guidelines (Davies et al. 2022) and ADA 2023 guidelines:

1. Sulfonylureas are recommended first, unless a contraindication is present to prevent confounding effect of using SGLT2 inhibitors or GLP-1 RA or tirzepatide.
2. If a contraindication to sulfonylurea is present, then
    a. SGLT2 inhibitors can be considered for participants randomized to orforglipron arm
    b. GLP-1 RA or tirzepatide can be considered for participants randomized to dapagliflozin arm
3. If glycemic control remains inadequate despite introduction of new antihyperglycemic medication, for example, after 90 days or within a time frame determined by the investigator, then addition of basal insulin therapy should be considered. If insulin is prescribed as a rescue therapy for hyperglycemia or as a new antihyperglycemic medication in patients requiring study intervention discontinuation, it must be differentiated from short-term use of insulin therapy for medical emergencies when reported in the CRF
4. Initiation of insulin as the first rescue intervention for hyperglycemia should be reserved for
    - participants with severe persistent hyperglycemia with an average blood glucose from the [redacted] ≥300 mg/dL (≥16.7 mmol/L)
    - participants with symptoms of hyperglycemia, if there is evidence of ongoing catabolism or in other clinical situations where the investigator believes more rapid glycemic control is warranted (ADA 2023).

Participants who receive rescue medicine for hyperglycemia management should also continue administering study intervention for the remaining period in the trial. Record the use of rescue medication as concomitant medication in the CRF.

If any new antihyperglycemic medication is initiated during the safety follow-up period, it will not be classified as rescue therapy.

Additional consideration for participants assigned to dapagliflozin:

Dapagliflozin is not recommended for improving glycemic control in adults with T2D with an eGFR less than 45 mL/min/1.73 m^2. If a participant's eGFR falls persistently below 45 mL/min/1.73 m^2, new antihyperglycemic medication should be considered (following the

order of preference above for rescue therapy) based on the investigator's clinical judgment. Record the use of new antihyperglycemic medication as concomitant medication in the CRF and not as rescue therapy.

6.9.5. Symptomatic Medication for Gastrointestinal Symptoms

The investigator may prescribe symptomatic medication for management of GI symptoms as needed during the study, for example, antiemetic or antidiarrheal medication, per local country availability and standard of care (see Section 6.6.1). Record the use of symptomatic medication as concomitant medication in the CRF.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation from Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention and will remain in the study to complete procedures for all remaining study visits, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant is diagnosed with acute or chronic pancreatitis, confirmed by adjudication. See Section 8.3.3.8
- the participant is diagnosed with MTC and MEN2 syndrome
- the participant develops significant elevation of serum calcitonin. See Section 8.3.3.9
- the participant is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer, for example, Gleason 6 or lower)
- the participant is diagnosed with T1D
- in the opinion of the investigator, for safety reasons
- the participant has intolerable GI symptoms despite management as described in Section 6.6.1
- the participant initiates any prohibited glucose-lowering medication (see Section 10.8.1.1) and will not or cannot discontinue the medication, or
- the participant develops any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken.

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

- If participants assigned to dapagliflozin,
    - experience persistent levels of eGFR <45 ml/min/1.73 m^2 , and
    - do not need to continue dapagliflozin for reasons other than glycemic control per local label as deemed appropriate by investigator.
- 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's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

Antihyperglycemic therapy after permanent discontinuation of study intervention

Following permanent discontinuation of study intervention for any reason, participants may require additional antihyperglycemic therapy to maintain glycemic control. Any locally approved antihyperglycemic therapy that is not a prohibited/restricted medication per Section 6.9.2 and is not contraindicated for use in the participant may be prescribed in accordance with local prescribing information.

The new antihyperglycemic intervention will be recorded on the concomitant medications CRF.

7.1.2. Hepatic Criteria for Study Intervention Interruption or Discontinuation

See Section 8.2.6.3 for hepatic criteria for study intervention interruption or discontinuation.

7.1.3. Temporary Study Intervention Interruption

Refer to Sections 6.6.1, 6.6.2, 7.1.2, and 8.3.3.8 for information on temporary dose interruptions.

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.

Participants will be discontinued from the study if the participant becomes pregnant.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, 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 ED visit and safety follow-up, 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.

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.

Section 10.2 lists the laboratory tests that will be performed for this study.

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

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.

See Section 3 for specific safety and efficacy endpoints.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

The primary efficacy assessment in this study is mean change in HbA1c values from baseline to 40 weeks, as determined by the central laboratory (Section 10.2). Blood samples for HbA1c measurements will be collected at visits specified in the SoA (Section 1.3).

8.1.2. Secondary Efficacy Assessments

- HbA1c (measured through central laboratory; Section 10.2).
- body weight (measuring method is described in Section 10.9).
- fasting serum glucose (measured CCI [redacted]; Section 10.2).

CCI [redacted]

CCI [redacted]

- blood pressure (measuring method is described in Section 10.9).
- lipid parameters (measured through central laboratory; Section 10.2).
- patient-reported outcomes (see Section 8.1.3).

8.1.3. Patient-Reported Outcomes

8.1.3.1. Short Form 36 Version 2 Health Survey, Acute Form, 1-Week Recall Version (SF-36 v2, Acute)

The SF-36v2 assesses health-related quality of life. The SF-36v2 acute form, 1-week recall version is a 36-item generic, participant-completed measure designed to assess the following 8 domains.

- physical functioning

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

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





8.1.3.6. Diabetes Treatment Satisfaction Questionnaire-Change Version (DTSQc)

The DTSQc (Bradley 1999) has the same 8 items as the status version but is reworded slightly to measure the change in treatment satisfaction rather than absolute treatment satisfaction.

Each item is scored on a 7-point scale ranging from -3 to +3. For most items (items 1, 4-7, and 8), higher scores indicate greater improvement in treatment satisfaction, lower scores indicate greater deterioration in treatment satisfaction, and a score of 0 represents no change. For item 2 (perceived frequency of hyperglycemia) and item 3 (perceived frequency of hypoglycemia), lower scores indicate better glycemic control.



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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:

- CV
- respiratory
- GI, and
- neurological.

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.

Additional assessments

Height, weight, CCI , and vital signs will also be measured and recorded. See Section 10.9 for further details.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and following the study specific recommendations included in Section 10.9.

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.

8.2.3. Electrocardiograms

Triplicate 12-lead ECGs will be obtained as outlined in the SoA (Section 1.3) using centrally provided ECG equipment. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. The recording of each ECG should occur at approximately 1-minute intervals. The collection of all replicates at a time point should not exceed 5 minutes. Collect ECG before blood samples for laboratory testing.

ECGs will be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present for immediate participant management, should any clinically relevant findings be identified. Any clinically relevant findings from ECGs that result in a diagnosis should be reported as an AE via CRF.

All digital ECGs 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).

The investigator, or qualified designee, must document their review of the ECG printed at the time of evaluation and any alert reports.

8.2.4. Clinical Safety Laboratory Tests

See 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 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, then report the information as an AE.

8.2.5. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA.

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.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected as outlined in Sections 8.3.1 and 8.3.2.

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

This table summarizes actions to take based on abnormal hepatic laboratory or clinical changes.

Participants with normal or near-normal baseline (ALT and/or AST and/or ALP <1.5x ULN)

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring (see Section 8.2.6.1)	Initiate comprehensive evaluation (see Section 8.2.6.2)	Interrupt or discontinue study intervention (see Section 8.2.6.3)
ALT or AST ≥3x ULN	X		
ALP ≥2x ULN	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥5x ULN	X	X	
ALP ≥2.5x ULN	X	X	
ALT or AST ≥3x ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥5x ULN for more than 2 weeks	X	X	X
ALT or AST ≥8x ULN	X	X	X
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x ULN	X	X	X
ALP ≥2.5x ULN and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x ULN with hepatic signs or symptoms[a]	X	X	X

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

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

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

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring (see Section 8.2.6.1)	Initiate comprehensive evaluation (see Section 8.2.6.2)	Interrupt or discontinue study intervention (see Section 8.2.6.3)
ALT or AST ≥2x baseline	X		
ALP ≥2x baseline	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥3x baseline or ≥250 U/L	X	X	

If this laboratory value is observed…	Then…		
	Initiate or continue close hepatic monitoring (see Section 8.2.6.1)	Initiate comprehensive evaluation (see Section 8.2.6.2)	Interrupt or discontinue study intervention (see Section 8.2.6.3)
(whichever occurs first)			
ALP ≥2.5x baseline	X	X	
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x baseline	X	X	X
ALP ≥2.5x baseline and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x baseline with hepatic signs or symptoms[a]	X	X	X

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

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

8.2.6.1. Close Hepatic Monitoring

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

Participants with normal or near-normal baseline liver enzymes (ALT and/or AST and/or ALP <1.5x ULN)	Participants with elevated baseline liver enzymes (ALT and/or AST and/or ALP ≥1.5x ULN)
ALT or AST ≥3x ULN **or**	ALT or AST ≥2x baseline **or**
ALP ≥2x ULN **or**	ALP ≥2x baseline **or**
TBL ≥2x ULN[b]	TBL ≥2x ULN[b]

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

Close hepatic monitoring should include

- laboratory tests (Section 10.2), including ALT, AST, ALP, TBL, D. Bil, GGT, CK, and complete blood count 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 normalize or return to approximate baseline values

- in addition to laboratory 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.

8.2.6.2. Comprehensive Hepatic Evaluation

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

Participants with normal or near-normal baseline liver enzymes (ALT and/or AST and/or ALP<1.5x ULN)	**Participants with elevated baseline liver enzymes (ALT and/or AST and/or ALP ≥1.5x ULN)**
ALT or AST ≥5x ULN **or**	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) **or**
ALP ≥2.5x ULN **or**	ALP ≥2.5x baseline **or**
ALT or AST ≥3x ULN with hepatic signs or symptoms[a] **or**	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a] **or**
ALT or AST ≥5x ULN for more than 2 weeks **or**	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks **or**
ALT or AST ≥8x ULN **or**	ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first) **or**
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR ≥1.5

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

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

Comprehensive hepatic evaluation should include these actions:

- at a minimum, comprehensive hepatic evaluation should include
    - physical examination and a thorough medical history, as outlined in Sections 1.3 and 8.2.1.
    - tests for
        - PT-INR
        - tests for viral hepatitis A, B, C, and E, and
        - tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

- based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for
    - hepatitis D virus
    - cytomegalovirus
    - Epstein-Barr virus
    - acetaminophen levels
    - acetaminophen protein adducts
    - urine toxicology screen
    - Wilson's disease
    - blood alcohol levels
    - urinary ethyl glucuronide, and
    - blood phosphatidylethanol.
- based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.
- clinical and laboratory monitoring should continue at a frequency of 1-2 times weekly until levels normalize or return to approximate baseline values.
- if the hepatic event continues past the anticipated end of the study (that is, data lock), the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, database lock date).
- all the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.6.3. Study Intervention Interruption or Discontinuation

If a participant develops any 1 of the following laboratory or clinical changes, interrupt the study intervention and continue close monitoring and comprehensive hepatic evaluation as described in Sections 8.2.6.1 and 8.2.6.2.

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

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

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

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

Interruption or discontinuation of study intervention should include these actions:

- While the participant is not receiving the study intervention, clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study, that is, data lock, the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study, that is, data lock date.
- All the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study 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.

8.2.7. 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 10.2.3. Laboratory results are provided to the sponsor via the central laboratory.

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

The definitions of the following events can be found in Appendix 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 or 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).

For PCs, 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 Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE[a]– after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	At least 30 days after the last dose	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	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.

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

- will obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent, will record pregnancy information on the appropriate form and submit it to the sponsor.

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

Female participants who become pregnant

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

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

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

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

Any 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, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will 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.

8.3.3. Adverse Events of Special Interest

8.3.3.1. Major Adverse Cardiovascular Events

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

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

Case adjudication and data entry

An independent CEC with cardiology expertise will adjudicate all suspected cases of major adverse cardiovascular events. The investigator must first report these events as an AE as described in Section 8.3.1 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (see Section 10.1.5). Clinical event reporting begins after randomization.

8.3.3.2. Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac arrhythmias and conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.3.2 must be reported as SAEs.

8.3.3.3. Hypotension, Orthostatic Hypotension, and Syncope

All events of hypotension or orthostatic hypotension and syncope should be evaluated and additional diagnostic tests performed as needed.

8.3.3.4. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia and how to treat hypoglycemia and instructed to record relevant information for each episode of hypoglycemia in the study eDiary.

Participants will record information on episodes of hypoglycemia starting from Visit 2 until the last study visit (ED visit or follow-up visit).

All hypoglycemic episodes will be recorded in the study eDiary. Because all hypoglycemic episodes will be recorded in the study eDiary, they should not be recorded on the AE CRF unless the event meets criteria of severe hypoglycemia which should then be recorded as serious on the AE CRF and reported to the sponsor as an SAE.

To avoid duplicate reporting, all consecutive BG 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).

In this study, increased risk of hypoglycemia is defined as having a single episode of severe hypoglycemia or having more than 1 episode of documented symptomatic hypoglycemia within a 1-week period at any time during the treatment period. In cases where a participant experiences hypoglycemia as described above, to confirm the increased risk, the study sites must ensure that the participant has been fully compliant with the assigned study intervention and also that there is no evidence of other possible causes of hypoglycemia, for example, omission of meal and unexpected increase in exercise.

If the participant fulfills the definition of increased risk of hypoglycemia even when metformin has been discontinued, the investigator should discontinue the participant from study intervention and follow the guidance for management of participants to permanently discontinue the study intervention as outlined in Section 7.1.1.

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 - Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)

Level 1 hypoglycemia should alert the participant 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 a glucose value of <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

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 the sponsor as an SAE.

Nocturnal hypoglycemia

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

8.3.3.5. Severe Persistent Hyperglycemia

Criteria for severe persistent hyperglycemia are provided in Section 6.9.3.

Occurrences of severe persistent hyperglycemia that meet these criteria for rescue therapy should be reported as an AE on the CRF.

8.3.3.6. Severe Gastrointestinal Adverse Events

Orforglipron may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs, as well as antiemetic or antidiarrheal use, will be collected in the AE and concomitant medications CRFs, respectively. For detailed information concerning the management of GI AEs, please refer to Sections 6.6.1 and 6.9.5.

8.3.3.7. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute renal failure or worsening of preexisting chronic renal failure. GI AEs have been reported with orforglipron, including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 RA (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

8.3.3.8. Pancreatitis

Diagnosis of acute pancreatitis

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

- abdominal pain, characteristic of acute pancreatitis, that is, epigastric pain radiating to the back, often associated with nausea and vomiting
- serum pancreatic amylase and/or lipase ≥3x ULN, and
- 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 and lipase
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI

  Note: Abdominal ultrasound may be used as an alternative method only if CT and MRI cannot be performed.
- evaluate for possible causes of acute pancreatitis, including alcohol use, gallstone or gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study intervention (Section 7.1.3). In this case, the participant needs to receive an appropriate alternative antihyperglycemic regimen. Afterwards, if pancreatitis is confirmed by the adjudication committee, the study intervention must be permanently discontinued (Section 7.1.1), and the participant should be followed throughout the duration of the study. If the case is not confirmed, then the participant can restart the study intervention if the investigator deems as clinically appropriate as described in Section 6.6.2.

Case adjudication and data entry

An independent CEC will adjudicate all suspected cases of pancreatitis. This committee will be blinded to treatment assignment. The investigator must first report these events as an AE as described in Section 8.3.1 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (see Section 10.1.5). Clinical event reporting begins after randomization.

Asymptomatic elevation of serum amylase and/or lipase

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

Cases of pancreatic hyperenzymemia with symptoms or asymptomatic cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up will be submitted for adjudication.

8.3.3.9. Thyroid Malignancies and C-Cell Hyperplasia

Participants who are diagnosed with MTC and/or MEN2 during the study will have study intervention stopped (Section 7.1.1) and should continue follow-up with an endocrinologist.

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

Calcitonin measurements for participants assigned to orforglipron

A significant increase in calcitonin for participants is defined as postrandomization calcitonin value of ≥35 ng/L that has increased at least 50% over baseline.

If this increased calcitonin value is observed in a participant who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped, and calcitonin levels should be measured after an appropriate washout period of that concomitant medication (that is, 5 times the half-life).

Study intervention should be discontinued if the increased concentration of calcitonin is confirmed. The participant must be recommended to immediately undergo additional endocrine

assessments and longer-term follow-up by an endocrinologist to exclude AEs on the thyroid gland.

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



8.3.3.11. Malignancies

All events of malignancy or other suspected events related to malignancy should be evaluated and additional diagnostic tests performed as needed.

8.3.3.12. Hepatic Disorders

All events of hepatic disorders or other suspected events related to hepatic disorders should be evaluated and additional diagnostic tests performed as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.6.

8.3.3.13. Gallbladder and Biliary Tract Disorders

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

8.3.3.14. Hypersensitivity Reactions

Refer to Section 8.2.7.

8.3.3.15. Abuse Potential

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

8.4. Pharmacokinetics

PK parameters are not evaluated in this study.

8.5. Pharmacodynamics

Efficacy measures will be used as indicators of PD response.

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 orforglipron and to investigate genetic variants thought to play a role in obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis. Assessment of variable response may include evaluation of AEs or differences in PD, mechanistic, safety, or efficacy measures.

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

8.7. Biomarkers

Plasma and serum samples will be collected and stored to enable exploratory nonpharmacogenetic biomarker research.

Biomarker research is performed on stored samples to address questions of relevance to

- drug disposition
- target engagement
- PD
- mechanism of action
- variability of participant response, including safety, and
- clinical outcomes.

Samples may be used for

- research on the drug target
- disease process
- variable response to orforglipron
- pathways associated with diabetes mellitus, obesity, and related clinical traits or complications, including nonalcoholic steatohepatitis
- mechanism of action of orforglipron, or
- research method or validating diagnostic tools or assay(s) related to obesity, diabetes mellitus, or related clinical traits or complications.

Samples will be collected according to the schedule described in the SoA.

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study.

8.9. Health Economics

Health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP will be approved before the first participant first visit , 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 important endpoints, including primary and key secondary endpoints.

Unblinding details will be specified in the blinding and unblinding plan.

9.1. Statistical Hypotheses

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



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



9.1.1. Multiplicity Adjustment

Multiplicity-adjusted analyses will be performed on the primary and key secondary objectives in order to control the overall family-wise Type I error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2009, 2011) will be used. This

approach is a closed testing procedure; hence, it strongly controls the family-wise Type I error rate across all hypotheses (Alosh et al. 2014).

Figure 1 illustrates the graphical multiple testing procedure used to assess the primary and key secondary efficacy objectives.

Treatment regimen estimand and efficacy estimand will be used to assess primary and key secondary efficacy objectives. Unless otherwise specified or requested by a regulatory agency, the "treatment regimen" estimand is planned to support future product registration applications, and the "efficacy estimand" will be considered for use in scientific disclosures and other purposes. Because these 2 types of estimands are intended for distinct purposes, no multiplicity adjustment will be made for conducting separate analyses on the same objectives. There will be no adjustment for multiple comparisons for any other analyses outside the primary and key secondary objectives.



9.2. Analyses Sets

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

Data Points Sets	Description
Treatment regimen estimand data points set	All data points obtained during the treatment period defined as after baseline and up to the last visit within the treatment period, regardless of study intervention discontinuation or initiation of additional antihyperglycemic medications.
Safety data points set	All data points obtained during the treatment period and the safety follow-up period defined as after baseline and up to the date of study withdrawal including the safety follow-up period regardless of study intervention discontinuation or initiation of additional antihyperglycemic medications [a].
Efficacy estimand data points set	All data points obtained during the treatment period defined as after baseline and up to the earliest date of discontinuation of study intervention or initiation of additional antihyperglycemic medications [a].

[a] "Additional antihyperglycemic medications" refers to any antihyperglycemic therapy that is used for more than 2 weeks (14 days).

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 of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the CI will be calculated at 95%, 2-sided.

Baseline is defined as the last available non-missing measurement prior to the first dose of study intervention, unless otherwise specified.

General descriptions of analyses

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. LS means 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 LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons. All baseline measures will be analyzed using an analysis of variance (ANOVA) model that has treatment group as the fixed effect.

The analysis model to make comparisons between treatment groups relative to continuous efficacy measurements will be an ANCOVA with a variance estimator that is robust to model misspecification and heteroscedasticity (Ye et al. 2022). The model will include treatment group, strata, and the continuous covariate of baseline values and their interactions with treatment group (strata*treatment group and baseline*treatment group).

For measures evaluated at multiple postbaseline visits, a restricted maximum likelihood-based MMRM (Wang and Du 2022) analysis will be used. The analysis model to make comparisons between treatment groups relative to continuous measurements assessed over time will include a MMRM, with fixed effects of visit, and treatment, stratification factors, and baseline measurement all nested within 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. If applicable, Fisher’s exact test or Pearson’s chi-square test will be used for treatment comparisons in other categorical outcomes.

Unless otherwise specified, safety and tolerability assessments will be guided by an estimand comparing safety of orforglipron doses with dapagliflozin for the entire study period (the treatment period plus safety follow-up) irrespective of adherence to study intervention for all study population.

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

Missing data should be minimized at 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 CSR.

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

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 randomized participants will be presented by treatment groups. A listing of randomized 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. The percentage of participants discontinuing from treatment groups will be compared using the Fisher's exact test. Kaplan-Meier analyses of time from randomization to premature discontinuation from study and premature discontinuation from study 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 randomized participants.

9.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy, will be summarized by treatment group for the randomized participants during treatment period.

9.3.2.4. Treatment Compliance

Treatment compliance is defined as taking at least 75% 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

The null hypotheses corresponding to the primary objective can be found in Section 9.1.

The primary objective will be evaluated relative to 2 estimands, "treatment regimen" and "efficacy" (see Section 3).

The primary objective aligned to the "treatment regimen" estimand will be evaluated using the randomized participants and the treatment regimen estimand data points set as described in Section 9.2.

For the assessment of the primary objective guided by the "treatment regimen" estimand, data for participants with missing values at Week 40 will be imputed and then analyzed using an ANCOVA with a variance estimator that is robust to model misspecification and heteroscedasticity (Ye et al. 2022). The model will include treatment group, strata, and the continuous covariate of baseline values and their interactions with treatment group (strata*treatment group and baseline*treatment group).

If there are occurrences of missing data despite the best precautions, missing data will be imputed in a manner consistent with what the values would likely have been had they been collected. In principle, missing data due to permanent discontinuation of study will be imputed using retrieved dropouts, namely using multiple imputation based on data retrieved from participants who permanently discontinued study intervention but continued in the study with non-missing measurements from the same treatment group. More details regarding the

imputation for missing values according to the reasons for study discontinuation will be described in the SAP.

The primary objective aligned to the "efficacy" estimand will be evaluated using the randomized participants and the efficacy estimand data points set (Section 9.2). The MMRM model described in Section 9.3.1 will be used for the assessment of the primary objective guided by the "efficacy" estimand. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. For the "efficacy" estimand, the hypothetical strategy is used to handle the ICEs, so only data collected before the occurrence of any ICEs will be used in the MMRM analysis. Through the MMRM, the potential efficacy measures (after the ICEs) will be implicitly imputed as if participants did not have ICEs.

For each hypothesis, orforglipron will be declared non-inferior to dapagliflozin in controlling HbA1c if the upper limit of the CI is below NIM (+0.3%), with the CI calculated at the alpha level allocated according to the graphical approach.

A multiple imputation-based tipping-point (MI-TP) analysis is planned as a sensitivity analysis to assess the robustness of primary efficacy results.

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

9.3.4. Secondary Endpoints and Estimands Analysis

The null hypotheses corresponding to the key secondary objectives can be found in Section 9.1.

Key secondary objectives will be evaluated relative to both the "treatment regimen" and "efficacy" estimands, as described in Section 9.3.3. Analyses for key secondary endpoints will be controlled for type 1 error through the graphical approach.

The assessment of key secondary objectives for continuous variables will be evaluated by an ANCOVA for the "treatment regimen" estimand and an MMRM for the "efficacy" estimand as described in Section 9.3.3.

For the assessment of key secondary objectives for binary variables, a logistic regression model with treatment group and strata as fixed effects and the continuous baseline value 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 (Ge et al. 2011). The estimated treatment group-specific risk, risk difference, relative risk, p-value, and 95% CI will be presented.

For binary efficacy measures derived from a continuous variable, the missing value in the underlying continuous variable will be imputed first and then the corresponding binary variable will be derived. The details about imputation under "treatment regimen" estimand is described in Section 9.3.3. Under the "efficacy" estimand, missing values for continuous variables at Week 40 will be imputed through multiple imputation using all non-missing data (excluding data collected after ICEs) from the same treatment group under the missing-at-random assumption.

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

9.3.5. Pharmacokinetics/Pharmacodynamic Analyses

Not applicable.

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 proportions of participants experiencing AEs will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

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 Section 8.3.3) will be provided in the SAP.

9.3.6.2. Gastrointestinal Events

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

9.3.6.3. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Actual and change from baseline to postbaseline values of selected 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 summarized and compared between treatment groups using Fisher's exact test or Pearson's chi-squared test.

9.3.7. Other Analyses

Subgroup analyses

Subgroup analyses to assess consistency of the effect of orforglipron across subgroups for the primary endpoint (HbA1c) will be detailed in the SAP. The following subgroups will be considered but not limited to:

- age group (<65, ≥65 years)
- sex (female, male)
- baseline HbA1c stratum CCI [redacted]
- [redacted]
- duration of T2D (<median, ≥median)

- race
- ethnicity, and
- country/region.

Additional subgroup analyses on the key secondary endpoints, for example, weight, may also be performed.

If the number of participants is too small (<10%) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. Further details on the statistical analysis will be provided in the SAP.

9.4. Interim Analysis

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

9.5. Sample Size Determination

Approximately 888 participants will be randomly assigned in a CCI ratio to orforglipron CCI mg, CCI mg, CCI mg, dapagliflozin CCI mg, respectively.

This trial is powered at over 90% to assess non-inferiority of orforglipron CCI mg to dapagliflozin CCI mg, orforglipron CCI mg is noninferior to dapagliflozin CCI mg, and/or orforglipron CCI mg is noninferior to dapagliflozin CCI mg respectively at the 2-sided CCI significance level (0.05 overall alpha split between comparisons), relative to the primary endpoint (change from baseline in HbA1c at Week 40), under the following assumptions:

- use of a 2-sample t-test using HbA1c data
- a dropout rate of CCI% in the dapagliflozin-treated and the orforglipron-treated participants
- CCI% greater reduction in HbA1c from baseline for CCI mg, CCI mg, and CCI mg of orforglipron compared to CCI mg of dapagliflozin
- CCI [redacted]
- common SD of CCI%.

Furthermore, this sample size will ensure CCI% power for superiority of orforglipron CCI mg to dapagliflozin CCI mg, orforglipron CCI mg compared with dapagliflozin CCI mg, and orforglipron CCI mg compared with dapagliflozin CCI mg assuming CCI% greater HbA1c reduction of orforglipron CCI mg compared with dapagliflozin CCI mg, orforglipron CCI mg compared with dapagliflozin CCI mg, and orforglipron CCI mg compared with dapagliflozin CCI mg.

Based on a network meta-analysis, the treatment effect (mean and 95% CI) for orforglipron CCI mg versus dapagliflozin CCI mg is expected to be approximately CCI [redacted] A conservative treatment effect of -0.1% was chosen based upon the upper limit of the CI.

Based on a meta-analysis, the difference in estimated placebo-adjusted changes in HbA1c observed in T2D studies with dapagliflozin CCI mg was approximately CCI [redacted]

This indicates that the NIM chosen is smaller than the smallest effect size that dapagliflozin [redacted] mg would be reliably expected to have compared with placebo.

These assumptions are considered to ensure the power for the primary endpoint for both efficacy and treatment regimen estimands.

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 GCP Guidelines
- applicable laws and regulations.

The protocol, protocol amendments, ICF, IB, 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, 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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 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 (or, when appropriate, a caregiver, surrogate, or the participant's legally authorized representative) and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's 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 the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. 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's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

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

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, SAP, CSR, and blank or annotated CRFs, 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 access to source documents.

Data monitoring and management

Quality tolerance limits 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 quality tolerance limits and remedial actions taken will be summarized in the CSR.

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 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.

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

Clinical outcome assessments

The eCOA data (participant-focused outcome instrument) for all other assessments will be directly recorded by the participant 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 storage and access

Data collected via the sponsor-provided data capture system(s) will be stored at third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture 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 the central vendor's database system, and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

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

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

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

10.1.9. Study and Site Start and Closure

First act of recruitment

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

Study or site termination

The sponsor or sponsor's 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's publication policy, 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 orforglipron or after orforglipron becomes commercially available.

This table lists the maximum retention period for sample types. The retention period begins after the last participant's last visit in this study.

Sample Type	Custodian	Maximum Retention Period After the Last Participant Visit
Exploratory biomarkers	Sponsor or designee	Up to 15 years
Genetics/PD	Sponsor or designee	Up to 15 years

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in this appendix will be performed by the laboratory(ies) stated in Sections 10.2.1 and 10.2.2 of this appendix.

For visits other than the prescreening visit (Visit 601): 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, 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/analyte results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

10.2.1. Prescreening Visit (Optional)

A blood sample for HbA1c measurement will be obtained per the collection methods available to support the prescreening visit (Visit 601). The location of laboratory analysis will be dependent on collection method performed and is described in this table.

Collection Method	Location of Laboratory Analysis
Point of care	Near patient assessment
Microsampling	Lilly-designated laboratory
Venipuncture	Lilly-designated laboratory or local laboratory

Point-of-care testing must be permissible by local regulations and requirements.

All prescreening laboratory assessments must be conducted according to the SoA, with standard collection requirements according to the laboratory manual, if applicable.

10.2.2. Other Study Visits

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential	
Absolutes count of	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	To be performed if abnormalities are detected.
Clinical chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	
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)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	

Clinical Laboratory Tests	Comments
Lipid panel	
CCI [redacted]	Assayed by Lilly-designated laboratory.
Total cholesterol	
Triglycerides	
CCI [redacted]	[redacted]
CCI [redacted]	Calculated by Lilly-designated laboratory.
Non-high-density lipoprotein cholesterol (non-HDL)	
Hepatitis serology	Assayed by Lilly-designated laboratory.
Hepatitis C Virus (HCV) testing:	
HCV antibody	
HCV RNA	Performed only for participants who test positive for HCV antibody.
Hepatitis B Virus (HBV) testing:	
HBV DNA	Performed only for participants who test positive for anti-HBc.
Hepatitis B core antibody (HBc-Ab)	
Hepatitis B surface antigen (HBsAg)	
Hepatitis B surface antibody (anti-HBs)	
Hormones (female)	Assayed by Lilly-designated laboratory unless stated otherwise.
Serum pregnancy	
Urine pregnancy	Evaluated locally.
Follicle-stimulating hormone (FSH)	
Urine chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	CKD-EPI cystatin-C equation (2012). Results will be used for eligibility criteria.
Urinary albumin/creatinine ratio (UACR)	
Other testing	
HbA1c	Testing may be performed locally at V601. All other visits assayed by Lilly-designated laboratory.
Calcitonin	Assayed by Lilly-designated laboratory.
Pancreatic amylase	
Lipase	

Clinical Laboratory Tests	Comments
Glucose	Serum
Cystatin-C	
Genetics sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Whole blood (EDTA)	
CCI	

10.2.3. 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 min to 4 hr after the start of the event. ● Note: The optimal collection time is from 1 to 2 hr after the start of event.	total tryptase

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

10.3. Appendix 3: 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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, 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 <u>NOT</u> meeting the AE definition

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

10.3.2. Definition of SAE

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

- Results in death
- Is life-threatening
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- Results in persistent disability/incapacity
    - The term disability means a substantial disruption of a person's ability to conduct normal life functions.
    - This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma, for example, sprained ankle, which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/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 PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

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

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

Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention so that the situation can be assessed.

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

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

AE, SAE, and PC recording

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

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

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

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.

There may be instances when copies of medical records for certain cases are requested by 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.

A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

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

The investigator will also consult the IB 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) 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 SAE form.

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 on the SAE 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 has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to local regulatory requirements. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/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
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone >40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women **should not** be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

Females

WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship as their preferred and usual lifestyle:

Must…	Must not…

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

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

Topic	Condition
Contraception	Agree to use 2 methods of effective contraception, where at least 1 form must be highly effective. These methods of contraception must be used during the study and for at least 30 days after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization[a] (including fallopian tube ligation, hysteroscopic sterilization) • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (for men in clinical trials and for female partner if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Methods	Examples

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

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea

[a] Hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy are the only types of permanent female sterilization that allow a participant to be a WNOCBP.

Males

No male contraception is required except in compliance with specific local government study requirements.

10.5. Appendix 5: Genetics

Use/analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.



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 orforglipron or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases continues but no longer than the sample retention limits described in Section 10.1.12, or other period as per local requirements.

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

Hepatic evaluation testing

See protocol Section 8.2.6 for guidance on appropriate test selection.

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

In circumstances where required in accordance with local regulations, local laboratory testing may be performed in lieu of Lilly-designated central laboratory testing (in the table below).

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

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

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

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

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

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

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

10.7. Appendix 7: World Health Organization Classification of Diabetes and Diagnostic Criteria

Type 1 diabetes

T1D is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death.

Type 2 diabetes

T2D, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in T2D but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with T2D later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

10.8. Appendix 8: Prohibited Medications or Medications with Special Use Restrictions

10.8.1. Excluded/Prohibited or Restricted Use Medications

Medications within the following categories are strictly prohibited during the study. The lists below provide examples of each category of medication, but the examples are not exhaustive. As stated in Section 6.9.2, participants who have to initiate certain prohibited concomitant medications during this study will be discontinued from the study (Section 7.1).

10.8.1.1. Antihyperglycemic Medications

The following antihyperglycemic medications are prohibited within 90 days of Visit 1 or between Visit 1 and Visit 3, as well as at any time during the study.

Orforglipron arm

- alogliptin
- dulaglutide
- exenatide
- linagliptin
- liraglutide
- pramlintide
- saxagliptin
- semaglutide
- sitagliptin
- tirzepatide, and
- other incretin-based therapy.

Dapagliflozin arm

- Any SGLT2 inhibitors including canagliflozin, empagliflozin

10.8.1.2. Weight Loss Medications

Weight loss medications are prohibited within 90 days of Visit 1, or between Visit 1 and Visit, as well as at any time during the study.

- ingested material that transiently occupies space in the stomach, for example, Plenity®
- liraglutide
- lorcaserin
- mazindol
- naltrexone/bupropion
- orlistat
- over-the-counter medications, for example, allī®
- phentermine

- phentermine/topiramate
- phenylpropanolamine
- semaglutide
- sibutramine, and
- other incretin-based therapies.

10.8.1.3. CCI

Participants cannot be taking CCI, drugs that are CCI CCI, or CCI. Participants may be eligible for this study if these medications can be washed out for at least 2 weeks and the participant can be on a stable dose of an alternative medication for at least 2 weeks prior to randomization (Visit 3).

Non-exhaustive lists of examples of these medications are provided in this table.

Drug class	Drug name
CCI	



10.8.2. Medications with Special Use Restrictions

10.8.2.1. Moderate CCI



10.8.2.2. Drugs Affected [redacted]

Drugs that may be affecte [redacted]. Examples include

Drug class	Drug name
[redacted]	

10.9. Appendix 9: Standardized Protocols for the Measurement of Height, Weight, CCI and Vital Signs

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

Measuring height

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

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

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

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

Measuring weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms to 1 decimal place.

  All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.

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 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.



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

Step 1*:* Ask the participant to wear little clothing (if available, 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 the participant to relax and measure the participant's CCI.

Vital sign measurements (blood pressure and heart rate)

- Vital sign measurements (BP and HR, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing.
- The participant should sit quietly for 5 minutes before vital signs measurements are taken.
- For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm.
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and BP needs to be recorded in the CRF.
- BP must be taken with an automated BP instrument.
- If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

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

10.10. Appendix 10: Country-specific Requirements

Country-specific requirements for non-EU countries will be described in separate protocol addenda, if any.

10.10.1. 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/Withdrawal from the Study 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.1.3. Informed Consent Process 10.12. Appendix 12: Abbreviations and Definitions	Deleted references to "legally authorized representative," "legal guardian," "parents"	The German Drug Law (Arzneimittelgesetz – 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.
10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances	Revision in temporary measures	In Germany, the temporary measures described in Section 10.11 are applicable only to the COVID-19 pandemic.

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:

- at any time at the participant's own request for any reason or without providing any reason
- ~~at the request of the participant's designee (for example, parents or legal guardian)~~
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, 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:

- 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~~).

10.1.3. Informed Consent Process

The investigator or the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant (or, when appropriate, a caregiver, surrogate~~, or the potential participant's legally authorized representative~~) and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants (or, when appropriate, a caregiver, surrogate~~ or the participant's legally authorized representative~~) be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 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 (or, when appropriate, a caregiver, surrogate~~, or the participant's legally authorized representative~~) and is kept on file.

Section 10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances

In Germany, the temporary measures described in the Section 10.11 are applicable only to the COVID-19 pandemic.

Note: Healthcare visits, including mobile healthcare visits for procedures including physical assessments and collection and assessment of adverse events, must be performed by the investigator or a designee who is a physician. The investigator holds accountability for procedures delegated to other individuals.

Section 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. Appendix 11: 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.

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's written approval, sites may implement changes if permitted by local regulations.

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

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section "Remote Visits,"
- 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

- collection of AEs
- review CCI values, and
- concomitant medications.

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

- review of concomitant medications
- vital signs (BP and PR)
- body weight, collection of blood samples
- physical assessments, and
- collection of health information.

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: Visit 1, Visit 3, Visit 9, Visit 11, ED, and Visit 801. 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's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, 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 are valid for a CCI . The following rules will be applied for active, nonrandomized participants whose participation in the study must be interrupted due to exceptional circumstances:

- If screening is interrupted for CCI from screening visits to randomization visit: the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted CCI from first screening visit.
  - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
  - The site should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is interrupted for CCI from screening visits to randomization visit: 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 SoA should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

Adjustments to visit windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 1 through 3	CCI days from Visit 1 to Visit 3
Visit 4 through 9	within CCI days before or after the intended date per the SoA
Visit 10 through 11	within CCI days before or after the intended date per the SoA
Visit 801	up to CCI days after the intended date

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

Documentation

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 investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.12. Appendix 12: Abbreviations and Definitions

Term	Definition
abuse	use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
ALT	alanine aminotransferase
ALP	alkaline phosphatase
ANCOVA	analysis of covariance
CCI	[redacted]
AST	aspartate aminotransferase
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an investigational medicinal product
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labelling of the medicinal product, which is used as an auxiliary medicinal product
AxMP	auxiliary medicinal product. See also NIMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
CCI	[redacted]
BG	blood glucose
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
CEC	clinical endpoint committee

Term	Definition
CI	confidence interval
CK	creatine kinase
CCI	[redacted]
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system
compliance	adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
CCI	[redacted]
D. Bil	direct bilirubin
DPP	Dipeptidyl peptidase
DNA	deoxyribonucleic acid
DTSQc	Diabetes Treatment Satisfaction Questionnaire-Change Version
CCI	[redacted]
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
ED	early discontinuation
EDC	electronic data capture
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

Term	Definition
ERB	ethics review board
GCP	good clinical practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GLP-1 RA	Glucagon-Like Peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HBcAb	hepatitis B core antibody
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICE	intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (see also "investigational product"). A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked
INR	international normalized ratio
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP"

Term	Definition
IRB	Institutional Review Board
CCI	[redacted]
IWRS	interactive web response system
CCI	[redacted]
LS	least squares
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges or prefilled pens, or both
MEN2	multiple endocrine neoplasia type 2
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen or indication, or both, or is obtained without a prescription
MMRM	Mixed Model for Repeated Measures
MTC	medullary thyroid cancer
CCI	[redacted]
NIMP	Non-investigational Medicinal Product See AxMP. A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment.
CCI	[redacted]
participant	Equivalent to CDISC term "subject": an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control

Term	Definition
PC	product complaint
CCI	[redacted]
PI	principal investigator
PK/PD	pharmacokinetics/pharmacodynamics
PT	prothrombin time
QD	once daily
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study
SD	standard deviation
SF-36v2, acute	Short Form-36 version 2 Health Survey acute form
SGLT2	sodium glucose transport protein 2
CCI	[redacted]
SmPC	Summary of Product Characteristics
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
TBL	total bilirubin level
T1D	type 1 diabetes
T2D	type 2 diabetes
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment
ULN	upper limit of normal
VAS	visual analog scale

Term	Definition
CCI	[redacted]
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

10.13. Appendix 13: Protocol Amendment History

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

Amendment (a)

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary purpose of this amendment is to address feedback from the European Union Regulatory Authorities. The changes are presented in the table below.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis 3. Objectives, Endpoints, and Estimands	Primary estimands subsection: Added a statement to refer to Section 9.1 for details on the plan for use of each estimand.	Clarification.
1.3. Schedule of Activities (SoA)	Added a urine pregnancy test at Visit 801.	To include additional pregnancy testing.
6.4. Blinding, Masking	Added text on emergency unblinding and the scenarios in which unblinding can be done by the investigator.	To add procedure for emergency unblinding.
9.1.1. Multiplicity Adjustment	Updated the procedure for multiplicity adjustment and added paragraph for treatment regimen and efficacy estimand.	To add procedure for multiplicity adjustment.
9.5. Sample Size Determination	Added text for the treatment effect and for justification of non-inferiority margin.	Clarification.
10.10. Appendix 10: Country-specific Requirements (Germany)	Added a note that healthcare visits, including mobile healthcare visits, must be performed by the investigator or a designee who is a physician.	To clarify that, for participants in Germany, the procedures will be done by investigator or a designee who is a physician.

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