Protocol: I8F-MC-GPID

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Comparing the Efficacy and Safety of Tirzepatide versus Placebo in Patients with Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT)

NCT04847557

Approval Date: 14-Feb-2024

Title Page

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Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Comparing the Efficacy and Safety of Tirzepatide versus Placebo in Patients with Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT)

Protocol Number: I8F-MC-GPID

Amendment Number: c

Compound: LY3298176

Study Phase: 3

Short Title: Tirzepatide vs Placebo in Obesity-related HFpEF

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Manufacturer: Eli Lilly and Company

Regulatory Agency Identifier Number

IND: 147352

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

Document ID: VV-CLIN-120976

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	*21-Jan-2022*
Amendment (a)	*15-Dec-2021*
Original Protocol	*13-Jan-2021*

Amendment c

This amendment is considered to be substantial.

The amendment is considered to be substantial because of the change in design and methodology, and revision to the primary endpoints, which impacts the scientific value of the study.

Overall Rationale for the Amendment:

The purpose of this protocol amendment is to revise the dual primary endpoints.

Given the significant weight loss, and associated cardiometabolic improvements, achieved with tirzepatide, assessment of CV death and HF events, in addition to KCCQ score as a primary endpoint, offers the unique opportunity to evaluate tirzepatide for the benefit of patients with HFpEF and obesity. The dual primary endpoints described in GPID Protocol Amendment (b) may not be able to capture the full potential benefit offered by tirzepatide in this patient population.

Additionally, this amendment broadens the heart failure endpoint definition based on growing evidence that supports outpatient intensification of oral diuretics indicating worsening of HF. This change results in a new definition of HF event, defined as worsening symptoms or signs of HF, which are treated either as an inpatient (by hospitalization, treated by oral or IV diuretic intensification) or as an outpatient (by IV or oral diuretic intensification).

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis 3. Objectives and Endpoints	Revised primary endpoints to • Change from baseline to Week 52 in the KCCQ-CSS • Occurrence of the composite endpoint of CV death and/or HF events over time	Assessment of CV death and HF events, in addition to change from baseline to Week 52 in the KCCQ-CSS score as a primary endpoint, offers the unique opportunity to evaluate tirzepatide for the benefit of patients with HFpEF and obesity. The hierarchical components using the win ratio were removed from alpha-adjusted endpoints as they present significant complexity in analytics and interpretation
	Key secondary endpoints revised to • change from baseline to Week ~~24~~52 in 6MWD • percent change from baseline to week 52 in body weight • Change from baseline to Week 52 in hsCRP • ~~NYHA class change at week 52~~ • ~~Change from baseline to week 52 in the KCCQ-CSS~~	Revisions aligned with change in primary endpoint. hsCRP added as key secondary as it is considered a clinically significant biomarker in HF population
	Removed “The maximum duration of participation depends on when the last participant completes 52 weeks of treatment” from Overall Design	This was duplicated text in same section
	EVa, EVb, EVc weeks from randomization updated to	Provides clarity of when the extended visits occur based

1.3. Schedule of Activities (SoA)	"(+3, 6, 9, 15, 18, 21 months from Visit 12)"	from Visit 12 and not from randomization
	EVd weeks from randomization updated to "(+12, 24 months from Visit 12)"	Provides clarity of when the extended visits occur based from Visit 12 and not from randomization
	"Including product complaints" removed from adverse events (AEs) row	Clarification; product complaints are not AEs
	Footnote "c" added sentence noting that if a participant requires a telephone visit, they must still pick up study drug from the site	Clarification
	Footnotes "d," "e," "f," "h," "j," "k," and "l" text in comment column of table moved to footnote section below SoA	Editorial
2.1. Study Rationale	Revised study objectives summary statement relative to updated endpoints	Alignment with updated endpoints
2.2. Background	Section revised and updated to provide additional background information and references	Alignment with updated endpoints
3. Objectives and Endpoints	Hierarchical composite assessed by win ratio moved to other secondary endpoint	Alignment with updated endpoints
	NYHA class, exercise capacity (6MWD at Week 24) moved from Key Secondary endpoints to Other Secondary endpoints	Exercise capacity analyzed as other secondary and NYHA class moved as part of the revised endpoint strategy

	Change from baseline to Week 24 in KCCQ-CSS added to other secondary endpoints Proportion of participants attaining KCCQ-CSS meaningful within-patient change (MWPC) threshold at Week 52 added to other secondary endpoints	MWPC analysis added to support KCCQ-CSS
	Exploratory endpoint "HF medication use" integrated into primary endpoint CV death and/or HF event	Heart failure event definition expanded to include oral diuretic augmentation; therefore, a separate HF medication use is no longer needed
	Exploratory endpoint "Evaluation of prespecified biomarkers" hsCRP; moved to key secondary endpoint	Alignment with updated endpoints
	Added exploratory endpoints: • Change from baseline to week 52 in waist to height ratio • eGFR slope	Alignment with updated endpoints
4.1. Overall Design	Study Closeout and Final Visit: study duration revised as the duration of the trial depends on the last patient visit	Provides guidance to sites regarding final visit scheduling and expectations
	Study Closeout and Final Visit: indicated sponsor will notify sites of the study closeout based on the visit date of the last patient randomized	Provides guidance to sites regarding final visit scheduling and expectations

	Study Closeout and Final Visit: added statement that participants who have completed 52 weeks of the study are expected to complete V99 during the 3-month period prior to study close; no investigational product will be dispensed at the final visit	Provides guidance to sites regarding final visit scheduling and expectations
	Study Closeout and Final Visit: added "Any participant who has discontinued the study prior to completing 52 weeks of study duration is expected to complete an early termination visit per the SoA."	Provides guidance to sites of when to schedule final visit for participants
4.2. Scientific Rationale for Study Design	Revised section to provide rationale regarding updated primary endpoints	Alignment with revised endpoints
4.4. End of Study Definition	Clarified to indicate that the end of the study will occur approximately 52 weeks after the last participant has been randomized	Clarification
6.4. Study Intervention Compliance	Compliance revised as follows: Treatment compliance ~~for each visit interval~~ is defined as taking at least 75% of the required doses of study drug	Clarification
6.5. Concomitant Therapy	Dosage information for concomitant therapy of special interest updated to include drugs for diabetes, obesity diuretics, and cardiovascular drugs	Clarification

6.6.1. Temporary Interruption	Indicated that for cases where increased ALT, AST, or ALP occur, close hepatic monitoring must be initiated	Language regarding hepatic safety streamlined for clarity and consistency
6.6.2. Restarting Study Drug after Interruption	Added "During re-escalation after a temporary dose interruption, participants should be followed every 4 weeks until either a new lower maintenance dose level or prior maintenance dose level is reached."	Clarification
	Clarified that if an unscheduled visit occurs in the same week or date of a regular scheduled visit per the SoA, the site should complete all procedures included for the regular scheduled visit	Clarification
7.1.1. Permanent Discontinuation from Study Drug	Revised permanent discontinuation to indicate that participants who permanently discontinue the study drug will remain in the trial	Clarification
	Revised discontinuation due to hepatic event to reference appropriate section	Clarification
	Added bariatric surgery to permanent discontinuation circumstances	Bariatric surgery may pose a safety risk to subject taking IP
	Added GLP-1RA to permanent discontinuation circumstances	Added as co-administration of GLP-1RA and study drug may have safety implications to the participant
7.2. Participant Discontinuation/Withdrawal from the Study	Added instruction for sites regarding participants unwilling/unable to return for follow-up visits	Clarification

7.3. Lost to Follow up	Revised section to include updated instructions to sites regarding determination of participant vital status	Clarification to guide sites to continue attempts to reach participants until end of study
8.1.1. Primary Efficacy Assessment	Updated primary efficacy assessment to KCCQ-CSS and CV death and/or HF event	Alignment with revised primary endpoints
	Hierarchical composite assessed by win ratio moved to other secondary endpoint	Alignment with updated endpoints
	6MWT moved to Section 8.1.2	Alignment with revised primary endpoints
	Removed Time to All-Cause Mortality	Alignment with revised primary endpoints
8.1.1.2. Kansas City Cardiomyopathy Questionnaire	Addition of information regarding KCCQ collection at V8, V12, and ET	Clarification
8.1.1.2. Definition of Heart Failure Events	Revised definition of HF events to include outpatient intensification of oral diuretics due to HF events	Alignment with revised primary endpoints
8.1.2. Secondary Efficacy Assessments	Revised section header to "~~Additional~~ Secondary Efficacy Assessments"	Clarification
	Addition of information regarding 6MWT collection at V8, V12, and ET	Clarification
	Revised secondary endpoint "Body Weight" to include hsCRP; revised section subheader: "Body Weight and hsCRP"	hsCRP assessment added to align with change to key secondary endpoints
8.1.3. Exploratory Efficacy Assessments	Moved NYHA Classification from Secondary Efficacy	Alignment with revised primary and secondary endpoints

	Assessments to Exploratory Efficacy Assessments	
8.2.5.1. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Drug Interruption or Discontinuation	Section header updated, addition of tables for hepatic safety monitoring which indicate when to initiate close hepatic monitoring, comprehensive evaluation, or interrupt or discontinue study drug	Updated to current Lilly procedures. No major changes
8.2.5.2. Close Hepatic Monitoring	Separate section header created, removed table, addition of CBC with differential to laboratory tests	Clarification
8.2.5.3. Comprehensive Hepatic Evaluation	Separate section header created, removed table	Clarification
8.2.5.4. Study Drug Interruption or Discontinuation due to a Hepatic Event	Section added; additional instruction provided regarding study drug interruption or discontinuation	Clarification
8.3.1. Timing and Mechanism for Collecting Events	Pregnancy reporting mechanism and back-up mechanism updated to pregnancy paper form eCRF and pregnancy paper form respectively	Correction
8.3.2. Primary, Secondary, and Additional Study Endpoint Reporting	Revised “hospitalization for HF or an urgent HF visit” to “HF events”	Alignment with revised primary and secondary endpoints
8.4. Treatment of Overdose	Removed reference to IB	Template update
	Definition of overdose updated to injection of study drug more than 1 time in 72 hours	Correction and clarification

	Revised required investigator action in the event of an overdose	Correction and clarification
9.1. Statistical Hypotheses	Revised primary hypotheses to • tirzepatide MTD is superior to placebo for the change from baseline in KCCQ-CSS at Week 52 • tirzepatide MTD is superior to placebo for the occurrence of the composite endpoint of CV death and/or HF events over time	Alignment with revised primary endpoints
	Revised key secondary hypotheses to that tirzepatide MTD is superior to placebo with regards to: • change from baseline in 6MWD at Week ~~24~~52 • percent change from baseline in body weight at Week 52 • change from baseline in hsCRP at Week 52	Alignment with revised endpoints
	Revised statistical methods related to updated primary and key secondary endpoints	Alignment with revised primary and key secondary endpoints
9.2. Sample Size Determination	Updated sample size justification description as related to revised primary endpoints	Alignment with revised primary endpoints
9.4.2. Primary Endpoint(s)	Revised statistical methods related to primary endpoints; removed hierarchical	Alignment with revised primary endpoints

	composite endpoint and change in 6MWD, added KCCQ-CSS (9.4.2.1) and HF outcomes (9.4.2.2)	
9.4.3. Key Secondary Endpoint(s)	Revised statistical methods related to key secondary endpoints: • KCCQ-CSS endpoint moved to primary endpoint • 6MWD revised from 24 weeks to 52 weeks • Analysis method of percent change in body weight revised from MMRM to ANCOVA • NYHA class removed • hsCRP endpoint added (ANCOVA analysis)	Alignment with revised key secondary endpoints and correct analysis method appropriate for the estimand
9.4.4. Tertiary/Exploratory Endpoint(s)	"Other secondary" removed from section	Alignment with revised secondary endpoints
10.4.2. Female participants	Revised contraception requirement from 2 months after the last administration of study drug to 4 weeks	Update to align with Investigator's Brochure
Throughout the protocol	Minor editorial corrections, minor clarifying changes	Minor editorial changes, therefore not described; clarification

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study Comparing the Efficacy and Safety of Tirzepatide versus Placebo in Patients with Heart Failure with Preserved Ejection Fraction and Obesity (SUMMIT)

Short Title: Tirzepatide vs Placebo in Obesity-related HFpEF

Rationale:

Heart failure with preserved ejection fraction is a heterogenous clinical syndrome resulting from various pathophysiological processes. Among the broad spectrum of HFpEF clinical presentation, obesity-related HFpEF displays a distinct phenotype where increased visceral and ectopic adiposity as well as volume expansion plays a causal role (Kitzman and Shah 2016; Packer 2018; Miller and Borlaug 2020). Given tirzepatide's anti-inflammatory and antifibrotic effects and a reduction in circulating plasma volume as a consequence of the treatment of obesity, tirzepatide may provide clinical benefit to patients with HFpEF and BMI ≥30 kg/m^2.

Study I8F-MC-GPID, also known as SUMMIT, is a Phase 3, randomized, multicenter, international, placebo-controlled, double-blinded, parallel-arm study. This study will evaluate the effect of SC QW injection of tirzepatide, MTD up to 15 mg, on the health status, risk of death, HF events, and exercise capacity in participants with HFpEF and BMI ≥30 kg/m^2.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that a maximally tolerated tirzepatide dose up to 15 mg administered SC QW is superior to placebo to improve patient-reported symptoms and physical limitations in participants with HFpEF and obesity	Change from baseline to Week 52 in the KCCQ-CSS
To demonstrate that a maximally tolerated tirzepatide dose up to 15 mg administered SC QW is superior to placebo based on the composite HF outcome endpoint in participants with HFpEF and obesity	Occurrence of the composite endpoint of CV death and/or HF events over time
Key Secondary (multiplicity controlled)	
Exercise capacity	Change from baseline to Week 52 in 6MWD

Long-term weight loss	Percent change from baseline to Week 52 in body weight
Evaluation of change in inflammation	Change from baseline to Week 52 in hsCRP

Abbreviations: 6MWD = 6-minute walk distance; CV = cardiovascular; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; QW = once weekly; SC = subcutaneous.

Overall Design

Study GPID is a randomized, outpatient, multicenter, international, placebo-controlled, double-blind, parallel-arm, Phase 3 study with 2 study periods. The study is designed to evaluate the efficacy and safety of SC QW tirzepatide, MTD up to 15 mg, compared to placebo, in participants with HFpEF and obesity.

Two intervention groups will be studied:

- Tirzepatide, MTD up to 15 mg, SC QW
- Placebo

The starting dose of tirzepatide is 2.5 mg QW, which is to be escalated at 4-week intervals to a maximum of 15 mg QW or to the highest maintenance dose tolerated by the participant (see Section 6).

Disclosure Statement: This is a parallel-treatment study with 2 intervention groups that is double blinded.

Number of Participants:

Approximately 700 participants will be randomly assigned to study drug with approximately 350 participants per intervention group.

Intervention Groups and Duration:

The study will compare treatment with tirzepatide and treatment with placebo. Assignment to tirzepatide or placebo groups will be randomly allocated in a 1:1 ratio.

The starting dose of tirzepatide 2.5 mg QW is to be escalated to 15 mg QW or the highest maintenance dose tolerated by the participant (5 mg, 10 mg, QW).

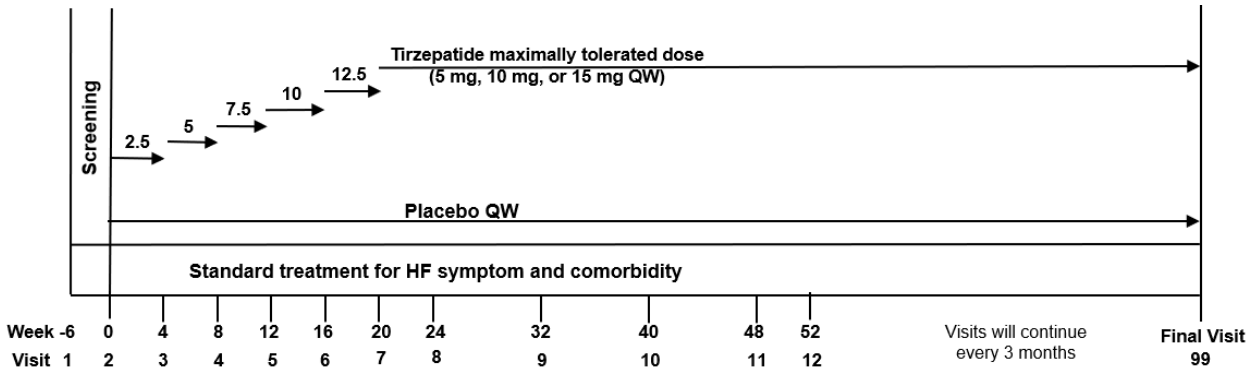
Study participation for each participant is sectioned into the following study periods:

- Study Period 1: screening period, approximately 6 weeks and not more than 12 weeks
- Study Period 2: treatment period, at least 52 weeks

The study will continue until approximately 52 weeks after the last participant is randomized. The maximum duration of an individual's participation is estimated to be 120 weeks and will depend on duration of study enrollment.

Data Monitoring Committee: Yes

1.2. Schema



Abbreviations: HF = heart failure; QW = weekly.

Note: Screening procedures may take longer or shorter than 6 weeks but no more than 12 weeks.

1.3. Schedule of Activities (SoA)

Visit 1 and 2 procedures may be conducted over more than 1 day each as long as all activities are completed within the allowable visit interval tolerance for each visit.

For early terminations (ET) from the study that occur before the final visit (V99) in treatment period, see the activities listed for ET in this table.

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Informed consent	X																			
Inclusion and exclusion criteria, review and confirm	X	X																		

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Demographics	X																			
Preexisting conditions and medical history, including relevant surgical history	X																			

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Prespecified medical history (indication and history of interest)	X																			Includes HF history, hospitalization for HF, CVD, MI, atrial fibrillation, stroke, CV risk (T2DM, HTN, dyslipidemia, metabolic syndrome)
Prior treatments for HFpEF	X																			
Substance use (alcohol, tobacco use)	X																			

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Physical Evaluation																				
Height	X																			
Weight	X	X	X	X	X	X	X	X		X		X		X	X	X		X	X	
Waist circumference	X	X						X				X		X				X	X	

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Vital Signs	X	X	X	X	X	X	X	X		X		X		X	X	X		X	X	Include 2 Sitting BP and HR. HR to be performed by apical auscultation. Vital signs should be collected prior to the first 6MWT of the day and before ECG.
Physical examination	X											X		X				X		

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Symptom-directed physical examination		X	X	X	X	X	X	X		X		X		X	X	X			X	As indicated based on participant status and standard of care, including dyspnea, orthopnea, paroxysmal nocturnal dyspnea (PND), edema, jugular venous distension (JVD), rales

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
NYHA class assessment	X	X						X				X		X				X[d]		NYHA class assessment must be performed by an independent assessor. See footnote d.
HF events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Evaluation of injection site reactions		X	X	X	X	X	X	X		X		X		X	X	X		X	X	

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Single-read 12-lead ECG	X	X						X				X						X[d]		Collect locally. Report atrial fibrillation or other abnormalities on the eCRF. Optional ECG is allowable if indicated. See footnote d
Echocardiography	X																			For those required to complete the ECHO examination

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Dilated fundoscopic examination	X																			Perform for participants with T2DM who have not had an evaluable dilated fundoscopic examination in the last 12 months. See exclusion criterion 25 (Section 5.2)

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
																				Follow-up dilated fundoscopic examination should be performed when clinically indicated by any AE suspected of worsening retinopathy.
6MWT	X[e]	X[f]						X				X						X[d]		Ensure that participant completes the associated Borg Questionnaire prior to and after the 6MWT. See footnotes e, f, and d
Participant Education																				

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Diary instruction		X																		
Participant Diary																				
Participant diary dispensed		X	X	X	X	X	X	X		X		X		X						
Diary compliance check/Assess study drug compliance[g]			X	X	X	X	X	X	X	X	X	X	X	X				X	X	
Diary return			X	X	X	X	X	X		X		X		X				X	X	
Patient-Reported Outcomes (PROs) (Electronic[h])																				See footnote h

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Kansas City Cardiomyopathy Questionnaire (KCCQ)	X	X						X				X						X		
EQ-5D-5L		X						X				X						X		
Patient Global Impression of Status – Overall (PGIS-Overall)	X	X						X				X						X		

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Patient Global Impression of Status – Physical Function (PGIS-Physical Function)	X	X						X				X						X		
Patient Global Impression of Status – Symptom Severity (PGIS-Symptom Severity)	X	X						X				X						X		
Laboratory Tests and Sample Collections																				

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Hematology	X	X			X			X				X		X	X[i]	X[i]		X	X	See footnote i
Hemoglobin A1c (HbA1c)	X	X	X	X	X	X	X	X		X		X		X				X	X	
Clinical chemistry (with glucose)	X	X[j]			X			X				X		X	X[i]	X[i]		X	X	See footnote j
Lipid panel	X	X[j]			X			X				X		X	X[i]	X[di]		X	X	See footnote j
Thyroid-stimulating hormone (TSH)	X																			

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Serum pregnancy	X	X[k]																		For women of childbearing potential only. See Appendix 4 (Section 10.4). See footnote k

Urine pregnancy (local)		X	X	X	X	X	X	X		X		X		X				X	X	A local urine pregnancy test must be performed at Visit 2 after patient eligibility has been confirmed with the result available prior to randomization and first injection of study drug(s) for WOCBP only. Additional local urine pregnancy tests may be performed at the investigator's discretion during the study. If required per local regulations and/or institutional guidelines, pregnancy testing can also occur at other times during the study treatment period. See Appendix 4 (Section 10.4).
Follicle-stimulating hormone (FSH)	X																			Collect FSH only in women whose menopausal status needs to be determined. For participants known to be either premenopausal or postmenopausal, these tests do not need to be collected
NT-proBNP	X	X			X			X				X						X [d]		See footnote d

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Cardiac troponin T (cTnT)		X			X			X				X						X[d]		See footnote d
Calcitonin	X							X				X		X				X	X	
Cystatin C		X			X			X				X						X[d]		See footnote d
C-reactive protein, high-sensitivity (hsCRP)		X			X			X				X						X[d]		See footnote d
Pancreatic amylase	X	X[j]			X			X		X		X		X				X	X	See footnote j

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Lipase	X	X[j]			X			X		X		X		X				X	X	See footnote j
eGFR (CKD-EPI)	X	X[l]			X			X				X		X				X	X	The CKD-EPI equation will be used by the central lab to estimate and report eGFR. See footnote l
Urinary albumin/creatinine ratio (UACR)	X							X				X		X				X	X	

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Pharmacokinetic (PK) samples		X	X		X			X				X		X				X	X	PK samples should be taken prior to dose administration at the visit and at the same time as immunogenicity samples.
Immunogenicity samples		X	X		X			X				X		X				X	X	
Stored Samples																				
Genetics sample		X																		
Exploratory biomarker samples		X			X			X				X								

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Randomization and Dosing																				
Randomization		X																		
Dispense study drug		X	X	X	X	X	X	X		X		X	X	X		X				
Injection training with autoinjector demonstration device		X																		

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
Observe participant administer study drug		X	X	X	X	X	X	X		X		X		X		X				Participants should administer the first dose of study drug at Visit 2 after study procedures and randomization have been completed. Review technique with the participant at each in clinic visit.

Study I8F-MC-GPID	Study Period I Screening	Study Period II - Treatment period																		
															Unscheduled Visit (UV)[a]					
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	EVa, EVb, EVc (13, 14, 15, 17, 18, 19, etc.)	EVd (16, 20, etc.)	UV	Dosing UV	Phone Follow-Up Dosing UV	ET	99	Comment
Weeks from randomization	-6	0	4	8	12	16	20	24	32	40	48	52	(+3, 6, 9, 15, 18, 21 months from Visit 12)	(+12, 24 months from Visit 12)				—	Final Visit	See footnote b
Visit interval tolerance (days)			±3	±3	±3	±3	±3	±3	±7	±7	±7	±7	±15	±15				—		
Telephone Visit									X		X		X				X			See footnote c
																				Sites should coach and oversee if participants self-administer study drug at a scheduled visit.
Dispense ancillary supplies to participant		X	X	X	X	X	X	X		X				X						
Participant returns study drugs and injection supplies			X	X	X	X	X	X		X		X		X				X	X	

Abbreviations: 6MWT = 6-minute walk test; BP = blood pressure; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CVD = cardiovascular disease; ECG = electrocardiogram; ECHO = echocardiography; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; EQ-5D-5L = 5-Level European Quality of Life Questionnaire; ET = Early Termination; EV = Extended Visit; HF = heart failure; HFpEF = heart failure with preserved ejection fraction; HR = heart rate; HTN = hypertension; MI = myocardial infarction; NT-proBNP = N-terminal pro b-type natriuretic peptide; NYHA = New York Heart Association; T2DM = type 2 diabetes mellitus; WOCBP = women of childbearing potential.

a There are 3 types of Unscheduled Visits (UV): These visits can occur during the dose-escalation period and maintenance period.
- Unscheduled Visits (UV) – Unscheduled Visit per investigator discretion. All activities with a check mark in UV visit are required.
- Dosing Unscheduled Visit (UV) – these visits will include dose re-escalation. The study drug must be restarted when it is safe to do so and only while at the clinic visit. The subsequent unscheduled dosing visits will be scheduled every 4 weeks (±7 days) until maximum tolerated dose is achieved.
- Phone Follow-up Dosing Unscheduled Visit (UV) – these visits are optional phone visits.

b At least 52 weeks (Visit 12) of treatment are planned. Additional visits after Visit 12 will occur every 3 months. The visits occurring after Visit 12 will follow the Extended Maintenance Visit schedule in sequence (EVa, EVb, EVc, and EVd) then repeat. If the final study visit is combined, site should only use the visit 12 lab kit; please refer to Study Closeout and Final Visit in Section 4.1.

c Telephone visits can become office visits. Site documentation will serve as the source for telephone visits. Additional, optional telephone visits may be conducted at investigator discretion. If patient requires study drug at a telephone visit, the participant will need to come to the clinic to pick up study drug in addition to telephone visit.

d Perform at ET only if participant early terminates at or prior to Week 52.

e Two 6MWTs conducted at screening visit.

f See Section 10.10.1 to determine if the 6MWT needs to be repeated for Visit 2.

g This includes glucose monitoring for participants with T2D, weekly study drug injection.

h Perform PRO at ET only if participant early terminates at or prior to Week 52.

i Unscheduled Visits: laboratory tests may be drawn according to investigator discretion. If only re-test labs required, site is not required to complete an unscheduled visit and associated procedures.

j Required at Visit 2 randomization if screening labs are older than 28 days for chemistry, lipid, and pancreatic lipase/amylase.

k Collect serum pregnancy at Visit 2 only if Visit 1 serum was ≥28 days prior.

l Only collect calculated eGFR with Clinical Chemistry sample if screening labs are older than 28 days.

2. Introduction

2.1. Study Rationale

Heart failure with preserved ejection fraction is a heterogenous clinical syndrome resulting from various pathophysiological processes. Among the broad spectrum of HFpEF clinical presentation, obesity-related HFpEF displays a distinct phenotype where increased visceral and ectopic adiposity as well as volume expansion plays a causal role (Kitzman and Shah 2016; Packer 2018; Miller and Borlaug 2020). Given tirzepatide's potential to decrease inflammation and fibrosis and a to reduce circulating plasma volume as a consequence of the treatment of obesity, tirzepatide may provide clinical benefit to patients with HFpEF and BMI ≥30 kg/m^2.

Study I8F-MC-GPID, also known as SUMMIT, is a Phase 3, randomized, multicenter, international, placebo-controlled, double-blinded, parallel-arm study. This study will evaluate the effect of SC QW injection of tirzepatide, MTD up to 15 mg, on the health status, risk of death, HF events, and exercise capacity in participants with HFpEF and BMI ≥30 kg/m^2.

2.2. Background

Obesity is one of the main attributes to worsen quality of life in patients with HFpEF (Reddy et al. 2020). There is a significant unmet need in treatment of patients with HFpEF. Tirzepatide, a GIP and GLP-1 dual agonist, has the potential to provide benefit to patients with HFpEF and BMI ≥30 kg/m^2. Tirzepatide may improve symptoms and exercise capacity and may also a reduce in HF events and/or increase survival. Supporting a causal association between obesity and HFpEF, bariatric surgery improved NYHA class, patient-reported outcomes, and echo parameters (LV wall thickness, LV relaxation) in patients with HFpEF and obesity (Mikhalkova et al. 2018). A meta-analysis of bariatric surgery also showed improvement in functional capacity 6 to 12 months after surgery in patients with obesity (Herring et al. 2016). In patients with HFpEF and obesity, diet-induced weight loss (Δ=−7 kg, 20 weeks) significantly improved symptoms (KCCQ) and exercise capacity (6MWD and peak oxygen uptake) (Kitzman et al. 2016). Furthermore, weight reduction is proven to be effective in reducing HF risk and HF hospitalizations. A large observational study has demonstrated a 62% decrease (over 8 years) of HF incidence after bariatric surgery in patients with T2DM (Aminian et al. 2019). The reduction of HF risk after bariatric surgery has been consistently demonstrated in broader patient populations and considered to be mediated by weight loss with a hazard ratio for a 10-kg weight loss being 0.77 (Sundström et al. 2017; Jamaly et al. 2019). Moreover, a self-controlled case study showed a 29% (0 to 12 months) and a 43% (13 to 24 months) risk reduction of HF events in patients with HFpEF after bariatric surgery (Shimada et al. 2016). Finally, in a recently published placebo-controlled study (STEP-HFpEF), semaglutide reduced body weight by 10.7% and improved KCCQ-CSS by 7.8 points at 52 weeks, both with p<0.001 (Kosiborod et al. 2023; Borlaug et al. 2023). In addition, superiority on the hierarchical composite endpoint (death, HF events, differences in the change in KCCQ-CSS, and 6MWD) was achieved, including the proportion of patients who had improved KCCQ score by at least 15 points in the semaglutide group. Semaglutide also improved 6MWD, with between-group difference of 20.3 meters. Most intriguingly, adjudicated events of hospitalization for heart failure or an urgent visit occurred in

12 patients in the placebo group, but only in 1 patient in the semaglutide group (HR 0.08; 95% CI 0.00 to 0.42)

It has been demonstrated that tirzepatide can provide significant body weight loss and improvement of lipid and glucose metabolism in patients with and without T2DM (Frias et al. 2018; Wilson et al. 2020; Jastreboff et al. 2022). It is known that the body weight reduction with GLP-1 RAs in patients without T2DM is higher than in patients with T2DM (Davies et al. 2015; Pi-Sunyer et al. 2015; Lingvay et al. 2018). If Study GPID is assumed to include 40% to 50% of patients with T2DM, the mean placebo-adjusted body weight percent reduction that tirzepatide can provide in 52 weeks in this study is estimated to be 15% to 16%. This is based on tirzepatide clinical data and the understanding of body weight loss differences between patients with and without T2DM treated with GLP-1 RAs. Thus, the predicted body weight loss with treatment with tirzepatide is close to that shown with bariatric surgery.

Tirzepatide may provide benefit to patients with HFpEF and obesity by virtue of cardiometabolic improvements (Wilson et al. 2020). Given the wide distribution of GIP receptor in the adipose tissue, GIP is thought to be actively involved in lipid and glucose metabolism. As suggested by the results of emerging data (Kosiborod et al. 2023) and the significant weight loss achieved with tirzepatide, the effect of tirzepatide on HF events in an obesity-related HFpEF population are expected to be robust. Therefore, it will be meaningful to assess the impact of tirzepatide not only on functional and symptomatic endpoints but also on the reduction in the risk of HF events in SUMMIT, thereby facilitating the holistic understanding of the clinical impact of tirzepatide treatment in patients with HFpEF and obesity.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of tirzepatide may be found in the Investigator’s Brochure.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that a maximally tolerated tirzepatide dose up to 15 mg administered SC QW is superior to placebo to improve patient-reported symptoms and physical limitations in participants with HFpEF and obesity	Change from baseline to Week 52 in the KCCQ-CSS
To demonstrate that a maximally tolerated tirzepatide dose up to 15 mg administered SC QW is superior to placebo based on the composite HF outcome endpoint in participants with HFpEF and obesity	Occurrence of the composite endpoint of CV death and/or HF events over time
Key Secondary (multiplicity controlled)	
Exercise capacity	Change from baseline to Week 52 in 6MWD
Long-term weight loss	Percent change from baseline to Week 52 in body weight
Evaluation of change in inflammation	Change from baseline to Week 52 in hsCRP
Other Secondary	
Hierarchical composite assessed by win ratio	A hierarchical composite of the following: 1. Time to all-cause mortality through the end of the study 2. Occurrence of heart failure (HF) events through end of the study, where HF events are defined as worsening heart failure with intensification of diuretics (oral or IV) during a hospitalization, urgent care visit or outpatient visit (adjudicated) • number of HF events • time to first HF events 3. Change from baseline in KCCQ-CSS category at Week 52

	4. Change from baseline in the 6-minute walk test distance (6MWD) category at Week 52 The categories for change from baseline in the KCCQ-CSS are: 1. ≥10-point worsening 2. ≥5- but <10-point worsening 3. No change (<5-point change) 4. ≥5- but <10-point improvement 5. ≥10- but <15-point improvement 6. ≥15-point improvement The categories for change from baseline in the 6MWD are: 1. ≥30% worsening 2. ≥20% and <30% worsening 3. ≥10% and <20% worsening 4. No change (<10% change) 5. ≥10% and <20% improvement 6. ≥20% and <30% improvement 7. ≥30% improvement.
Clinical outcome events of HF	• Time to all-cause death • Time to first occurrence of HF events or all-cause death • Time to recurrent events of HF events and all-cause death • Time to first occurrence of HF events • Time to recurrent events of HF events
New York Heart Association (NYHA) Class	Proportion of participants with NYHA Class change at Week 52
Exercise capacity	Change from baseline to Week 24 in 6MWD
Patient-reported symptoms and physical limitations	• Change from baseline to Week 24 in KCCQ-CSS • Proportion of participants attaining KCCQ-CSS meaningful within-patient change (MWPC) threshold at Week 52
Exploratory	

Atrial fibrillation	Proportion of participants with atrial fibrillation
Waist circumference	Change from baseline (centimeters)
Patient-reported health-related quality of life	Change from baseline in KCCQ: • Total Symptom Score (TSS) • Overall Summary Score (OSS)
Patient-reported health status	Change from baseline in EQ-5D-5L: o Index Score o VAS Score
Patient-reported global health status	Proportion of participants with improvements in global health status from baseline as assessed by the PGIS-Overall
Patient-reported global impression of physical function	Proportion of participants with improvements in physical function from baseline as assessed by the PGIS-Physical Function
Patient-reported global symptom severity	Proportion of participants with improvements in symptom severity from baseline as assessed by the PGIS-Symptom Severity
Evaluation of prespecified biomarkers	• NT-proBNP • cTnT
Waist to height ratio	Change from baseline to Week 52 in waist to height ratio
Kidney function	eGFR slope

Abbreviations: 6MWD = 6-minute walk distance; BMI = body mass index; CV = cardiovascular; hsCRP = high-sensitivity C-reactive protein; HF = heart failure; HFE(s) = heart failure event(s); HFpEF = heart failure with preserved ejection fraction; KCCQ-CSS = Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score; NYHA = New York Heart Association; QW = once weekly; SC = subcutaneous.

4. Study Design

4.1. Overall Design

Study GPID is a randomized, outpatient, multicenter, international, placebo-controlled, double-blinded, parallel-arm, Phase 3 study with 2 study periods. The study is designed to evaluate the efficacy and safety of SC QW tirzepatide, MTD up to 15 mg, compared to placebo, in participants with HFpEF and obesity.

Two intervention groups will be studied:

- Tirzepatide MTD up to 15 mg SC QW
- Placebo

The study will compare treatment with tirzepatide and treatment with placebo. Assignment to tirzepatide or placebo groups will be randomly allocated in a 1:1 ratio.

The starting dose of tirzepatide or placebo is 2.5 mg QW, which is to be escalated at 4-week intervals to a maximum of 15 mg QW or to the highest maintenance dose tolerated by the participant (see Section 6).

The study will consist of 2 periods:

- Study Period 1: screening period, lasting no more than 12 weeks.
- Study Period 2: treatment period, with a 20-week escalation followed by at least a 32-week maintenance period.

The study will continue until approximately 52 weeks after the last participant is randomized. The maximum duration of an individual's participation is estimated to be 120 weeks and will depend on duration of study enrollment.

Participant Visit Scheme

Study participants will undergo screening assessments and procedures, randomization, and double-blinded treatment with tirzepatide or placebo. Assessments and procedures to be conducted in each treatment period are described in the SoA (Section 1.3) and in Study Assessments and Procedures (Section 8).

Screening

Screening procedures will be performed at Visit 1. Visit 1 procedures may be conducted over more than 1 day as long as all activities are completed within the allowable visit tolerance for each visit. The duration of Visit 1 is anticipated to be <6 weeks but may be longer. Visit 1 should no more than 12 weeks from date of informed consent.

At Visit 1, two 6MWTs will be conducted. The investigator must ensure that the participant is recovered from completion of the first 6MWT prior to conducting the second 6MWT (at least 1 hour between each test). The screening 6MWTs may be conducted over more than 1 day.

Randomization

At Visit 2, prior to randomization, the participant needs to complete the 6MWT. Visit 2 may need to be conducted over 2 in-clinic visits (considered Visit 2a and Visit 2b) if a repeat 6MWT is necessary to assess participant eligibility. If the participant is required to return to repeat the 6MWT, the remaining procedures should be conducted at the second in-clinic visit for randomization (Visit 2b), more than 10 days from Visit 2a. See Section 10.10.1 for details on when a participant must return for a second Visit 2 6MWT.

Participants will be randomized and receive blinded study drug at the end of Visit 2 after all screening procedures are completed. The participant must not receive study drug until all eligibility criteria, including the 6MWT, are met.

Treatment

Starting from randomization, the participant receives study drug and procedures are conducted as described in the SoA (Section 1.3). Every effort should be made by the investigator to maintain participants on study drug.

Study drug dose will be escalated as illustrated in the study schema (Section 1.2). Dose escalation will continue until the participant reaches the maintenance dose of either 5 mg, 10 mg, or 15 mg. Participants who do not tolerate the first dose escalation (that is, from 2.5 mg to 5 mg [or placebo equivalent]) will need to discontinue from study drug.

Participants begin treatment with either tirzepatide or placebo starting at 2.5 mg given as a subcutaneous (SC) injection every week (QW). The dose level is increased by 2.5 mg increments approximately every 4 weeks for the first 20 weeks according to the participant's tolerability, reaching a MTD up to 15 mg. Once a MTD has been achieved, participants will continue at this MTD until study end, treatment discontinuation, or study discontinuation. Dose modifications will be permitted during the study under the circumstances specified in Section 6.6.

During the study treatment period, if an unscheduled visit or telephone visit is deemed necessary to support participant compliance, this is allowable at the discretion of the investigator site personnel. Optional telephone visits can be performed approximately 2 weeks after starting study drug and after each dose increase.

Participants will continue into the extended maintenance period with the same treatment assignment starting with Visit 13. Extended visits (EV) continue until criteria for study discontinuation is met or study ends (see Study Closeout and Final Visit below).

Study Closeout and Final Visit

The study will continue until approximately 52 weeks after the final participant is randomized The final study visit (Visit 99) for the study is based from the date of when the last patient for the trial was randomized.

Approximately 3 months prior to the anticipated end of study, the sponsor will notify sites of upcoming study closeout based on projected last patient visit date of the last patient randomized to the study. During the study closeout, a final visit (Visit 99) will be planned for each participant, with the exception of those who have died or prematurely discontinued from the study (Section 7.2). Any participant that has completed at least 52 weeks of study duration should be scheduled to complete the final visit (Visit 99) during this 3-month period prior to the

study final visit. No additional investigational product will be dispensed at this final visit. Study procedures for the final visit will be performed as outlined in the SoA (Section 1.3). Subjects completing 52 weeks of treatment during the last 3 months of the study will have a combined Visit 12 (52-week treatment visit) and Visit 99 (final visit) on the same day. During this combined visit, sites should only use the Visit 12 lab kit for blood draws and processing.

All unused study drug (unused single-dose pens) must be returned for compliance and final drug accountability. The sharp items container should also be returned to site or disposed of per local regulations.

Any participant who has discontinued the study prior to completing 52 weeks of study duration is expected to complete an early termination visit per the SoA.

4.2. Scientific Rationale for Study Design

Study GPID is a Phase 3 study designed to examine the efficacy and safety of SC QW tirzepatide MTD compared with placebo in participants with HFpEF and BMI ≥30 kg/m^2.

A placebo comparator was selected for this trial in accordance with regulatory guidance (FDA 2007; EMA 2016). Inclusion of a placebo comparator in Study GPID will allow for a direct assessment of the safety and efficacy of tirzepatide in participants with HFpEF and obesity.

Additionally, there is currently no approved therapy to be used as an active comparator in this population.

An endpoint assessment at 52 weeks of treatment is considered appropriate to assess the improvement of symptom and functional capacity. An extended maintenance treatment period increases the opportunity to evaluate HF events and outcomes.

The parallel-group design for treatment comparison was chosen to avoid any interaction between treatments that may interfere with the interpretation of the trial outcome. To minimize potential confounding effect of changes to concomitant medications, participants will be permitted to use the stable dose of concomitant medications that they require during the study. Medications that may interfere with the assessment of efficacy and safety characteristics of the study drug will not be allowed (see Section 6.5).

Assessment of HF events is relevant to HFpEF, which is characterized by a high frequency of recurrent HF hospitalizations. Moreover, hospitalization events reflect disease progression and high subsequent risk and predisposition, both of readmission and death (Solomon et al. 2007). Recent studies have shown that outpatient oral diuretic intensification in ambulatory care carries similar risk as an urgent HF visit and is independently associated with subsequent cardiovascular events, including death (Chatur et al. 2023; Ferreira et al. 2022; Madelaire et al. 2020).

Obesity is associated with important degrees of exercise intolerance and a markedly impaired quality of life and health status (Reddy et al. 2020). In patients with HFpEF, due to increased filling pressures, functional capacity is severely impaired, and patients can develop symptoms with light exercise. As a result, the ability to perform activities of daily living is deteriorated. Therefore, KCCQ is a meaningful endpoint to evaluate the clinical benefit of tirzepatide in patients with HFpEF and obesity.

Given the significant weight loss, and associated cardiometabolic improvements, achieved with tirzepatide, assessment of CV death and HF events, in addition to KCCQ-CSS as a primary endpoint, offers the unique opportunity to evaluate tirzepatide for the benefit of HFpEF patients with obesity.

4.2.1. Patient Input into Design

The sponsor involved patients in the design of this study by engaging patients in virtual collaborative events. The insights gained from these events were used to ensure that the study design is supportive of the well-being of the study participants and that the study procedures can be implemented effectively at the investigative sites.

4.3. Justification for Dose

Tirzepatide doses of up to 15 mg administered SC QW will be evaluated in this study.

Participants may be treated with lower maintenance doses of 5 mg or 10 mg if they do not achieve full dose escalation to 15 mg and/or do not tolerate 15 mg.

These doses and associated escalation schemes were selected based on assessment of safety, efficacy (glycemic and weight loss benefit), and GI tolerability data followed by exposure response modeling of data in participants with T2DM in Phase 1 and Phase 2 studies. Dosing algorithms starting at a low dose of 2.5 mg accompanied by dose escalation of 2.5 mg increments every 4 weeks should permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

The dose selection of tirzepatide is based on the findings of the Phase 2 study results. Tirzepatide doses of 5 mg, 10 mg, and 15 mg QW have been tested and compared with dulaglutide 1.5 mg QW or placebo in a Phase 2 study (Frias et al. 2018). While all 3 doses of tirzepatide significantly improved the glycemic control versus dulaglutide, the largest difference was observed in the 15-mg tirzepatide treatment group. Moreover, the reduction in body weight with tirzepatide was also dose-dependent and greatest in the 15 mg QW treatment group.

4.4. End of Study Definition

The end of study will occur approximately 52 weeks after the last participant has been randomized to the study globally. The study end will occur based on this definition and is not impacted by the status of the last randomized participant.

The criteria used to determine if a participant has completed the study will be described in the SAP.

5. Study Population

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. Participant must be at least 40 years of age inclusive, at the time of signing the ICF.

Type of Participant and Disease Characteristics

2. 6MWD ≤465 meters at both Visit 1 tests, between ≥100 meters and ≤425 meters at Visit 2 and change from the preceding qualifying 6MWD is <20% and <40 meters. See Section 10.10.1 for the flow diagram of the below qualifiers.
   - *If* Visit 2a 6MWD is both between 100 and 425 meters and…
     - <20% AND <40 meter change from the higher of the two 6MWDs conducted at Visit 1, *then* participant meets this inclusion criterion.
     - ≥20% OR ≥40 meter change from the higher of the two 6MWDs at Visit 1, *then* participant must attend Visit 2b. If at Visit 2b, the 6MWD is between 100 and 425 meters and <20% AND <40 meter change from preceding (Visit 2a) 6MWD, then participant meets this inclusion criterion.
3. Chronic HF (NYHA Class II-IV) diagnosed for at least 3 months before Visit 1.
4. LVEF ≥50% demonstrated by echocardiogram performed at Visit 1 or within 6 months of Visit 1.
5. At least 1 of the following to document evidence of HF:
   - Elevated NT-proBNP >200 pg/mL for participants without atrial AF or >600 pg/mL for participants with AF, as analyzed at the central laboratory at Visit 1

     OR
   - Evidence of structural heart disease:
     - LA enlargement (any of the following: LAV index ≥29 mL/m^2, or LAV >58 mL in male participants and >52 mL in female participants, or LA area >20 cm^2, or LA diameter >40 mm in male and >38 mm in female participants) determined by echocardiogram at Visit 1 or within 6 months of Visit 1

     OR
   - Evidence of elevated filling pressure:
     - At rest (PCWP ≥15 mmHg or LVEDP ≥15 mmHg) or with exercise (PCWP ≥25 mmHg) (based on historical record, not associated with hospitalization for decompensation of HF, within 2 years of Visit 1), or
     - E/e' ratio >15 (septal) or >13 (average of septal and lateral) determined by echocardiogram at Visit 1 or within 6 months of Visit 1

Note: Supporting medical documentation is required in all instances.

6. Either one of:
   - eGFR <70 mL/min/1.73 m^2 at Visit 1, OR
   - HF decompensation within 12 months of Visit 1, defined as hospitalization for HF requiring IV diuretic treatment or urgent HF visit requiring IV diuretic treatment
     Note: Supporting medical documentation is required in all instances.
7. Stable dose of all concomitant HF medications (these may include beta blockers, ACEis, ARBs, MRAs, ARNI, and/or SGLT2is), except for oral diuretics, for at least 4 weeks prior to Visit 1 and throughout the screening period.
8. If treated with oral diuretics, dose must be stable for at least 2 weeks prior to Visit 1 and throughout the screening period; volume control must be optimally achieved in the opinion of the investigator.
9. KCCQ-CSS ≤80 at Visit 1.

Weight

10. BMI ≥30.0 kg/m^2 at Visit 1.

Sex

11. At the time of signing the ICF:

a. **Male participants**: Male participants with partners of childbearing potential should be willing to use reliable contraceptive methods for the duration of the trial and for 4 months thereafter (see Appendix 4 [Section 10.4]).

b. Female participants:

- Female participants not of childbearing potential may participate and include those who are infertile due to surgical sterilization and/or postmenopausal. Please refer to Appendix 4 (Section 10.4) for definitions.
- Female participants of childbearing potential (not surgically sterilized and between menarche and 1-year postmenopausal) must:
  - test negative for pregnancy at Visit 1 based on a serum pregnancy test followed by a negative urine pregnancy test within 24 hours prior to exposure and agree to use 2 forms of effective contraception, if sexually active, where at least 1 form is highly effective, for the duration of the trial and for 2 months after the last injection, and
  - not be breastfeeding.

Contraceptive use by men or women of childbearing potential should be consistent with local regulations regarding the methods of contraception for those participating in clinical trials. See Appendix 4 (Section 10.4) for guidance.

Informed Consent

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

5.2. Exclusion Criteria

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

Medical Conditions

13. Myocardial infarction, coronary artery bypass graft surgery, or other major CV surgery/intervention, stroke or transient ischemic attack in past 90 days, or unstable angina pectoris in past 30 days, prior to Visit 1 or during screening; Have NYHA Class I heart failure at either Visit 1 or Visit 2.

14. Dominant contribution of noncardiac causes to exercise impairment or symptoms
    - Lung disease: pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension (CTEPH), or severe pulmonary disease including (COPD)
    - Other medical conditions: severe anemia (hemoglobin level <9 g/dL) at Visit 1, untreated thyroid disease or TSH >4.78 mU/L at Visit 1, or significant musculoskeletal disease
    - Orthopedic conditions that limit the ability to walk, such as severe arthritis in the leg, knee, hip injuries, hemiplegia, or amputation with artificial limb without stable prosthesis function for the past 3 months
    - Any condition that in the opinion of the investigator would interfere with the assessment of 6MWT

15. LVEF <40% by local echocardiography, MRI or other modalities documented any time within 2 years of Visit 1.
16. Acute decompensated HF (exacerbation of HF) requiring IV diuretics, IV inotropes, or IV vasodilators, or left ventricular assist device (LVAD) within 4 weeks prior to Visit 1, and/or during the screening period until randomization.
17. Impaired renal function, defined as eGFR <15 mL/min/1.73 m^2 (CKD-EPI) or requiring dialysis at Visit 1.
18. Any one of the following:
    - Systolic blood pressure (SBP) ≥180 mmHg at Visit 1
    - SBP >160 mmHg both at Visit 1 and at Visit 2
    - Have symptomatic hypotension or SBP <100 mmHg at Visit 1 or Visit 2
19. Resting heart rate (sinus rhythm) ≥100 bpm at either Visit 1 or Visit 2.
20. Atrial fibrillation or atrial flutter with a resting heart rate >110 bpm documented by ECG at either Visit 1 or Visit 2.
21. Cardiac amyloidosis or cardiomyopathy based on accumulation disease (for example, haemochromatosis, Fabry disease), muscular dystrophy, cardiomyopathy with reversible causes (for example, stress cardiomyopathy), hypertrophic cardiomyopathy, Chagas cardiomyopathy or known pericardial constriction, or any severe (obstructive or regurgitant) valvular heart disease likely to lead to surgery during the study period.
22. Completed prior surgical treatment for obesity or had liposuction or abdominoplasty within 1 year prior to Visit 1. Participants who plan to have surgical treatment for obesity or liposuction or abdominoplasty during the duration of the study are excluded.

23. Participation in a structured exercise training program in the 1 month prior to Visit 1 or planning to start a program during the study.
24. Have T1DM.
25. For participants with T2DM:
- Have uncontrolled diabetes requiring immediate therapy (such as diabetic ketoacidosis) at Visit 1 or Visit 2, in the judgement of the physician
- Have had 1 or more events of severe hypoglycemia and/or 1 or more events of hypoglycemia unawareness within 6 months prior to Visit 1 (see Section 10.5.1.1 for definition of hypoglycemia)
- Have HbA1c ≥9.5% (80 mmol/mol) at Visit 1, as analyzed at the central laboratory
- Have a history of proliferative diabetic retinopathy or diabetic maculopathy. Patients with severe nonproliferative diabetic retinopathy that requires acute treatment are also excluded.
- Treated with premix or prandial insulins or intensified insulin regimens (multiple daily injection with basal and prandial insulins or insulin pump therapy) at Visit 1.

26. History of acute or chronic pancreatitis or at high risk for acute pancreatitis (for example, serum triglyceride level >500 mg/dL [5.65 mmol/L]).
27. Have acute or chronic hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory during Visit 1:
- ALT or AST levels >2.5X the ULN for the reference range.

Note: Participants with nonalcoholic fatty liver disease are eligible to participate in this trial if their ALT level is ≤3.0X the ULN for the reference range.

28. Have a calcitonin level at Visit 1 of:
    - ≥20 ng/L, if eGFR is ≥60 mL/min/1.73 m^2
    - ≥35 ng/L, if eGFR is <60 mL/min/1.73 m^2
29. Have a family or personal history of medullary thyroid carcinoma (MTC) or Multiple Endocrine Neoplasia (MEN) Syndrome type 2.
30. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal- or squamous-cell skin cancer, in situ carcinoma of the cervix, or in situ prostate cancer) for less than 5 years.
31. Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.
32. Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility.

Prior/Concomitant Therapy

33. Treatment with any incretin, GLP-1 RA, or pramlintide in the 3 months prior to Visit 1.

34. Discontinuation of any incretin, GLP-1 RA, or pramlintide due to intolerability any time prior to Visit 1.
35. Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1 RA.
36. Implantable cardioverter defibrillator (ICD) implantation within 1 month prior to Visit 1 or planned implantation during the course of the study.
37. Currently implanted left ventricular assist device (LVAD).
38. Cardiac resynchronization therapy (CRT) implanted within 6 months prior to Visit 1 or planned implantation during the course of the trial.
39. Current use of medication associated with weight gain or weight loss, except when on stable dose for at least 3 months prior to Visit 1, and expected to be stable during the study period.

Prior/Concurrent Clinical Study Experience

40. Have participated within the last 6 months in a clinical study involving an investigational product.

Other Exclusions

41. 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.
42. Lilly employees.

5.3. Lifestyle Considerations

Study participants should be instructed not to donate blood or blood products during the study and for 8 weeks following the study.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study drug. 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, eligibility criteria, and any SAE.

Individuals who do not meet certain criteria for participation in this study (screen failure) may be rescreened once. Additionally, individuals who do not complete screening within 12 weeks from ICF date should be screen failed and may be rescreened. Rescreened participants should sign a new ICF and be assigned a new participant number. The interval between rescreenings should be at least 2 weeks. For participants who may have screen failed due to HbA1c criterion not met, the time to permit rescreening is at least 8 weeks. If, in the opinion of the investigator, an ineligible laboratory test result is the result of an error or extenuating circumstance, then that parameter can be retested once without the participant having to be rescreened. For rescreened participants, a repeat echocardiogram is not permitted.

Participants may be rescreened for the following reasons:

- Have become eligible to enroll in the study as the result of a protocol amendment
- Status has changed such that the eligibility criterion that caused the participant to screen fail would not cause the participant to screen fail again
- Completed screening and met all inclusion and exclusion requirements but are unable to be enrolled due to extenuating circumstances (such as severe weather, death in family, or child illness)

6. Study Intervention

Study drug is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol. For this study, 'study intervention' and 'study drug' are equivalent.

6.1. Study Interventions Administered

Intervention Name	Placebo	Tirzepatide (LY3298176)
Type	Drug (placebo)	Drug
Dose Formulation	Single-dose pen	Single-dose pen
Unit Dose Strengths	Not applicable	2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg
Dosage Levels	Not applicable	15 mg QW (or maximum tolerated dose of 5 mg QW or 10 mg QW)
Route of Administration	Subcutaneous	Subcutaneous
Use	Placebo	Experimental
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor and dispensed via IWRS	
Packaging and Labeling	Study drug will be provided in autoinjectors (single-dose pens), packaged in cartons to be dispensed. Clinical study materials will be labeled according to country regulatory requirements.	

Abbreviations: QW = weekly; IMP = investigational medicinal product; IWRS = interactive web-response system; NIMP = non-investigational medicinal product.

The following table shows the randomized study drugs for the entire study.

Treatment Group	Treatment Period Interval					
	Weeks 0 to 3	**Weeks 4 to 7**	**Weeks 8 to 11**	**Weeks 12 to 15**	**Weeks 16 to 19**	**Weeks 20 to End of Treatment Period**
Tirzepatide	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg or MTD
Placebo	→					

Abbreviation: MTD = maximum tolerated dose.

There are no restrictions on the time of day each weekly dose of study drug is given, but it is advisable to administer the SC injections on the same day and same time each week. The actual date, time, and injection site location of all dose administrations will be recorded in the diary by the participant. If a dose of study drug is missed, the participant should take it as soon as possible, unless it is within 72 hours of the next dose, in which case that dose should be skipped, and the next dose should be taken at the appropriate time. The day of weekly administration can be changed if necessary, as long as the last dose was administered 72 or more hours previously.

All participants will inject study drug subcutaneously in the abdomen or thigh using the injection supplies provided; a caregiver may also administer the injection in the participant's upper arm. The injection site location of all dose administrations will be recorded by the participant. A new autoinjector will be used for each injection. If study drug is to always be injected in the same body region, participants should be advised to rotate injection sites each week.

6.1.1. Medical Devices

The combination product provided for use in the study is a tirzepatide or matching placebo autoinjector.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only participants enrolled in the study may receive study drug. Only study personnel may supply study drug.
- All study drug must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug (includes study drug and autoinjector or single-dose pen) accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition of records).
- Study site staff must regularly assess whether the participant is correctly administering the assigned study drug and storing study drug according to the provided instructions.

Further guidance and information for the final disposition of unused study drugs are provided in the study training materials.

The investigator or designee is responsible for the following:

- Explaining the correct use of the study drug to the participant
- Verifying that instructions are followed properly
- Maintaining accurate records of study drug dispensing and collection as well as records of interruptions in study drug administration
- Instructing the participant to discard all used autoinjectors for study drug in a closeable, puncture-resistant container and dispose according to local regulations, and
- Considering dose adjustment of antihyperglycemic medications (see Section 6.5) at Visit 2 from first administration of study drug.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study.

Participants who meet all criteria for enrollment will be randomized to one of the study treatment groups at the end of Visit 2. Assignment to treatment groups will be determined by a computer-generated, random sequence using an IWRS. Participants will be randomized in a 1:1 ratio to receive tirzepatide or placebo. The randomization will be stratified by HF decompensation (hospitalization for HF requiring IV diuretic treatment or urgent HF visit requiring IV diuretic treatment) within 12 months of screening (Y/N), diagnosed T2DM (Y/N), and BMI ≥35 kg/m^2 (Y/N).

Before the study is initiated, the log in information and directions for the IWRS will be provided to each site.

Study drug will be dispensed at the study visits shown in the SoA.

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

The IWRS will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's drug assignment is warranted. Participant safety must always be the first consideration in making such a determination. If a participant's drug assignment is unblinded, the sponsor must be notified immediately after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF, as applicable.

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

6.4. Study Intervention Compliance

Participant compliance with study drug and adherence to study visits and procedures will be vitally important to meet the study objectives. This will be emphasized through comprehensive site training and consistently monitoring participant retention throughout the duration of the study.

Study drug compliance will be determined by the following:

- Study drug administration data will be recorded by the participants in the participant study diary and reviewed by the investigator at each study visit.
- The participants will be instructed to return any unused study drug and/or empty cartons at the next visit to the study site for the purpose of performing drug accountability.

Treatment compliance is defined as taking at least 75% of the required doses of study drug. 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 the study drug administration, other aspects of compliance with the study drug will be assessed at each visit based on the participant's adherence to the visit schedule, completion of study diaries, 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.

6.5. Concomitant Therapy

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:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency for concomitant therapy of special interest (drugs used for diabetes, diuretics, drugs used for obesity, and cardiovascular drugs)

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

Initial doses of tirzepatide delay gastric emptying and have the potential to transiently impact the rate of absorption of concomitantly administered oral medicinal products. Tirzepatide should be used with caution in participants receiving oral medicinal products that require rapid GI absorption following the initial doses of tirzepatide, as exposure to oral medications may be increased.

Prevention of Hypoglycemia

Similar to GLP-1 RAs, tirzepatide does not generally cause hypoglycemia, but it is recommended to decrease the dose of concomitant sulfonylurea or insulin to reduce the risk of hypoglycemic episodes in patients with T2DM. For participants with T2DM, specific, individually tailored adjustments of the respective antihyperglycemic medications should be considered during the entire study.

At Visit 2, with the initiation of study drug, the dose adjustments to the following concomitant glucose lowering medications are recommended.

Sulfonylureas: Sulfonylurea dose is recommended to be reduced at least 50% or discontinued, especially if the participant is receiving a low dose at randomization.

Insulins: For participants on basal insulin and with screening HbA1c ≤8.5%, the daily dose is recommended to be reduced by at least 20%.

During the dose escalation period, consider adjusting the total daily dose of insulin, if required for controlling worsening hyperglycemia and its acute complications.

During the maintenance period, further insulin dose reduction for the prevention of hypoglycemia is to be considered at the investigator's discretion.

Standard of Care for T2DM

The standard of care for diabetes may be adjusted at the discretion of the investigator as clinically indicated in accordance with local standard of care and professional society guidelines.

Participants will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study drug. Prohibited medications include all GLP-1 RAs and pramlintide. Discontinuation of dipeptidyl peptidase 4 inhibitors at randomization is recommended in line with guidelines. Similarly, the use of dipeptidyl peptidase 4 inhibitor therapies during the study is also discouraged (Davies et al. 2018).

Regarding the use of insulin, participants can be included if treated with basal insulin only; and are allowed to use prandial insulin if needed during the study to attain optimal glucose control.

Hyperglycemia Rescue

Other medications for glycemic control for participants with T2DM meeting severe, persistent hyperglycemia criteria for rescue may be added during the study at the investigator's discretion.

Rescue therapy with glucose-lowering agents, including basal and prandial insulins, may be medically indicated in situations after randomization due to severe, persistent hyperglycemia or early discontinuation of study drug.

Hyperglycemia rescue criteria will be determined from values recorded in T2DM participant diaries. If a diary value equal to or greater than the glycemic threshold for rescue (see definitions below) is recorded, that value should be confirmed by a repeat fasting glucose text within 48 hours (for example, local laboratory). Intensification of T2DM therapy should be initiated if confirmed fasting glucose values are:

- ≥15.0 mmol/L (270 mg/dL) from baseline to Week 6 over at least a 2-week period (at least 2 consecutive values) after randomization
- ≥13.3 mmol/L (240 mg/dL) from Week 6 to Week 12 over at least a 2-week period (at least 2 consecutive values)
- ≥11.1 mmol/L (200 mg/dL) from Week 12 to end of trial over at least a 2-week period (at least 2 consecutive values)

In addition, if HbA1c is >9.0% at Week 12 or >8.0% at Week 24 or later in the study, glucose-lowering therapy should be adjusted to improve glycemic control as outlined above. In the event a participant's HbA1c values are less than these thresholds but are higher than what the investigator feels comfortable leaving untreated, glucose-lowering medication can be adjusted. In addition, if participants develop symptoms of hyperglycemia (for example, polyuria and polydipsia), the investigator should implement measures to determine glycemic control and adjust as necessary. For participants newly diagnosed with T2DM during the trial, appropriate glucose-lowering therapy should be initiated per standard of care.

Standard of Care for Heart Failure

Anticipated treatment for heart failure should be decided prior to randomization.

Both American College of Cardiology/American Heart Association and European Society of Cardiology guidelines recommend symptom management with diuretic agents in patients with excess volume, as well as aggressive risk factor management for comorbidities for the treatment of HFpEF (van der Meer JACC 2019). Optimization of volume status and proactive adjustment of diuretic doses will help control symptoms and volume overload.

Participants should remain on stable doses of medications to treat heart failure condition and comorbidities such as hypertension. With the exception of diuretics, dose modification or alteration of such background therapies should be avoided unless all other measures fail to improve the participant's condition. However, if the participant's condition warrants a change in any of these medications, it will be allowed at the discretion of the investigator.

Management of Participants with Gastrointestinal Symptoms

In the Phase 2 program, the most commonly reported TEAEs for participants receiving tirzepatide were nausea, vomiting, and diarrhea. To mitigate GI symptoms and manage participants with intolerable GI AEs, the investigator should:

- Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4, or more smaller meals, and to stop eating when they feel full. Also, participants may be informed that lower-fat meals could be better tolerated.
- Prescribe symptomatic medication (for example, anti-emetic or antidiarrheal medication) per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
- Temporarily interrupt study drug. See Section 6.6.1. The data related to temporary interruption of study drug should be documented in source documents and entered on the eCRF.
- After the interruption, follow the guidance for restarting study drug (Section 6.6.2).

If intolerable GI symptoms or events persist despite the above measures, other dose modifications (see Section 6.6) may be considered.

6.6. Dose Modification

Interventions to optimize study drug tolerance and adherence may be employed throughout the study and include, but are not limited to, brief temporary interruptions and use of additional medications to manage symptoms.

Dose modifications, including temporary interruption and de-escalation may occur to manage issues with tolerability. It is preferred to attempt a temporary dose interruption (at any time) (Section 6.6.1) to manage tolerability issues. After a temporary dose interruption, participants may resume study drug at the same dose, re-escalate to the prior dose level (if re-escalation is desired or required), or resume at a lower MTD dose level, as tolerated. Guidance for resuming study drug after a temporary dose interruption should be followed (Section 6.6.2).

Unwarranted excessive weight reduction: **Dose interruption is preferred over de-escalation for slowing unwarranted excessive weight loss; however, the method used is at the investigator's discretion.** After the dose escalation period and at the investigator's discretion, when excessive weight reduction is not warranted due to safety concerns, the investigator may choose to adjust the study drug dose without first attempting a temporary dose interruption. The participant's study drug dose will be permanently reduced to 5 mg, in a blinded fashion for the remainder of the study and the dose cannot be re-escalated. A dose adjustment for unwarranted excessive weight reduction is completed through the IWRS. Participants on 5 mg will have blinded study drug temporarily interrupted (Section 6.6.1).

Dose reductions for unwarranted excessive weight loss may occur at scheduled and unscheduled visits.

6.6.1. Temporary Interruption

Temporary study drug interruption should be utilized to manage tolerability issues. After randomization, the investigator may interrupt study drug, for example, due to an AE (such as nausea vomiting, excessive unwarranted weight loss or a clinically significant laboratory value). Guidance for resuming study drug after a temporary dose interruption should be followed (Section 6.6.2). If study drug interruption is due to an AE, the event is to be followed and documented.

For cases where increased ALT, AST, or ALP occurs, study drug may be interrupted (Section 6.6.2), and close hepatic monitoring must be initiated (Section 8.2.5.1). The interruption of study drug is not equivalent to discontinuation from study treatment. Any interruption of study drug does not affect the study visit structure/schedule per the SoA (Section 1.3). Even if study drug is interrupted, study procedures should continue during the dose interruption. Every effort should be made by the investigator to maintain participants in the study and to restart study drug promptly after any interruption, as soon as it is safe to do so (see Section 6.6.2. for restarting study drug). Dose interruptions are managed through the IWRS. The data related to interruption of study drug will be documented in source documents and entered on the eCRF, however participant noncompliance should not be recorded as interruption of study drug on the eCRF.

Participants who have a temporary interruption of the study drug will continue participating in the trial according to the protocol to collect all planned efficacy and safety measurements (Section 1.3).

6.6.2. Restarting Study Drug after Interruption

In certain situations, the investigator may need to temporarily interrupt study drug. Every effort should be made by the investigator to maintain participants on study drug and to restart study drug after any temporary interruption, as soon as it is safe to do so. Distribution of study drug at the correct dose will be per IWRS instructions.

If study drug interruption is…	then…
1 or 2 consecutive doses	Participant restarts study drug at last administered dose, per escalation schedule. If the participant has reached maintenance dose level, the study drug dose level will restart at the same prior achieved maintenance dose level.
3 or more consecutive doses	Participant restarts study drug (at 5 mg, managed by IWRS) and repeats dose escalation scheme until maintenance dose is reached. If maintenance dose has previously been established, the dose escalation cannot not exceed the prior achieved maintenance dose level.
Due to an AE	The event is to be documented and followed according to the procedures in Section 8.3.
Due to intolerable persistent GI AE	Participants should be treated as suggested in Section 6.5.

Abbreviations: AE = adverse event; GI = gastrointestinal; IWRS = interactive web response service.

Investigators should inform the sponsor that study drug has been temporarily interrupted.

Participants are not required to re-escalate to the prior maintenance dose level if a tolerability issue recurs during dose re-escalation.

If this attempted dose re-escalation to the prior maintenance dose level is not tolerated, the dose should be reduced to the next lower 5 mg incremental dose that was tolerated (for example, 5 mg or 10 mg). The participant will remain at that dose level for the duration of the study. During re-escalation after a temporary dose interruption, participants should be followed every 4 weeks until either a new lower maintenance dose level or prior maintenance dose level is reached.

For participants receiving 5 mg maintenance dose, no dose de-escalation is permitted. Only dose interruption is permitted to manage tolerability issues (Section 6.6.2). This can be performed through IWRS.

In the event that a participant has a temporary interruption that requires extending the escalation beyond Visit 8, unscheduled visits are allowed in the IWRS to facilitate a 4-week dispensing schedule to complete the escalation.

If an unscheduled visit occurs in the same week or date of a regular scheduled visit per the SoA, the site should complete all procedures included for the regular scheduled visit. Unscheduled

visits either in the clinic or by telephone may be conducted to provide support and guidance to participants as needed.

6.7. Intervention after the End of the Study

Tirzepatide will not be made available to participants after conclusion of the study. Due to the double-blind study drug assignment, it is not known if a participant received active study drug or placebo. Participants will not be unblinded until study end and the final analyses are complete.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation from Study Drug

Before permanently discontinuing study drug, attempts to maintain the participant should be documented (see Dose Modification, Section 6.6 and Temporary Dose Interruption, Section 6.6.1). Contact the sponsor before study treatment discontinuation occurs to discuss potential options to maintain the participant on study drug until final study ends. It is the goal for participants to remain on study drug treatment until study ends.

Permanent discontinuation of study drug will not automatically lead to discontinuation from the study. If study drug is permanently discontinued, the participant will remain in the study and attend all scheduled visits to be evaluated for safety and efficacy as described in the SoA.

Possible reasons leading to permanent discontinuation of study drug:

- **Participant decision**
  - The participant or the participant's designee (for example, legal guardian) requests to discontinue study drug
- **Investigator Decision**
  - The investigator decides that the participant should be discontinued from study drug
- **Discontinuation due to a hepatic event or liver test abnormality**
  Please refer to Section 8.2.5.1 for liver chemistry stopping criteria and Section 8.2.5.4 for study drug interruption or discontinuation due to an hepatic event. Participants who experience a hepatic event or liver test abnormality should have additional hepatic safety data collected via CRF (see Section 8.2.5.1 for details). Resumption of the study drug can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited non-drug etiology is identified.

- In addition, participants will be permanently discontinued from the study drug in the following circumstances:
  - acute or chronic pancreatitis (see Section 10.5.1.2)
  - if a participant is diagnosed with thyroid C-cell hyperplasia, MEN-2, or MTC, or pancreatic cancer after randomization
  - if any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
  - if a participant is diagnosed with T1DM
  - if a female participant becomes pregnant
  - if an investigator, site personnel performing assessments, or participant is unblinded

- if the investigator, after consultation with the sponsor-designated medical resource, determines that a clinically significant systemic hypersensitivity reaction has occurred. A clinically significant systemic hypersensitivity reaction is one that occurs after administration of the study drug (for example, drug-related symptomatic bronchospasm, allergy-related edema/angioedema, or hypotension) and requires parenteral medication, does not respond to symptomatic medication, results in clinical sequelae, or is an anaphylactic reaction.
- if the participant undergoes any bariatric surgery during the study
- if the participant begins treatment with a GLP-1RA during the study,
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons.

7.2. Participant Discontinuation/Withdrawal from the Study

In order 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, irrespective of the following:

- compliance to study drug
- adherence to visit schedule
- missing assessments
- study drug discontinuation due to AE (Section 7)
- development of comorbidities, and
- development of clinical outcomes.

The circumstances listed above are ***not*** valid reasons for participant discontinuation from the study.

Participant will be discontinued from study in the following circumstances:

- enrollment in any other clinical study involving a study drug or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP, and
- if the participant becomes pregnant.

A participant may discontinue from the study:

- at any time at his/her own request
- at the request of his/her designee (for example, legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study, or

- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

Study discontinuation is expected to be rare and participants should be provided with options for alternative follow-up methods and/or end of study vital status/endpoint ascertainment.

If the participant is unwilling or unable to return for all scheduled follow-up visits in person, the site will attempt to collect as much follow-up information as possible via telephone or other virtual methods of direct patient contact with the patient. Sites are expected to conduct these alternative visit methods according to the visit interval outlined in the Schedule of Activities.

An ET visit should be conducted, as shown in the SoA. If the participant refuses to have an ET visit in the clinic, efforts should be made to collect data via telephone. See the SoA for data to be collected at the time of ET visit. 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, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Inadvertently Enrolled Participants

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should remain in the study and be discontinued from study drug when continued treatment would not be medically appropriate. If the investigator and the sponsor CRP agree it is medically appropriate to continue the study drug, the investigator must obtain documented approval from the sponsor Chief Medical Officer (CMO) to allow the inadvertently enrolled participant to continue study drug. Safety follow-up should be performed as outlined in Section 8.2 (Safety Assessments) and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow up

A participant will be considered high risk for lost to follow-up if he or she repeatedly fails to return for scheduled visits. 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. If a participant refuses all means of completing study visits, contact with the patient's family or the patient's primary physician or medical record review during the study and at the end of the study to ascertain vital status and record safety and efficacy endpoints is required.

The disposition of lost to follow-up will be documented in the eCRF at the time of study end. Site personnel should continue to enter missed visits into both IWRS and eCRF. A patient will be considered as lost to follow-up only if the patient is unable to be contacted by the study site during the study close-out period, and no data on vital status (alive or dead) is available through accepted methods for ascertainment, including query of public databases, contact with patient's

family or designee/personal contact (e.g., friend), family doctor, or attempt to determine vital status and endpoints via other means (if not prohibited by local laws) (e.g., national registries/databases, medical records, voter records, and third-party patient locator services).

If vital status is determined, this will be documented and the patient will not be considered lost to follow-up. If no final visit is available, and vital status is not determined during the study close-out period, this will be documented and the patient will be considered lost to follow-up.

Note: If the investigator site personnel are unable to contact the patient, they may give the patient's name and last known contact information to a patient locator service to try to find current information, if not prohibited by local laws and regulations. The patient locator service will **not** contact the patient directly and any new information they find will be shared with investigator site personnel.

Sponsor personnel will not be involved in any attempts to collect vital status information.

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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

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.

Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

Other visit methods (i.e. remote, telephone) may be considered at the discretion of the investigator if a participant is unable to come to their scheduled on-site visit. Alternative options to visit procedures must be considered with prior consultation and written approval of the sponsor.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

The primary efficacy endpoints are

- change from baseline to Week 52 in KCCQ-CSS.
- occurrence of the composite endpoint of CV death and/or HF events over time, and

Death and heart failure events will be recorded by the investigator at the time of event discovery. An independent CEC will adjudicate death (CV, non-CV, unknown cause) and HF events. The CEC charter will contain the final detailed event definitions for all adjudicated events.

8.1.1.1. Kansas City Cardiomyopathy Questionnaire

The KCCQ is a 23-item, participant self-administered questionnaire that assesses impacts of HF "over the past 2 weeks" on the following 7 domains (Green et al. 2000; Joseph et al. 2013):

- Physical Limitation (6 items)
- Symptom Stability (1 item)
- Symptom Frequency (4 items)
- Symptom Burden (3 items)
- Self-Efficacy (2 items)
- Quality of Life (3 items), and
- Social Limitation (4 items).

Each of the 23 individual items are answered on Likert scales of varying lengths (5-point, 6-point, or 7-point scales). Domain scores are obtained by averaging the associated individual

items and transforming the score to a 0 to 100 range. Higher scores indicate better health status. Summary scores are obtained by combining select domain scores:

- Total Symptom Score: mean of the Symptom Frequency and Symptom Burden scores
- Clinical Summary Score: mean of the Physical Limitation and Total Symptom scores, and
- Overall Summary Score: mean of the Physical Limitation, Total Symptom, Quality of Life, and Social Limitation scores.

The Clinical Summary Score will be used for the primary and key secondary endpoints.

KCCQ collections are required per the SoA at Visits 8 and 12 for all participants in the study regardless study drug status (on or off study drug).

If Visit 12 is missed or not performed within the SoA window of the Visit 12 KCCQ (52 ± 7 days from Visit 2), it is requested that the KCCQ be performed within 30 days of missed Visit 12 date. If a participant discontinues study before reaching Visit 12, a KCCQ must be conducted at the early termination visit.

The KCCQ and all other self-reported questionnaires will be translated into the native language of the region, linguistically validated, and administered according to the SoA (Section 1.3). At these visits, the questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff.

8.1.1.2. Definition of Heart Failure Events

The heart failure event definition within the protocol includes worsening symptoms or signs of HF, which are meaningful to the participant and require intensification of treatment characterized by one or more of the following: hospitalization for heart failure regardless of duration or treatment received; use of intravenous drug, usually an intravenous diuretic, but may include intravenous vasodilators or positive inotropic drugs; or augmentation or increase in oral diuretic therapy.

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Six-Minute Walk Test

Participants will perform an exercise capacity assessment using the 6MWT. Testing of the 6MWT should be performed as directed in the SoA (Section 1.3). The 6MWT is to be performed indoors on a straight, flat, hard surface that is at least 30 meters in length.

The 6MWTs at Visits 1 and 2 will be performed to assess participant eligibility. The Visit 1 tests will also serve as the training test to familiarize participants with the procedure. Additional details can be found in Section 10.10.1.

Prior to and at the end of each 6MWT, participants will be asked to rate their breathing discomfort and overall fatigue using the Borg Scale, separately, at each timepoint.

6MWT are required per the SoA at Visits 8 and 12 for all participants in the study regardless study drug status (on or off study drug).

If Visit 12 is missed or not performed within the SoA window of the Visit 12 6MWT (52 ± 7 days from Visit 2), it is requested that the 6MWT be performed within 30 days of missed Visit 12 date.

If a participant discontinues study before reaching Visit 12, a 6MWT must be conducted at the early termination visit.

8.1.2.2. Body Weight and hsCRP

Body weight will be assessed as described in Section 8.2.1. hsCRP will be assessed as described in Section 8.2.4.

8.1.3. Exploratory Efficacy Assessments

8.1.3.1. Patient Global Impression of Status

Three patient global impression items will be assessed and are described below.

8.1.3.1.1. Patient Global Impression of Status – Overall

Study participants will be asked to complete a Patient Global Impression of Status – Overall item specifically developed for this study. This is a participant-rated assessment of their overall health "in the past 2 weeks" and is rated on a 5-point scale ranging from "1-Excellent" to "5-Poor."

8.1.3.1.2. Patient Global Impression of Status – Physical Function

Study participants will be asked to complete a Patient Global Impression of Status – Physical Function item specifically developed for this study. This is a participant-rated assessment of the overall impact of HF symptoms on their ability to perform physical activities "in the past 2 weeks" and is rated on a 5-point scale ranging from "1- Not impacted" to "5- Extremely impacted, cannot perform physical activities."

8.1.3.1.3. Patient Global Impression of Status – Symptom Severity

Study participants will be asked to complete a Patient Global Impression of Status – Symptom Severity item specifically developed for this study. This is a participant-rated assessment of the overall severity of their HF symptoms "in the past 2 weeks" and is rated on a 5-point scale ranging from "1- No symptoms" to "5- Very severe."

8.1.3.2. EQ-5D-5L

Generic health-related quality of life will be assessed using the EQ-5D-5L (EuroQoL Research Foundation 2019). The EQ-5D-5L is a standardized 5-item instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L comprises 5 dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). The 5L version, introduced in 2005, scores each dimension at 5 levels (no problems, slight problems, moderate problems, severe problems, and unable to perform/extreme problems), for a total of 3125 possible health states. In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between less than 0 (where 0 is a health state equivalent to death; negative values are valued as worse than

dead) to 1 (perfect health). In addition, the EQ Visual Analog Scale records the respondent's self-rated health status on a vertical graduated (0 to 100) visual analog scale. In conjunction with the health state data, it provides a composite picture of the respondent's health status.

The EQ-5D-5L is used worldwide and is available in more than 170 languages. Details on the instrument, scoring, organizing, and presenting the data collected can be found in the EQ-5D-5L User Guide (EuroQoL Research Foundation 2019).

8.1.3.3. NYHA Classification

The NYHA classification will be assessed and recorded at the time points indicated in the SoA (Section 1.3) by an independent, blinded assessor. The NYHA classification is provided in Appendix 11 (Section 10.11).

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the CV, respiratory, GI and neurological systems, as well as a thyroid examination.
    - Body weight, waist circumference, and height should be measured. All weights for a given participant should be measured in a consistent manner using a calibrated scale (mechanical or digital scales are acceptable), using the same scale whenever possible, and after the participant has emptied their bladder. Participants should be lightly clothed but not wearing shoes while their weight is measured.
- Symptom-directed physical examinations will be conducted as described in the SoA.
    - Investigators should pay special attention to clinical signs and symptoms related to HF as well as related to previous serious illnesses. Particular interest would include dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, jugular venous distension, and rales.

The physical examination should be performed before the first 6MWT, if more than one 6MWTs are done.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3). An apical heart rate should be assessed during the collection of vital signs. The vital signs collection associated with the 6MWT should be separate and may be performed using automated equipment.

Any clinically significant findings from vital signs measurements that result in a diagnosis and that occur after the participant receives the first dose of study drug should be reported to the sponsor or its designee as an AE via the eCRF.

8.2.3. Electrocardiograms

Single 12-lead ECGs will be obtained locally as outlined in the SoA (see Section 1.3).

All ECGs should be recorded after the participant has been supine for 5 minutes in a quiet room.

The ECGs must be interpreted by a qualified physician (the investigator or 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, if needed. The investigator (or qualified designee) is responsible for determining if any change in participant management is needed, and must document his/her review of the ECG printed at the time of evaluation. If a clinically relevant abnormality is observed on the participant's ECG, then the investigator should assess the participant for symptoms (such as palpitations, near syncope, syncope, or chest pain). The investigator must report the presence of AF on the eCRF.

The original ECG must be retained at the investigative site.

The investigator or qualified designee's interpretation will prevail for immediate participant management purposes.

8.2.4. Clinical Safety Laboratory Assessments

With the exception of laboratory test results that may unblind the study, the sponsor or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, if a central vendor is used for the clinical trial.

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed. The SoA describes 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 that 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 levels or are no longer considered clinically significant by the investigator or medical monitor.

- If such values do not return to normal/baseline levels within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

All urine pregnancy tests will be performed locally according to the SoA. Guidance for contraception and definitions are defined in Appendix 4 (Section 10.4).

8.2.5. Safety Monitoring

The sponsor will periodically review evolving aggregate safety data within the study by appropriate methods. The study team will review safety reports in a blinded fashion according to the schedule provided in the Trial-Level Safety Review Plan. The sponsor will also review SAEs within time frames mandated by company procedures. The Sponsor CRP will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

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

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

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

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

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

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

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

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

[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.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study participants who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5X ULN on 2 or more consecutive blood tests (if baseline ALT <1.5X ULN)
    - In participants with baseline ALT ≥1.5X ULN, the threshold is ALT ≥3X baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2X ULN (if baseline TBL <1.5X ULN) (except for cases of known Gilbert's syndrome)
    - In participants with baseline TBL ≥1.5X ULN, the threshold should be TBL ≥2X baseline
3. Elevation of serum ALP to ≥2X ULN on 2 or more consecutive blood tests (if baseline ALP <1.5X ULN)

- In participants with baseline ALP ≥1.5X ULN, the threshold is ALP ≥2X baseline on 2 or more consecutive blood tests

4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the two consecutive blood tests should be at least 2 days.

8.2.5.2. Close Hepatic Monitoring

Close hepatic monitoring should include these actions:

- Laboratory tests (Appendix 8 [Section 10.8]), including ALT, AST, ALP, TBL, D. Bil, GGT, CK, and CBC with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2-3 times weekly until levels normalize or return to approximate baseline values.
- In addition to lab tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

8.2.5.3. Comprehensive Hepatic Evaluation

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study, for example, ultrasound or CT scan.
- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), 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 (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), 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.
- All the medical information and test results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety case report form (CRF).

8.2.5.4. Study Drug Interruption or Discontinuation due to a Hepatic Event

Interruption or discontinuation of study drug should include these actions:

- While the participant is not receiving the study drug, clinical and laboratory monitoring should continue at a frequency of 1 to 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 test results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety case report form (CRF).
- Resumption of the study drug after interruption for a hepatic reason can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results returned to near baseline and if a self-limited non-study-drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

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

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

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Product complaints (PCs)

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study drug or study procedures, or that caused the participant to discontinue the study drug 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/contacts. All SAEs 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 product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to study drug or procedure. United States 21 CFR 312.32, European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidance or national regulatory requirements in participating countries require the reporting of SUSARs. The sponsor has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidance.

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 the informed consent form (ICF)	Participation in study has ended	As soon as possible upon site awareness	AE eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study drug **and** deemed reasonably possibly related with study procedures	Signing of the informed consent form (ICF)	Start of study drug	Within 24 hours of awareness	SAE eCRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE* and SAE updates – after start of study drug	Start of study drug	Participation in study has ended	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE* – 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 drug	Four months after the last injection for female partners of male participants and 2 months after the last injection for female participants	Within 24 hours of learning of the pregnancy	Pregnancy paper form eCRF	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study drug	End of study drug	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study drug	End of study drug	Within 1 business day of awareness	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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	N/A

Abbreviations: eCRF = electronic case report form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

*Serious adverse events, including death, caused by disease progression as described in Section 8.3.2 should not be reported unless the investigator deems them to be possibly related to study drug.

8.3.2. Primary, Secondary, and Additional Study Endpoint Reporting

The following investigator-reported events are considered potential endpoints and must be reported first as an AE on the AE eCRF (with the appropriate designation for seriousness). They must then be reported as an endpoint on the eCRF with all required source documents provided for adjudication to the CEC. These potential endpoints (even if they meet criteria for a serious event) are not to be reported on the SAE eCRF unless considered as possibly related to study drug, the drug delivery system, or study procedure. Potential endpoints that are serious and considered as possibly related to study drug, the drug delivery system, or study procedure must also be reported as an SAE using the SAE eCRF:

- all-cause mortality (death), and
- HF events.

In the case where 1 of the above endpoint events is reported but does not meet a prespecified event definition detailed in the CEC charter, as reviewed by the independent CEC, no further action will be taken by the study site.

8.3.3. Adverse Events of Special Interest

The following are AESI and will be adjudicated by an external adjudication committee. This committee will be blinded to treatment assignment.

- pancreatitis
- major adverse CV events (see Section 10.5.1.5), and
- deaths

The following are additional AESI for this program that will not be adjudicated by an external committee:

- hepatobiliary disorders
- severe hypoglycemia
- thyroid malignancies and C-cell hyperplasia
- supraventricular arrhythmias and cardiac conduction disorders
- allergic/hypersensitivity reactions, including injection site reactions and ADA formation
- severe GI AEs, and
- acute renal events.

Sites should collect additional details and data regarding AESI, as instructed on the applicable eCRFs, and detailed in Section 10.5.

The details on the definition of AESI will be provided in SAP.

8.4. Treatment of Overdose

Considering the mechanism of action of tirzepatide, potential overdose effects can be GI disorders and hypoglycemia. In the event of overdose, appropriate supportive treatment should be initiated according to the participant's clinical signs and symptoms.
Study drug overdose (defined as injection of study drug more than 1 time within 72 hours) will be reported as an AE.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced, and
- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate.

8.5. Pharmacokinetics

Pharmacokinetic samples will be collected from all participants in this study.

Tirzepatide plasma concentrations will be determined from blood samples obtained from participants receiving tirzepatide treatment. Blood samples collected from participants assigned to the placebo arm will not be included in the bioanalysis of drug concentrations.

Blood samples for PK assessment will be collected prior to the dose administration and at the same time as the planned immunogenicity samples (that is, at Week 0 and then at Weeks 4, 12, 24, and 52 per the Study Schedule or additionally at follow-up and ET (reference SoA).

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

Concentrations of tirzepatide will be assayed using a validated liquid chromatography mass spectrometry method. Bioanalytical samples collected to measure tirzepatide concentrations will be retained for a maximum of 1 year following last participant visit for the study (Section 10.1.10). During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, and/or bioanalytical method cross-validation.

8.6. Pharmacodynamics

Pharmacodynamic parameters will not be evaluated in this study.

8.7. Genetics

A whole blood sample will be collected for pharmacogenetic analysis where local regulations allow.

See Appendix 2, Clinical Laboratory Tests (Section 10.2), and Section 1.3 (SoA) for sample collection information.

See Section 10.6 for genetic research, custody, and sample retention information.

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, pharmacodynamics, mechanism of action, variability of participant response (including safety), and clinical outcome. Sample collection is incorporated into clinical studies to enable examination of these questions through measurement of biomolecules including DNA, RNA, proteins, lipids, and other cellular elements.

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

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

Samples will be stored and analysis may be performed on biomarkers thought to play a role in disease processes, mechanism of action of tirzepatide, pathways associated with HFpEF, and/or research methods validating diagnostic tools or assay(s) related to HFpEF and associated diseases. Biomarkers may be evaluated to determine their association with observed clinical responses to tirzepatide and the disease state.

Samples will be retained at a facility selected by the sponsor or its designee for the duration detailed in Section 10.1.10, or for a shorter period if local regulations and ERBs impose shorter time limits. This retention period enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of tirzepatide or after tirzepatide becomes commercially available.

8.9. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against tirzepatide. Antibodies may be further characterized for cross-reactive binding to endogenous counterparts (native GIP and GLP-1) and their ability to neutralize the activity of tirzepatide and endogenous counterparts. To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of tirzepatide. All samples for immunogenicity should be taken predose when applicable and possible.

Samples will be retained for a maximum of 15 years after the last participant visit, or for a shorter period if local regulations and ERBs allow, at a facility selected by the sponsor. The duration allows the sponsor to respond to future regulatory requests related to tirzepatide. Any samples remaining after 15 years will be destroyed.

8.10. Medical Resource Utilization and Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

Two primary hypotheses will be tested in this study:

- Tirzepatide MTD is superior to placebo for the change from baseline to Week 52 in KCCQ-CSS.
- Tirzepatide MTD is superior to placebo for the occurrence of the composite endpoint of CV death and/or HF events over time.

Key secondary hypotheses (all under multiplicity control) are that tirzepatide MTD is superior to placebo with regards to

- change from baseline to Week 52 in 6MWD
- percent change from baseline to Week 52 in body weight, and
- change from baseline to Week 52 in hsCRP.

All primary and key secondary hypotheses will be tested with the overall family-wise type I error rate at a 2-sided alpha level of 0.05 through the multiplicity control approach based on the graphical multiple testing procedure. For the primary hypotheses, the HF outcome will be tested at a 2-sided alpha level of 0.04, and change in KCCQ-CSS will be tested at a 2-sided alpha level of 0.01 in parallel for statistical significance. If significant, the respective alpha of the primary endpoints will be propagated to test the key secondary endpoints. If any of the primary endpoints is not significant, then the appropriate alpha after the key secondary endpoints testing will be recycled to that primary endpoint. The detailed graphical testing scheme will be outlined in the SAP.

9.2. Sample Size Determination

A sample size of 700 participants (350 in each treatment group) will provide roughly 80% power for the change from baseline to Week 52 in KCCQ-CSS using Wilcoxon rank sum test under the assumptions that the change from baseline to Week 52 in KCCQ-CSS follows normal distribution with mean of 5 and standard deviation of 19 in placebo and mean of 10 and standard deviation of 19 in tirzepatide group at a 2-sided alpha of 0.01 significance level. The expected events at the end of the study will provide roughly 80% power to demonstrate the superiority of tirzepatide MTD to placebo in occurrence of the composite endpoint of CV death and/or HF events at a 2-sided alpha of 0.04 significance level under the treatment effect estimate assumption of 0.5. The study power is calculated using nQuery Version 9.1.

9.3. Populations for Analyses

The following populations are defined:

Analysis Population	Description
Entered	All participants who sign the informed consent form
Randomized/Intent-to-Treat (ITT) Population	All participants assigned to treatment, regardless of whether they take any doses of study treatment, or if they took the correct treatment. Participants will be analyzed according to the treatment group to which they were assigned.
Safety Population	All participants in ITT population who take at least 1 dose of study treatment. Participants will be analyzed according to the treatment group to which they were assigned.

9.4. Statistical Analyses

9.4.1. General Considerations

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

Unless specified otherwise, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05 and all confidence intervals will be given at a 2-sided 95% level. Efficacy will be assessed using ITT Population and safety will be assessed using the Safety Population.

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

The SAP will be completed prior to first unblinding and any subsequent amendments will be documented, with final amendments finalized prior to final database lock. The SAP will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints including primary and key secondary endpoints.

9.4.2. Primary Endpoint(s)

The primary estimand for primary endpoints is to assess the treatment difference between tirzepatide and placebo relative to the efficacy measures for all randomized participants, and treatment policy strategy will be used to handle all intercurrent events, which is, all the observed values for the variable of interest are used regardless of whether the intercurrent event occurs. The endpoint and population-level summary for the estimand is described in Section 9.4.2.1 and Section 9.4.2.2 for each primary endpoint.

9.4.2.1. Change from Baseline in KCCQ-CSS

For the primary endpoint of change from baseline to Week 52 in KCCQ-CSS, a stratified Wilcoxon (Van Elteren) test will be used as the primary analysis method, controlling for the stratification factors of HF decompensation within 12 months of screening (Y/N), diagnosed T2DM (Y/N), and baseline BMI ≥35 kg/m^2 (Y/N). Population-level summary of Hodges-Lehmann estimate for the median difference and corresponding confidence interval will be reported.

The last measurement prior to randomization KCCQ-CSS will be used as baseline. Missing KCCQ-CSS at Week 52 will be imputed through multiple imputations based on the reason of missingness with details described in the SAP. The statistical inference over multiple imputations will be guided by the method proposed by Rubin (1987).

9.4.2.2. Occurrence of CV Death and/or HF Event over time

The primary analysis model will include fixed factors of treatment and the stratification factors of HF decompensation within 12 months of screening (Y/N), diagnosed T2D (Y/N), and baseline BMI ≥35 kg/m^2 (Y/N). The analysis model with a full list of covariates will be specified in the SAP. The censoring date for a participant is the date of participant's end of follow-up. The missing data due to censoring will be implicitly handled by the model, assuming censoring is independent of the outcome. The treatment effect estimate, with its 95% CI and p-value, will be provided using the primary analysis model.

The estimated cumulative event curve over time will be provided. Counts and proportions of participants who experience a primary endpoint event will be calculated as well as counts of primary endpoint events. The total person-years of follow-up, the incidence rate per 100 person-years of follow-up, and the absolute risk difference will be provided.

9.4.3. Key Secondary Endpoint(s)

Analyses for the key secondary endpoints will also be guided by the treatment policy strategy.

Change from baseline in 6MWD at Week 52 will be analyzed using the same nonparametric approach as described in Section 9.4.2.1.

Percent change from baseline in body weight will be analyzed using an analysis of covariance (ANCOVA) analysis. The ANCOVA model will include the categorical effect of treatment, stratification factors, and the continuous covariate of baseline body weight value. Missing data will be imputed through multiple imputations based on the reason of missingness with details described in the SAP.

Change from baseline in hsCRP will be analyzed using an ANCOVA model. The ANCOVA model will include the categorical effect of treatment, stratification factors, and the continuous covariate of baseline hsCRP value. The ANCOVA model will be based on the log-transformed values of hsCRP. Missing data will be imputed through multiple imputations based on the reason of missingness with details described in the SAP.

9.4.4. Tertiary/Exploratory Endpoint(s)

The analyses for exploratory endpoints will be described in the SAP. Statistical tests will be performed at the two-sided significance level of 0.05. There will be no multiplicity adjustment for any analysis of exploratory variables unless specified otherwise. Missing values will not be explicitly imputed unless specified otherwise.

9.4.5. Other Safety Analyses

Safety will be assessed by summarizing and analyzing AEs, special safety topics, laboratory analytes, and vital signs. All safety analyses will be made on the Safety Population. Unless specified otherwise, all data obtained during study period from Safety Population, regardless of adherence to study drug, will be used for safety analyses. The details for safety analysis will be described in the SAP.

Adverse events will be coded from the actual term using MedDRA and reported with preferred terms and system organ class.

9.4.5.1. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADAs and with treatment-emergent ADAs to tirzepatide will be tabulated. Treatment-emergent ADAs are defined as those with a titer 2-fold (1 dilution) greater than the minimum required dilution of the ADA assay if no ADAs were detected at baseline (treatment-induced ADA), or those with a 4-fold (2 dilutions) increase in titer compared with baseline if ADAs were detected at baseline (treatment-boosted ADA). The details of analyses for immunogenicity will be specified in SAP.

9.4.6. Subgroup Analyses

Subgroup variables to be evaluated for the primary efficacy endpoint may include demography (for example, race, ethnicity), baseline disease characteristics (for example, diagnosed T2DM) and others. Subgroup analyses may also be performed for selected secondary efficacy endpoints. Details for the subgroup analyses will be provided in the SAP.

9.5. Interim Analyses

Based on the projected enrollment, approximately 4 interim analyses of safety will be conducted. The first interim analysis is planned to occur when approximately 20% of the anticipated number of participants are randomized or 6 months after the first participant is randomized, whichever occurs later, followed by subsequent reviews approximately every 6 months throughout the study.

The DMC is authorized to evaluate unblinded interim analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

Unblinding details are specified in a separate unblinding plan document.

The DMC charter will describe the planned interim analyses in detail.

9.6. Data Monitoring Committee

An independent DMC with members all external to the sponsor will be used to monitor participant safety in an unblinded fashion. For details on the DMC, refer to the DMC charter.

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 CIOMS International Ethical Guidelines
    - Applicable ICH GCP guidelines
    - International Organization for Standardization (ISO) 14155
    - 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 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- 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 his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA 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.

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

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

Participants who are rescreened are required to sign a new ICF.

10.1.4. Data Protection

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

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

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

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

10.1.5. Dissemination of Clinical Study Data

Report Preparation

An investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Public Access to Reports and 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.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK, immunogenicity, or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once they 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.clinicalstudydatarequest.com.

Publications/Publication Policy

The publication policy is described in Section 10.1.9.

10.1.6. Data Quality Assurance

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

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

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

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).

Study monitors will perform ongoing source data verification 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, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

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

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.

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

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

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

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

Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

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

The first act of recruitment is the first site open and will be the study start date.

The sponsor 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:

- 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 of participants by the investigator
- Discontinuation of further study drug development.

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 assures appropriate participant therapy and/or follow-up.

10.1.9. 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.

10.1.10. Long-Term Sample Retention

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

This table describes the retention period for potential sample types.

Sample Type	Custodian	Retention Period After Last Participant Visit
Genetics sample	Sponsor or designee	up to 15 years
Exploratory biomarker sample	Sponsor or designee	up to 15 years
Immunogenicity (antidrug antibody) sample	Sponsor or designee	up to 15 years
Pharmacokinetic sample	Sponsor or designee	up to 1 years

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

10.2. Appendix 2: Clinical Laboratory Tests

- Clinical laboratory testing will be performed according to the SoA (Section 1.3).
- Central and local laboratories will be used. The table below describes when the local or central laboratory will be used
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Pregnancy testing will be performed according to the SoA.
- Investigators must document their review of the laboratory safety results. Laboratory results that will not be reported to investigative sites or other blinded personnel are noted in the table below.

Refer to Section 10.7 for recommended laboratory testing for hypersensitivity events.

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory.
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs [red blood cells])	
Mean cell volume	
Mean cell hemoglobin concentration	
Leukocytes (WBCs [white blood cells])	
Differential	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Clinical Chemistry	Assayed by Lilly-designated laboratory.
Sodium	
Potassium	
Chloride	
Bicarbonate	

Clinical Laboratory Tests	Comments
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Lipids	
Total cholesterol	
Direct LDL-C	
HDL-C	
VLDL-C	
Triglycerides	
Pancreas (Exocrine)	Assayed by Lilly-designated laboratory.
Pancreatic amylase	
Lipase	
Special Chemistry	Assayed by Lilly-designated laboratory.
Hemoglobin A1c (HbA1c)	
Calcitonin	
Cystatin C	
N-terminal pro b-type natriuretic peptide (NT-proBNP)	
Cardiac troponin T (cTnT)	
C-reactive protein, high-sensitivity (hsCRP)	
Thyroid stimulating hormone	
Urine Chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculation	
eGFR (calculated by CKD-EPI equation)	Will be calculated by the Lilly-designated laboratory at all visits.
Urine albumin, creatinine, UACR	
Hormones (female)	
Urine Pregnancy	Local laboratory
Serum Pregnancy	Assayed by Lilly-designated laboratory.

Clinical Laboratory Tests	Comments
Follicle Stimulating Hormone (FSH)	Assayed by Lilly-designated laboratory.
Pharmacokinetic Samples	• Assayed by Lilly-designated laboratory. • Results will not be provided to the investigative sites. • In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, PK, and exploratory biomarker samples. PK samples for immunogenicity must be taken prior to drug administration.
Genetics sample Whole blood (EDTA)	• Assayed by Lilly-designated laboratory. • Results will not be provided to the investigative sites.
Exploratory Biomarker Samples	• Assayed by Lilly-designated laboratory. • Results will not be provided to the investigative sites.
Serum	
EDTA Plasma	
P800 Plasma	
Immunogenicity Samples	
Anti-tirzepatide antibodies Anti-tirzepatide neutralizing antibodies	• Assayed by Lilly-designated laboratory. • Results will not be provided to the investigative sites. • In the event of systemic drug hypersensitivity reactions (immediate or nonimmediate), additional blood samples will be collected including ADA, PK, and exploratory biomarker samples. PK samples for immunogenicity must be taken prior to drug administration.

Abbreviations: ADA = antidrug antibody; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lilly = Eli Lilly and company; PK = pharmacokinetic; UACR = urine albumin/creatinine ratio; VLDL-C = very low-density lipoprotein cholesterol.

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

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

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

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

10.3.1. Definition of AE

AE Definition
• 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 drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. • An AE is any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory finding) in study participants, users, or other persons, whether or not related to the investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved except for events in users or other persons, which only include events related to investigational devices.
Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, 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 conditions detected or diagnosed after study drug administration even though they may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such an overdose should be reported regardless of 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 an 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 which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/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

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. 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.
c. Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the participant has been admitted to the hospital 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.

d. 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.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised 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.

g. Resulted in medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

Definition of Serious Adverse Device Effect (SADE)

An SADE is defined as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

Definition of Unanticipated Adverse Device Effect (UADE)

An UADE is a serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application) or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of the participant.

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study drug. When the ability to use the study drug safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study drugs used in clinical trials are collected in order 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 product complaint or problem with the study drug so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

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

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

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

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

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

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

Assessment of Intensity

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

- Mild: A type of adverse event 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 adverse event 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 adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study drug and each occurrence of each AE/SAE.
- 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.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study drug administration will be considered and investigated.
- The investigator will also consult the IB in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

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

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 paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline 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 paper SAE form (see next section) or to the sponsor by telephone. • Contacts for SAE reporting can be found in the study training.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting
• Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study drug 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 drug under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators. • An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements. • As required by local regulations, the investigator will report to their IRB/IEC any UADE (unanticipated problem that resulted in an SAE), or any product complaint that could have led to an SAE had precautions not been taken.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Male participants:

Men, regardless of their fertility status, with nonpregnant WOCBP partners must agree to either remain abstinent (if this is their preferred and usual lifestyle) or use condoms, as well as 1 additional highly effective (<1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) or effective method of contraception (such as diaphragms with spermicide or cervical sponges) for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days plus 5 half-lives following the last dose of study drug, which is approximately 4 months after the last injection.

a) Men and their partners may choose to use a double-barrier method of contraception. (Barrier protection methods without concomitant use of a spermicide are not an effective or acceptable method of contraception. Thus, each barrier method must include use of a spermicide. It should be noted, however, that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these barrier methods are combined.)

b) Periodic abstinence (for example, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Men with pregnant partners should use condoms during intercourse for the duration of the study and until the end of the estimated, relevant potential exposure in WOCBP (4 months).

Men should refrain from sperm donation for the duration of the study and until their plasma concentrations are below the level that could result in a relevant potential exposure to a possible fetus, predicted to be 90 days plus 5 half-lives following the last dose of study drug, which is approximately 4 months.

Men who are in exclusively same-sex relationships (as their preferred and usual lifestyle) are not required to use contraception.

10.4.2. Female participants:

Women of childbearing potential who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, or postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Otherwise, WOCBP participating must agree to use 2 forms of effective contraception, where at least 1 form is highly effective (<than 1% failure rate), for the entirety of the study. Contraception must continue following completion of study drug administration for the entirety of the study and for 4 weeks after the last injection.

a) WOCBP participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure.

b) Two forms of effective contraception, where at least 1 form is highly effective (such as combination oral contraceptives, implanted contraceptives, or intrauterine devices) will be used for the duration of the trial and for 2 months after the last injection. Effective contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) may be used as the second therapy. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide (that is, condom with spermicide, diaphragm with spermicide, or female condom with spermicide). It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

c) Not be breastfeeding.

Women not of childbearing potential may participate and include those who are:

a) Infertile due to surgical sterilization, or

b) Postmenopausal.

Definitions:

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female is defined as follows:
    a. A woman at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note
    b. A woman at least 40 years of age and up to 55 years old with an intact uterus, not on hormone therapy*, 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

c. A woman 55 or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or
d. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

* Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators (SERMs), or chemotherapy that could induce transient amenorrhea.

Contraception Guidance:

Highly Effective Methods of Contraception:

- Combined oral contraceptive pill and mini pill
- NuvaRing®
- Implantable contraceptives
- Injectable contraceptives (such as Depo-Provera®)
- Intrauterine device (such as Mirena® and ParaGard®)
- Contraceptive patch – ONLY women <198 pounds or 90 kg
- Total abstinence (if this is their preferred and usual lifestyle) or in a same-sex relationship with no sexual relationship with males (as part of their preferred and usual lifestyle).

Note: periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

Note: Implantable contraceptives and injectable contraceptives (such as Depo-Provera) are only permitted if started prior to screening. Participants should not start these methods of contraception after being enrolled in the study.

- Vasectomy - for men in clinical trials

Effective Methods of Contraception (must use combination of 2 methods):

- Male condom with spermicide
- Female condom with spermicide
- Diaphragm with spermicide
- Cervical sponge
- Cervical cap with spermicide

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.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and

submit it to the sponsor within 24 hours of learning of the partner's pregnancy. 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 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 fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy, pregnancy-related SAE considered reasonably related to the study drug by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study drug and be withdrawn from the study.

10.5. Appendix 5: Adverse Events of Special Interest: Definitions and Procedures for Recording, Evaluating, Follow-Up, and Reporting.

10.5.1. Special Safety Topics

10.5.1.1. Hypoglycemia

Upon ICF signing, all participants will be educated about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to collect appropriate information for each episode of hypoglycemia.

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

All participants with T2DM and who develop diabetes during the study will be provided with glucometers.

Participants with T2DM will be provided a diary to record relevant information (for example, glucose values, symptoms).

All hypoglycemic episodes are to be recorded on a specific eCRF and should not be otherwise recorded as AEs unless the event meets severe criteria. If a hypoglycemic event meets severe criteria (see definition below), it should be recorded as serious on the AE eCRFs, 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 to be a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

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

Glucose Alert Value (Level 1):

- Documented symptomatic hypoglycemia is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <70 mg/dL (<3.9 mmol/L).
- Documented asymptomatic hypoglycemia is defined as any event not accompanied by typical symptoms of hypoglycemia, but with a measured BG <70 mg/dL (<3.9 mmol/L).
- Documented unspecified hypoglycemia is defined as any event with no information about symptoms of hypoglycemia available, but with a measured BG <70 mg/dL (<3.9 mmol/L).

Clinically Significant Hypoglycemia (Level 2):

- Documented symptomatic hypoglycemia is defined as any time a participant feels that he or she is experiencing symptoms and/or signs associated with hypoglycemia and has a BG level of <54 mg/dL (<3.0 mmol/L).

- Documented asymptomatic hypoglycemia is defined as any event not accompanied by typical symptoms of hypoglycemia but with a measured BG <54 mg/dL (<3.0 mmol/L).
- Documented unspecified hypoglycemia is defined as any event with no information about symptoms of hypoglycemia available but with a measured BG <54 mg/dL (<3.0 mmol/L).

Severe Hypoglycemia (Level 3):

- Severe hypoglycemia is defined as an episode with severe cognitive impairment requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG to normal is considered sufficient evidence that the event was induced by a low BG concentration.

Nocturnal Hypoglycemia:

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

10.5.1.2. Pancreatitis

Acute pancreatitis is defined as an AE of interest in all trials with tirzepatide, including this trial.

Acute pancreatitis is an acute inflammatory process of the pancreas that may also involve peripancreatic tissues and/or remote organ systems (Banks and Freeman 2006). The diagnosis of acute pancreatitis requires 2 of the following 3 features:

- abdominal pain, characteristic of acute pancreatitis (generally located in the epigastrium and radiates to the back in approximately half the cases) (Banks and Freeman 2006; Koizumi et al. 2006); the pain is often associated with nausea and vomiting
- serum amylase (total and/or pancreatic) and/or lipase ≥3X ULN, and
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, appropriate laboratory tests (including levels of pancreatic amylase and lipase) should be obtained via the central laboratory (and locally, if needed).

Imaging studies, such as abdominal CT scan with or without contrast, MRI, or gallbladder ultrasound, should be performed. Abdominal ultrasound may be used as an alternative method only if CT and MRI cannot be performed. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the participant must discontinue therapy with tirzepatide but will continue in the study. A review of the participant's concomitant medications should be conducted to assess any potential causal relationship with pancreatitis.

Each AE of pancreatitis must be reported. If typical signs and/or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study drug(s).

Each participant will have measurements of p-amylase and lipase (assessed at the central laboratory) as shown on the SoA (Section 1.3) to assess the effects of the investigational doses of tirzepatide on pancreatic enzyme levels. Serial measurements 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). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (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. Only cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up and/or are accompanied by symptoms suggestive of pancreatitis will be submitted for adjudication.

All suspected cases of acute or chronic pancreatitis will be adjudicated by an independent clinical endpoint committee. In addition, AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease. Relevant data from participants with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

10.5.1.3. Thyroid Malignancies and C-Cell Hyperplasia

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

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

10.5.1.4. Calcitonin Measurements

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

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

Calcitonin Measurements in Participants with eGFR ≥60 mL/min/1.73 m^2

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

- calcitonin value ≥20 ng/L and <35 ng/L AND ≥50% increase from the screening value.
    - These participants will be asked to repeat the measurement within 1 month. If this repeat value is increasing (≥10% increase), study drug should be stopped, and the

participant encouraged to undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude any serious adverse effect on the thyroid.

- calcitonin value ≥35 ng/L AND ≥50% over the screening value.
    - In these participants, study drug should be stopped, and the participant recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist.

Calcitonin Measurement in Participants with eGFR <60 mL/min/1.73 m^2

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

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

10.5.1.5. Major Adverse Cardiovascular Events

Deaths and nonfatal CV AEs will be adjudicated by a committee of physicians external to the sponsor 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
- coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

10.5.1.6. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Participants who develop any event from these groups of disorders should undergo an ECG, which will be retained at the site as a source document. 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. If a clinically significant finding is identified by ECG (including, but not limited to, AF or changes from baseline in corrected QT interval), the investigator or qualified designee will determine if any change in study participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

10.5.1.7. Hypersensitivity Events

All allergic or hypersensitivity reactions will be reported by the investigator as either AEs, or if any serious criterion is met, as SAEs.

In the event of suspected drug hypersensitivity reactions (immediate or nonimmediate) in subjects who experience moderate-to-severe reactions as assessed by the investigator, unscheduled blood samples will be collected as outlined in Appendix 7 (Section 10.7).

Additional data, such as type of reaction and treatment received, will be collected on any AEs or SAEs that the investigator deems related to study drug via the eCRF created for this purpose.

Study drug should be temporarily interrupted in any individual suspected of having a severe or serious allergic reaction to study drug. Study drug may be restarted when/if it is safe to do so, in the opinion of the investigator.

10.5.1.8. Injection Site Reactions

Injection site reactions will be collected on the eCRF separate from the hypersensitivity reaction eCRF. At the time of AE occurrence, samples will be collected for measurement of tirzepatide ADA and tirzepatide concentration.

10.5.1.9. Antidrug Antibodies

The occurrence of ADA formation will be assessed as outlined in Section 8.9.

10.5.1.10. Hepatobiliary Disorders

All events of treatment-emergent biliary colic, cholecystitis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Appendix 8 (Section 10.8).

10.5.1.11. Severe Gastrointestinal Adverse Events

Tirzepatide may cause severe GI AEs such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form. For detailed information concerning the management of GI AEs, please refer to Section 6.5.

10.5.1.12. Acute Renal Events

Renal safety will be assessed based on repeated renal function assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. Gastrointestinal AEs have been reported with tirzepatide, including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 RAs (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.

10.6. Appendix 6: Genetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to study drug, susceptibility to, severity, and progression of disease. Variable response to study drug may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to tirzepatide or HF and related diseases. They may also be used to develop tests/assays including diagnostic tests related to tirzepatide or HF. Genetic research may consist of the analysis of one or more candidate genes, the analysis of genetic markers throughout the genome, or analysis of the entire genome (as appropriate).
- DNA sample analysis may be performed on pharmacogenetic variants thought to play a role in T2DM or CV disease to evaluate their association with observed clinical outcomes to tirzepatide in this study. In the event the observation of a study drug response, the samples may be genotyped, and analysis may be performed to evaluate a genetic association with response to tirzepatide. These investigations may be limited to a focused, candidate-gene study or, if appropriate, genome-wide association studies may be performed to identify regions of the genome associated with the variability observed in drug response. Samples may be used for investigations related to the disease, drug, or class of drugs under study in the context of this clinical program; however, samples may not be used for broad, exploratory, unspecified disease or population genetic analysis. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to tirzepatide or study drugs of this class to understand the study disease or related conditions.
- The results of genetic analyses may be reported in the CSR or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- The samples will be retained while research on tirzepatide continues but no longer than 15 years or another period as per local requirements (see Section 10.1.10).

10.7. Appendix 7: Recommended Laboratory Testing for Hypersensitivity Events

Laboratory testing should be performed at the time of a systemic hypersensitivity event. The management of the AE may warrant lab testing beyond that described below and should be performed as clinically indicated. Laboratory assessments should be performed if the participant experiences generalized urticaria or if anaphylaxis is suspected.

- Collect the sample after the participant has been stabilized and within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after approximately 4 weeks, whichever is later.

Clinical Laboratory Tests for Hypersensitivity Events

Hypersensitivity Tests	**Notes** Selected test may be obtained in the event of anaphylaxis or systemic allergic/hypersensitivity reactions.
Tirzepatide antidrug antibodies (immunogenicity/ADA)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tirzepatide concentrations (PK)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Tryptase	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. Urine N-methylhistamine testing is performed in addition to tryptase testing. Collect the first void urine sample following the event. Collect a follow-up urine sample after approximately 4 weeks. **Note:** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2-12 hours), or is not obtained because more than 12 hours have lapsed since the event, collect a urine sample for N-methylhistamine testing.
N-methylhistamine	Will be performed if validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Drug-specific IgE	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Basophil activation test	Will be performed if a validated assay is available. Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites. **NOTE:** The basophil activation test is an in vitro, cell-based assay that only requires a serum sample. It is a surrogate assay for drug specific-IgE but is not specific for IgE.
Complement (C3, C3a and C5a)	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Cytokine panel: IL-6, IL-1β, IL-10	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.

Abbreviations: ADA = antidrug antibody; IgE = immunoglobulin E; IL = interleukin; PK = pharmacokinetic.

10.8. Appendix 8: Liver Safety: Suggested Actions and Follow-Up Assessments

Hepatic Evaluation Testing

See Section 8.2.5.1 for guidance on appropriate test selection.

The Lilly-designated central laboratory must complete the analysis of all selected testing except for microbiology testing.

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

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (red blood cells [RBCs])	Alkaline phosphatase (ALP)
Leukocytes (white blood cells [WBCs])	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen protein adducts
Platelets	Alkaline phosphatase isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl alcohol (EtOH)
Prothrombin time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (quantitative)
Hepatitis A virus (HAV) testing:	Immunoglobulin IgG (quantitative)
HAV total antibody	Immunoglobulin IgM (quantitative)
HAV IgM antibody	Phosphatidylethanol (PEth)
Hepatis B virus (HBV) testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug screen
Hepatitis B surface antibody (anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Antinuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA)[a]

HBV DNA[b]	Anti-actin antibody[c]
Hepatis C virus (HCV) testing:	Epstein-Barr virus (EBV) testing:
HCV antibody	EBV antibody
HCV RNA[b]	EBV DNA[b]
Hepatitis D virus (HDV) testing:	Cytomegalovirus (CMV) testing:
HDV antibody	CMV antibody
Hepatitis E virus (HEV) testing:	CMV DNA[b]
HEV IgG antibody	Herpes simplex virus (HSV) testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA[b]	HSV (Type 1 and 2) DNA[b]
Microbiology[d]	Liver kidney microsomal type 1 (LKM-1) antibody
Culture:	
Blood	
Urine	

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio; PT = prothrombin time.

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

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

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

[d] Assayed ONLY by investigator-designated local laboratory; no central testing available.

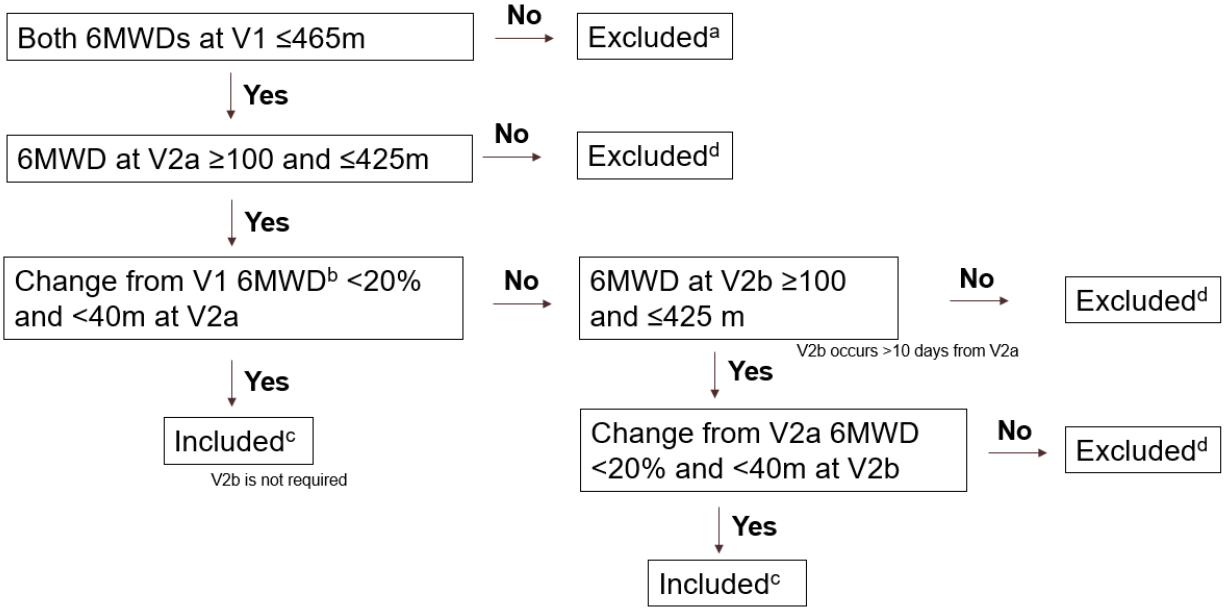
10.9. Appendix 9: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-Up, and Reporting

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

10.10. Appendix 10: Six-Minute Walk Test Screening Procedures

10.10.1. Screening Procedures and Flow Diagram

The flow diagram below details the participant flow and eligibility with the 6MWT.



Abbreviations: 6MWD = 6-minute walk test distance; 6MWT = 6-minute walk test; V1 = Visit 1; V2a = Visit 2a; V2b = Visit 2b.

[a] Rescreening is not allowed

[b] Use the higher value of the two Visit 1 6MWD as a reference for Visit 2a.

[c] Continue with other Visit 2 assessments according to the SoA.

[d] Participants excluded on 6MWT may be re-screened after a minimum of 2 weeks.

10.11. Appendix 11: New York Heart Association Classification of Heart Failure

Class	Symptomatology
I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
III	Symptoms with less than ordinary physical activity. Walking 1-2 blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

10.12. Appendix 12: Abbreviations

Term	Definition
6MWD	6-minute walk test distance
6MWT	6-minute walk test
ADA	antidrug antibody
AE	adverse event
AESI	adverse events of special interest
AF	atrial fibrillation
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his 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/his 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.
BG	blood glucose
BMI	body mass index
CEC	clinical endpoint committee
CFR	Code of Federal Regulations
CIOMS	Council for International Organizations of Medical Sciences
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
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.

Term	Definition
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
D Bil	direct bilirubin
DMC	data monitoring committee
Device Deficiencies	Equivalent to product complaint
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
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.
ERB	ethical review board
ET	early termination
EV	extended visit
GCP	good clinical practice
GGT	gamma-glutamyl transferase
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
HIPAA	Health Insurance Portability and Accountability Act

Term	Definition
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
informed consent	A process by which a participant voluntarily confirms his or her 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.
INR	international normalized ratio
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.
IRB	institutional review board
ISO	International Organization for Standardization
ITT	intention to treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IV	intravenous
IWRS	interactive web-response system
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ-CSS	Kansas City Cardiomyopathy Questionnaire – Clinical Summary Scale
LA	left atrial
LAV	left atrial volume
LVDEP	left ventricular end-diastolic pressure
LVEF	left ventricular ejection fraction
MedDRA	Medical Dictionary for Regulatory Activities
MEN-2	multiple endocrine neoplasia type 2
MMRM	mixed model repeated measures
MRI	magnetic resonance imaging

Term	Definition
MTC	medullary thyroid cancer
MTD	maximum tolerated dose
NT-proBNP	N-terminal pro b-type natriuretic peptide
NYHA	New York Heart Association
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
PCWP	pulmonary capillary wedge pressure
PK	pharmacokinetics
PT	prothrombin time
QTc	corrected QT interval
QW	weekly
RA	receptor agonist
SADE	serious adverse device effect
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SoA	schedule of activities
study intervention	for this study, study intervention may be interpreted/synonymous with study drug
SUSAR	suspected unexpected serious adverse reaction
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin

Term	Definition
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.
UADE	unanticipated adverse device effect
ULN	upper limit of normal
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 b: 21 January 2022

Overall Rationale for the Amendment:

The purpose of this protocol amendment is to incorporate feedback received from the FDA on exclusion criterion and concomitant therapy.

Section # and Name	Description of Change	Brief Rationale
Section 5.1 Inclusion Criteria	Criterion #7: removed "and/or" wording; added "or" between ARNI and SGLT2is	For clarification
Section 5.2 Exclusion Criteria	Criterion #13: for NYHA Class, added word "or" in sentence to ensure participants with NYHA Class I are excluded from the study Criterion #20: for AF, changed "and" to "or" between "Visit 1" and "Visit 2"	For clarification
Section 6.5 Concomitant Therapy	Removed sentence on use of SGLT2i for treatment of T2DM	Per FDA feedback
Section 7.1.1 Permanent Discontinuation from Study Drug	A sentence inadvertently added and then was removed	For clarification

Amendment a: 15 December 2021

Overall Rationale for the Amendment:

The purpose of this protocol amendment is to clarify dosing information to allow for more participant retention and clarity on the dosing regimen, add additional unscheduled visits, and make inclusion/exclusion criteria updates.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	• In Intervention Groups and Duration, changed 15 mg to QW • Added wording to Study Period 1 to specify timing	• To Clarify dose • For Clarification in timing
Section 1.2 Schema	Adjusted wording in Note for screening procedures timing	To Clarify screening period timing
Section 1.3 Schedule of Activities (SoA)	• Added 3 columns to Unscheduled Visits (UV): UV, Dosing UV, and Phone follow up Dosing UV, added Xs for specific tests • Footnote "a" added in regard to Unscheduled Visits; subsequent footnotes adjusted • For Telephone Visit, X added to Phone Follow-Up Dosing UV	• To specify UV • To explain UV; for accuracy • For Accuracy
Section 3 Objectives and Endpoints	• Added Other Secondary title & moved Incidence HF events and CV Death from Exploratory • Added timing to first occurrence and recurrent events for HF events and CV death • The Endpoint wording for the exploratory Objective Atrial fibrillation is updated	• Change in Endpoints • To specify timings • Correction
Section 4.1 Overall Design	• For Study Period 1, timing period adjusted • For Screening, sentence added to clarify time period for V1 • For Treatment, dose escalation described; paragraphs added to specify that participant be	• Correction • Clarification for timing for duration of V1 • New information added to clarify dose escalation,

	maintained on study drug; some sentences regarding dose and discontinuation removed	maintenance on study drug; To reduce redundancy
Section 5.1 Inclusion Criteria	• For Inclusion Criterion #7 added additional HF medications	• Clarification for Concomitant Medication use
Section 5.2 Exclusion Criteria	• For Exclusion Criterion #13, NYHA Class information added • For Exclusion Criterion #15 changed wording to include MRI or other local modalities • For Exclusion Criterion #21 added sentence on participants with Chagas disease • For Exclusion Criterion #25 removed sentence regarding fundoscopic examination and clarified definition of nonproliferative diabetic retinopathy	• Additional information • For Clarification • For Clarification • Correction and Clarification
Section 5.4 Screen Failures	Added upper limit of screening period to clarify screen failure	For Clarification
Section 6.4 Study Intervention Compliance	Wording added to clarify participant compliance	For Clarification
Section 6.5 Concomitant Therapy	• Added information on ARNI, SGLT2i, and GLP-1/GIPR use in the study • Changed Hyperglycemia Rescue at Week 26 to Week 24 • Wording added in Standard of Care for Heart Failure • Wording changed to Clarify dosing modification for GI Symptoms	• Clarification of Concomitant Medication Use • Correction • For Clarification • For Clarification
Section 6.6 Dose Modification	Information changed to clarify dose modification	For Clarification

Section 6.7 Intervention after the End of the Study	Wording added in regard to unblinding information	For Clarification
Section 7.1.1 Permanent Discontinuation from Study Drug	• Wording added to clarify permanent discontinuation of study drug • Wording changed to specific criteria when participant has Pancreatic Cancer	• For Clarification • For Clarification
Section 7.1.2 Temporary Interruption	Wording changed to clarify that study interruption, is not study discontinuation; Moved to Section 6.6.1	For Clarification
Section 7.1.3 Restarting Study Drug after Interruption	Added wording on Maintenance dose levels; Moved to Section 6.6.2	For Clarification
Section 7.2 Participant Discontinuation/Withdrawal from the Study	Wording changed to clarify participant retention in the study	For Clarification
Section 7.2.1 Inadvertently Enrolled Participants	Wording Changed to clarify medical appropriateness of treatment	For Clarification
Section 8 Study Assessments and Procedures	Information added regarding remote visits	For Clarification
Section 8.1.1.3 Six-Minute Walk Test	Clarified wording on Borg Scale	For Clarification
Section 8.2.3 Electrocardiograms	Clarified on use of ECG machine type	For Clarification
Section 8.2.4 Clinical Safety Laboratory Assessments	Urine pregnancy wording added	For Clarification
Section 10.1.1 Regulatory and Ethical Considerations	Added bullet point, International Organization for Standardization (ISO) 14155 and wording on substantiality of amendments	To align with current Harmonized Protocol Template v10

Section 10.1.11 Investigator Information	Added Investigator Information Section	To align with current Harmonized Protocol Template v10
Section 10.2 Appendix 2: Clinical Laboratory Tests	Removed Lactate dehydrogenase	Error Correction
Section 10.5.1.5 Major Adverse Cardiovascular Events	Removed hospitalization for HF	This is an efficacy point
Section 10.10 Appendix 10: Six Minute Walk Test Screening Procedures	Flow Diagram corrected for 6MWD	Error Correction

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