Protocol I8F-MC-GPHR(d)

A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing the Efficacy and Safety of Tirzepatide versus Placebo in Patients with Nonalcoholic Steatohepatitis (NASH)

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Title Page

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Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment C	15 November 2019
Amendment B	21 October 2019
Amendment A	13 August 2019
Original Protocol	26 July 2019

Amendment d

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union

Overall Rationale for Amendment d:

A recently published algorithm, the FibroScan-AST (FAST) score, has optimized the use of transient elastography (FibroScan) and a laboratory test (aspartate aminotransferase [AST]) to identify patients who have nonalcoholic steatohepatitis (NASH) with a nonalcoholic fatty liver disease (NAFLD) Activity Score (NAS) ≥4 and fibrosis stages ≥2, which is the target population for this study (Newsome et al. 2020). Review and analyses of early blinded biopsy data from Study I8F-MC-GPHR indicate that use of the FAST score would reduce the number of patients who undergo liver biopsies that do not qualify for inclusion into the study. Therefore, the FAST score is added as an additional screening criterion for patients who have a reliable FibroScan. Furthermore, the lower limit of AST for inclusion has been increased to reduce the number of screen-fails by biopsy.

The protocol is also being amended to put procedures into place that would enable participants to continue safely in the study and maintain the integrity of the study under exceptional circumstances.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Added FAST score to screening	Included the FAST score in the Schedule of Activities.
	Added footnote to imaging (transient elastography and MRI) to allow a longer visit window at Visit 10 (Week 26)	The visit window for obtaining the transient elastography and MRI were increased to ± 2 weeks at Visit 10 due to challenges in scheduling the procedures. The enhanced visit window for imaging does not affect the quality of the data or the study.
	Added footnote reference regarding timing of imaging at Week 52.	Correction of an oversight. Reference was already in the footnote (p) but was not in the SOA.
5.1. Inclusion Criteria	(#5) Added FAST score and increased the screening lower AST lower limit from >20 U/L to >23 U/L (#5b) Increased screening AST lower limit from >20 U/L to >23 U/L for patients whose FibroScan is not reliable	Reduce the number of patients undergoing a biopsy that do not qualify for the study.

8.1.3.3. Transient Elastography (TE)	Added description of the FAST score	Provided description of the FAST score.
9.3. Populations for Analyses	Deleted text	Deleted text is covered in the table below.
	Modified previously defined populations in the study table by adding more granularity to the description	Differentiates between efficacy and safety analyses sets more clearly.
	Added Safety Analysis Set (SS) population	For safety analysis purposes by adding safety follow-up period to FAS.
9.4.4. Safety Analyses	Replaced FAS with SS	With addition of SS population, safety analysis is conducted using SS.
10.2. Appendix 2: Clinical Laboratory Tests	Added FAST score	The central laboratory will be calculating the FAST score; therefore, FAST has been added to laboratory calculations.
10.10. Appendix 10. Provisions for Changes in Study Conduct During Exceptional Circumstances	Added procedures for exceptional circumstances	There may be exceptional circumstances that may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures. Procedures have been added that would enable participants to continue safely in the study and maintain the integrity of the study.
11. References	Added Newsome reference for FAST score	Added Newsome reference that gives the background to the FAST score that being incorporated into the Inclusion Criteria.
	Updated Hartman et al reference	Published journal article cited instead of abstract

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study Comparing the Efficacy and Safety of Tirzepatide versus Placebo in Patients with Nonalcoholic Steatohepatitis (NASH)

Short Title: Tirzepatide versus placebo in NASH

Rationale:

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the glucose-dependent insulinotropic polypeptide gastric inhibitory polypeptide (GIP) receptor and the glucagon-like peptide-1 receptor. Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety. It is administered once weekly by subcutaneous (SC) injection. Treatment with tirzepatide results in glucose lowering, weight loss, and improved metabolic health in patients with type 2 diabetes mellitus (Frias et al. 2018). The beneficial effects of weight loss in patients with nonalcoholic steatohepatitis (NASH) are well-characterized (Promrat et al. 2010; Vilar-Gomez et al. 2015). Study I8F-MC-GPHR (GPHR) will investigate the effects of 52-week treatment with tirzepatide in patients with biopsy-proven NASH. The primary endpoint is NASH resolution with no worsening of fibrosis, based on liver histology. These data will support dose selection for Phase 3.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that tirzepatide 5 mg, 10 mg or 15 mg administered SC QW is superior to placebo for NASH resolution with no worsening of fibrosis at Week 52.	Proportion of participants classified with absence of NASH with no worsening of fibrosis on liver histology as defined in Section 8.1.1.
Secondary	
To demonstrate that tirzepatide 5 mg, 10 mg or 15 mg administered SC QW is superior to placebo at Week 52 for:	From baseline:
• Regression of fibrosis with no worsening of NASH	• Proportion of participants with ≥1 point decrease in fibrosis stage with no worsening of NASH on liver histology
• Prevention of fibrosis progression	• Proportion of participants with ≥1 point increase in fibrosis stage on liver histology
• Decreasing NAS by ≥2 points	• Proportion of participants that achieve a ≥2 point decrease in NAS on liver histology, with ≥1 point reduction in at least 2 NAS components (steatosis, hepatocellular ballooning, lobular inflammation)
• Decreasing liver fat content	• Mean absolute change in liver fat content by MRI-PDFF
• Decreasing body weight	• Mean change in body weight

Abbreviations: MRI-PDFF = magnetic resonance imaging – proton density fat fraction; NAS = nonalcoholic fatty liver disease (NAFLD) activity score; NASH = nonalcoholic steatohepatitis; SC = subcutaneous; QW = once weekly.

Overall Design:

Study GPHR is a Phase 2, multicenter, randomized, double-blind, parallel group, placebo controlled, treat-through study to evaluate the safety and efficacy of tirzepatide compared with placebo in patients with nonalcoholic steatohepatitis.

Disclosure Statement:

This is a parallel, double-blinded treatment study with 4 treatment groups.

Number of Participants:

Approximately 196 participants will be randomly assigned to study intervention such that approximately 157 evaluable participants complete the study.

Intervention Groups and Duration:

Participants will be randomized in a 1:1:1:1 ratio to receive:

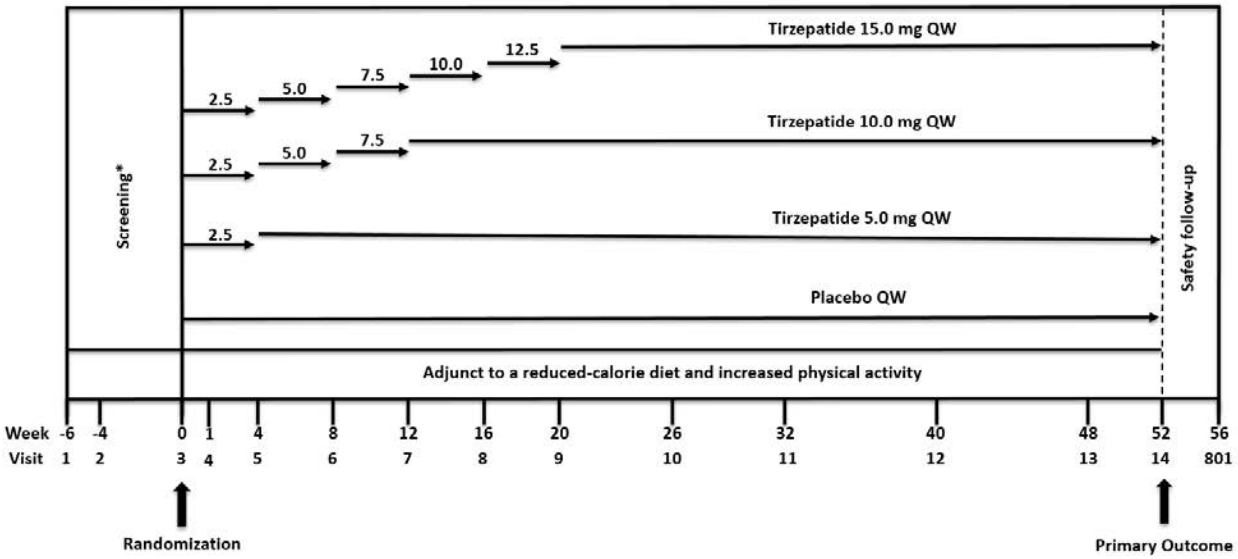
- Tirzepatide 15 mg SC every week
- Tirzepatide 10 mg SC every week
- Tirzepatide 5 mg SC every week
- Placebo SC every week

The maximum total duration of study participation for each participant is up to 68 weeks, across the following study periods:

- Screening: approximately 6 weeks and should not exceed 12 weeks
- Treatment: 52 weeks
- Safety follow-up: 4 weeks

Data Monitoring Committee: No

1.2. Schema



Abbreviation: QW = once weekly.

* Screening procedures may take longer or shorter than 6 weeks and will not be considered a protocol deviation.

1.3. Schedule of Activities (SoA)

Visit	1[a]	2[a,b]	3[a]	4	5	6	7	8	9	10	11	12	13	14	801	ET
Week of Treatment	−6	−4	0	1	4	8	12	16	20	26	32	40	48	52	56	
Study Day/(Dose number)			0/(1)	7/(2)	28/(5)	56/(9)	84/(13)	112/(17)	140/(21)	182/(27)	224/(33)	280/(41)	336/(49)	364/ND	392/ND	
Visit Window (days)				±3	±3	±7	±7	±7	±7	±7	±10	±14	±7	±7	±7	
Fasting Visit	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Administrative																
Informed consent	X															
Diabetes/therapy	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Medical history	X															
Health habits (alcohol use, tobacco use)	X															
Cardiovascular risk factors history			X													
Alcohol use questionnaire (AUDIT)	X													X		X
Concomitant medications	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Inclusion/Exclusion	X		X													
Randomization			X													
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
BG meter/supplies, counseling (T2DM patients only) (resupply as needed)			X													
Diet, physical activity coaching			X		X	X	X			X		X				
Study diary, dispense			X		X	X	X	X	X	X	X	X	X	X		
Review diaries for BG values (T2DM patients only)			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Subcutaneous injection training[c]			X	X												
Study drug and injection supplies, dispense[d]			X	X	X	X	X	X	X	X	X	X	X			
Participant returns study drug supplies					X	X	X	X	X	X	X	X	X	X		X
Drug accountability and compliance			X	X	X	X	X	X	X	X	X	X	X	X		X

Visit	1[a]	2[a,b]	3[a]	4	5	6	7	8	9	10	11	12	13	14	801	ET
Week of Treatment	−6	−4	0	1	4	8	12	16	20	26	32	40	48	52	56	
Study Day/(Dose number)			0/(1)	7/(2)	28/(5)	56/(9)	84/(13)	112/(17)	140/(21)	182/(27)	224/(33)	280/(41)	336/(49)	364/ND	392/ND	
Visit Window (days)				±3	±3	±7	±7	±7	±7	±7	±10	±14	±7	±7	±7	
Fasting Visit	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Participant Demographics																
Age/Gender	X															
Race/Ethnicity	X															
Clinical Variables																
Adverse events			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical examination[e]	X															
Height	X													X		X
Weight	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Waist circumference	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (BP, pulse rate, and body temperature)	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Dilated fundoscopic examination[f]	X															
Diagnostics (Safety)																
Screening laboratory tests[g]	X															
Transferrin saturation	X															
TSH	X															
Pregnancy test[h]	X		X		X	X	X	X	X	X	X	X	X	X	X	X
Estradiol, FSH, LH[i]	X															
Chemistry panel	X		X	X	X	X	X	X	X	X		X		X	X	X
FIB-4[j]	X		X		X	X	X	X	X	X				X	X	X
Lipid panel	X		X				X			X		X		X	X	X
eGFR	X		X		X	X	X	X	X	X		X		X	X	X
Hematology	X		X		X	X	X	X	X	X			X	X	X	X
APTT and PT (INR)	X		X				X			X			X	X	X	X
Urinalysis	X		X				X			X				X	X	X
Urine albumin and creatinine, UACR	X		X				X			X				X	X	X
Calcitonin	X		X				X			X		X		X	X	X
ECGs[k]	X		X							X				X	X	X

Visit	1[a]	2[a,b]	3[a]	4	5	6	7	8	9	10	11	12	13	14	801	ET
Week of Treatment	−6	−4	0	1	4	8	12	16	20	26	32	40	48	52	56	
Study Day/(Dose number)			0/(1)	7/(2)	28/(5)	56/(9)	84/(13)	112/(17)	140/(21)	182/(27)	224/(33)	280/(41)	336/(49)	364/ND	392/ND	
Visit Window (days)				±3	±3	±7	±7	±7	±7	±7	±10	±14	±7	±7	±7	
Fasting Visit	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Diagnostics (Efficacy)																
Liver biopsy		X[l]												X[m]		X[n]
Transient Elastography (Fibroscan)[o]	X		X[p]							X[r]				X[op]		X[n]
FAST Score	X															
MRI (PDFF and cT1)[o]			X[p]							X[or]				X[op]		X[n]
HbA1c	X		X		X	X	X	X	X	X		X		X	X	X
Insulin and C-peptide			X				X		X	X		X		X	X	X
Biomarkers K-18, Pro-C3, ELF, Adiponectin, Leptin, NIS4, Ferritin, Free Fatty Acid			X				X		X	X				X		X
Patient Reported Outcomes																
PGIS			X										X			X
PROMIS Fatigue Short Form 8a			X										X			X
PROMIS Pain Interference Short Form 4a			X										X			X
CLDQ-NAFLD			X										X			X
Other																
Pharmacogenetic stored samples			X													
Nonpharmacogenetic stored samples			X				X		X	X				X		
Immunogenicity			X		X		X			X		X		X	X	X
PK sample for immunogenicity					X		X			X		X		X	X	X
Pharmacokinetics[q]							X			X				X		

Abbreviations: ALT = alanine aminotransferase; APTT = activated partial thromboplastin time; AST = aspartate aminotransferase; AUDIT = Alcohol Use Disorders Identification Test; BG = blood glucose; BP = blood pressure; CLDQ-NAFLD = chronic liver disease questionnaire – nonalcoholic fatty liver disease; cT1 = corrected T1; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; ELF = enhanced liver fibrosis; ET = early termination; FAST = FibroScan-AST; FIB-4 = fibrosis-4; FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; INR = international normalized ratio; IWRS = Interactive Web Response System; LH = luteinizing hormone; MRI = magnetic resonance imaging; ND = no dose of study drug; NIS4 = noninvasive score 4; PDFF = proton density fat fraction; PK = pharmacokinetics; PGIS = patient global impression of severity; PROMIS = Patient Reported Outcome Measurement Information System; PT = prothrombin time; T2DM = type 2 diabetes mellitus; TSH = thyroid stimulating hormone; UACR = urine albumin-to-creatinine ratio.

a Screening procedures for Visit 1 and Visit 2 may take more or less time than listed. Randomization (Visit 3) may occur once all screening procedures have occurred, biopsy results received, and the participant qualifies for the study; thus, randomization may occur more or less than 6 weeks from screening. Longer or shorter than 6 weeks from screening will not be considered a protocol deviation. All procedures (screening and baseline) need to be completed prior to the first dose of study drug.

b Participants with acceptable previous liver biopsy do not need to attend Visit 2.

c Sites should coach and oversee participants self-administer study drug at every scheduled visit.

d Study drug should be administered at the end of a visit after all other scheduled procedures have been collected.

e Additional physical examinations may be performed throughout the study if determined necessary due to participant symptoms.

f Dilated fundoscopic examination will be performed between Visit 1 and Visit 2 by an eye care professional (ophthalmologist or optometrist) for T2DM patients who have not had a dilated fundoscopic examination in the last 12 months to exclude patients with proliferative diabetic retinopathy, diabetic maculopathy, or severe nonproliferative diabetic retinopathy that requires acute treatment. Follow-up dilated fundoscopic examination should be performed when clinically indicated by any adverse event suspected of worsening retinopathy.

g Screening laboratory tests also include serum hepatitis B surface Ag, hepatitis C antibody (Ab), and HIV (human immunodeficiency virus) Ab tests for all participants. Participants treated for hepatitis C should have a hepatitis C RNA test rather than an antibody test.

h Serum pregnancy test will be performed by the central laboratory at Visit 1 for women of child-bearing potential. A urine pregnancy test to be analyzed locally should be given to all women of child-bearing potential at Visit 3 prior to administration of first dose of study drug to confirm lack of pregnancy. Additional urine pregnancy tests (analyzed locally) should be given to women of child-bearing potential at all other visits beginning at Visit 5. Other urine pregnancy tests may be performed locally at the investigator's discretion if pregnancy is suspected during the study.

i Collect serum estradiol, FSH, and LH 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.

j FIB-4 will be calculated by the central laboratory.

k ECGs should be collected centrally at Visits 3, 10, 14, and 801, and locally at screening and early termination.

l Participants with an acceptable liver biopsy (See Section 8.1.1) prior to screening do not need to have an additional screening liver biopsy. Patients who require a screening biopsy should have the biopsy performed once the participant has been found eligible with respect to all other inclusion and exclusion criteria.

m End of treatment liver biopsy may be collected between Weeks 49 and 53. Hematology and INR should be measured prior to liver biopsy according to the SOA. Additional safety testing may be performed at the discretion of the investigator.

n Early termination liver biopsy and all imaging procedures should only be performed on participants who have had at least 9 months (36 weeks) study drug exposure; for those participants, the biopsy and imaging procedures should be collected within 2 weeks (+/- 2weeks) of the last dose of study drug. Hematology and INR should be measured prior to liver biopsy according to the SOA. Additional safety testing may be performed at the discretion of the investigator.

o Transient elastography imaging should be collected after at least a 3-hour fast. MRI imaging should be collected after at least a 6-hour fast. However, drinking a small amount of water is acceptable for transient elastography and MRI.

p Baseline imaging should occur after the liver biopsy confirming eligibility for the study and prior to the first study drug administration (Visit 3). Imaging at Week 52 will occur up to 2 weeks prior to the last treatment visit (Visit 14) but not after the end-of-treatment liver biopsy.

q PK samples will be collected at these visits at time windows of 1 to 24 hours or 24 to 96 hours postdose, as assigned by IWRS. Dependent on the time windows to which a patient is assigned, the patient may be required to come to site for PK-specific visits.

r Transient elastography and MRI may occur ±2 weeks of Visit 10 (Week 26).

2. Introduction

2.1. Study Rationale

Tirzepatide is a 39-amino acid synthetic peptide with agonist activity at both the glucose-dependent insulinotropic polypeptide gastric inhibitory polypeptide (GIP) receptor and the glucagon-like peptide-1 (GLP-1) receptor. Its structure is based on the GIP sequence and includes a C20 fatty diacid moiety. It is administered once weekly (QW) by subcutaneous (SC) injection. Treatment with tirzepatide results in glucose lowering, weight loss, and improved metabolic health in patients with type 2 diabetes mellitus (T2DM) (Frias et al. 2018). The beneficial effects of weight loss in patients with nonalcoholic steatohepatitis (NASH) are well-characterized (Promrat et al. 2010; Vilar-Gomez et al. 2015). Study I8F-MC-GPHR (GPHR) will investigate the effects of 52-week treatment with tirzepatide in patients with biopsy-proven NASH. The primary endpoint is NASH resolution with no worsening of fibrosis, based on liver histology. These data will support dose selection for Phase 3.

2.2. Background

Nonalcoholic Steatohepatitis

Nonalcoholic steatohepatitis (NASH) is the progressive stage of nonalcoholic fatty liver disease (NAFLD), characterized histologically by the presence of steatosis, lobular inflammation, and hepatocyte injury (ballooning), with or without fibrosis (Chalasani et al. 2018). Noncirrhotic NASH is a silent disease with few clinical symptoms and requires a liver biopsy for diagnosis. As a consequence, the prevalence of NASH in the general population is unclear, but estimated to be between 1.5% and 6.45% (Younossi et al. 2016). Obesity, T2DM, and dyslipidemia are considered important risk factors for NAFLD (Chalasani et al. 2018). The risk of NASH is ~2-fold higher for patients with diabetes versus patients who do not have diabetes (Williams et al. 2011; Loomba et al. 2012). The prevalence of NASH in patients with morbid obesity has been reported to be 37% (Machado et al. 2006). Those with NASH, especially in the presence of fibrosis, are at a higher risk for adverse outcomes, including liver cirrhosis, liver-related mortality, and cardiovascular mortality (Angulo et al. 2015). NASH is currently the third-most common cause of hepatocellular carcinoma (Van Thiel and Ramadori 2011; Chalasani et al. 2018). Due to its increasing prevalence, NASH is expected to become the most common indication for liver transplantation in forthcoming years overtaking viral hepatitis (Charlton et al. 2011).

There are currently no approved pharmacological therapies available for treatment of NASH. The beneficial effects of weight loss on NASH are well-documented (Promrat et al. 2010; Vilar-Gomez et al. 2015; Chalasani et al. 2018); therefore, currently diet and exercise are considered the standard treatment for NASH. For example, losing ≥5% body weight was shown to improve hepatic steatosis, induce resolution of NASH, and stabilize or improve fibrosis. A ≥10% body weight decrease is associated with improvements in all features of NASH, including fibrosis regression (Vilar-Gomez et al. 2015; Chalasani et al. 2018). The relationship between NASH, increased body weight, and T2DM provides a strong rationale to investigate therapies that induce weight loss and improve insulin sensitivity.

Tirzepatide

The Phase 2 tirzepatide clinical trial, I8F-MC-GPGB (GPGB) in participants with T2DM with inadequate glycemic control on diet and exercise alone or on a stable dose of metformin monotherapy demonstrated dose-dependent reductions in hemoglobin A1c (HbA1c) and body weight. At Week 26, at doses of 5 mg, 10 mg and 15 mg, the proportion of subjects with ≥5% loss of baseline body weight was 50.0%, 77.3% and 85.7%, respectively, and the proportion of subjects with ≥10% loss of baseline body weight was 16.8%, 45.5% and 54.3%, respectively.

Several NASH-related biomarkers from Study GPGB were evaluated to explore whether tirzepatide may have potential efficacy in NASH (Hartman et al. 2019). The following biomarkers were included: alanine aminotransferase (ALT), aspartate transaminase (AST), keratin-18 M30 fragment (K-18, apoptosis marker), Pro-C3 (fibrosis marker, a fragment of the NH_2-terminal propeptide of type III procollagen), and adiponectin (adipokine that protects the liver from inflammation and fibrosis). Statistically significant ($p<.05$) decreases from baseline with tirzepatide occurred in ALT (all doses), AST (1 mg, 5 mg, 15 mg), K-18 (5 mg, 10 mg, 15 mg) and Pro-C3 (15 mg). Decreases were statistically significant for tirzepatide versus placebo in K-18 (10 mg) and Pro-C3 (15 mg), and for tirzepatide versus dulaglutide in ALT (10 mg, 15 mg). Increases in adiponectin with tirzepatide were statistically significant compared with placebo for the 10-mg and 15-mg dose groups. These NASH-related biomarker data in patients with T2DM, along with the weight loss findings, support the hypothesis that tirzepatide may have beneficial effects in NASH (Hartman et al. 2019).

Additional nonclinical and clinical trial data are summarized in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

More information about the known and expected benefits, risks, serious adverse events (SAEs), and reasonably anticipated adverse events (AEs) of tirzepatide are to be found in the IB.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To demonstrate that tirzepatide 5 mg, 10 mg or 15 mg administered SC QW is superior to placebo for NASH resolution with no worsening of fibrosis at Week 52.	Proportion of participants classified with absence of NASH with no worsening of fibrosis on liver histology as defined in Section 8.1.1.
Secondary	
To demonstrate that tirzepatide 5 mg, 10 mg or 15 mg administered SC QW is superior to placebo at Week 52 for:	From baseline:
• Regression of fibrosis with no worsening of NASH	• Proportion of participants with ≥1 point decrease in fibrosis stage with no worsening of NASH on liver histology
• Prevention of fibrosis progression	• Proportion of participants with ≥1 point increase in fibrosis stage on liver histology
• Decreasing NAS by ≥2 points	• Proportion of participants that achieve a ≥2 point decrease in NAS on liver histology, with ≥1 point reduction in at least 2 NAS components (steatosis, hepatocellular ballooning, lobular inflammation)
• Decreasing liver fat content	• Mean absolute change in liver fat content by MRI-PDFF
• Decreasing body weight	• Mean change in body weight
Tertiary/Exploratory	
Investigate the effect of tirzepatide 5 mg, 10 mg or 15 mg SC QW versus placebo at various time points for:	From baseline:
• Additional histological measures	• Mean change in the liver histology score

	for: o Expanded ballooning score o Expanded portal inflammation score o Expanded fibrosis stage 1 scores o Mallory-Denk body score o Glycogenosis score
• Liver inflammation and fibrosis measured by MRI	• Mean change in extracellular hepatic water content measured by iron-corrected T1 imaging (cT1, in ms) by MRI
• Liver stiffness measured by TE	• Mean change in liver stiffness (in kPa) measured by TE
• Liver enzymes and serum biomarkers of NASH and fibrosis	• Mean change in ALT, AST, GGT, K-18, Pro-C3, ELF, FIB-4, Adiponectin, Leptin, and Ferritin
• Insulin sensitivity	• Mean changes in fasting insulin and HOMA-IR
• Decreasing waist circumference	• Mean change in waist circumference (centimeters)
• PROs	• Change in: o PROMIS Fatigue short form 8a v1.0 score o PROMIS Pain Interference short form 4a v1.0 score o Chronic Liver Disease Questionnaire for nonalcoholic fatty liver disease total and domain scores o Patient Global Impression of Severity (PGIS) score
• NASH resolution	• NASH resolution based on overall assessment of histology by pathologists
• Decreasing NAFLD Activity Score (NAS)	• Mean change in NAS on liver histology
• Decreasing steatosis, hepatocellular ballooning or lobular inflammation	• Mean change in the liver histology score for: o Steatosis o Hepatocellular ballooning o Lobular inflammation

• Decreasing steatosis, hepatocellular ballooning, or lobular inflammation by ≥1 point	• Proportion of participants that achieve a ≥1 point improvement in the liver histology score for: o Steatosis o Hepatocellular ballooning o Lobular inflammation
• Decreasing fibrosis stage	• Mean change in fibrosis stage on liver histology
• Regression of fibrosis with no worsening of NASH	• Proportion of participants with: o ≥2 point decrease in fibrosis stage, and no worsening of NASH on liver histology
• Prevention of progression to cirrhosis	• Proportion of participants classified with cirrhosis (F4) on liver histology
• Resolution of fibrosis	• Proportion of participants classified with absence of fibrosis on liver histology
• Relative decreases in liver fat content	• Mean percentage change in liver fat content by MRI-PDFF
• Decreasing liver fat content	• Mean absolute change in liver fat content by MRI-PDFF
• Decreasing liver fat content by ≥30% from baseline	• Proportion of participants that achieve a ≥30% relative decrease in liver fat content by MRI-PDFF
• Relative decreases in body weight	• Mean percentage change in body weight
• Decreasing body weight by 5%, 10%, 15%, and 20%	• Proportion of participants that achieve ≥5%, ≥10%, ≥15%, or ≥20% decrease in body weight

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; ELF = enhanced liver fibrosis; FIB-4 = fibrosis-4; GGT = Gamma-glutamyl transferase; K-18 = keratin-18 M30 fragment; HOMA-IR = Homeostatic Model Assessments for Insulin Resistance; MRI = magnetic resonance imaging; MRI-PDFF = magnetic resonance imaging – proton density fat fraction; ms = millisecond; NAFLD = nonalcoholic fatty liver disease; NAS = NAFLD activity score; NASH = nonalcoholic steatohepatitis; PGIS = Patient Global Impression of Severity; PRO = patient reported outcome; PROMIS = Patient Reported Outcome Measurement Information System; SC = subcutaneous; TE = transient elastography; QW = once weekly.

4. Study Design

4.1. Overall Design

Study GPHR is a Phase 2, multicenter, randomized, double-blinded, placebo-controlled study that will investigate the effects of treatment with tirzepatide 5 mg, 10 mg and 15 mg SC QW compared with placebo on NASH resolution with no worsening of fibrosis in patients with biopsy-proven NASH and fibrosis, with or without T2DM.

Four intervention groups will be studied:

- Tirzepatide 5 mg SC QW, initially 2.5 mg SC QW for 4 weeks then 5 mg SC QW
- Tirzepatide 10 mg SC QW, initially 2.5 mg SC QW then dose escalated by 2.5 mg every 4 weeks until target dose is reached
- Tirzepatide 15 mg SC QW, initially 2.5 mg SC QW then dose escalated by 2.5 mg every 4 weeks until target dose is reached
- Placebo

All participants will receive diet and physical activity counseling throughout the study.

Study GPHR will consist of 3 periods:

- Screening (Visits 1 and 2)
- Treatment (Visits 3 to 14)
    - 4- to 20-week dose escalation (4-week for 5 mg group, 12-week for 10 mg group, 20-week for 15 mg group)
    - 32- to 48-week maintenance (48-week for 5 mg group, 40-week for 10 mg group, 32-week for 15 mg group)
- Safety follow-up (4 weeks post-treatment, through Visit 801)

The maximum total duration of the combined treatment periods is 52 weeks.

The approximate maximum total duration of study participation for each participant, including screening and post-treatment follow-up periods, is 68 weeks. Some participants may require additional follow-up after V801 for evaluation of treatment-emergent antidrug antibodies (ADA).

Enrichment Strategy

Participants with biopsy-proven NASH will be enrolled into this study. The study population will be enriched for participants who have T2DM, such that 40% to 65% of the total study population will consist of participants with NASH who have also been diagnosed with T2DM. The other 35% to 60% of the study population will consist of participants with NASH who do not have T2DM.

Participant Visit Scheme

Study participants will undergo screening assessments and procedures, double-blinded treatment with investigational product or placebo, and a post-treatment safety follow-up visit. Assessments and procedures to be conducted in each treatment period are described in the Schedule of Activities (SoA; Section 1.3), and in Study Assessments and Procedures (Section 8).

Screening procedures will be performed at Visit 1 through Visit 2. All screening procedures must be completed prior to or at Visit 3. These measurements will occur prior to randomization and prior to the first administration of study drug.

Participants with a qualifying liver biopsy performed within 6 months of screening who meet the other required inclusion and exclusion criteria can participate in the study after evaluation of the histology by 2 central pathologists with experience in NASH to confirm presence of NASH and the study-specific histological inclusion criteria. Visit 2 will be omitted for these participants.

Participants without a qualifying liver biopsy will undergo assessments of their controlled attenuation parameter (CAP) and liver stiffness measurement (LSM) at Visit 1 using transient elastography (TE) (refer to Section 5.1, inclusion criterion 5b for further detail) to determine if they have a high probability of fatty liver disease with fibrosis. Participants meeting prespecified criteria for a high probability of fatty liver disease with fibrosis by TE will undergo a liver biopsy at Visit 2 to assess study eligibility, provided they meet all other required inclusion and exclusion criteria. Liver biopsies will be evaluated by 2 central pathologists with experience in NASH prior to Visit 3 to confirm presence of NASH and study-specific histological inclusion criteria.

Participants will be treated for a total of 52 weeks. Tirzepatide will be dose escalated as illustrated in the study schema (Section 1.2).

Participants will remain in the study for a 4-week safety follow-up period, during which participants are off study drug.

4.2. Scientific Rationale for Study Design

Study GPHR is a Phase 2 study designed to examine the efficacy and safety of QW tirzepatide compared with placebo in patients with biopsy-proven NASH and fibrosis. Body weight and NASH biomarker data from the tirzepatide Phase 2 study in T2DM (GPGB; Section 2.2) provide a strong rationale for development of tirzepatide as a potential treatment for NASH.

Inclusion of a placebo comparator in Study GPHR will allow for a direct comparison of the safety and efficacy of tirzepatide in patients with NASH over a 12-month time period. The currently recommended treatment for NASH is diet and exercise in order to reduce body weight. All patients will receive diet and exercise counseling (See Appendix 6, Section 10.6), thus placebo patients will be receiving the recommended treatment for NASH. Although some Phase 2 studies of other compounds being investigated for treatment of NASH have had treatment durations less than 12 months, a treatment duration of 52 weeks was chosen because of the need for a 20-week dose escalation period for the 15 mg dose of tirzepatide. This slow dose escalation approach was chosen to minimize gastrointestinal (GI) side effects of tirzepatide, which were common in the Phase 2 T2DM study that included a shorter dose escalation period (6 weeks to reach 15 mg SC QW). Thus, the 52-week treatment period will be sufficient to compare the effects of tirzepatide and placebo to resolve NASH. Several noninvasive methods to evaluate NASH and fibrosis, utilizing serum biomarkers and imaging modalities, have been included in the study with the objective of developing future alternatives to liver biopsy for diagnosis of NASH and evaluation of treatment effects of tirzepatide in patients with NASH. The data from this study will inform the decision of whether to continue evaluation of tirzepatide in Phase 3 studies for treatment of NASH.

4.3. Justification for Dose

Tirzepatide doses of 5 mg, 10 mg and 15 mg administered SC QW will be evaluated in this study. These doses and associated escalation schemes were selected based on assessment of safety, efficacy (weight loss benefit), and GI tolerability data followed by exposure response modeling of data in T2DM patients in Phase 1 and 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 would permit time for development of tolerance to GI events and are predicted to minimize GI tolerability concerns.

The tirzepatide 5 mg, 10 mg, and 15 mg doses provided clinically relevant weight loss relative to placebo in the 26-week Phase 2 Study GPGB. The percent of patients achieving ≥10% body weight loss was progressively higher with increasing dose levels. In contrast, the proportion of patients with gastrointestinal adverse events was progressively higher with increasing dose levels in the Phase 2 study. Thus, inclusion of these 3 doses in Study GPHR will enable assessment of dose-response and balance between efficacy and tolerability. The NASH biomarker results from Study GPGB demonstrated statistically significant differences compared with placebo for most of the NASH biomarkers with the 10 mg and/or the 15 mg doses.

The selected doses and escalation schemes will enable further evaluation of benefit/risk considerations for the 5 mg, 10 mg, and 15 mg doses of tirzepatide.

4.4. End of Study Definition

End of trial is defined as the last visit or the last scheduled procedure shown in the SoA for the last participant.

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit or the last scheduled procedure shown in the SoA.

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 18 to 80 years of age (inclusive), at the time of signing the informed consent form (ICF).

Type of Participant and Disease Characteristics

2. Body mass index (BMI) ≥27 kg/m^2 and ≤50 kg/m^2
3. For participants with T2DM:
    a. HbA1c ≤9.5% at time of screening
    b. Treated with diet and/or exercise, or treated with oral antihyperglycemic medication (metformin, sulfonylureas, SGLT-2 inhibitors, DPP-4 inhibitors, and/or TZDs) with
        i. Stable dose for at least 3 months before screening (6 months for TZDs)

        OR

        ii. Stable dose for at least 3 months before baseline liver biopsy, if baseline liver biopsy was performed prior to screening (6 months for TZDs)
    c. For participants treated with a DPP-4 inhibitor, the medication must be discontinued prior to randomization (See Section 5.2)
4. For participants without diagnosed T2DM:
    a. HbA1c <6.5% at screening
    b. Fasting glucose <7.0 mmol/L (126 mg/dL)
5. Diagnosis of NASH by liver biopsy:
    a. Individuals may be eligible if they have had a liver biopsy not more than 6 months prior to screening. The liver biopsy slides need to be available for review, and presence of definite NASH according to the NASH Clinical Research Network (CRN) classification needs to be confirmed by 2 sponsor-designated central pathologists. All study-specific histological inclusion criteria must be met and confirmed by the central pathologists.
    b. Individuals for whom *(i.)* no liver biopsy has been performed within 6 months of screening, *(ii.)* the previously performed liver biopsy is not of adequate quality, or *(iii.)* the previously performed liver biopsy is not available for review are required to undergo a baseline liver biopsy as part of screening to determine definite NASH according to the NASH CRN classification prior to randomization. To be

eligible for a liver biopsy at baseline, these individuals need to meet the following criteria:

i. T2DM or at least 1 of the following weight-related comorbidities:
   1. Central obesity (waist circumference ≥35 inches [89 cm] for women; ≥40 inches [102 cm] for men)
   2. Impaired fasting glucose (≥100 mg/dL [5.56 mmol/L])
   3. Elevated fasting triglycerides (treated and/or ≥150 mg/dL [1.7 mmol/L])
   4. Hypertension (treated and/or systolic blood pressure ≥130 mm Hg or diastolic blood pressure ≥85 mm Hg)
   5. Low high-density lipoprotein cholesterol (treated and/or <50 mg/dL [1.29 mmol/L] for women or <40 mg/dL [1.03 mmol/L] for men)

ii. CAP >288 dB/m by TE, or higher at the discretion of the investigator

iii. LSM >7.6 kPa and < 20 kPa by TE

iv. AST >23 U/L

v. FibroScan-AST (FAST) score >0.35 (see Section 8.1.3.3.1 for details)

When TE is of insufficient quality (See definitions in Section 8.1.3.3) or LSM is >7.1 but ≤7.6 kPa and/or the CAP is >283 but ≤288 dB/m, following criteria may be used:

i. T2DM or at least 2 weight-related comorbidities (as defined above)

ii. Fibrosis -4 (FIB-4) >1.3 and <3.2

iii. AST >23 U/L

6. NAFLD Activity Score (NAS) ≥4 with ≥1 point for each component
7. Fibrosis stage 2 or 3 according to the NASH CRN scoring system
8. Stable body weight (≤5% body weight change) for at least 3 months. For participants entering the study with a liver biopsy done between 3 to 6 months from the screening visit, body weight must be stable (<5% body weight change) for the period of time between the biopsy and the screening visit.
9. Participants currently treated with vitamin E (≥400 IU QD) or TZDs for NASH need to remain on treatment during the study, and need to be on a stable dose for at least 6 months prior to screening or need to be off treatment for at least 6 months prior to screening
10. Participants with a documented history of Gilbert's syndrome may be enrolled if the direct bilirubin is within normal reference range
11. Individuals who are, in the investigator's opinion, well-motivated, capable, and willing to:
    a. Self-inject study drug or have the assistance of a trained individual who will inject the study drug
    b. Undergo baseline and endpoint liver biopsies

c. Maintain a study diary, as required for this protocol

Sex

12. Males and females will be eligible for this study
    a. Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies
    b. Male participants:
        i. Men with partners of child-bearing potential, for the duration of the study and for 5 half-lives of the study drug plus 90 days after the last dose of study drug (corresponding to 4 months), will either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives [estrogen and progestogen containing hormonal contraception associated with inhibition of ovulation], implanted contraceptives or intrauterine device) or an effective method of contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges). 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. 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). Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
        ii. Men should refrain from sperm donation for the duration of the study and for 5 half-lives of the study drug plus 90 days after the last dose of study drug (corresponding to 4 months).
        iii. Men who are in exclusively same sex relationships (when it is their preferred and usual lifestyle) are not required to use contraception.
    c. Female participants:
        i. Women of child-bearing 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 (e.g., calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

ii. Otherwise, women of child-bearing potential participating must agree to use 2 forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study and for 30 days thereafter.
    A. Women of child-bearing potential 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 one form is highly effective, (such as combined [estrogen and progesterone containing] hormonal contraception associated with inhibition of ovulation, implanted contraceptives or intrauterine devices) will be used. 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 (i.e., condom with spermicide, diaphragm with spermicide, 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.

iii. Women not of child-bearing potential may participate and include those who are:
    A. infertile due to surgical sterilization (hysterectomy, bilateral oophorectomy, or tubal ligation), congenital anomaly such as mullerian agenesis; or
    B. postmenopausal – defined as either
        a. A woman at least 40 years of age with an intact uterus, not on hormone therapy, who has cessation of menses for at least 1 year without an alternative medical cause, AND a follicle-stimulating hormone >40 mIU/mL; or
        b. A woman 55 years of age or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea; or
        c. A woman at least 55 years of age with a diagnosis of menopause prior to starting hormone replacement therapy.

iv. Must not be breastfeeding

Informed Consent

13. Capable of giving signed informed consent as described in Appendix 1 (Section 10.1.2), 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

14. Alcohol consumption >14 units/week for women and >21 units/week for men
15. Fibrosis stages 0 and 1 according to the NASH CRN scoring system on liver biopsy
16. Cirrhosis (fibrosis stage 4)
17. Platelet count <150,000/mm^3
18. Evidence of other forms of chronic liver disease:
    a. Alcoholic liver disease
    b. Hepatitis B as defined by presence of hepatitis B surface antigen (HBsAg)
    c. Hepatitis C as defined by presence of hepatitis C virus (HCV) RNA or positive hepatitis C antibody (anti-HCV). Participants treated for hepatitis C (and diagnosed as cured) must have an RNA test at screening and also be RNA negative for at least 3 years prior to screening in order to be eligible for the study
    d. Primary biliary cholangitis as defined by the presence of at least 2 of the following:
        i. Biochemical evidence of cholestasis based mainly on alkaline phosphatase (ALP) elevation
        ii. Presence of antimitochondrial antibody
        iii. Historical evidence of nonsuppurative destructive cholangitis and destruction of interlobular bile ducts
    e. Evidence of autoimmune liver disease as defined by compatible liver histology
    f. Primary sclerosing cholangitis
    g. Current drug-induced liver disease as defined on the basis of typical exposure and history
    h. Suspected or proven liver cancer
    i. Any other type of liver disease other than NASH
19. Transferrin saturation >50%, except when it has been demonstrated that a diagnosis of hemochromatosis has been excluded by genetic testing and when a previous liver biopsy has demonstrated no evidence of iron overload
20. Clinical evidence of hepatic decompensation as defined by the presence of any of the following abnormalities:
    a. Serum albumin <3.5 g/dL
    b. International normalized ratio (INR) >1.3

c. Direct bilirubin > upper limit of normal (ULN) at screening
d. History of esophageal varices, ascites, or hepatic encephalopathy

21. ALT or AST levels >5 times upper limit of normal (ULN) at screening
22. ALP ≥1.5 the ULN at screening
23. Inability to safely obtain a liver biopsy
24. History of biliary diversion
25. Known positive for human immunodeficiency virus infection
26. Active, serious medical disease with likely life expectancy <5 years
27. Active substance abuse including oral, inhaled or injection drugs in the year prior to screening
28. Use of marijuana within 3 months of enrollment and unwilling to abstain from marijuana use during the trial. Patients should also refrain from use of cannabidiol (CBD) oil for the duration of the study
29. Any current or historical condition (for example, diagnosed eating disorder or other psychiatric disorder) that, in the opinion of the investigator, may preclude the participant from following and completing the protocol
30. Other condition which, in the opinion of the investigator, would impede compliance or hinder completion of the study

Diabetes-Related

31. Uncontrolled T2DM defined as HbA1c >9.5% within 3 months prior to screening
32. Type 1 diabetes mellitus (T1DM), latent autoimmune diabetes in adults, history of ketoacidosis, and/or hyperosmolar state/coma
33. Patients with T2DM who have a history of proliferative diabetic retinopathy, diabetic maculopathy or severe nonproliferative diabetic retinopathy that requires acute treatment. Patients with T2DM should have had a dilated fundoscopic exam, performed by an ophthalmologist or optometrist, within 12 months of screening.

Obesity-Related

34. Prior (within 5 years) or planned (during the study) surgical treatment for obesity
35. Obesity which is induced by other endocrine disorders (such as Cushing's syndrome or Prader-Willi syndrome)

Other Medical Conditions

36. Renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by chronic kidney disease-epidemiology as determined by central laboratory during screening; for patients on metformin, eGFR <45 mL/min/1.73m^2 (or lower than the country-specific threshold for using the prescribed dose of metformin per local label)

37. Known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect gastrointestinal motility
38. History of chronic or acute pancreatitis. A patient with a history of acute pancreatitis caused by gallstones may be included in the study if the patient had a cholecystectomy to resolve the problem
39. Uncontrolled hypertension (systolic blood pressure ≥160 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg). For participants with uncontrolled hypertension at the screening visit, antihypertensive medication may be started and blood pressure must meet the protocol criterion for hypertension control by the randomization visit
40. Uncontrolled inflammatory bowel disease (IBD) and/or not on stable therapy for the last 3 months or clinically symptomatic IBD with C-reactive protein >4 mg/L.
41. Any medical condition that, in the opinion of the investigator, may increase the risk of complications related to a liver biopsy (e.g., a known coagulopathy)
42. Any of the following cardiovascular conditions within 6 months prior to screening:
    a. acute myocardial infarction (MI),
    b. cerebrovascular accident (stroke),
    c. unstable angina, or
    d. hospitalization due to congestive heart failure (CHF)
43. New York Heart Association Functional Classification IV CHF
44. Have a serum calcitonin of
    (a) ≥20 ng/L at Visit 1 if eGFR is ≥60 mL/min/1.73 m^2
    (b) ≥35 ng/L at Visit 1 if eGFR is <60 mL/min/1.73 m^2
45. Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma (MTC)
46. Evidence of untreated hypothyroidism or hyperthyroidism based on clinical and laboratory evaluation. Individuals on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.
47. 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 carcinomas of the cervix, or in situ prostate cancer) for less than 5 years
48. Any other condition (for example, hypersensitivity) that is a contraindication to GLP-1 receptor agonist
49. A transplanted organ (corneal transplants [keratoplasty] allowed) or awaiting an organ transplant
50. Any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease)

Prior/Concomitant Therapy

51. Have used insulin for treatment of diabetes within the prior year. However, short-term use of insulin for acute conditions is allowed (≤14 days) in certain situations, such as during a hospitalization or perioperatively (See Section 6.5.1.2)
52. Current or previous (within 3 months of screening) use of GLP-1 receptor agonists or any history of allergies to these medications.
53. Use of drugs associated with hepatic steatosis (e.g., amiodarone, methotrexate, tamoxifen) for more than 2 weeks in the 3 months prior to screening. If the use of such drugs is anticipated to be medically necessary within the next year, the patient should also be excluded.
54. Current use of medication associated with weight gain, except when on stable dose for at least 3 months prior to screening and remaining on stable dose during the study
55. Receiving or having received (within 3 months of screening) chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, intra-articular, or inhaled preparations) or have evidence of a significant active autoimmune disease (such as systemic lupus erythematosus or rheumatoid arthritis) that has required (within the last month) or is likely to require (in the opinion of the investigator) concurrent treatment with systemic glucocorticoids (excluding topical, intra-ocular, intranasal, intra-articular or inhaled preparations) in the next 12 months
56. Use of medications or alternative remedies (within 3 months prior to screening; prescribed or over-the-counter) intended to promote weight loss. These include, but are not limited to: Saxenda [liraglutide 3.0 mg], Alli®/Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion]. (See also Inclusion criteria #9)
57. Unwillingness to discontinue over-the-counter (herbal) medication that, in the opinion of the investigator, can interfere with the study
58. Active and chronic use of anticoagulants (other than aspirin or nonsteroidal anti-inflammatory drugs [NSAIDs]) that, in the opinion of the investigator, increases the risk of severe bleeding during the liver biopsy.

Prior/Concurrent Clinical Study Experience

59. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
60. Have participated within the last 6 months in a clinical study involving an investigational product

Other Exclusions

61. 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
62. Lilly employees
63. Unwilling or unable to comply with study diary or questionnaire completion required to record data from the participant

5.2.1. Rationale for Select Exclusion Criteria

Marijuana should not be used during the study because there are mixed data on its effect on the liver, particularly in NASH. Use of CBD oil is also discouraged because there are data indicating that it can raise liver enzymes, which could result in unnecessary follow up tests.

5.3. Lifestyle Considerations

Medical staff will provide weight management counseling per the SoA (Section 1.3), which will include recommendations on diet and physical activity according to site programs. Based on the counseling provided by the site personnel, participants should follow a healthy lifestyle plan throughout the course of the study. Diet and physical activity counseling may be reviewed throughout the study as needed. Appendix 6 (Section 10.6) provides suggested diet and physical activity recommendations for sites that do not have programs and that may be modified as appropriate locally.

Patients will report to the clinical research site for safety assessments and will remain in the clinic until all procedures for that visit are complete and the investigator has deemed it safe to release the patient from the clinic. There will be no inpatient stays. In addition, patients will report to the clinical research site for pharmacokinetic (PK)-specific visits.

Meals/Diet – Patients will fast for at least 8 hours overnight prior to each outpatient visit where fasting samples are drawn or for at least 8 hours when weight measurements are taken.

Alcohol – Alcohol will not be permitted 8 hours prior to the study site visits, until the patient has been discharged from the clinical research site.

Blood Donation – 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 intervention due to not meeting inclusion and/or exclusion criteria. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (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 the criteria for participation in this study (screen failures) may be rescreened only once at the discretion of the investigator. Before rescreening is performed, the patient must sign a new ICF and receive a new identification number. If, in the opinion of the investigator, an ineligible lab test result is the result of an error or extenuating circumstance, then that parameter can be retested once without the patient having to be rescreened.

Patients who did not meet eligibility criteria for liver biopsy or the histological inclusion criteria based on liver biopsy results may not be rescreened.

Patients whose screening HbA1c is outside of inclusion/exclusion criteria may be rescreened 3 months after adjustments in allowed glucose-lowering medications are made. While patients on stable doses of DPP-4 inhibitors are eligible for study entry, treatment with DPP-4 inhibitors needs to be discontinued prior to randomization. For patients treated with a DPP-4 inhibitor and whose HbA1c is ≤8% at the screening visit, this medication must be discontinued with no repeat screening required; the randomization visit should occur approximately 3 months after the screening visit and discontinuation of the DDP-4 inhibitor so that a new baseline HbA1c may be established at randomization. For patients treated with a DPP-4 inhibitor and whose HbA1c is >8% but ≤9.5% at the screening visit, this medication must be discontinued for eligibility into the study, but a rescreening laboratory collection will be required to ensure that the HbA1c is ≤9.5% prior to the liver biopsy (Visit 2).

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

The following table shows the randomized study interventions for the entire study. All doses will be administered SC QW using a single-dose prefilled syringe.

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 52
15 mg tirzepatide	2.5 mg	5 mg	7.5 mg	10 mg	12.5 mg	15 mg →
10 mg tirzepatide	2.5 mg	5 mg	7.5 mg	10 mg →		
5 mg tirzepatide	2.5 mg	5 mg →				
Placebo	→					

The sponsor will provide tirzepatide and placebo in prefilled syringes. These will be dispensed via an interactive web-response system (IWRS). Prefilled syringes will be packaged in cartons to be dispensed. Clinical trial materials will be labeled according to the country's regulatory requirements.

The actual time of dose administrations will be transcribed in patient diaries and provided to the sponsor.

The investigator or designee is responsible for the following:

- Explaining the correct use of the investigational agent to the participant
- Verifying that instructions are followed properly
- Maintaining accurate records of investigational product dispensing and collection as well as records of interruptions in study drug administration
- Instructing the participant to discard all used syringes for tirzepatide in a closeable, puncture-resistant container and dispose according to local regulations

6.1.1. Medical Devices

Tirzepatide and matching placebo will be provided in prefilled syringes.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are

reported and resolved before use of the study intervention. Refer to the study drug label for specific storage conditions.

2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is: receipt, reconciliation, and final disposition records).

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a double-blind study. Patients will be stratified at randomization based on T2DM status (Yes or No) and the region (Japan, US including Mexico, and Europe including Israel). Stratification will ensure the number of patients in each stratum will be balanced across different treatment arms.

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

Emergency unblinding for AEs may be performed through the IWRS, which may supplement or take the place of emergency codes generated by a computer drug-labeling system. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All calls resulting in an unblinding event are recorded and reported by the IWRS.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

6.4. Study Intervention Compliance

Study drug compliance will be determined by the following:

- Study drug administration data will be recorded by the patient in the patient study diary and reviewed by the investigator at each study visit.
- The patients 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 for each visit interval is defined as taking at least 75% of the required doses of study drug. Similarly, a patient will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more or less than the prescribed amount of medication.

In addition to the assessment of a patient's compliance with the study drug administration, other aspects of compliance with the study treatments will be assessed at each visit based on the patient's adherence to the visit schedule, completion of study diaries, and any other parameters the investigator considers necessary.

Initially, patients 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 and acetaminophen/paracetamol), vitamins, and/or herbal supplements 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

The Medical Monitor 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 patients receiving oral medicinal products that require rapid gastrointestinal absorption following the initial doses of tirzepatide as exposure to oral medications may be increased.

6.5.1. Hyperglycemia Rescue

Although the use of rescue medications is allowable during the study, the use of rescue medications should be delayed, if possible, for at least 1 month after initiation of study drug. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

6.5.1.1. Hyperglycemia Rescue Criteria

Hyperglycemia rescue criteria will be determined from weekly fasting self-monitored blood glucose (SMBG) values recorded in T2DM participant diaries. If an SMBG value equal or greater to the glycemic threshold for rescue (See definitions below) is recorded, that value should be confirmed by repeat fasting SMBG within 48 hours. 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) post-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 26 or later in the study, glucose-lowering therapy should be adjusted to improve glycemic control as outlined in Section 6.5.1.2. 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 patients develop symptoms of hyperglycemia (e.g. polyuria and polydipsia), the investigator should implement measures to determine glycemic control, and adjust as necessary. For patients newly diagnosed with T2DM during the trial, SMBG and appropriate glucose-lowering therapy should be initiated per protocol (Section 6.5.1.2).

6.5.1.2. Hyperglycemia Rescue Medication

Participants with T2DM who develop persistent severe hyperglycemia during the treatment period may be candidates for glucose-lowering rescue therapy and should be considered for addition of, or dose increases of, glucose-lowering medications.

The study site will supply rescue medication that will be obtained locally. Initiation or dose increase of the following may be used as rescue therapy:

- Metformin
  - Do not initiate or increase the dose of metformin when the eGFR <45 mL/min/1.73 m^2 (or lower than country-specific threshold for using the prescribed dose of metformin per local label)
- Sulfonylureas
- Long-acting basal insulin, when
  - Participant has persistent severe hyperglycemia, and
  - Participant is at maximal tolerated doses of metformin and/or sulfonylurea (or has an intolerance or contraindication to these medications)

Dose increases of the following are NOT allowed during the study:

- SGLT-2 inhibitors
- TZDs

Initiation of the following is NOT allowed during the study:

- GLP-1 receptor agonists (See Section 5.2)
- DPP-4 inhibitors (See Section 5.2).
- SGLT-2 inhibitors
- TZDs

While avoiding the classes of glucose-lowering medications not allowed by the protocol, investigators should follow national standards of care for diabetes management in respective

participating countries or the American Diabetes Association/European Association for the Study of Diabetes guidance (Inzucchi et al. 2015).

6.5.2. Management of Participants with Gastrointestinal Symptoms

In the Phase 2 program, the most commonly reported treatment-emergent adverse events (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 patients 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, patients 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 patient needs. Use of symptomatic medication should be captured as concomitant medication in the eCRF.
- Temporarily interrupt study drug (omit 1 dose, the patient will take 3 of 4 doses at that dose level). The data related to temporary interruption of study treatment should be documented in source documents and entered on the eCRF.
- After the interruption, restart at the same dose with the patient taking medication to alleviate their GI symptoms.

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

6.6. Dose Modification

Patients who do not tolerate the first dose escalation, in other words from 2.5 mg to 5 mg (or placebo equivalent), will need to discontinue from study treatment. If a patient does not tolerate a dose level higher than 5 mg for 2 weeks (e.g., moderate-to-severe nausea, vomiting, or diarrhea) and the investigator does not believe that the patient will tolerate the dose with further exposure, then the investigator may reduce the dose to the next lower 5 mg incremental dose (e.g., 5 mg or 10 mg). If this dose is tolerated after 4 weeks, the dose should be increased by 2.5 mg every 4 weeks until the target dose is achieved. If this dose escalation is not tolerated, the dose should be reduced to the next lower 5 mg incremental dose that was tolerated (e.g., 5 mg or 10 mg). The patient will remain at that dose level for the duration of the study. Maintenance doses of 2.5 mg, 7.5 mg, or 12.5 mg will not be allowed.

In order to maintain blinding of the investigator and patient, the investigator should call the IWRS to explain that the patient needs the dose reduced and IWRS will provide dispensing information. Dose reductions may occur at unscheduled visits.

6.7. Intervention after the End of the Study

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

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Possible reasons leading to permanent discontinuation of investigational product:

- Subject Decision
  - the participant or the participant's designee (for example, parents or legal guardian) requests to discontinue investigational product.
- Investigator Decision
  - the investigator decides that the patient should be discontinued from the study medication
- Any medication for weight loss is given for more than 1 week
- Participants will be discontinued from the investigational product in the following circumstances:
  - Diagnosis of cirrhosis after randomization (refer to Section 8.3.7.1 for details)
  - Pancreatitis or pancreatic cancer (refer to Section 8.3.7.2 for details)
  - Diagnosis of MTC after randomization
  - Diagnosis of an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) after randomization
  - Any severe injection site reaction, or 2 or more moderate injection site reactions occurring a week or more apart
  - Any significant study drug-related hypersensitivity reaction
  - Any TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study drug discontinuation is the appropriate measure to be taken
  - Any TEAE or SAE considered possibly or probably related to study drug that is severe or medically significant but not immediately life-threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living
  - Any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or urgent intervention is indicated
  - A female participant becomes pregnant
  - Diagnosis of T1DM or latent autoimmune diabetes in adults
- If the patient develops any exclusion criteria during the course of the study, the investigator should call the sponsor to determine whether discontinuation of study drug is necessary

- Significant non-compliance with the protocol

If study drug is permanently discontinued, the patient should remain in the study if possible. The patient may continue participation in the study, attend all visits, and undergo most protocol procedures.

Participants discontinuing from the investigational product prematurely for any reason should complete AE and other follow-up procedures per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of the protocol.

7.1.1. Interruption of Study Intervention

After randomization, the investigator may interrupt study drug, for example, due to an AE (e.g., nausea and vomiting), or a clinically significant laboratory value. If study drug interruption is due to an AE, the event is to be followed and documented. Every effort should be made by the investigator to maintain patients in the study and to restart study drug promptly after any interruption, as soon as it is safe to do so (See Section 7.1.2 for restarting study drug). The dates of study drug interruption and restart must be documented. The data related to interruption of study treatment will be documented in source documents and entered on the eCRF. Patient noncompliance should not be recorded as interruption of study drug on the eCRF.

7.1.2. Restarting Study Drug after Interruption

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

- If the number of consecutive missed doses is ≥3, then the treatment should be restarted at 5 mg irrespective of the dose the patient was receiving before the interruption and subsequently follow the original dose escalation scheme (i.e., beginning at 5 mg with 2.5 mg dose increments every 4 weeks to reach the assigned dose level). See Section 6.6 for guidance on dose escalation/maintenance for patients who do not tolerate a dose level of tirzepatide.
- The investigator will use the IWRS to receive the appropriate study drug dispensing information to preserve blinding of the study drug

7.1.3. Interruption/Discontinuation due to a Hepatic Event or Liver Test Abnormality

Participants who are interrupted/discontinued from investigational product due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via case report form (CRF).

Interruption/discontinuation of the investigational product for abnormal liver tests should be considered by the investigator when a participant meets one of the following conditions after consultation with the Lilly-designated medical monitor. These criteria differ based on the baseline liver test findings and are summarized below (Regev et al. 2019). If study drug is interrupted, it can be restarted only if another etiology is identified and liver enzymes return to baseline.

For participants with baseline ALT <1.5 X ULN and normal baseline bilirubin:

- ALT or AST >8 X ULN
- ALT or AST >5 X ULN for more than 2 weeks
- ALT or AST >3 X ULN and total bilirubin level (TBL) >2 X ULN or INR >1.5
- ALT or AST >5 X ULN with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 X ULN
- ALP >2.5 X ULN and TBL >2 X ULN
- ALP >2.5 X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

For participants with baseline ALT ≥1.5 X ULN and normal baseline bilirubin:

- ALT >5 X baseline or ≥500 U/L (whichever occurs first)
- ALT >2 X baseline or ≥300 U/L (whichever occurs first) and TBL >2 X ULN
- ALT >3 X baseline or ≥300 U/L (whichever occurs first) with the appearance of fatigue, nausea, vomiting, right upper-quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)
- ALP >3 X ULN
- ALP >2.5 X ULN and TBL >2 X ULN
- ALP >2.5 X ULN with the appearance of fatigue, nausea, vomiting, right quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

7.2. Participant Discontinuation/Withdrawal from the Study

Participants will be discontinued in the following circumstances:

- Enrollment in any other clinical study involving an investigational product 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 good clinical practice (GCP)
- Investigator decision
  - the investigator decides that the participant should be discontinued from the study
  - if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- Participant decision
  - the participant or the patient's designee, (for example, parents or legal guardian) requests to be withdrawn from the study

Participants discontinuing from the study prematurely for any reason should complete AE and other safety follow-up per Section 1.3 (Schedule of Activities), Section 8.3 (Adverse Events and Serious Adverse Events), and Section 8.2 (Safety Assessments) of this protocol.

7.2.1. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a participant who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site. Site personnel 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.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get investigational product. Public sources may be searched for vital status information. If vital status is determined, this will be documented and the participant will not be considered lost to follow-up.

Lilly 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 Section 10.1.7.2.

8. Study Assessments and Procedures

Unless otherwise stated in the subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

Study procedures and their timing are summarized in the SoA (Section 1.3). Protocol waivers or exemptions are not allowed.

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

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

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

Procedures conducted as part of the participant's routine clinical management (e.g., ophthalmic exam) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

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

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessment

The primary efficacy measurement in this study is NASH resolution with no worsening of fibrosis based on liver histology at Week 52 compared with baseline.

In alignment with United States (US) Food and Drug Administration (FDA) draft guidance (FDA 2018) and the EMA reflection paper (EMA 2018), NASH resolution will be defined as:

- absence of fatty liver disease or simple steatosis without steatohepatitis;
- the absence of hepatocellular ballooning (NAS 0 for ballooning)
- with or without mild lobular inflammation (NAS 0 or 1 for inflammation), and
- any value for steatosis.

No worsening of fibrosis will be defined as no increase in fibrosis stage from baseline to Week 52.

Liver histology will be evaluated via liver biopsies collected at baseline in participants for whom a liver biopsy of adequate quality performed within 6 months of screening is unavailable, and at Week 52 (end-of-treatment) in all participants who remained on study drug. Patients who discontinued study drug prior to Week 36 will not have a second liver biopsy.

Histology will be scored according to the NASH CRN guidelines (Kleiner et al. 2005; Puri and Sanyal 2012). Pathologists reviewing the liver biopsies will be blinded to treatment group. Intra- and inter-observer variability in assessment of histology will be assessed. The glass slides may be scanned to facilitate future additional exploratory analyses of the whole slide images.

Liver biopsy tissue block and slides will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and 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.

8.1.1.1. Baseline Liver Biopsy

The baseline liver biopsy used for assessment may be a biopsy performed in the line of standard care or be a new biopsy performed as part of screening, as described below.

A prior liver biopsy may be used for screening and assessment purposes when the biopsy

- was taken within 6 months of screening,
- is available for review, and
- is of adequate quality.

In the case that a liver biopsy was performed previously, the investigator should confirm if the tissue block and/or additional slides can be obtained. The liver biopsy will then be analyzed by 2 central pathologists to confirm that the biopsy is of adequate quality and there is histological evidence of NASH and fibrosis stage as defined in inclusion criterion 5 (Section 5.1). Clinical staff should note that the date of the historical liver biopsy establishes a hard window for completion of screening: screening must take place within 6 months of the date of the liver biopsy. If the liver biopsy is more than 6 months old when the participant enters screening, a new baseline liver biopsy is required.

When an acceptable liver biopsy is unavailable, one must be obtained for analyses by the 2 central pathologists. A screening liver biopsy must only be collected after patients have completed all screening assessments designated at Visit 1, met inclusion/exclusion criteria, and thus, have a high likelihood of having NASH. For participants using aspirin and/or NSAIDs, it is left to the discretion of the investigator whether or not to temporarily discontinue these medications prior to the liver biopsy procedure.

8.1.1.2. Liver Biopsy Method

The quality of the histologic data obtained by liver biopsy is affected by several factors including the manner of procurement, the type of biopsy, biopsy location, dimensions of the biopsy core and the inherent variability in the subjective assessment of liver histology (Sanyal et al. 2011). For this trial, the recommended method is a percutaneous biopsy obtained from the right lobe of the liver, if possible, and with at least a 16-gauge instrument. Other biopsy methods, including transvenous (e.g., transjugular) methods or more than one sample obtained with a narrower bore (e.g., 18 gauge) instrument, may be used based on specific clinical considerations (e.g., morbid obesity) or local expertise (Rockey et al. 2009). The method employed for liver biopsy should be recorded in source documents and entered on the eCRF. Whichever method is employed, the

liver biopsy tissue should be of adequate size (20 mm or more in length is preferred). Two central pathologists will assess the quality of the biopsy. Specimens that are inadequate for evaluation of histology will not be acceptable for inclusion of patients in the trial.

8.1.1.3. End-of-Treatment Biopsy

The biopsy should be obtained as described above for the baseline liver biopsy at the time specified in the SoA. Ideally, the same procedure that was used for the baseline liver biopsy should be employed, so that a change in procedure is not a reason for changes in histological features. Similarly, the end-of-treatment biopsy should be obtained from the same lobe of the liver as the initial biopsy whenever possible. In the event a participant either discontinues study drug or terminates early from the study, end-of-treatment liver biopsies may be performed if the:

- participant has been on treatment for at least 36 weeks, and
- the liver biopsy should be performed within 2 weeks of treatment discontinuation.

8.1.1.4. Risk Mitigation for Liver Biopsies

The risk of bleeding is greatest initially after liver biopsy; thus, it is recommended that patients are observed carefully over the first several hours after biopsy. Consensus guidelines for mitigating the risk of liver biopsies have been published (Rockey et al 2009). This guidance states that vital signs should be frequently monitored (at least every 15 minutes for the first hour) after liver biopsy. The minimum recommended observation time after biopsy is between 2 to 4 hours but may vary depending on local expertise and practice. Platelet count and INR should be measured prior to liver biopsy, as noted in the SOA. The decision to perform liver biopsy in the setting of abnormal laboratory parameters of hemostasis should be reached as the result of local practices.

8.1.2. Secondary Efficacy Assessments

8.1.2.1. Histology Determined from Liver Biopsy

- NAS
- Fibrosis stage

8.1.2.2. Liver Fat Content Determined from Magnetic Resonance Imaging

As part of the magnetic resonance imaging (MRI) evaluation, liver fat content will be determined using MRI – Proton Density Fat Fraction (MRI-PDFF). The fat fraction is the proportion of mobile protons in liver tissue attributable to fat, and is a noninvasive MRI-based biomarker of liver triglyceride concentration.

Participants will undergo 3 liver-directed MRI evaluations as outlined in the SoA (Section 1.3). MRI images will be transmitted to a central reader for evaluation of the MRI-based efficacy endpoints. For patient safety, images should also be over-read locally to assure there are no underlying liver pathologies other than NASH.

In the event of early termination from the study drug or the study,

- the second MRI exam may be performed when
  - the participant has been on treatment for at least 16 weeks, and
  - within 2 weeks of treatment discontinuation

- the third MRI exam may be performed
  - when the participant has been on treatment for at least 36 weeks, and
  - within 2 weeks of treatment discontinuation

MRIs will be performed after a fast of at least 6 hours. Participants are allowed to take necessary medications and small quantities of water during the fast. Additional exclusion criteria apply for MRI examination eligibility, which do not count toward eligibility for study participation. These exclusions are:

- a contraindication to MRI examinations
- extreme claustrophobia
- weight or girth exceeds the scanner capabilities
- any condition or circumstance that, in the opinion of the investigator, would interfere with completion of MRI examinations

For patients with claustrophobia in MRI machines, investigators may offer, at their discretion, a light sedative. However, if the patient is not willing to attempt MRI with light sedation, the patient should be excluded from the MRI evaluation but should not be excluded from the study.

8.1.2.3. Body Weight

Patients will be weighed on an electronic scale in light clothing at approximately the same time after an overnight fast (or fast of at least 8 hours) and evacuation of any bowel and bladder contents. See Appendix 5 (Section 10.5). The scale's performance will be monitored at least monthly using standard weights, and records of these assessments will be kept in the study binder.

8.1.3. Exploratory Efficacy Assessments

8.1.3.1. Histology Determined from Liver Biopsy

Additional histological measures will be scored by the pathologists. These will include

- Expanded ballooning score
- Expanded portal inflammation score
- Expanded fibrosis stage 1 scores
- Mallory-Denk body score
- Glycogenosis score
- Scores for steatosis, hepatocellular ballooning, and lobular inflammation
- NASH resolution based on overall assessment by pathologists

8.1.3.2. Magnetic Resonance Imaging – Iron-Corrected T1 Imaging

During the MRI exam described above (Section 8.1.2.2), iron-corrected T_1 imaging of the liver will be performed to measure hepatic extracellular fluid content, which has been shown to correlate with hepatic inflammation and fibrosis (Pavlides et al. 2017). MRI images will be transmitted to a central reader for evaluation.

8.1.3.3. Transient Elastography (TE)

CAP and LSM will be measured by TE (FibroScan) by experienced operators and per manufacturer's recommendations. TE measurements will be performed after a fast of at least 3 hours. Participants are allowed to take necessary medications and small quantities of water during the fast.

For screening purposes, TE may be considered unreliable if the LSM interquartile range (IQR) divided by median LSM is greater than 30% (Hsu et al. 2019) or if the CAP IQR is >30 dB/m (Caussy et al. 2018). In the event that TE is unreliable, the alternate criteria for eligibility for liver biopsy may be used (See Section 5.1, inclusion criterion 5). In addition, the alternate criteria for eligibility for liver biopsy may be used if the LSM is >7.1 but ≤7.6 kPa and/or the CAP is >283 but ≤288 dB/m.

In the event of early termination from the study drug or the study,

- the second TE exam may be performed when
  - the participant has been on treatment for at least 16 weeks, and
  - within 2 weeks of treatment discontinuation
- the third TE exam may be performed
  - when the participant has been on treatment for at least 36 weeks, and
  - within 2 weeks of treatment discontinuation

8.1.3.3.1. Screening FibroScan-AST (FAST) Score

The FAST score is used to identify patients with NASH who have NAS ≥4, and fibrosis stage ≥2 as part of the inclusion criteria to reduce the number of patients who have a non-qualifying liver biopsy. The score is based on a calculation (below) that includes the FibroScan LSM, the CAP, and AST level. A value of FAST ≤0.35 had a negative predictive value of 0.85 in the derivation cohort (n=350) and 0.94 in the pooled external validation cohorts (n=1026) (Newsome et al. 2020). For Study GPHR, the FAST score must be >0.35 for a patient with a valid FibroScan to be eligible for screening liver biopsy. The FAST score will be provided by the central laboratory.

FAST Score Calculation:

$$\text{FAST} = \frac{e^{-1.65+1.07\times\ln(\text{LSM})+2.66\times10^{-8}\times\text{CAP}^3-63.3\times\text{AST}^{-1}}}{1+e^{-1.65+1.07\times\ln(\text{LSM})+2.66\times10^{-8}\times\text{CAP}^3-63.3\times\text{AST}^{-1}}}.$$

In this formula, "*e*" denotes the exponential constant, also known as Euler's number, and "ln" denotes the natural logarithm function.

8.1.3.4. Biomarkers

Biomarkers will be collected during the study according to the SoA (Section 1.3) and change from baseline will be analyzed.

See Section 8.8 for more information on biomarkers.

8.1.3.5. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

The effect of tirzepatide on insulin sensitivity will be evaluated based on the change from baseline in HOMA-IR.

8.1.3.6. Waist Circumference

Waist circumference will be collected according to the SoA (Section 1.3). Waist circumference should be measured at the midpoint between the lower margin of the least palpable rib and the top of the iliac crest. The patient should stand with feet close together, arms at the side and body weight evenly distributed, and should wear little clothing. The patient should be relaxed, and the measurements should be taken at the end of a normal expiration. The measurement should be repeated. If the difference between the 2 measurements exceeds 1 cm, the 2 measurements should be repeated.

8.1.3.7. Patient Reported Outcomes (PRO)

Patient Global Impression of Severity (PGIS)

The PGIS is designed to assess the patients' overall perception of disease condition. This is a single global item that asks participants to rate the overall severity of their NASH disease condition in the past 7 days on a 5-point scale ranging from "no symptoms" to "very severe."

Chronic Liver Disease Questionnaire for Nonalcoholic Fatty Liver Disease (CLDQ-NAFLD)

The Chronic Liver Disease Questionnaire – Nonalcoholic Fatty Liver Disease (CLDQ-NAFLD) is a disease-specific instrument consisting of 36 items that assess 6 domains: Abdominal Symptoms (3 items), Activity/Energy (5 items), Emotional Health (9 items), Fatigue (6 items), Systemic Symptoms (6 items), and Worry (7 items) (Younossi et al. 2017). Items are rated on a 7-point scale ranging from "1 – All of the time" to "7 – None of the time." Scores are calculated separately for each domain by taking the average of the domain's items. A total score is calculated by taking the average of the domain scores. Higher scores reflect better health. The CLDQ-NAFLD was originally developed with a recall period of "the last 2 weeks," but for this study, permission has been obtained from the developers to modify the recall period to "the last week." The CLDQ-NAFLD has previously been validated in people with NASH with F3 and F4 fibrosis (Younossi et al. 2019).

PROMIS Short Form Fatigue 8a v1.0

The Patient-Reported Outcome Measurement Information System (PROMIS) is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children (Health Measures [WWW]). It can be used with the general population and with individuals living with chronic conditions. The PROMIS Short Form Fatigue 8a assesses self-reported symptoms from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally. The PROMIS Short Form Fatigue 8a consists of 8 items each rated on a 5-point scale ranging from "1 - not at all" to "5 - very much." Items have a recall period of "the past 7 days." Individual item scores are totaled to obtain a raw score, with higher scores indicating more interference. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a standard deviation (SD) of 10.

PROMIS Short Form Pain Interference 4a v1.0

The PROMIS Short Form Pain Interference 4a assesses consequences of pain on relevant aspects of one's life. This includes the extent to which pain hinders engagement with social, cognitive, emotional, physical, and recreational activities. The PROMIS Short Form Pain Interference 4a

consists of 4 items that asks participants to rate their pain interference over the past 7 days on a 5-point scale ranging from "1 - not at all" to "5 - very much." Individual item scores are totaled to obtain a raw score, with higher scores indicating more interference. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and an SD of 10.

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 be performed at screening. Additional physical examinations may be performed throughout the study if determined necessary due to participant symptoms.

8.2.2. Vital Signs

Sitting BP, pulse rate, and body temperature will be measured according to Section 1.3. Vital sign measurements should be taken before obtaining an electrocardiogram (ECG) tracing and before collection of blood samples for laboratory testing, at visits where required (See Section 1.3). The participant should be required to sit quietly for 5 minutes before vital sign measurements are taken. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure the accuracy of BP measurements. The arm used for the BP measurement should be supported at heart level. At Visit 1 (screening), to determine which arm should be used to collect BP and pulse rate throughout the study, BP and pulse rate will be measured once in each arm, and the arm that had the higher systolic BP should be used to collect both measurements of both BP and pulse rate at all study visits. For each parameter (PR, systolic BP, and diastolic BP), 2 measurements will be taken using the same arm; the recordings should be taken at least 1 minute apart, and each measurement of sitting pulse rate and BP will be recorded in the eCRF; temperature does not need to be recorded in the eCRF. Any AE related to changes in BP and pulse rate should be reported.

8.2.3. Electrocardiograms

For each patient, 12-lead ECGs should be collected according to Section 1.3. Patients must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.

Electrocardiograms should be recorded in triplicate according to study-specific recommendations included in the Manual of Operations for the study, using standardized equipment provided by the sponsor.

Consecutive replicate ECGs will be obtained at approximately 1-minute intervals.

Electrocardiograms may be obtained at additional times, when deemed clinically necessary. Collection of more ECGs than expected at a particular time point is allowed when needed to ensure high-quality records.

Electrocardiograms will initially be interpreted by a qualified physician (the investigator or qualified designee) at the site as soon after the time of ECG collection as possible, and ideally while the patient is still present, to determine whether the subject meets entry criteria and for

immediate subject management, should any clinically relevant findings be identified. Any clinically significant findings from ECGs that result in a diagnosis and that occur after the patient receives the first dose of the investigational treatment should be reported to Lilly or its designee as an AE. The investigator (or qualified designee) is responsible for determining if any change in patient management is needed, and must document his/her review of the ECG printed at the time of evaluation.

After enrollment, if a clinically significant increase in the QT/QTc interval from baseline or other clinically significant quantitative or qualitative change from baseline is identified, the patient will be assessed by the investigator for symptoms (e.g., palpitations, near syncope, and syncope) and to determine whether the patient can continue in the study. The investigator or qualified designee is responsible for determining if any change in patient management is needed and must document his/her review of the ECG printed at the time of evaluation from at least 1 of the replicate ECGs from each time point.

All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory. The central ECG laboratory will perform a basic quality control check (e.g., demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be over-read by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and heart rate may be used for data analysis and report-writing purposes, unless a cardiologist over-reading of the ECGs is conducted prior to completion of the final study report (in which case, the over-read data would be used).

In addition, for each patient, a single ECG will be recorded at screening and if the patient discontinues from the study prematurely for immediate patient management. These ECGs will be stored at the investigation site.

Any treatment-emergent clinically significant ECG finding resulting in a diagnosis should be reported as an AE in the eCRF.

8.2.4. Clinical Safety Laboratory Assessments

With the exception of laboratory test results that may unblind the study, Lilly 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 and to the SoA (Section 1.3) for the timing and frequency.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 1 month after the last dose of study intervention should be repeated until

the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

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

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

If laboratory values from nonprotocol specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.4.1. Immunogenicity Assessment

Where local regulations and ERBs allow, blood samples for immunogenicity testing will be collected to determine antibody production against tirzepatide as specified in the SoA (Section 1.3).

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against tirzepatide. To interpret the results of immunogenicity, a PK sample will be collected at the same time points as the immunogenicity samples in all post-baseline samples to determine the plasma concentrations of tirzepatide. All samples for immunogenicity should be collected predose when applicable and possible.

Additional samples (including ADA, PK, and exploratory immune safety samples) may be collected if there is a possibility that an AE is immunologically mediated (See Section 8.3.7.10) "Hypersensitivity Events"). Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded. Sample collected at Visit 801 will assess immunogenicity at washout of tirzepatide (5 half-lives post end of treatment).

Treatment-emergent ADA are defined in Section 9.4.6.

A risk-based approach will be used to monitor patients who develop treatment-emergent ADA after treatment with tirzepatide. Clinically significant treatment-emergent ADA will be defined as any treatment-emergent ADA at the follow-up visit (Visit 801) with:

- A high (≥1:1280) or increasing titer at the follow-up visit (V801)
- An association of treatment-emergent ADA with a moderate-to-severe injection site reaction or infusion-related reaction

Patients who are treatment-emergent-ADA positive at the last scheduled assessment or discontinuation visit will have additional samples taken at 3, 6, 9 (optional), and 12 months postlast assessment until the titer returns to within 2-fold of baseline titer or for up to 1 year, whichever is less. Patients followed for at least 1 year since last dose who have not returned to baseline as defined above will be assessed for safety concerns. If no clinical sequelae is recognized by the clinical team, then no further follow-up will be required.

Immunogenicity will be assessed by a validated assay designed to detect and titer ADA in the presence of tirzepatide at a laboratory approved by the sponsor. Samples with detected ADA

will be tested for cross-reactivity binding to native GIP and GLP-1. Antidrug antibodies may be further evaluated for their ability to neutralize the activity of assigned treatment (tirzepatide neutralizing antibodies). Antidrug antibody samples with detected cross-reactive binding to native GIP and/or GLP-1 may be further evaluated for neutralizing antibodies against native GIP and/or GLP-1, respectively.

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 the tirzepatide. Any samples remaining after 15 years will be destroyed.

8.2.4.2. Hepatic Safety Monitoring

Participants with NASH may have normal or elevated ALT and fluctuations of ALT are part of the natural course of the disease. Therefore, assessment of possible drug-induced liver injury (DILI) must take into account the baseline ALT (Regev et al. 2019). Possible DILI will be adjudicated by a committee of physicians external to Lilly with hepatic expertise. This committee will be blinded to study assignment. Additional clinical and laboratory monitoring (Appendix 3 Section 10.3) is required if a participant experiences any of the following elevations of liver tests while in the study.

For participants with baseline ALT <1.5 X ULN and normal baseline bilirubin:

- Elevation of ALT ≥5 X ULN
- Elevation of ALT ≥3 X ULN and presence of severe fatigue, nausea, vomiting, right upper quadrant pain
- Elevation of ALP ≥2 X ULN
- Elevation of TBL ≥2 X ULN

For participants with baseline ALT ≥1.5 X ULN and normal baseline bilirubin:

- Elevation of ALT ≥3 X baseline or ≥300 U/L (whichever occurs first)
- Elevation of ALT ≥2 X baseline or ≥300 U/L (whichever occurs first) and presence of severe fatigue, nausea, vomiting, right upper quadrant pain
- Elevation of ALP ≥2 X ULN
- Elevation of TBL ≥2 X ULN

Baseline ALT is derived from an average of 2 pretreatment ALT measurements at least 2 weeks apart. Elevated baseline is defined as ALT ≥1.5 X ULN. In participants with a sizable stable decrease in ALT (>50% of the baseline value) during treatment, a new baseline, corresponding to the ALT nadir, should be established on an individual basis for subsequent determination of a possible DILI signal.

For participants with Gilbert's syndrome, the criterion of elevation of TBL ≥2X ULN should be replaced by a doubling of direct bilirubin or increased INR to >1.5.

If a study participant meets any of the above criteria during the study, liver testing (Section 10.3) should be repeated within 48 to 72 hours including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical

monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Additional safety data should be collected via eCRF if 1 or more of the following conditions occur:

- participant meets any of the above criteria that trigger additional hepatic safety monitoring on 2 or more consecutive blood tests
- participant discontinued from treatment due to a hepatic event or abnormality of liver tests
- hepatic event considered to be an SAE

8.3. Adverse Events and Serious Adverse Events

Investigators are responsible for monitoring the safety of participants who have entered this study and for alerting Lilly or its designee to any event that seems unusual, even if this event may be considered an unanticipated benefit to the participant.

The investigator is responsible for the appropriate medical care of participants during the study.

Investigators must document their review of each laboratory safety report.

The investigator remains responsible for following, through an appropriate health care option, AEs that are serious or otherwise medically important, considered related to the investigational product or the study, or that caused the participant to discontinue the investigational product before completing the study. The participant should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is otherwise explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

After the ICF is signed, study site personnel will record via eCRF the occurrence and nature of each participant's preexisting conditions, including clinically significant signs and symptoms of the disease under treatment in the study. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure or investigational product via eCRF.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment or pathologies.

A "reasonable possibility" means that there is a cause and effect relationship between the investigational product, study device, and/or study procedure and the AE.

The investigator answers yes/no when making this assessment.

Planned surgeries and nonsurgical interventions should not be reported as AEs unless the underlying medical condition has worsened during the course of the study.

If a participant's investigational product is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via eCRF, clarifying if possible, the circumstances leading to any dosage modifications, or discontinuations of treatment.

Serious Adverse Events

An SAE is any AE from this study that results in one of the following outcomes:

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs occurring after signing the ICF are recorded in the eCRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the participant has signed the ICF and has received investigational product. However, if an SAE occurs after signing the ICF, but prior to receiving investigational product, the SAE should be reported to the sponsor as per SAE reporting requirements and timelines (See Section 8.3.1) if it is considered reasonably possibly related to study procedure.

Study site personnel must alert Lilly or its designee of any SAE within 24 hours of investigator awareness of the event via a sponsor-approved method. If alerts are issued via telephone, they are to be immediately followed with official notification on study-specific SAE forms. This 24-hour notification requirement refers to the initial SAE information and all follow-up SAE information. Participants with a serious hepatic AE should have additional data collected using the eCRF.

Pregnancy (during maternal or paternal exposure to investigational product) does not meet the definition of an AE. However, to fulfill regulatory requirements any pregnancy should be reported following the SAE process to collect data on the outcome for both mother and fetus.

Investigators are not obligated to actively seek AEs or SAEs in subjects once they have discontinued and/or completed the study (the participant disposition CRF has been completed). However, if the investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event reasonably possibly related to the study treatment or study participation, the investigator must promptly notify Lilly.

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 investigational product or procedure. United States 21 CFR 312.32 and European Union Clinical Trial Directive 2001/20/EC and the associated detailed guidances or national regulatory requirements in participating countries

require the reporting of SUSARs. Lilly 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 guidances.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All SAEs and AEs will be collected from the signing of the ICF through the follow-up visit at the time points specified in the SoA (Section 1.3).

Medical occurrences that begin before the start of study intervention but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the CRF not the AE section.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

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

8.3.2. Follow-Up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs, and nonserious AEs of special interest (as defined in Section 8.3.7), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 1.3).

8.3.3. Regulatory Reporting Requirements for SAEs

- 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 intervention under clinical investigation are met.
- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., 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.

8.3.4. Pregnancy

- Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until 1 month after the last dose of study drug for female participants and 3 months after the last dose of study drug for male participants.
- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 8 (Section 10.8).
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.5. Medical Device Incidents (Including Malfunctions)

Medical devices (prefilled syringes) are being provided for use in this study for administration of the study drug. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition and directions for reporting of a Medical Device Incident can be found in Appendix 7 Section 10.7).

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3.2.

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.3.6. Complaint Handling

Lilly collects product complaints on investigational products and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product or drug delivery system so that the situation can be assessed.

8.3.7. Adverse Events of Special Interest

The following are adverse events of special interest (AESI) and will be adjudicated by an external adjudication committee:

- NASH-related clinical events
- Pancreatitis
- Major adverse cardiovascular events
- Deaths

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

- Hepatobiliary disorders
- Hypoglycemia
- Thyroid malignancies and C-cell hyperplasia
- Supraventricular arrhythmias and cardiac conductive disorders
- Diabetic retinopathy complications
- Allergic/hypersensitivity reactions. Includes injection site reactions and ADA formation.
- Severe GI AEs
- Acute renal events

Sites should collect additional details and data regarding AESIs, as instructed on the applicable eCRFs, and detailed below.

8.3.7.1. NASH-Related Clinical Events

All TEAEs of cirrhosis, ascites (clinically evident), esophageal variceal hemorrhage, hepatic encephalopathy, subacute liver failure (including liver transplantation), hepatocellular carcinoma, increase in Model for End Stage Liver Disease (MELD) score >15 or liver-related mortality should be evaluated and additional diagnostic tests performed, as needed. These events will be adjudicated by an external adjudication committee.

Study drug should be discontinued for any patient who develops a clinical diagnosis of cirrhosis (e.g., evidence of hepatic decompensation, etc.) after randomization. For purposes of safety evaluation, patients with treatment-emergent cirrhosis may be followed in the study until study end, unless the investigator decides that the participant should be discontinued from the study.

8.3.7.2. 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 ≥3 X ULN
- Characteristic findings of acute pancreatitis on computed tomography (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. If laboratory values and/or abdominal imaging support the diagnosis of acute pancreatitis, the patient must discontinue therapy with tirzepatide but will continue in the study. A review of the patient'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 patient will have measurements of p-amylase and lipase (assessed at the central laboratory) as shown in Section 1.3 (SoA) to assess the effects of the investigational doses of tirzepatide on pancreatic enzyme levels. Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic patients (Nauck 2016; Steinberg et al. 2017a; Steinberg et al. 2017b). Thus, further diagnostic follow-up of cases of asymptomatic pancreatic hyperenzymemia (lipase and/or pancreatic amylase ≥3 X ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the patient'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 patients with acute or chronic pancreatitis and those with severe or serious abdominal pain will be entered into a specifically designed eCRF page by study site. The adjudication committee representative will enter the results of adjudication in a corresponding eCRF page.

8.3.7.3. Major Adverse Cardiovascular Events

Nonfatal cardiovascular (CV) AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment.

The nonfatal CV AEs to be adjudicated include:

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

8.3.7.4. Deaths

All deaths will be adjudicated by a committee of physicians external to Lilly. This committee will be blinded to treatment assignment.

8.3.7.5. Hepatobiliary Disorders

All events of TE 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 enzymes, hepatic monitoring should be initiated as outlined in Sections 8.2.4.2 and 10.3.

8.3.7.6. Hypoglycemia

Upon ICF signing, all participants will be educated about signs and symptoms of hypoglycemia and how to treat it. Additionally, at Visit 3 participants with T2DM will receive glucometers to monitor glycemia and will be trained on how to collect appropriate information for each episode of hypoglycemia in the study.

When diagnosing and categorizing an episode considered to be related to hypoglycemia, investigators should use definitions and criteria in accordance with the 2017 American Diabetes Association position statement on glycemic targets (ADA 2017), as described in Appendix 4 (Section 10.4).

Management of Hypoglycemia

Participants who develop persistent or recurrent hypoglycemic episodes (clinical symptoms of hypoglycemia and/or blood glucose [BG]-confirmed symptomatic BG hypoglycemia [BG concentration ≤3.0 mmol/L (54 mg/dL)]) during the treatment period will be asked to reduce the dose or discontinue any concomitant glucose-lowering medications.

- The occurrence of hypoglycemia with GLP-1 receptor agonists has been reported to be higher in patients receiving concomitant sulfonylurea therapy (Trujillo et al. 2015). For patients treated with a sulfonylurea, the occurrence of (a) hypoglycemic episode(s) should prompt consideration by the investigator of a dose reduction or discontinuation of the sulfonylurea.
- For participants who are not on a sulfonylurea but are on dual oral treatment of metformin and SGLT-2 inhibitors, in case of (a) hypoglycemic episode(s), the dose of metformin should be reduced or discontinued prior to reducing/discontinuing SGLT-2 inhibitors. The rationale for discontinuing metformin prior to SGLT-2 inhibitors is that the latter may have an effect on liver fat content (Ohki et al. 2016).
- When hypoglycemia develops in patients on any oral monotherapies, the dose of this oral medication should be reduced or discontinued.

Hypoglycemic episodes will be recorded on a specific eCRF. Information regarding severity, time of day, and investigator's opinion of relatedness to study drug and procedure will be recorded. Hypoglycemia episodes should not be recorded as AEs unless the event meets serious criteria.

Avoidance of Hypoglycemia

Temporary discontinuation of concomitant antihyperglycemic medications <14 consecutive days is allowed for certain clinical situations in order to avoid hypoglycemia (for example, severe dehydration, elective surgery, or need for radiologic examination involving intravenous iodinated contrast dye).

Tirzepatide has glucose-lowering efficacy (Frias et al. 2018). Thus, it is possible that some participants may achieve normal glycemia (e.g., HbA1c <5.7%) during the study. To avoid the potential for future hypoglycemia as the patient continues in the study, investigators may, at their discretion, choose to discontinue glucose-lowering medication other than study drug.

8.3.7.7. Thyroid Malignancies and C-Cell Hyperplasia

Individuals with personal or family history of MTC and/or multiple endocrine neoplasia type 2 (MEN-2) will be excluded from the study.

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.

Study drug should be discontinued (after first confirming the value) if postrandomization serum calcitonin value increases.

- For eGFR ≥60 mL/min: ≥20 pg/mL and has increased ≥50% over the screening value.
- For eGFR <60 mL/min: ≥35 pg/mL and has increased ≥50% over baseline.

A consultation with a thyroid specialist (if not available, an endocrinologist) should be obtained. If the increased calcitonin value is observed in a patient who has administered a medication that is known to increase serum calcitonin, this medication should be stopped and calcitonin levels should be measured after an appropriate washout period. If the confirmed calcitonin value is <20 pg/mL (eGFR ≥60 mL/min) or <35 pg/mL (eGFR <60 mL/min), tirzepatide should be restarted once safe to do so.

8.3.7.8. Supraventricular Arrhythmias and Cardiac Conduction Disorders

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

8.3.7.9. Diabetic Retinopathy Complications

Patients with T2DM who have a history of proliferative diabetic retinopathy, diabetic maculopathy, or severe nonproliferative diabetic retinopathy that requires acute treatment will be excluded from the protocol due to the potential risk of early worsening of retinopathy with the significant glucose lowering that is possible with tirzepatide.

For patients with T2DM, the results of a dilated retinal fundoscopic exam performed by an eye care professional (ophthalmologist or optometrist) within 12 months prior to randomization will

be recorded on the preexisting conditions and medical history eCRF as a baseline measure of retinopathy. A follow-up, dilated fundoscopic exam should be performed when clinically indicated by any AE suspected of worsening retinopathy, and the findings should be recorded as an AE.

8.3.7.10. 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. 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 if and when it is safe to do so, in the opinion of the investigator. If study drug is permanently discontinued, the patient should continue in the trial to collect all planned efficacy and safety measurements.

Lab testing should be performed at the time of a systemic hypersensitivity event. The management of the AE may warrant laboratory testing beyond that described below and should be performed as clinically indicated.

In the presence of generalized urticaria or if anaphylaxis is suspected and after the subject has been stabilized, samples described below should be obtained within 1-2 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. The time at which the sample was collected should be recorded and a follow-up sample should be obtained at the next regularly scheduled visit or after 4 weeks, whichever is later.

Analytes to be evaluated in the sample:

- Tryptase
- ADA and tirzepatide concentration (PK)
  - If a drug specific immunoglobulin E (IgE) assay is not available, a commercially available alternative test that can indicate the presence of drug-specific IgE in serum is the basophil activation test (BAT)
- Complement
  - C3a and C5a
- Cytokines
  - IL-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

8.3.7.11. Injection Site Reactions

All injection site reactions and information regarding their time of day, time relative to injection, size, amount of erythema, induration, and pruritus, as well as severity, will be recorded on specific CRFs. In addition, if the reaction is clinically significant, the site should attempt to contact the sponsor for potential follow-up procedures. Injection site reactions do not need to be recorded as AEs as well unless they meet SAE criteria.

8.3.7.12. Severe Gastrointestinal Adverse Events

Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the eCRF/AE form.

8.3.7.13. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute or worsening of chronic renal failure. GI AEs may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Patients should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

8.4. Treatment of Overdose

For this study, any dose of study drug greater than the highest possible dose (15 mg) and estimated from where the patient is in the dose-escalation regimen or treatment-maintenance regimen within a 2-day time period will be considered an overdose and should be reported as an AE. For example, if a patient is in the second month of the dose-escalation period, the presumed dose is 5 mg. A patient who takes presumed 5 mg injections 1 day apart would not be considered to have an overdose. However, if the patient was in the fourth month of dosing, was taking the presumed dose of 10 mg, and took injections 1 day apart, the patient would have received a presumed dose of 20 mg within 2 days and would be considered to have had an overdose.

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

1. Contact the Medical Monitor immediately.
2. Closely monitor the participant for any AE/SAE and laboratory abnormalities for at least 1 week. Based on the AE profile of tirzepatide, the following are the possible AEs related to an overdose:
    a. Severe GI events that lead to dehydration and require medical intervention.
    b. CV abnormalities such as increase in heart rate, decrease in BP, supraventricular arrhythmias/cardiac conduction disorders.
    c. Hypoglycemia.
3. Implement medical intervention/monitoring according to the clinical presentation.
4. Obtain a plasma sample for PK analysis as soon as possible from the date of the last dose of study intervention if requested by the Medical Monitor (determined on a case-by-case basis).
5. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic samples will be obtained from all patients. Plasma tirzepatide concentrations will be determined from blood samples obtained from patients randomized to tirzepatide

treatment at the visits and times specified in the SoA (Section 1.3). At each PK visit, the patient will be assigned to 1 of the 2 PK sampling windows (1 to 24 hours or 24 to 96 hour postdose) via IWRS. In addition, a PK sample will be obtained at each immunogenicity visit. For all PK samples, the actual date and 24-hour clock time of each sample will be recorded.

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

Concentration of tirzepatide will be assayed using a validated method.

Bioanalytical samples collected to measure investigational product concentration will be retained for a maximum of 1 year following last participant visit for the study.

8.6. Pharmacodynamics

Samples to assess the pharmacodynamic (PD) properties of tirzepatide are included in the efficacy measures and associated subsections (Section 8.1).

8.7. Genetics

8.7.1. Whole Blood Samples for Pharmacogenetic Research

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future. Samples will be used to investigate variable response to tirzepatide and to investigate genetic variants thought to play a role in NASH. Assessment of variable response may include evaluation of AEs or differences in efficacy.

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

Samples will be retained at a facility selected by Lilly or its designee for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and/or ethical review boards ERBs/IRBs 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 become(s) commercially available.

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

8.8. Biomarkers

Biomarker research is performed to address questions of relevance to drug disposition, target engagement, PD, 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, proteins, lipids, and other cellular elements.

Samples for biomarker research will be collected at the times specified in the SoA (Section 1.3) where local regulations allow.

Samples will be used for research on the drug target, disease process, variable response to tirzepatide, pathways associated with NASH, mechanism of action of tirzepatide, and/or research method or in validating diagnostic tools or assay(s) related to NASH.

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 retained at a facility selected by Lilly or its designee for a maximum 15 years after the last participant visit for the study, 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. Medical Resource Utilization and Health Economics

Health Economics and Medical Resource Utilization parameters are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The primary hypothesis that is being tested in this study is that tirzepatide 5 mg, 10 mg or 15 mg administered SC QW is superior to placebo with regards to resolution of NASH with no worsening of fibrosis at week 52.

Major secondary hypotheses are that tirzepatide is superior to placebo with regards to

- Regression of fibrosis with no worsening of NASH at Week 52.
- Prevention of fibrosis progression at Week 52.
- Decrease of NAS by ≥2 points at Week 52.
- Absolute decrease in liver fat content by MRI-PDFF at Week 52.
- Decrease in body weight at Week 52.

9.2. Sample Size Determination

Approximately, 196 participants will be randomized to placebo, tirzepatide 5 mg, tirzepatide 10 mg, or tirzepatide 15 mg in a 1:1:1:1 ratio; assuming a 20% dropout rate, this results in approximately 40 completers per arm. Sample size selection is guided by the objective of establishing superiority of each tirzepatide dose to placebo relative to the proportion of participants achieving NASH resolution without worsening of fibrosis at 52 weeks from randomization. The evaluation of superiority to placebo will be conducted for each of the 3 tirzepatide doses at 2-sided significance level of 0.05 using a test of 2 proportions. The tirzepatide group mean response rate is assumed to be 42.5% and the placebo group mean response rate is assumed to be 12.5%. The chosen sample size provides at least 80% power to establish superiority of tirzepatide 5 mg, tirzepatide 10 mg, or tirzepatide 15 mg doses to placebo. No adjustment for multiplicity will be performed.

9.3. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Screened	All participants who sign informed consent.
Randomized	All participants who are randomly assigned to a treatment arm.
Efficacy analysis set (EAS)	Data obtained during treatment period from all randomized participants who take at least 1 dose of double-blind study treatment for at least 46 weeks and have a post-baseline liver biopsy that is collected within 2 weeks of the last dose of study treatment. Data excludes data after discontinuation of study drug. Participants will be included in the treatment group to which they were randomized.

Population	Description
Exploratory analysis set (EXAS)	Data obtained during treatment period from all randomized participants who take at least 1 dose of double-blind study treatment for at least 36 weeks and have a post-baseline liver biopsy that is collected within 2 weeks of the last dose of study treatment. Data after discontinuation of study drug will be excluded. Participants will be included in the treatment group to which they were randomized.
Full analysis set (FAS)	Data obtained during treatment period from all randomized participants who take at least 1 dose of double-blind study treatment, regardless of adherence to study drug or having post-baseline liver biopsy. Participants will be included in the treatment group to which they were randomized.
Safety analysis set (SS)	Data obtained during treatment period plus safety follow-up period from all randomized participants who take at least 1 dose of double-blind study treatment, regardless of adherence to study drug or having post-baseline liver biopsy. Participants will be included in the treatment group to which they were randomized.

9.4. Statistical Analyses

9.4.1. General Statistical Considerations

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

Any change to the data analyses methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to data analyses methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) or the clinical study report (CSR). Additional exploratory analyses of the data will be conducted as deemed appropriate.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval (CI) will be calculated at 95%, 2-sided. In statistical summaries and analyses, patients will be analyzed as randomized.

The Cochran-Mantel-Haenszel (CMH) test will be used to make comparisons among treatment groups for the efficacy analyses of the primary endpoint and all other endpoints that are measured as proportions. The analyses will adjust for stratification factors in the study. Summary statistics for other categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Comparisons between treatment groups for such variables may be assessed using Pearson's Chi-squared test.

The summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum, and for categorical measures will include sample size, frequency, and percentage. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time (in addition to the baseline and end of treatment measurements) will be a mixed model for repeated measures (MMRM).

9.4.2. Treatment Group Comparability

9.4.2.1. Participant Disposition

Frequency counts and percentages of all patients screened, randomized, and receiving at least 1 dose of study drug will be presented by treatment groups. A listing of randomized patients not receiving study drug will be provided. All patients who discontinue the study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment. The percentage of patients discontinuing from each treatment will be compared using the Fisher's exact test.

9.4.2.2. Participant Characteristics

Demographics, medical history, and concomitant illness will be summarized by treatment group using the full FAS.

9.4.2.3. Concomitant Therapy

Concomitant medications, including previous therapy for diabetes, will be summarized by anatomical therapeutic chemical classification and treatment group using the FAS. In particular, the incidence of rescue therapy for severe, persistent hyperglycemia will be analyzed as an exploratory safety endpoint. Dose modifications of oral antihyperglycemic therapy will also be compared between treatment groups.

9.4.2.4. Treatment Discontinuation

Treatment discontinuation will be listed using the FAS. Of the patients in the FAS, frequency counts and percentages of patients discontinuing study drug, including the reason for discontinuation, will be presented by treatment group.

9.4.2.5. Treatment Compliance

Treatment compliance is defined as taking at least 75% of required injections of study drug while on study drug. Frequency counts and percentages of patients compliant to study drug will be summarized by treatment arm using the FAS.

9.4.3. Efficacy Analyses

9.4.3.1. Primary Analyses

The primary efficacy analyses will be conducted to establish superiority of tirzepatide 5 mg, 10 mg or 15 mg to placebo using the proportion of participants classified with absence of NASH with no worsening of fibrosis on liver histology, as defined in Section 8.1.1, in their post-baseline biopsy. The primary analyses will be performed on EAS using CMH test that compares treatment groups and placebo while adjusting for stratification factors. Stratification factors are T2DM status (Yes or No) and the region (Japan, US including Mexico, and Europe including Israel). Details will be provided in the SAP. Participants with a missing post-baseline biopsy will be removed from the primary analyses.

9.4.3.2. Secondary Analyses

In addition to the primary efficacy analysis of NASH resolution with no worsening of fibrosis in study population, the following secondary study objectives will be analyzed on the EAS:

- Regression of fibrosis with no worsening of NASH at Week 52.
- Prevention of fibrosis progression at Week 52.
- Decreasing NAS by ≥2 points at Week 52.
- Decreasing liver fat content by MRI-PDFF at Week 52.
- Decreasing body weight at Week 52.

Analyses for regression of fibrosis with no worsening of NASH, prevention of fibrosis progression, and decreasing NAS by ≥2 points will be conducted in a manner similar to the primary efficacy analyses discussed in Section 9.4.3.1.

Decreasing liver fat content by MRI-PDFF and body weight will be analyzed by MMRM. The corresponding baseline value, treatment, visits, treatment by visit interaction, and stratification factors are the terms in the MMRM analysis.

9.4.3.3. Tertiary/Exploratory Analyses

All exploratory efficacy analyses that require a post-baseline biopsy result will be done using the EAS. The rest of the analyses may be done using either the FAS or EAS. Depending on the number of patients that drop out between Weeks 36 and 46, primary, secondary, and exploratory efficacy analyses may be repeated with the EXAS. Details will be provided in the SAP.

9.4.4. Safety Analyses

The SS will be used for safety analyses. The overall comparison of tirzepatide doses versus placebo will be reported for these safety analyses. Safety measures will include vital signs, body weight, TEAEs (including SAEs and AEs of special interest), laboratory measures (including ADAs), and ECGs.

Summary statistics will be presented by treatment for the safety measures. Counts and proportions of subjects experiencing AEs will be reported for each treatment group. Fisher's exact test may be used to compare the treatment groups.

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities (MedDRA) and reported with preferred terms and system organ class.

9.4.5. Pharmacokinetic/Pharmacodynamic Analyses

The relationships between tirzepatide dose, concentration and efficacy, tolerability and safety measures will be characterized using population PK and PK/PD nonlinear mixed-effects modeling techniques implemented on Nonlinear Mixed Effects Modeling (NONMEM) software. Additionally, the impact of intrinsic and extrinsic factors (such as age, weight, sex, renal, and hepatic functions) on PK and/or PD parameters may be evaluated.

If ADA titers are detected in the immunogenicity samples, the impact of titers on tirzepatide PK and/or PD may be evaluated.

9.4.6. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with treatment-emergent ADA+ 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 if no ADAs were detected at baseline (treatment-induced ADA) or those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline (treatment-boosted ADA). The minimum required dilution of the ADA assay is 1:10. For the treatment-emergent ADA+ participants, the distribution of maximum titers will be described. The frequency of neutralizing antibodies, if performed, will also be tabulated in treatment-emergent ADA+ participants. If cross-reactivity to native GLP-1 and GIP or neutralizing antibodies against native GLP-1 and GIP assays are performed, the frequency of each will be reported.

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

9.4.7. Subgroup Analyses

Subgroup analyses of important factors, including fibrosis stage, amount of weight loss, baseline BMI, baseline liver fat content, T2DM status, and other factors to be specified in the SAP are planned for the key outcomes. The models used for these analyses will vary depending on the subgroups and the outcome. More details of the modeling will be provided in the SAP. Other exploratory subgroup analyses may be performed as deemed appropriate.

9.5. Interim Analyses

A futility interim analysis based on 26-week liver fat reduction from baseline measured by MRI-PDFF will be conducted. The study will be stopped or modified if none of the tirzepatide treatment arms meet the required criteria to continue the study. The trial will not be stopped based on the superiority of the treatment versus placebo. Therefore, there will be no inflation of the type 1 error rate and no need to employ an alpha spending function or multiplicity adjustment. The details regarding number of patients, type of analysis, and success criteria will be provided in the assessment committee (AC) charter. In addition, other interim analyses may be conducted.

An AC will be formed to review the interim analyses in an unblinded manner. Study team members who have potential contact with the sites will remain blinded throughout the study. Information that may unblind the study during the analyses will not be reported to study sites or blinded study team members before the study has been unblinded. Study sites will receive information about interim results only if deemed necessary for the safety of their patients. Details on the timing of the interim analyses and unblinding will be specified in the unblinding plan.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- 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 the conduct of the study at the site 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

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study 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, Health Insurance Portability and Accountability Act (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 enrolled 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.

For patient rescreening, see Section 5.4.

10.1.3. Data Protection

- Participants will be assigned a unique identifier by IWRS. Any participant records or datasets 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 his/her 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.
- The participant must be informed that his/her 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.

10.1.4. 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 publically 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 or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and European Union (EU) 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, blank or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal. For details on submitting a request, see the instructions provided at www.clinicalstudydatarequest.com.

Publications/Publication Policy

The publication policy is described in the letters of agreement between the sponsor and the investigators and institutions.

10.1.5. Data Quality Assurance

To ensure accurate, complete, and reliable data, Lilly or its representatives will do the following:

- provide instructional material to the study sites, as appropriate
- provide sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures.
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

In addition, Lilly 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 Lilly or its representatives and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

The investigator will keep records of all original source data. This might include laboratory tests, medical records, and clinical notes. If requested, the investigator will provide the sponsor, applicable regulatory agencies, and applicable ERBs with direct access to original source documents.

Data Capture System

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

An electronic data capture system (EDC) will be used in this study for the collection of eCRF 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 eCRF.

Additionally, clinical outcome assessment data (questionnaires and diary data) will be collected by the investigator site personnel, via a paper source document and will be transcribed by the investigator site personnel into the EDC system.

Data collected via the sponsor-provided data capture system will be stored at third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. 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/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

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

10.1.6. 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 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 10.1.5.

10.1.7. Study and Site Closure

10.1.7.1. Discontinuation of the Study

The study will be discontinued if Lilly or its designee judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

Medical Oversight and Safety Review

Ongoing safety review(s) by designated sponsor personnel will occur and be documented. Such reviews will include:

- Monitoring and assessing the safety information collected during the trial both in real time and periodically
- Reviewing safety data for trends that need action
- Detecting adverse drug/device effects.

A safety investigation will be triggered to determine if the study should be terminated early based on the following criteria:

- Two study participants develop the same TEAE or SAE considered possibly or probably related to study drug that is severe or medically significant but not immediately life-threatening; or where hospitalization or prolongation of hospitalization is indicated; or is disabling; or limits self-care activities of daily living.
- One study participant develops any TEAE or SAE regardless of attribution to study drug that has life-threatening consequences or requires urgent intervention
- Death of any study participant at any time
- Any other clinically significant safety signal

10.1.7.2. Discontinuation of Study Sites

Study site participation may be discontinued if Lilly or its designee, the investigator, or the ERB of the study site judges it necessary for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and GCP.

10.1.8. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.
- The sponsor will comply with the requirements for publication of study results.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the central laboratory unless otherwise stated.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- 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.
- Refer to Section 5.1 (Inclusion Criteria) for screening pregnancy criteria.

Investigators must document their review of each laboratory safety report.

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

Clinical Laboratory Tests[a]

Hematology
- Hemoglobin
- Hematocrit
- Erythrocyte count (RBC)
- Mean cell volume
- Mean cell hemoglobin concentration
- Leukocytes (WBC)
- Neutrophils, segmented
- Lymphocytes
- Monocytes
- Eosinophils
- Basophils
- Platelets

Hemaglobin A1c

Coagulation
- Prothrombin time
- Prothrombin time, INR

Urinalysis
- pH
- Protein
- Glucose
- Blood
- Leukocyte esterase

Urine Chemistry
- Albumin
- Creatinine

Lipid Panel
- Total cholesterol
- HDL-C
- LDL-C
- Triglycerides

Biomarkers[f]
- Free Fatty Acid
- K-18
- Ferritin
- Pro-C3
- Insulin
- C-peptide
- ELF (procollagen III amino terminal peptide, hyaluronic acid, tissue inhibitor metalloproteinase type 1)
- Adiponectin (Total and HMW)
- NIS4 (alpha-2-macroglobulin, chitinase-3-like protein 1, HbA1c, and microRNA-34a)

Optional urine drug screen (local, at the discretion of the investigator)

Clinical Chemistry
- Sodium
- Potassium
- Total bilirubin
- Direct bilirubin
- GGT
- ALP
- ALT
- AST
- BUN
- Creatinine
- Uric acid
- Calcium
- Total protein
- Albumin
- Glucose
- Pancreatic amylase
- Lipase

Special Chemistry
- Thyroid stimulating hormone (TSH)[b]
- Transferrin saturation[b]
- Calcitonin

Hormones (females)
- Pregnancy test, serum[b,c] and/or urine[c]
- Estradiol[b,d]
- FSH[b,d]
- Luteinizing hormone (LH)[b,d]

Serology[b,e]
- Hepatitis B Surface Ag
- HIV (human immunodeficiency virus)
- Hepatitis C Ab (or virus RNA for patients cured of hepatitis C to confirm absence of virus)

Immunogenicity[f]
- Anti-tirzepatide antibodies
- Anti-tirzepatide antibody neutralization

Pharmacogenetics Stored Sample[b]

Nonpharmacogenetic Stored Samples
- EDTA plasma
- Serum
- P800 plasma

Pharmacokinetic Samples[f,g]

Calculations
- UACR
- eGFR (calculated by CKD-EPI equation)
- FIB-4[h] (ALT, AST, platelets)
- FAST score (CAP, LSM, AST)

Abbreviations: Ab = antidrug antibody; Ag = antigen; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CAP = controlled attenuation parameter; CKD-EPI = chronic kidney disease epidemiology collaboration; EDTA = ethylenediaminetetraacetic acid; ELF = enhanced liver fibrosis; eGFR = estimated glomerular filtration rate; FIB-4 = fibrosis-4; FSH = follicle stimulating hormone; GGT = Gamma-glutamyl transferase; HDL-C = high density lipoprotein cholesterol; HIV = human immunodeficiency virus; HMW = high molecular weight; INR = international normalized ratio; IWRS = interactive web response system; LDL-C = low density lipoprotein cholesterol; LSM = liver stiffness measurement; NIS4 = noninvasive score 4; RBC = red blood cells; UACR = urine albumin to creatinine ratio; WBC = white blood cells.

a All tests will be performed by a Lilly-designated central laboratory, unless otherwise noted.

b Screening only.

c Serum pregnancy test will be performed by the central laboratory at Visit 1 for women of child-bearing potential. A local urine pregnancy test should be given to all women of child-bearing potential at Visit 3 prior to administration of first dose of study drug to confirm lack of pregnancy. For the remainder of the study, a urine pregnancy test may be performed locally at the investigator's discretion if pregnancy is suspected during the study.

d Collect serum estradiol, FSH, and LH 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.

e Screening laboratory tests also include serum hepatitis B surface Ag, hepatitis C antibody (Ab), and HIV (human immunodeficiency virus) Ab tests for all participants. Participants treated for hepatitis C should have a hepatitis C RNA test rather than an antibody test.

f Results will not be provided to the investigative sites.

g Pharmacokinetic (PK) samples for immunogenicity should be collected prior to dose administration. At specified visits, additional PK samples will be collected after dosing at a schedule determined by IWRS for individual patients.

h FIB-4 will be calculated by the central laboratory.

10.3. Appendix 3: Liver Safety: Actions and Follow-Up Assessments

Selected tests may be obtained in the event of a treatment-emergent hepatic abnormality and may be required in follow-up with participants in consultation with the Lilly, or its designee, clinical research physician/clinical research scientist (CRP/CRS).

The initial panel of tests are shown below.

Based on the patient's history and initial results, further testing may be considered, in consultation with the Lilly CRP/CRS, including tests for hepatitis D virus, cytomegalovirus, Epstein Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethylglucuronide, and serum phosphatidylethanol. These additional tests should be performed through local laboratories. 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/gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-nuclear antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-smooth muscle antibody (or anti-actin antibody)[a]

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatinine phosphokinase; GGT = gamma-glutamyl transferase; Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated or local laboratory.

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

10.4. Appendix 4: Definitions of Hypoglycemia

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 2017 American Diabetes Association position statement on glycemic targets (ADA 2017).

- *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 defined as any hypoglycemic event that occurs between bedtime and waking.

10.5. Appendix 5: World Health Organization Standardized Protocols for the Measurement of Height and Weight

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

Measuring Height

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

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

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

Step 4 Ask the patient to breathe in and stand tall. If using a stadiometer or fixed measuring device, move the device's measurement arm gently down onto the top of the patient's head. Record the patient's height in centimeters (cm).

Measuring Weight

Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms (kg) to one decimal place. All weights for a given patient should be measured using the same scale, whenever possible, after the patient has emptied their bladder. Patients should be lightly clothed but not wearing shoes while their weight is measured.

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

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

Step 3 Ask the patient to step onto the scale with one foot on each side of the scale.

Step 4 Ask the patient to stand still with their arms by their sides and then record their weight in kilograms (kg).

10.6. Appendix 6: Diet and Physical Activity Suggestions for Sites without Programs

10.6.1. Diet

Diet recommendations are based on the World Health Organization (WHO 2018) for everyone and a consensus report from the American Diabetes Association and the European Association for the Study of Diabetes (Davies et al. 2018) for treatment of hyperglycemia, all of which are based on a Mediterranean eating pattern.

The Mediterranean eating pattern for a healthy diet consist of:

- Legumes (e.g., lentils and beans)
- Nuts
- Whole grains (e.g., unprocessed wheat, maize, millet, oats, and brown rice)
- At least 5 portions of fruit and vegetables per day (excluding potatoes, sweet potatoes, cassava, and other starchy roots)
- Less than 10% of total energy intake from free sugars (equivalent to 50 g or 12 level teaspoons), but ideally less than 5% of total energy intake. Free sugars are sugars added to foods and drinks, as well as sugars present in honey, syrups, fruit juices, and fruit juice concentrates.
- Less than 30% of total energy intake from fats. Unsaturated fats are preferred over saturated fats. Unsaturated fats are found in fish, avocado, nuts, and in sunflower, canola, and olive oils. Consumption of saturated fats, which are fats in fatty meat, butter, palm and coconut oil, cream cheese, ghee, and lard, should be reduced to less than 10% of total energy intake. Trans-fats, which are found in industrially produced foods, should be avoided.
- Salt intake should not be more than 5 g (about 1 teaspoon) per day and should be iodized.

Although the Mediterranean eating pattern does not prohibit alcohol, particularly red wine, patients with NASH should be encouraged to reduce or eliminate alcohol intake due to the effects of alcohol on the liver.

10.6.2. Physical Activity

Regular physical activity can improve a patient's health. Moving more and sitting less have benefits everyone, regardless of age, sex, race, ethnicity, or current fitness level. Benefits accumulate with even small amounts and start immediately.

To safely engage in physical activity, types of physical activity appropriate for the patient's current fitness should be chosen. Furthermore, the amount and duration of physical activity should be gradually increased over time. Patients with chronic conditions and symptoms should be under the care of a health care provider about the types and amounts of physical activity that are appropriate for the patient.

Physical activity recommendations are based on WHO recommendations (WHO 2018) and also align with the ADA and European Association for the Study of Diabetes consensus report (Davies et al. 2018) and with the US Health and Human Services (HHS 2019) recommendations.

- Any physical activity is better than none. Adults should move more and sit less.
- Adults should do 150 minutes (2 hours 30 minutes) to 300 minutes (5 hours) of moderate-intensity aerobic physical activity throughout the week or 75 minutes (1 hour 15 minutes) to 150 minutes (2 hours and 30 minutes) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activity. Preferably, aerobic activity should be spread throughout the week.
- Aerobic activity should be performed in bouts of at least 10 minutes duration.
- For additional health benefits, adults should increase their moderate-intensity aerobic physical activity to 300 minutes per week, or engage in 150 minutes of vigorous-intensity aerobic physical activity per week, or an equivalent combination of moderate- and vigorous-intensity activity. Additional health benefits are gained by engaging in physical activity beyond the equivalent of 300 minutes (5 hours) of moderate-intensity physical activity a week.
- Muscle-strengthening activities should be done involving major muscle groups on 2 or more days a week.
- Older adults, with poor mobility, should perform physical activity to enhance balance and prevent falls on 3 or more days per week, as well as aerobic and muscle-strengthening activities. They should be as physically active as their abilities and conditions allow. When older adults cannot do 150 minutes of moderate-intensity aerobic activity a week because of chronic conditions, they should be as physically active as their abilities and conditions allow.

10.7. Appendix 7: Medical Device Incidents: Definition and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study.

Medical Device Incident Definition

- A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labeling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a participant/user/other person or to a serious deterioration in his/her state of health.
- Not all incidents lead to death or serious deterioration in health. The nonoccurrence of such a result might have been due to other fortunate circumstances or to the intervention of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical intervention to prevent one of the above
- Fetal distress, fetal death, or any congenital abnormality or birth defects

Examples of Incidents

- A participant, user, caregiver, or health care professional is injured as a result of a medical device failure or its misuse.
- A participant's study intervention is interrupted or compromised by a medical device failure.
- A misdiagnosis due to medical device failure leads to inappropriate treatment.
- A participant's health deteriorates due to medical device failure.

Documenting Medical Device Incidents

Medical Device Incident Documenting
• Any medical device incident occurring during the study will be documented in the participant's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF. • For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Section 8.3. • The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee. • It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident. • A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

10.8. Appendix 8: Contraceptive Guidance and Collection of Pregnancy Information

Definitions:

Woman of Child-Bearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (See below).
If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, 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, (e.g., mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determine study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
     - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement >40 IU/L or mIU/mL is required.
   - Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Collection of Pregnancy Information

Male participants with partners who become pregnant

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

- After 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. 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 will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.2. 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 intervention or be withdrawn from the study.

10.9. Appendix 9: List of Prohibited Medications by Protocol Section

Protocol Section	Prohibited Medication
5.2. Exclusion Criteria	
Medical Conditions	
#28	Marijuana and CBD oil
Prior/Concomitant Therapy	
#51	Insulin – Long-term treatment
#52	GLP-1 Receptor Agonists
#53	Drugs associated with hepatic steatosis (amiodarone, methotrexate, tamoxifen)
#54	Medications associated with weight gain unless on stable dose. Note – examples such as atypical antipsychotics are included in the investigator training materials.
#55	Long term systemic glucocorticoids
#56	Weight loss drugs and weight loss herbal supplements. These include, but are not limited to: Saxenda [liraglutide 3.0 mg], Alli®/Xenical® [orlistat], Meridia® [sibutramine], Acutrim® [phenylpropanolamine], Sanorex® [mazindol], Apidex® [phentermine], BELVIQ® [lorcaserin], Qsymia™ [phentermine/topiramate combination], Contrave® [naltrexone/bupropion].
#57	Anticoagulants (other than aspirin or NSAIDs) that may increase the risk of bleeding with the liver biopsy
6.5.1.2 Hyperglycemia Rescue Medication	Dose increases of the following are NOT allowed during the study: • SGLT-2 inhibitors • TZDs Initiation of the following is NOT allowed during the study: • GLP-1 receptor agonists • DPP-4 inhibitors • SGLT-2 inhibitors • TZDs

10.10. Appendix 10: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local Ethical Review Boards, regulatory bodies and any other relevant local authorities, implementation of exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific conditions in which notification is required. To protect the safety of study participants, urgent changes may be implemented before approval, but need to be reported as soon as possible. All approvals must be retained in the study records.

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

Considerations for making a change

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

Informed consent

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

- participation in remote visits, as defined in Section "Remote visits,"
- dispensation of additional study intervention during an extended treatment period,
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

1. **Remote visits**

Remote visits only apply to Visit 4 through Visit 13, and follow-up visits. Every effort should be made for the participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of the participants and investigational site staff. The study site should capture the method of data collection and procedure conduct with a specific explanation for any data missing in the source document due to missed in-person site visits.

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Any procedures that cannot be accomplished at a remote visit should be conducted at the next on-site visit and captured as a protocol deviation related to the exceptional circumstances. Of note, procedures from the missed visit that were not collected and are the same as ones at the next site visit do not need to be duplicated. However, imaging procedures (Fibroscan and MRI) scheduled for Visit 10 (Week 26) should be collected as close to the schedule as possible. Electrocardiograms scheduled for Visit 10 (Week 26) should be collected locally and reviewed by the investigator for patient safety; however, centralized ECGs should be collected at the next on-site visit.

Mobile healthcare:

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

- Weight measurement
- Collecting blood samples
- Brief physical assessment or general wellness check
- Efficacy measures and safety assessments
- Patient-reported outcome measures administration
- Collecting health information

Other alternative locations:

During exceptional circumstances, laboratory samples may be drawn locally, if needed outside of mobile healthcare visits.

2. **Local laboratory testing option**

To ensure participant safety and with the Sponsor's prior written approval, local laboratory testing may be conducted in lieu of central laboratory testing, except for PK, immunogenicity, and biomarkers, which must be analyzed by the central laboratory. The local laboratory must be

qualified in accordance with local regulations. Clinically significant laboratory findings must be recorded as an AE in the AE eCRF. However, if possible, laboratory samples collected locally or by mobile healthcare visits should be sent to the central laboratory for analyses.

3. Study intervention and ancillary supplies (including participant diaries)

When a participant is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include:

- asking the participant to go to the site and receive study supplies from site staff without completion of a full on-site study visit,
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies.

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

4. Screening period guidance

The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If paused for less than 60 days from Visit 1 to Visit 2: The participant will proceed to the next study visit (Visit 2, liver biopsy) per the usual SoA.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay in the CRF.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If paused for more than 60 days from Visit 1 to Visit 2 and the patient qualified for a liver biopsy following Visit 1, then safety laboratory parameters and ECGs should be collected to assure that a patient may still safely undergo a liver biopsy. If paused for more than 120 days from Visit 1 to Visit 2, sites should contact the sponsor medical

monitor to discuss whether the patient should be a screen-failure, and re-entered as a new patient, and then follow the SoA to determine eligibility for a liver biopsy.

- If a patient has an historical liver biopsy (that is, a biopsy that was performed prior to entering Study GPHR) and there is a pause that results in more than 6 months from the date the biopsy was performed to the date of submission of the biopsy slides to the central laboratory, then the liver biopsy will need to be repeated, provided the patient continues to meet inclusion criteria for a liver biopsy.

5. Adjustments to visit windows

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

- Participants should complete the primary treatment endpoint visit (Visit 14) and the final study endpoint follow-up visit (Visit 801) as per the original SoA whenever possible and safe to do so, at the investigator's discretion. During periods of exceptional circumstance, flexibility in Visits 10 (secondary endpoint), 14 (primary treatment endpoint), and 801 (final study endpoint follow-up) may occur after consultation with, and prior approval by the sponsor.
- For the secondary endpoint visit (Visit 10, Week 26), the visit windows may be adjusted upon specific guidance from the sponsor.
- For participants requiring the visit windows to be extended, additional study drug may need to be provided to avoid study drug interruption and maintain overall integrity of the trial.

Documentation

Changes to study conduct will be documented:

- Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances.
- Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.
- Source documents generated at a location other than the study site should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.11. Appendix 11: Protocol Amendment History

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

DOCUMENT HISTORY	
Document	**Date**
Amendment C	15 November 2019
Amendment B	21 October 2019
Amendment A	13 August 2019
Original Protocol	26 July 2019

Amendment a

Overall Rationale for the Amendment:

Changes were made to Section 5.1, inclusion criterion 12 to align with regulatory guidance based on the results of preclinical fetal toxicity studies.

Inclusion criterion 12.b.i has been changed to include the following:

- Men with partners of child-bearing potential, for the duration of the study and for 5 half-lives of the study drug plus 90 days after the last dose of study drug (corresponding to 4 months), will either remain abstinent (if this is their preferred and usual lifestyle) or use condoms plus 1 additional highly effective (less than 1% failure rate) method of contraception (such as combination oral contraceptives, implanted contraceptives or intrauterine device) or an effective method of contraception (such as male or female condoms with spermicide, diaphragms with spermicide or cervical sponges). Men and their partners may choose to use a double-barrier method of contraception.

Inclusion criterion 12.b.ii has been changed to clarify that 5 half-lives of the study drug plus 90 days after the last dose of study drug corresponds to 4 months.

Inclusion criterion 12.c.ii has been changed to include the following:

- Otherwise, women of child-bearing potential participating must agree to use 2 forms of effective contraception, where at least one form is highly effective (less than 1% failure rate), for the entirety of the study and for 30 days thereafter.

Furthermore, a statement requiring that female participants must not be breastfeeding has been added (criterion 12.c.iv).

Section # and Name	Description of Change	Brief Rationale
5.1 Inclusion Criteria	Updated contraceptive information	The contraceptive information for men and women has been updated and a statement that female participants must not be breast feeding has been added.
1.3 Schedule	Corrected visit window for Visit 14	Clerical error.

Section # and Name	Description of Change	Brief Rationale
of Activities	in headers subsequent to the first page.	

Amendment b

Overall Rationale for the Amendment:

Regulatory feedback from both the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) through the Voluntary Harmonisation Process (VHP) has resulted in changes to the protocol. These changes incorporate additional measures to ensure patient safety or clarify procedures. Other changes are either a result of those additions or due to inadvertent typographical errors.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities	Added temperature to vital signs	Regulatory request
	Added laboratory assessments during the dose escalation period	Evaluating laboratory parameters at the end of the first dose and each dose escalation.
	Added Thyroid Stimulating Hormone and Free Fatty Acid	This was inadvertently omitted from laboratory assessments
	Deleted AST and ALT and glucose lines	Line items were deleted because they are part of additional safety chemistry parameters added by this amendment
	Urine pregnancy tests have been added to all visits beginning at Visit 5.	Regulatory request
	Removed text from footnote *j* since FIB4 will be reported to sites with all appropriate measured parameters	Correction based on feedback from coordinating laboratory
4.4. End of Study Definition	Added wording to clarify end of study.	Regulatory request
5. Study Population (Inclusion and Exclusion Criteria)	(#2) Added an upper limit on BMI (#12) Defined combined contraception (#17) Increased minimum limit for platelet count (#20) Increased minimum limit for serum albumin	Regulatory request

Section # and Name	Description of Change	Brief Rationale
	(#20) Reduced maximum direct bilirubin (#36) Increased minimum eGFR for patients on metformin	
6.3. Measures to Minimize Bias: Randomization and Blinding	Explained purpose of stratification	Regulatory request
6.5 Concomitant Medication	Added cautionary statement regarding rapid gastrointestinally absorbed drugs	Tirzepatide initially delays gastric emptying, which may result in higher exposures of concomitantly administered drugs with rapid gastrointestinal absorption.
6.5.1.1. Hyperglycemia Rescue Criteria	Lowered the HbA1c criteria for initiating hyperglycemia rescue medication	Regulatory request
6.5.1.2. Hyperglycemia Rescue Medication	Added directions for using metformin rescue based on eGFR	Regulatory request
7.1. Discontinuation of Study Intervention	Added patient discontinuation criteria based on TEAE and SAE severity and relatedness	Clarifies common practice due to regulatory request
7.2.1. Discontinuation of Inadvertently Enrolled Patients	Removed language stating that patients who did not meet enrollment criteria may stay in the study in extenuating circumstances	Regulatory request
8.1.1. Primary Efficacy Assessment	Added information on duration of storage of liver biopsy tissue blocks and slides	Regulatory request
8.2.2. Vital Signs	Removed statement regarding sponsor supply of equipment	Lilly will not be providing equipment for measurement of vital signs
8.2.2. Vital Signs	Added collection of temperature to align with modified Schedule of Activities SOA.	Regulatory request
8.2.4.2. Hepatic Safety Monitoring	Reduced the time for follow up liver testing	Regulatory request
8.3.7.6. Hypoglycemia	Corrected blood glucose values to align with Appendix 4	Typographical errors

Section # and Name	Description of Change	Brief Rationale
9.5. Interim Analyses	Clarified the interim analyses	Regulatory request
10.1.7.1. Discontinuation of Study	Outlined safety reviews based on Lilly Standard Operating Procedures (SOPs) Added study discontinuation criteria based on TEAE and SAE severity and relatedness	Provides information within Lilly SOPs and due to regulatory request
10.2. Laboratory Tests	Moved calcitonin to special laboratory tests	Calcitonin will be collected at times specified in the SOA and not with every general chemistry collection
	Removed text from footnote *h* since FIB4 will be reported to sites with all appropriate measured parameters	Correction based on feedback from coordinating laboratory
10.3. Liver Safety	Added text on additional liver tests	Regulatory request

Amendment c

Overall Rationale for the Amendment:

Regulatory feedback from European Regulatory Agencies through the Voluntary Harmonisation Process (VHP) has resulted in changes to the protocol. These changes incorporate additional measures to ensure patient safety or clarify procedures. Other changes are either a result of those additions or due to inadvertent typographical errors.

Section # and Name	Description of Change	Brief Rationale
4.1. Overall Design	Changed 3 to 6 months	Regulatory request
5.1. Inclusion Criteria	(#5a) Changed 3 to 6 months	Regulatory request
	(#5b) Changed 3 to 6 months	Regulatory request
	(#8) Added additional language clarifying stable body weight	Additional language added in response to regulatory request for liver biopsies up to 6 months
	(#12bi) Language added to clarify oral contraceptives	Regulatory request
Section # and Name	**Description of Change**	**Brief Rationale**

8.1.1. Primary Efficacy Assessment	Changed 3 to 6 months	Regulatory request
8.1.1.1. Baseline liver biopsy	Changed 3 to 6 months in multiple places	Regulatory request
10. Supporting Documentation and Operational Considerations	A table including a list of prohibited medications by protocol section was added as an appendix (Appendix 9).	Regulatory request
10.3 Appendix 3 Liver Safety: Actions and Follow-Up Assessments	In paragraph 3 the word “should” was replaced with “may”.	Regulatory request

10.12. Appendix 12: Abbreviations

Term	Definition
ADA	antidrug antibody
AC	Assessment committee
AE	adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
AESI	adverse events of special interest
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
BP	blood pressure
CAP	controlled attenuation parameter
CBD	cannabidiol
CLDQ-NAFLD	Chronic Liver Disease Questionnaire – Nonalcoholic Fatty Liver Disease
CHF	congestive heart failure
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
Companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.

Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form
CRN	Clinical Research Network
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.
CRS	clinical research scientist
CSR	clinical study report
CT	computed tomography
CV	cardiovascular
DILI	drug-induced liver injury
DPP-4	dipeptidyl peptidase-4
EAS	efficacy analysis set
eCFR	electronic case report form
ECG	electrocardiogram
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/IRB	Ethical Review Board/Institutional Review Board
FAS	full analysis set
FAST	FibroScan-AST score
FDA	Food and Drug Administration
FIB-4	fibrosis-4
Fibroscan	method of transient elastography used for assessment of liver fibrosis
Fibroscan-AST	combination of fibroscan with measurement of AST
GCP	good clinical practice

GI	gastrointestinal
GIP	gastric inhibitory polypeptide
GLP-1	glucagon-like peptide-1
HbA1c	hemoglobin A1c
HCV	hepatitis C virus
HOMA-IR	Homeostatic Model Assessments for Insulin Resistance
HRT	hormone replacement therapy
IB	Investigator's Brochure
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgE	immunoglobulin E
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
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IQR	interquartile range
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.
IVRS/IWRS	interactive voice-response system/interactive web-response system
LSM	liver stiffness measurement
MI	myocardial infarction

MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MRI-PDFF	MRI – Proton Density Fat Fraction
MTC	medullary thyroid carcinoma
NAFLD	nonalcoholic fatty liver disease
NAS	NAFLD Activity Score
NASH	nonalcoholic steatohepatitis
NSAID	nonsteroidal anti-inflammatory drug
PGIS	Patient Global Impression of Severity
PK/PD	pharmacokinetics/pharmacodynamics
PR	pulse rate
PROMIS	Patient-Reported Outcome Measurement Information System
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
QW	once weekly
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SGLT-2	sodium-glucose co-transporter-2
SoA	Schedule of Activities
SS	safety analysis set
SUSARs	suspected unexpected serious adverse reactions
T1DM	type 2 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TE	transient elastography

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.
TZD	thiazolidinediones
ULN	upper limits of normal
US	United States
WOCBP	women of child-bearing potential

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