

Protocol VTX3232-204

A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of VTX3232 Alone or in Combination With Semaglutide in Participants With Obesity

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TITLE PAGE

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Brief Title: Phase 2a Placebo-Controlled Study of VTX3232 Alone or in Combination with Semaglutide in Obesity

Sponsor Name: Zomagen Biosciences Ltd., a wholly owned subsidiary of Ventyx Biosciences, Inc.

Sponsor's Legal Registered Address:

5 New Street Square
London EC4A 3TW
United Kingdom

Sponsor's Clinical Lead:

PPD [REDACTED]

PPD [REDACTED], Clinical Development

Telephone: PPD [REDACTED]

Email: PPD [REDACTED]

Sponsor's Medical Expert

PPD [REDACTED]

PPD [REDACTED]

CCI [REDACTED]

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VERSION HISTORY

A summary of changes is provided in [Appendix 2](#).

VTX3232-204 Protocol Version History

Protocol Version	Amendment Type	Date
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LIST OF ABBREVIATIONS

Abbreviation	Explanation
ADHD	attention-deficit/hyperactivity disorder
ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATP	adenosine triphosphate
CCI	
β-hCG	beta-human chorionic gonadotropin
BLQ	below the limit of quantification
BMI	body mass index
BP	blood pressure
CFR	Code of Federal Regulations
CI	confidence interval
CCI	
CNS	central nervous system
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
CSR	clinical study report
CCI	
CT	computed tomography
CCI	
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CTFG	Clinical Trial Facilitation Group
CV%	coefficient of variation
CCI	
DDI	drug-drug interaction
DIO	diet-induced obese

Abbreviation	Explanation
DNA	deoxyribonucleic acid
CCI	
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
ELISA	Enzyme-Linked Immunosorbent Assay
CCI	
ET	early termination
FAS	full analysis set
FDA	Food and Drug Administration
FOCBP	female of childbearing potential
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GI	gastrointestinal
GLP-1	glucagon-like peptide-1
CCI	
HbA1C	hemoglobin A1C
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IMP	investigational medicinal product
IND	Investigational New Drug

Abbreviation	Explanation
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
JAK	Janus kinase
CCI	
LDL	low-density lipoprotein
CCI	
LS	least squares
MASH	metabolic dysfunction-associated steatohepatitis
MASLD	metabolic dysfunction-associated steatotic liver disease
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
MEN2	multiple endocrine neoplasia type 2
min	minimum
MMRM	mixed effect model with repeated measure
CCI	
MTC	medullary thyroid cancer
NAFLD	nonalcoholic fatty liver disease
NGAL	neutrophil gelatinase-associated lipocalin
NLRP3	NACHT, LRR and pyrin domains-containing protein 3
NOAEL	no-observed-adverse-effect level
NSAID	nonsteroidal anti-inflammatory drug
PD	pharmacodynamic(s)
CCI	
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PK	pharmacokinetic(s)
QD	once daily
QTcF	Fridericia's corrected QT interval
CCI	
SAE	serious adverse event

Abbreviation	Explanation
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SD	standard deviation
SoA	Schedule of Assessments
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
CCI	
TMF	trial master file
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
VLDL	very low-density lipoprotein
WHO	World Health Organization

1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Number: VTX3232-204

Protocol Title: A Phase 2a, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of VTX3232 Alone or in Combination with Semaglutide in Participants with Obesity

Compound: VTX3232

Study Phase: 2a

Indication: Obesity

Brief Title: Phase 2a Placebo-Controlled Study of VTX3232 Alone or in Combination with Semaglutide in Obesity

Sponsor Name: Zomagen Biosciences Ltd., a wholly owned subsidiary of Ventyx Biosciences, Inc.

Country/region: United States

Study Rationale:

Nonclinical and clinical studies have shown that NACHT, LRR, and pyrin domains-containing protein 3 (NLRP3) inflammasome activation is associated with obesity and cardiovascular disease but the therapeutic potential of NLRP3 inflammasome inhibition is unknown. In nonclinical studies, the combination of VTX3232 plus semaglutide has demonstrated a synergistic effect on weight loss and decrease in cardiometabolic parameters in a mouse diet-induced obesity model compared with NLRP3 inhibitor alone.

Individuals with obesity will be recruited in this Phase 2a study to test the safety/tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of a novel compound (VTX3232) that selectively targets the NLRP3 inflammasome in the periphery and central nervous system (CNS), alone or in combination with semaglutide.

Study Population:

Males or females ages ≥ 18 to ≤ 80 years at the time of consent who meet the criteria for obesity with a body mass index (BMI) ≥ 30.0 to ≤ 42.0 kg/m² at screening, stable body weight for at least 3 months prior to screening, and at least one self-reported unsuccessful dietary effort to lose body weight. A high-sensitivity C-reactive protein (hs-CRP) of ≥ 2 mg/L at screening is required. For eligible participants with hypertension or hyperlipidemia, these conditions must be controlled with stable therapy prior to initiating study treatment. Individuals with diabetes mellitus (Type 1 or Type 2 diabetes mellitus, or rare forms of diabetes mellitus) will be excluded.

Complete inclusion/exclusion criteria are provided in Section 5.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of active treatment compared with placebo	Incidence and severity of AEs, SAEs, and AEs leading to study treatment discontinuation from the first dose through end of the Follow-Up Period
Secondary	
To evaluate the effect of active treatment on hs-CRP compared with placebo	Change from baseline in hs-CRP over time through Week 12
Exploratory	
To evaluate the effect of active treatment on body weight compared with placebo	Percent change from baseline in body weight over time through Week 12
	Change from baseline in body weight over time through Week 12
	Proportion of participants achieving at least 5% and at least 10% body weight reduction at Week 12
To evaluate the effect of active treatment on BMI compared with placebo	Change from baseline in BMI over time through Week 12
CCI [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
To evaluate the effect of active treatment on vital signs compared with placebo	Change from baseline in blood pressure (systolic and diastolic) over time through Week 12
	Change from baseline in pulse rate over time through Week 12
To evaluate the effect of active treatment on lipid parameters in blood compared with placebo	Change from baseline in measures of lipid levels (total cholesterol, HDL, LDL, VLDL, triglycerides, free fatty acids) over time through Week 12
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
To evaluate the effect of active treatment on glycemic parameters in blood compared with placebo	Change from baseline in fasting glucose and fasting insulin over time through Week 12
	Change from baseline in Hemoglobin A1C at Week 12

Objectives	Endpoints
To evaluate the effect of active treatment on liver parameters compared with placebo	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
Pharmacokinetic	
To investigate the pharmacokinetics of VTX3232 (and metabolites, as appropriate) in plasma	CCI [REDACTED] [REDACTED]
Safety	
To evaluate the effect of study treatment on additional measures of safety and tolerability	Incidence and severity of laboratory abnormalities Change from baseline in laboratory values (hematology, serum chemistry, coagulation, and urinalysis), ECG, and vital signs Incidence of clinically significant changes to vital signs and ECGs CCI [REDACTED] [REDACTED]

AE, adverse event; BMI, body mass index; CCI [REDACTED]
[REDACTED] ECG, electrocardiogram; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; CCI [REDACTED] LDL, low-density lipoprotein; MRI, magnetic resonance imaging; CCI [REDACTED]
[REDACTED]
[REDACTED]

SAE, serious adverse event; VLDL, very low-density lipoprotein.

A complete list of endpoints and definitions, as well as analysis methods will be provided in the Statistical Analysis Plan (SAP).

Overall Design Synopsis:

This is a Phase 2a multicenter, randomized, placebo-controlled study to evaluate the safety and tolerability of VTX3232 alone or in combination with semaglutide in participants with obesity. The PK of VTX3232, the effect of study treatment on inflammatory and cardiometabolic biomarkers in blood and urine, and the effect of study treatment on weight loss will also be evaluated. CCI [REDACTED]
[REDACTED]

Number of Participants:

Approximately 160 participants are planned to be enrolled and randomized in 4 treatment groups of approximately 40 participants each.

Study Treatment Groups:

Participants will be randomly assigned (1:1:1:1 allocation ratio) to receive VTX3232 or placebo as an oral 30 mg tablet once daily (QD) alone or in combination with semaglutide (dose titration regimen from 0.25 mg to 1 mg dose) as a weekly subcutaneous injection in the 12-week Double-Blind Treatment Period. The study treatment groups are:

- Placebo QD
- VTX3232 30 mg QD
- Placebo QD and weekly semaglutide injection
- VTX3232 30 mg QD and weekly semaglutide injection

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-
-
-

Study treatment includes the investigational medicinal product (IMP), defined as a pharmaceutical form of the active substance being tested (test product) and the placebo being used as a reference (reference therapy) and includes both study treatment tablets (i.e., VTX3232 or placebo) and study treatment injections (i.e., semaglutide).

Study Duration:

The overall study duration will be up to approximately 20 weeks, including:

- Screening Period: up to 30 days
- Double-Blind Treatment Period: 12 weeks
- Follow-Up Period: through 30 days after the last study treatment administration

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Statistical Methods:

Sample Size Determination

No formal sample size or power calculations were performed. For this initial study in participants with obesity, it is planned to treat and complete safety, tolerability, PK, and PD assessments in approximately 160 participants (approximately 40 per treatment group), which is reasonable to assess the primary, secondary, and exploratory study objectives. It is expected that this number of participants will provide guidance for the assessment of safety in this patient population.

Methodology

Categorical variables will be presented in tables as frequencies and percentages. Continuous variables will be summarized in tables and will include the number of participants, mean, standard deviation (SD), median, first quartile, third quartile, minimum (min), and maximum (max).

All details regarding the efficacy, safety, PK, and PD variable definitions, analyses strategy, statistical justification, and techniques for handling missing values will be detailed in the SAP that will be finalized prior to the database lock and undertaking of any analyses. Any deviation(s) from the SAP will be described and justified in the final clinical study report, as appropriate.

Testing Strategy

All statistical tests will be 2-sided and will be performed with a nominal significance (alpha) level of 0.05, unless otherwise specified in the SAP.

Stratification

CCI

Analysis Sets

- The Full Analysis Set (FAS) consists of all participants who received at least 1 dose of study treatment. For this analysis set, participants are analyzed according to the treatment group to which they were randomized, regardless of the treatment they received during the study. The FAS will be used for all demographics, disposition, and efficacy analyses.
- The Safety Set consists of all participants who received at least 1 dose of study treatment. For this analysis set, participants are analyzed according to the treatment they received, regardless of randomization. The Safety Set will be used for all safety and tolerability analyses. The primary safety analysis will be completed based on the Safety Set.
- The Pharmacokinetic Set consists of all participants in the Safety Set who have at least 1 quantifiable postdose PK measurement for VTX3232. The Pharmacokinetic Set will be used for all PK analyses.
- The Pharmacodynamic Set consists of all participants in the Safety Set who have at least 1 measured PD assessment value at a scheduled timepoint after the first dose of study treatment. The Pharmacodynamic Set will be used for all pharmacodynamic analyses.

Safety Analyses

Primary Analyses: Incidence and severity of adverse events (AEs) will be summarized by treatment group from the first dose through the end of the Follow-Up Period.

All safety data will be listed and summarized by treatment group. All treatment-emergent adverse events (TEAEs) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and tabulated by System Organ Class and Preferred Term. Incidence of AEs, serious AEs (SAEs), and AEs leading to study treatment discontinuation will be summarized and presented in descending order of frequency.

Laboratory parameters will be summarized at each scheduled assessment timepoint using descriptive statistics. Associated laboratory parameters such as hepatic enzymes, renal function, and hematology values may be grouped and presented together. Individual participant values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from Day 1/baseline may be produced.

Descriptive statistics for vital signs (blood pressure [systolic/diastolic], pulse rate, respiratory rate, body temperature) will be presented by treatment group. The change from baseline for each of the vital signs will be summarized and the incidence of abnormal vital signs parameters will be tabulated.

Other safety assessments will also be analyzed in a descriptive manner. CCI

Pharmacodynamic Analyses

For the secondary endpoint analysis, the change from baseline in hs-CRP will be summarized by treatment group. A descriptive summary of all biomarkers will be provided by treatment group.

Pharmacokinetic Analyses

A descriptive summary of observed plasma concentrations of VTX3232 will be displayed by time and by treatment group.

Disease-Specific Analysis

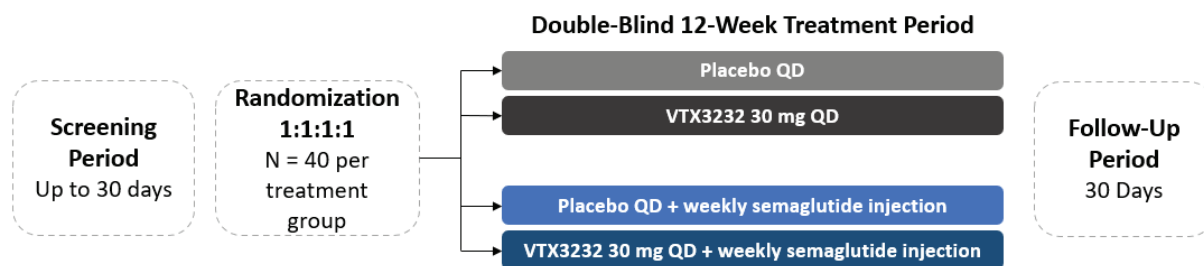
Exploratory objectives related to the effectiveness of study treatment in obesity (CCI) will be summarized by treatment group at each scheduled assessment timepoint using descriptive statistics and listed for individual participants.

Interim Analysis

No formal interim analysis is planned for this study.

1.2. Schema

Figure 1: Schematic Diagram of Study Design



QD, once daily.

CCI

1.3. Schedule of Activities

Procedure	Screening	12-Week Double-Blinded Treatment Period ^a						ET ^b	FU ^c
		W0/D1	W1/D8	W2/D15	W4/D29	W8/D57	W12/D85		
Window	D -30 to D -1	NA	± 2D	± 2D	± 2D	± 2D	± 2D	NA	+ 5D
Informed consent	X								
Eligibility criteria	X	X							
Demographics	X								
Social history	X								
Medical history	X								
FSH ^d	X								
Pregnancy test ^e	X	X			X	X	X	X	X
QuantiFERON-TB test	X								
Urine drug screen ^f	X								
Serology (HIV, HBV, HCV)	X								
Prior and concomitant medication and procedure review	X	X	X	X	X	X	X	X	X
AE review	X	X	X	X	X	X	X	X	X
CCI									
Vital signs ^g	X	X	X	X	X	X	X	X	X
12-Lead ECG ^h	X	X			X	X	X	X	X

Procedure	Screening	12-Week Double-Blinded Treatment Period ^a						ET ^b	FU ^c
		W0/D1	W1/D8	W2/D15	W4/D29	W8/D57	W12/D85		
Window	D -30 to D -1	NA	± 2D	± 2D	± 2D	± 2D	± 2D	NA	+ 5D
Height	X								
CCI									
Physical examination ^l	X	X	X	X	X	X	X	X	X
Urinalysis	X	X					X	X	X
CCI									
Clinical chemistry ^m	X	X	X	X	X	X	X	X	X
TSH	X	X			X		X	X	
Hematology ^m	X	X	X	X	X	X	X	X	X
Coagulation	X	X					X	X	X
Hemoglobin A1C	X						X	X	
CCI									
Blood collection for central lab biomarker analysis ^m		X		X	X		X	X	X

Procedure	Screening	12-Week Double-Blinded Treatment Period ^a						ET ^b	FU ^c
		W0/D1	W1/D8	W2/D15	W4/D29	W8/D57	W12/D85		
Window	D -30 to D -1	NA	± 2D	± 2D	± 2D	± 2D	± 2D	NA	+ 5D

CCI

Blood collection for VTX3232 PK analysis ^p		X	X	X	X	X	X	X	
Diet and exercise counselling ^q		X			X	X			
Randomization		X							
Dispense/redispense study treatment		X	X	X	X	X			
Return study treatment			X	X	X	X	X	X	
Review drug compliance ^r			X	X	X	X	X	X	
Administer study treatments at clinic ^s		X	X	X	X	X			

AE, adverse event; β-hCG, beta-human chorionic gonadotropin; BMI, body mass index; BP, blood pressure; CCI, Confidential Clinical Information; D, day; CCI, Confidential Clinical Information; ECG, electrocardiogram; ET, early termination; FSH, follicle-stimulating hormone; FU, Follow-Up; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IMP, investigational medicinal product; MRI, magnetic resonance imaging; NA, not applicable; CCI, Confidential Clinical Information; PK, pharmacokinetic; CCI, Confidential Clinical Information; SAE, serious adverse event; TB, tuberculosis.

Note: Study treatment includes the IMP, defined as a pharmaceutical form of the active substance being tested (test product) and the placebo being used as a reference (reference therapy) and includes both study treatment tablets (i.e., VTX3232 or placebo) and study treatment injections (i.e., semaglutide).

Note: If assessments are scheduled for the same nominal time, then the assessments should occur in the following order: 1) vital signs; 2) 12-lead ECG; 3) blood draw.

Note: If, for any reason, clinical samples (e.g., clinical chemistry, urine or blood collection, etc.) are considered indeterminate for the evaluation of safety or of the study endpoints, additional samples should be collected during the study as determined necessary by the Investigator or Medical Monitor.

- ^a At study visits, it is recommended that procedures are performed in a consistent order and at approximately the same time of day for each visit. The recommended sequence of events during study visits is provided in Section 8.1.2.
- ^b All participants who discontinue the study prematurely will be asked to return to the clinic for the ET visit within 1 week of the last dose of study treatment. The ET Visit may occur on the same day as another scheduled study visit.
- ^c A Follow-Up Visit will be conducted 30 days (window + 5 days) after the last dose of study treatment. Participants should be instructed to report any new AEs (including SAEs and AEs of interest) through 30 days after the last dose of study treatment (refer to Sections 8.1.8 and 8.4.2.3). The Investigator should monitor all participants through the Follow-Up Period. The Investigator is responsible for monitoring of AEs that may be ongoing at the time of the participant's last contact, as well as follow-up of any clinically significant abnormal laboratory results according to local standard of care. If the Investigator determines additional visits are clinically indicated, such visits will be captured as unscheduled visits.
- ^d The Investigator will determine the participant's reproductive potential during screening (refer to Section 8.3.5). FSH is required at screening only in females not using hormonal contraception or hormonal replacement therapy and with no menses for ≥ 12 months without alternative medical cause to confirm postmenopausal status.
- ^e For females of childbearing potential, the first pregnancy test at screening is a serum β -hCG test; all subsequent pregnancy testing will be performed using a urine dipstick pregnancy test. The serum β -hCG test is evaluated by a central laboratory and results are required to determine eligibility prior to randomization in addition to the results of the urine dipstick pregnancy test on Day 1. Any positive urine pregnancy test will be confirmed with a serum β -hCG test by a central laboratory; refer to Section 8.3.5.
- ^f A standard urine drug screen will be performed (refer to Table 5).
- ^g BP and pulse rate measurements should be preceded by at least 5 minutes of rest (where possible) without distractions and collected with the participant in the seated position (refer to Section 8.3.2). At screening/prerandomization, up to 3 BP readings may be recorded at intervals of at least 1 minute to confirm abnormal results. At subsequent timepoints, a single BP reading will be recorded. If scheduled for the same nominal time, vital signs should be collected prior to ECG and any blood draws.
- ^h All ECGs will be recorded with the participant in a supine position (refer to Section 8.3.3). In the event of an abnormal reading, the ECG should be completed in triplicate, regardless of Investigator's assessment of clinical significance; 3 individual ECG tracings should be obtained as closely as possible in succession, if possible, no more than 2 minutes apart. If scheduled for the same nominal time, ECG should be collected after collection of vital signs, but prior to any blood draws.
- ⁱ Refer to Section 8.2.1. BMI will be calculated using weight and baseline height to determine eligibility and at subsequent timepoints.
- ^j Refer to Section 8.2.2. The W0/D1 assessment may be obtained up to 14 days prior to Day 1.
- ^k CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
- ^l A complete physical examination is conducted at screening and at the W0/D1 and W12/D85 or ET visits and symptom-directed physical examinations are conducted at all other visits, unless clinically indicated. Refer to Section 8.3.1 for assessments to be performed during complete and symptom-directed physical examinations.
- ^m Blood samples to be obtained from participants in a fasted state (no food or drink aside from water for at least 10 hours). CCI [REDACTED]
[REDACTED]. Refer to Section 8.3.4. Clinical laboratory assessments are outlined in Table 5.

- ⁿ CCI [REDACTED]
[REDACTED]
[REDACTED]
- ^o Blood samples will be collected and processed as detailed in the Laboratory Manual.
- ^p CCI [REDACTED]
[REDACTED]
[REDACTED].
- ^q Conducted by a qualified healthcare professional via visits/phone contact.
- ^r Participants should be instructed to bring all dispensed bottles of study treatment tablets (including empty bottles) and, for participants randomized to receive semaglutide, bring all dispensed injection supplies (including used supplies) with them to their next visit.
- ^s Study treatments (injections and tablets) should be administered after completion of all predose assessments on the day of visit (refer to Section 8.1.2). The last dose of study treatment tablet is administered on the day prior to the last study visit. For participants assigned to a semaglutide treatment group, the last dose of study treatment injection (i.e., the 12th dose) is administered in Week 11 (Table 4). In addition, on weeks without scheduled study visits, participants in the semaglutide injection treatment groups may return to the study site for their once weekly administration of study treatment injections by site staff.

2. INTRODUCTION

2.1.1. Obesity

Obesity is a chronic complex disease defined by excessive fat deposits throughout the body with proven deleterious impact on health and lifespan. Obesity can lead to increased risk of heart disease, type 2 diabetes, obstructive sleep apnea, and fatty liver disease, affect bone health and reproduction, and increase the risk of certain cancers. Weight loss is a critical intervention for improving overall health in patients with obesity. For adults, the WHO defines an individual with obesity as having a BMI greater than or equal to 30 kg/m² (1).

In the United States, the prevalence of obesity was 41.9% in 2017 to 2020, which increased from a prevalence of 30.5% in 1999 (2). The estimated annual cost in the US as of 2019 is approximately \$173 billion to treat comorbidities that are associated with obesity (3).

Globally, in 2022, over 890 million adults were living with obesity (1). High BMI accounted for 4.0 million deaths worldwide in 2015, of which more than two-thirds were caused by cardiovascular disease (4). Though it is widely accepted that obesity is a major risk factor for cardiovascular disease, the impact of weight reduction in lowering the underlying cardiometabolic risks has not been fully elucidated and the strategies to reduce this risk have included managing hyperlipidemia, hyperglycemia, blood pressure, heart failure, inflammation, and/or thrombosis via medication rather than via weight-loss. Given that obesity is also a contributing factor in these related cardiometabolic conditions, effective and sustained weight loss may have an independent benefit (5, 6).

The CNS plays a major role in the regulation of metabolic balance and energy homeostasis (7). Activation of nonneuronal cells, such as microglia and astrocytes, has been demonstrated to be associated with excessive weight gain in animal models through impairment of the hypothalamic energy homeostasis system (8-10). This “reactive gliosis” response involves entry of saturated fatty acids into the CSF through diet, which leads to inflammatory activation of hypothalamic microglia (11, 12). This neuroinflammatory response is a potentially important aspect in the pathogenesis of diet-induced obesity (9). For the energy homeostasis system to function properly, key hypothalamic neurons provide “adiposity negative feedback” from signals such as insulin and leptin. Impaired neuronal responsiveness to these signals likely result in the obesogenic effect of hypothalamic gliosis (9, 13).

2.1.2. Investigational Product

VTX3232, a brain-penetrant small molecule inhibitor of the NLRP3 inflammasome, is being evaluated by Zomagen Biosciences Ltd. as a potential oral treatment for participants with obesity.

One of the major pathways by which innate immune cells integrate pathogen- and damage-associated signals with inflammation is via assembly and activation of intracellular protein complexes known as inflammasomes. Inflammasome activation is implicated in a host of autoinflammatory and autoimmune disorders, including neurodegenerative diseases (14, 15).

Saturated fatty acids, present during obesity, are potential activators of the NLRP3 inflammasome (16, 17). Nonclinical research has demonstrated this relationship between NLRP3

and obesity, as NLRP3-knockout mice have been shown to be protected from diet-induced obesity (18). In addition, dosing with a potent, selective, but non-CNS penetrant NLRP3 inhibitor (MCC950) limited weight gain in response to high-fat diet feeding in mice (19).

Recently, 2 clinical-stage NLRP3 inhibitors demonstrated reversal of diet-induced obesity in mice (20). The effect of NLRP3 inhibition was associated with enhanced reductions in hypothalamic gliosis and circulating biomarkers of cardiovascular disease risk in comparison with semaglutide treatment or calorie restriction. In the evaluation of these 2 NLRP3 inhibitors, inflammatory responses played a key role in driving obesity and NLRP3 activation in the brain was implicated in the pathogenesis of obesity.

CCI

Nonclinical Data with VTX3232

Nonclinical studies demonstrate that VTX3232 is a potent, selective inhibitor of NLRP3 that binds the NACHT-LRR domain of NLRP3 with high affinity and potently inhibits its ATPase activity. As a result, VTX3232 inhibits NLRP3-driven pyroptosis and IL-1 β /IL-18 release from myeloid cells, including microglia (CNS resident myeloid cells). In vitro cellular studies indicate that VTX3232 is approximately 15-fold more potent in human compared to mouse/rat NLRP3, and in whole blood, VTX3232 is approximately 7-fold more potent in human compared to mouse. VTX3232 demonstrated the relevant pharmacologic effects in nonclinical neuroinflammation models. In a mouse acute inflammation model, VTX3232 dose-dependently inhibits IL-1 β release in serum. Furthermore, VTX3232 inhibits NLRP3 pathway activation to the brain of female mice, specifically targeting caspase-1 activation and IL-1 β release.

CCI

In nonclinical species, orally administered VTX3232 was readily absorbed and distributed to the CNS in all species tested and CSF levels were demonstrated to consistently approximate unbound plasma and (where measured) unbound brain VTX3232 levels. CCI

VTX3232 was evaluated in repeat dose toxicology studies in rats and dogs for up to 6 and 9 months, respectively. CCI

The effects of VTX3232 on body weight, food consumption, and cardiometabolic parameters were evaluated in a mouse high-fat (DIO) model. Treatment with VTX3232 resulted in

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Clinical Data with Semaglutide

Semaglutide is a GLP-1 receptor agonist that was initially approved as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to reduce the risk of cardiovascular events in adults with type 2 diabetes mellitus and cardiovascular disease (OZEMPIC® Prescribing Information, Novo Nordisk). Subsequently, semaglutide has received approval in combination with a reduced calorie diet and increased physical activity to reduce the risk of major adverse cardiovascular events in adults with either obesity or overweight and established cardiovascular disease and to reduce excess body weight and maintain weight reduction long term in patients age 12 and older with obesity (21) (WEGOVY® Prescribing Information, Novo Nordisk). Across multiple clinical studies in adults with overweight or obesity (without diabetes), once weekly treatment with subcutaneous injections of semaglutide plus lifestyle intervention was associated with substantial, sustained, clinically relevant mean weight loss compared to placebo (21-28).

In addition, semaglutide has been shown to improve cardiometabolic risk factors and cardiovascular outcomes in both patient populations (6, 21, 22, 29, 30); notably, obesity is a strong risk factor for the development of diabetes, and both diabetes and obesity are associated with cardiovascular disease (5, 24). Semaglutide monotherapy or as a combination therapy also reduced liver steatosis in patients with NAFLD (i.e., MASLD) or steatohepatitis (31-33). CCI

[REDACTED]

[REDACTED]

2.2. Benefit/Risk Assessment

Treatment with NLRP3 inhibitors such as VTX3232 represents a potential novel mechanism with potential to treat obesity by inhibiting inflammatory processes associated with the disease. This study will evaluate the biological effects of VTX3232 when administered alone or in combination with semaglutide therapy in patients with obesity.

Potential Risks and Mitigations for VTX3232

Data from the nonclinical safety studies and Phase 1 Study VTX3232-101 in healthy participants supports the administration of VTX3232 in this study. In nonclinical studies, VTX3232 was well-tolerated without evidence of significant toxicity in animal species at the proposed human doses/exposures, and potential risks, such as changes in hematology and clinical chemistry, can be monitored and are considered manageable at the planned dose range in the current study.

CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Safety monitoring for potential risks of VTX3232 will be instituted in this study. Such monitoring will include, but is not limited to, AE monitoring, recording vital signs, neurological examination, evaluating clinical laboratory and ECG results, CCI. The eligibility criteria have been selected to include participants representative of a population with

obesity and exclude participants potentially vulnerable to treatment with an NLRP3 inhibitor

CCI

Potential Risks and Mitigations for Semaglutide

In clinical studies with semaglutide, the safety profile was consistent with the known profile of GLP-1 receptor agonists, with gastrointestinal events being the most commonly reported AEs. This study will implement a gradual dose-escalation that may help alleviate or prevent such side effects (21, 22). This study also permits dose modification for study treatment injections if an individual participant does not tolerate a dose increase of semaglutide treatment. Risks associated with semaglutide use in patients with overweight or obesity include acute pancreatitis, acute gallbladder disease, hypoglycemia, acute kidney injury, hypersensitivity reactions, diabetic retinopathy complications in patients with type 2 diabetes, heart rate increase, and CCI

Safety monitoring for the risks associated with semaglutide will be instituted in this study. Such monitoring will include, but is not limited to, monitoring AEs throughout the treatment period and after study treatment discontinuation, recording vital signs, neurological examination, evaluating clinical laboratory and ECG results, CCI assessment at regular intervals. The eligibility criteria will exclude participants potentially vulnerable to treatment with semaglutide (e.g., participants with medullary thyroid carcinoma). In addition, the study will include treatment discontinuation criteria for the conditions considered risks of semaglutide use (e.g., participants with confirmed pancreatitis will be discontinued) as determined by clinical study monitoring (e.g., clinical laboratory test results).

Potential Risks and Mitigations for Combination Therapy

CCI

The safety monitoring and risk mitigations described for each treatment alone (e.g., AE monitoring, treatment discontinuation criteria, regular clinical laboratory assessments) are also applicable for combination therapy. CCI

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Potential Benefits

Participants will be treated within a regimen anticipated to be better than or equal to the weight management they receive at the time of entry into the study. In addition, it is expected that all study participants (including those randomized to placebo) will benefit from participation through counselling by a qualified healthcare professional, which may result in improved weight management. As even moderate weight loss has been shown to have significant health benefits, participants in this study are expected to benefit from an improvement in weight-related comorbidities, indicated by cardiovascular risk factors, lipid profile and glycemic factors, as well as improvements in clinical outcome assessments.

In nonclinical studies with VTX3232 in diet-induced obese mice, VTX3232 administered alone or in combination with semaglutide decreased body weight gain, body weight, and food intake, and showed improvements in systemic inflammatory and cardiometabolic markers of disease.

The efficacy of semaglutide for chronic weight management was studied in 5 randomized, double-blind placebo-controlled studies. Results from these studies demonstrated that semaglutide was effective for weight loss in participants with obesity as an adjunct to a reduced-calorie diet and increased physical activity (21-28).

2.2.1. Risk/Benefit Conclusion

Accounting for the nonclinical and clinical data to date, as well as the assessments in this study to protect participants safety, the potential risks identified in association with VTX3232 are justified by the anticipated benefits that may be afforded to study participants, which supports further clinical development of VTX3232. CCI

[REDACTED]

[REDACTED]

Detailed information regarding the known and expected benefits, risks, and reasonably expected AEs of VTX3232 can be found in the IB. Detailed information regarding the known and expected benefits, risks, and reasonably expected AEs of semaglutide can be found in the Prescribing Information for WEGOVY® (Novo Nordisk).

3. OBJECTIVES AND ENDPOINTS

The objectives and endpoints in this study are provided in [Table 1](#). A complete list of endpoints and definitions, as well as analysis methods will be provided in the SAP.

Table 1: Study VTX3232-204 Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the safety and tolerability of active treatment compared with placebo	Incidence and severity of AEs, SAEs, and AEs leading to study treatment discontinuation from the first dose through end of the Follow-Up Period
Secondary	
To evaluate the effect of active treatment on hs-CRP compared with placebo	Change from baseline in hs-CRP over time through Week 12
Exploratory	
To evaluate the effect of active treatment on body weight compared with placebo	Percent change from baseline in body weight over time through Week 12
	Change from baseline in body weight over time through Week 12
	Proportion of participants achieving at least 5% and at least 10% body weight reduction at Week 12
To evaluate the effect of active treatment on BMI compared with placebo	Change from baseline in BMI over time through Week 12
CCI [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]
To evaluate the effect of active treatment on vital signs compared with placebo	Change from baseline in blood pressure (systolic and diastolic) over time through Week 12
	Change from baseline in pulse rate over time through Week 12
To evaluate the effect of active treatment on lipid parameters in blood compared with placebo	Change from baseline in measures of lipid levels (total cholesterol, HDL, LDL, VLDL, triglycerides, free fatty acids) over time through Week 12
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED]

Objectives	Endpoints
To evaluate the effect of active treatment on glycemic parameters in blood compared with placebo	Change from baseline in fasting glucose and fasting insulin over time through Week 12
	Change from baseline in Hemoglobin A1C at Week 12
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED]
[REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
Pharmacokinetic	
To investigate the pharmacokinetics of VTX3232 (and metabolites, as appropriate) in plasma	To determine the plasma concentration of VTX3232 over time through 12 weeks
Safety	
To evaluate the effect of study treatment on additional measures of safety and tolerability	Incidence and severity of laboratory abnormalities Change from baseline in laboratory values (hematology, serum chemistry, coagulation, and urinalysis), ECG, and vital signs Incidence of clinically significant changes to vital signs and ECGs CCI [REDACTED] [REDACTED]

AE, adverse event; BMI, body mass index; CCI [REDACTED]
[REDACTED] ECG, electrocardiogram; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; CCI [REDACTED]; LDL, low-density lipoprotein; MRI, magnetic resonance imaging; CCI [REDACTED]
[REDACTED]
[REDACTED] SAE, serious adverse event; VLDL, very low-density lipoprotein.

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2a multicenter, randomized, placebo-controlled study to evaluate the safety and tolerability of VTX3232 administered alone or in combination with semaglutide in participants with obesity. The PK of VTX3232, the effect of study treatment on inflammatory and cardiometabolic biomarkers in blood and urine, and the effect of study treatment on weight loss will also be evaluated.

This study consists of a Screening Period of up to 30 days, an outpatient Double-Blind Treatment Period of 12 weeks, and a safety Follow-Up Period of 30 days (approximately 4 weeks). The study design schema is presented in Section 1.2. The maximum duration of study participation for an individual participant will be approximately 20 weeks.

During the Screening Period, participants will undergo eligibility assessments.

On Day 1, participants will commence study treatment in the Double-Blind Treatment Period where approximately 160 participants will be randomized (1:1:1:1, with approximately 40 participants in each treatment group) to one of the following treatment groups:

- Placebo QD
- VTX3232 30 mg QD
- Placebo QD and weekly semaglutide injection
- VTX3232 30 mg QD and weekly semaglutide injection

CCI [REDACTED] VTX3232 30 mg or placebo will be administered orally once daily. For participants assigned to a semaglutide treatment group, semaglutide injections will be administered once weekly in an escalating dose regimen in accordance with the Prescribing Information for WEGOVY®, refer to Table 4, with a maximal semaglutide dose level of 1.0 mg.

CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

During the study, participants will be evaluated for safety and other outcome measures in accordance with the SoA (Section 1.3). For all participants (including those participants who discontinue the study prematurely), the Follow-Up Period is 30 days after the last dose of study treatment.

The primary objective of this study is to evaluate the safety and tolerability of study treatment (i.e., VTX3232 alone or in combination with semaglutide) in participants with obesity. A secondary objective is to assess the effect of study treatment on hs-CRP over 12 weeks of treatment. CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

Safety will be assessed by

recording AEs (including SAEs and AEs of interest), vital signs, performing complete and targeted physical examinations (including neurological examination), CCI [REDACTED], and evaluating clinical laboratory and ECG results measures in accordance with the SoA (Section 1.3).

The target study population includes adult males or females ages ≥ 18 to ≤ 80 years at the time of consent who meet the criteria for obesity with a BMI ≥ 30.0 to ≤ 42.0 kg/m² at screening, stable body weight for at least 3 months prior to screening, and at least one self-reported unsuccessful dietary effort to lose body weight. A hs-CRP of ≥ 2 mg/L at screening is also required. For eligible participants with hypertension or hyperlipidemia, these conditions must be controlled with stable therapy prior to initiating study treatment. Individuals with diabetes mellitus (Type 1 diabetes mellitus or Type 2 diabetes mellitus, or rare forms of diabetes mellitus) will be excluded.

4.2. Scientific Rationale for Study Design

Study VTX3232-204 is a 12-week Phase 2a study designed to examine the effects of administration of VTX3232 alone or in combination with semaglutide on safety, tolerability, efficacy, and PK in participants with obesity. This study is randomized, double-blind, and placebo-controlled (for VTX3232), CCI [REDACTED]

[REDACTED] In this proof of principle study with the combination therapy of VTX3232 and semaglutide, the primary objective is evaluation of safety and tolerability.

The secondary endpoint of the study is the change from baseline in hs-CRP. CCI [REDACTED]

Additional biomarkers will be assessed as exploratory endpoints in the study. Assessments of efficacy such as percent change in body weight and body composition will also be evaluated in this study. CCI [REDACTED]

The 12-week duration of the Double-Blind Treatment Period is adequately supported by nonclinical toxicology studies where there was no evidence of significant toxicology in animal species at the human doses/exposures evaluated in this study. CCI [REDACTED]

CCI

This study will also include lifestyle (e.g., diet and exercise) counselling as a component as an adjunct to interventional pharmacologic treatment. When lifestyle interventions are used alone, these forms of weight management are difficult for patients to achieve and maintain. Diet and exercise, though widely considered a mainstay of treatment for obesity, are therefore associated with only modest weight-loss that is often regained. In this study, pharmacotherapy used in conjunction with lifestyle counselling will therefore mimic the real-world experience of patients undertaking diet and exercise to achieve sustained weight-loss and improve cardiorespiratory outcomes. This treatment paradigm is also consistent with prior drug approvals for weight reduction medications by the US FDA and European Medicines Agency (24).

CCI

4.3. Dose Justification

The dose and dosing regimen in this study was selected based on the PK and tolerability profile of VTX3232 in Study VTX3232-101, a Phase 1 single- and multiple-ascending dose study.

CCI

The highest dose of semaglutide 1 mg was selected based on the 12-week treatment duration of this study, which is considered an adequate time to evaluate body-weight change in this initial study (refer to Section 4.2).

CCI from the WEGOVY[®] Prescribing Information through 12 weeks will therefore be used as the dose regimen for this study (Table 4).

CCI

4.4. End-of-Study Definition

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

5. STUDY POPULATION

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if ALL of the following criteria are met:

General

1. Participants are male or female ≥ 18 years up to ≤ 80 years of age.
2. Capable of giving signed informed consent, which includes compliance with the requirements and restrictions listed in the ICF and in the study protocol, including compliance with the SoA.
3. Ability to comply with study requirements.

Disease Characteristics

4. BMI ≥ 30.0 to ≤ 42.0 kg/m² at screening.
5. Stable body weight ($\pm 5\%$) for at least 3 months prior to screening.
6. hs-CRP ≥ 2 mg/L at screening.
7. Hypertension or hyperlipidemia which are known to be associated with increased risk of cardiovascular events, if present, must be controlled with stable dose/therapy on study and for the 3 months prior to Day 1. Changes to dose/therapy prior to Day 1 may be permitted if approved by the Medical Monitor on a case-by-case basis.
8. History of at least one self-reported unsuccessful dietary effort to lose body weight.

Sex and Contraceptive/Barrier Requirements

9. A female participant is eligible to participate if she is not pregnant or breastfeeding, and 1 of the following conditions (either a or b) applies:
- Is not a FOCBP (as defined in [Appendix 1](#)).
 - Is a FOCBP and using a highly effective contraceptive method with a failure rate of < 1% per year, as described in [Appendix 1](#), during the study treatment period. For participants receiving study treatment tablets only, such contraception must also be used for at least 30 days after the last dose of study treatment. For participants receiving both study treatment tablets and semaglutide injections, such contraception must be used for at least 60 days after the last dose of study treatment. The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study treatment. Methods considered highly effective for birth control are listed in [Appendix 1](#).
 - A FOCBP must have a negative serum pregnancy test at screening.
 - A FOCBP must refrain from donating oocytes for at least 90 days after the last dose of study treatment.
10. A male participant is eligible to participate if they agree to the following during the study treatment period and for at least 90 days after the last dose of study treatment:
- Refrain from donating sperm.
 - Agree to use a male condom with a FOCBP. Female partners of male participants should be instructed to use an additional highly effective contraceptive method with a failure rate of < 1% per year (as listed in [Appendix 1](#)).

5.2. Exclusion Criteria

Participants are excluded from the study if ANY of the following criteria are met:

Current or Past Medical History

1. Obesity induced by endocrinologic disorders (CCI [REDACTED]), or diagnosed genetic or syndromic forms of obesity (CCI [REDACTED]).
2. Have any prior diagnosis of diabetes mellitus (Type 1 or Type 2 diabetes mellitus, CCI [REDACTED]).
3. Current participation (or within the last 3 months) in an organized weight reduction program.
4. History or presence of clinically significant gastric emptying abnormality (e.g., severe gastroparesis or gastric outlet obstruction) or chronically take drugs that directly affect GI motility, have undergone prior surgical treatment for obesity (e.g., gastric bypass).

[bariatric] surgery or restrictive bariatric surgery), or have an endoscopic and/or device-based therapy for obesity. CCI :

- CCI

- _____

The Medical Monitor should be contacted if there are any questions regarding eligibility.

5. Clinically relevant medical condition(s) that put the participant at risk or will make implementation of the protocol or interpretation of the study difficult. This includes:

- a. CCI
-
- | Response | Percentage |
|----------|------------|
| Yes | 100% |
| No | 0% |

- n. Personal or family history of medullary thyroid carcinoma (MTC)
- o. Personal or family history of Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

6. CCI

CCI

Prior or Concomitant Treatment

7. Use of any medication (e.g., GLP-1 agonists), nutritional supplement, or over the counter product for weight loss within the previous 6 months or during study participation, unless administered as a part of assigned study treatment in this study.

8. CCI

13. Receipt of the following medications within the time period described:

- Any immunosuppressive biologic or targeted therapy within 90 days (CCI) prior to Day 1.
- Use of anti-inflammatory medications within 30 days prior to Day 1; CCI
- Colchicine within 30 days prior to Day 1.
- Glucose-lowering agent(s) administered for conditions other than diabetes within 90 days before screening.

14. CCI

15. CCI

Diagnostic Assessments

18. Clinically significant abnormalities in safety test results at screening, including hepatic and renal panels, complete blood count, chemistry panel, and urinalysis, CCI [REDACTED]

[illegible]

Government	Percentage
Current government	85%
Previous government	15%

Other

22. CCI
23. Hypersensitivity to semaglutide or any of its excipients.
24. Positive pregnancy test or lactating female participant.
25. CCI

26. Individuals in the same household are currently receiving approved or investigational GLP-1-targeted medications.
27. Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability or lack of efficacy.

5.3. Lifestyle Considerations

Medical and/or recreational use of marijuana is not permitted during study participation. Participants need to also refrain from use of cannabidiol oil during the study.

5.3.1. Diet and Physical Activity Counselling

All participants will receive counselling with regards to their diet and physical activity. Counselling will be done by a qualified healthcare professional.

5.4. Screen Failures

A screen failure occurs when a participant who has consented to participate in the clinical study is not subsequently randomized in the study for any reason.

Individuals who do not meet the eligibility criteria for participation in this study (i.e., screen failure) may be rescreened once, if deemed acceptable by the Investigator. Additional screening attempts beyond the first should be approved by the Medical Monitor prior to rescreening.

- Rescreened participants should be assigned a new participant number for every screening/rescreening event.
- All procedures planned at the Screening Visit, including signature of a new ICF, will be performed.
- Only results from the latest Screening Visit will be considered to establish eligibility.
- Duration of existing treatments and required discontinuation periods will be considered relative to the new Screening Visit and/or randomization.

If a participant fails any screening criteria, the assessment(s) may be repeated once at the discretion of the Investigator, and the participant may be enrolled if the criteria are then met, provided the assessments are completed within the Screening Period. If additional retests are considered, the ability to repeat the laboratory assessment should be discussed with the Medical Monitor and the outcome of the conversation should be documented.

For hematology and chemistry laboratory assessments, only those collected during the Screening Period should be used to determine participant eligibility; such results must be obtained and reviewed prior to randomization. Results of hematology and chemistry laboratory assessments collected predose as a part of the Day 1 Visit are not considered exclusionary.

6. STUDY TREATMENT AND CONCOMITANT THERAPY

6.1. Study Treatment Administered

Study treatment includes the IMP, defined as a pharmaceutical form of the active substance being tested (test product) and the placebo being used as a reference (reference therapy) and includes both study treatment tablets (i.e., VTX3232 or placebo) and study treatment injections (i.e., semaglutide).

Study treatment is listed in [Table 2](#) and treatment groups are outlined in [Table 3](#).

CCI

For participants randomized to receive semaglutide, injection treatment will be administered in an escalating dose regimen in accordance with the Prescribing Information for WEGOVY[®], refer to [Table 4](#).

Study treatment tablets and injections may be administered in any order.

On study visit days, participants are required to be in a fasted state (no food or drink aside from water for at least 10 hours). Participants should be instructed to document the date and time of their last dose of study treatment (tablets and injections) prior to the study visit and that should be documented in the eCRF.

The date and time of each dose of study treatment (tablets and injections) administered in the clinic will be recorded in the source documents and eCRF. Refer to [Section 8.1.2](#) for the recommended sequence of procedures to be conducted during study visits.

Table 2: Study Treatment Information

Study Treatment	Tablet		Injection
	VTX3232	Placebo	Semaglutide
Dose formulation	Film-coated tablet	Film-coated tablet	Solution for injection
Unit dose strength(s)	30 mg	Not applicable	0.25, 0.5, 1.0 mg/mL
Dosage level(s)	30 mg	Not applicable	0.25, 0.5, 1.0 mg/mL
Route of administration	Oral	Oral	Subcutaneous
Use	Experimental	Placebo	Active Combination Treatment
Sourcing	Provided centrally from Sponsor	Provided centrally from Sponsor	Provided centrally from Sponsor
Packaging and labeling	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]

Study Treatment	Tablet		Injection
	VTX3232	Placebo	Semaglutide
Storage requirements	Kept in accordance with the label condition at 15 to 25°C (59 to 77°F)	Kept in accordance with the label condition at 15 to 25°C (59 to 77°F)	Kept in accordance with the label condition at 2 to 8°C (36 to 46°F)

Table 3: Treatment Group(s)

Treatment Group	Tablet		Injection
	VTX3232 30 mg	Matching Placebo	Semaglutide
Placebo QD		X	
VTX3232 30 mg QD	X		
Placebo QD and weekly semaglutide subcutaneous injection		X	X
VTX3232 30 mg QD and weekly semaglutide subcutaneous injection	X		X

QD, once daily; X, each X represents 1 tablet or injection.

Study Treatment Tablets

All participants will self-administer study treatment tablets each day by mouth, with water (approximately 240 mL or 8 fluid oz) [REDACTED]. Study treatment tablets should be taken at approximately the same time each day, except on study visit days when the dose of study treatment tablets will be administered at the study site after all predose assessments and procedures have been completed (as applicable per the SoA Section 1.3).

Study Treatment Injections

For participants randomized to a treatment group including semaglutide injections, study treatment injections are administered once weekly on approximately the same day each week, at any time of day, [REDACTED]

Study treatment injections will be administered at the study site or off-site by the participant, according to the schedule provided in Table 4. In addition, on weeks without scheduled study visits, participants in the semaglutide injection treatment groups may return to the study site for their once weekly administration of study treatment injections by site staff.

On study visit days, study treatment injections should be administered after all predose assessments and procedures have been completed (as applicable per the SoA Section 1.3).

Injections are administered according to the Prescribing Information for WEGOVY®; participants will be trained by the Investigator or delegate in the proper injection technique. Prior to each injection, the injector pen should be visually examined; treatment should only be used if the solution is clear, colorless, and contains no particles. Injections are administered subcutaneously in the abdomen, thigh, or upper arm. Participants should be encouraged to inject

in the same body part throughout the study, but the injection site may be changed without dose adjustment.



Instructions for Missed Dose

Guidance on study treatment interruption for reasons other than a missed dose is described in Section 7.2.

Missed Dose of Study Treatment Tablets

Participants should be instructed that if they forget to take a dose of study treatment tablets, they can take the dose within 8 hours of the normal dosing time; otherwise, they should take their next dose of study treatment tablets at the regular time on the following day.

If the participant vomits the tablet(s), they should be instructed not to take additional tablets on the same day, but to take the next dose at the regular time on the following day.

Any interruption of study treatment tablets of ≥ 2 consecutive doses must be documented on the corresponding eCRF, with the start date, end date, and reason for interruption (if known) specified.

Missed Dose of Study Treatment Injection

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Any interruption of study treatment injection (i.e., any missed dose) must be documented on the corresponding eCRF, with the start date, end date, and reason for interruption (if known) specified.

If ≥ 2 consecutive doses of study treatment injection are missed, the Medical Monitor should be contacted to discuss the treatment reinitiation plan. Generally, study treatment should be continued as early as the situation allows and the missed doses should not affect the scheduled dosing day of the week.

6.2. Preparation, Handling, Storage, and Accountability

6.2.1. Study Treatment Packaging and Labeling

Study treatment tablets will be provided in bottles containing VTX3232 film-coated tablets or placebo, as appropriate. Each bottle will be labeled as required per local requirements.

Study treatment injection supplies will include prefilled injector pens with the correct dosage level according to the dose escalation regimen in [Table 4](#). All study treatment injection supplies will be labeled as required per local requirements.

6.2.2. Study Treatment Storage

All study treatment (including both study treatment tablets and injections) 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.

The Investigator or designee must confirm appropriate conditions (e.g., temperature) have been maintained during transit for all study treatment received, and any discrepancies are reported and resolved before use of the study treatment.

6.2.3. Study Treatment Preparation

No preparation by study site personnel is required.

6.2.4. Study Treatment Accountability, Handling, and Disposal

The Investigator is responsible for ensuring that study treatment is dispensed only from official study sites by authorized personnel according to local regulations and dispensed only to study participants.

The Investigator is responsible for study treatment accountability and reconciliation, and must maintain adequate records documenting the receipt, use, loss, or other disposition of study treatment. Reasons for departure from the expected dispensing regimen must also be recorded. All treatment supplies should be accounted for in the IRT/EDC Drug Accountability Form and will be monitored by counting unused study treatment tablets.

All study treatment materials will be reconciled by the clinical monitor and then returned or destroyed according to applicable country regulations and in accordance with applicable site standard operating procedures. Final reconciliation will be performed at the study's completion. For additional details regarding the final disposition of unused study treatment and all the study treatment supplies/containers, refer to the Pharmacy Manual.

6.3. Assignment to Study Treatment

For treatment during the Double-Blind Treatment Period, participants will be randomly assigned (1:1:1:1 allocation ratio) at the Day 1 (Baseline) Visit to receive VTX3232 30 mg or placebo once daily alone or in combination with weekly injections of semaglutide. CCI

Unique participant identification numbers will be as described in the Study Manual.

All participants will be centrally assigned to randomized study treatment using an IRT system that will hold treatment codes. Before the study is initiated, the log-in information and directions for the IRT system will be provided to each site.

Blinded treatment assignment will be managed using the IRT system, which will also control IMP supply with study treatment dispensed at applicable study visits as specified in the SoA (Section 1.3).

6.4. Blinding

The study will employ a double-blind design with respect to the assignment of study treatment tablets (i.e., VTX3232 or placebo). Participants, Investigators, study center staff, persons performing the assessments, and the Sponsor or other authorized designees are to remain blinded to the identity of study treatment tablets in the Double-Blind Treatment Period from the time of randomization until after database lock, unless that knowledge is necessary to determine emergency medical care for a participant. Whether a participant has been assigned to receive semaglutide injections plus to study treatment tablets, or study treatment tablets alone will not be blinded.

The study treatment tablets (VTX3232 and placebo) and tablet bottles are identical in physical appearance and each daily dose is made up of an active or placebo tablet to provide the correct treatment and maintain the blind (Table 2).

Circumstances for Unblinding:

- The IRT system is programmed with blind-breaking instructions to guide the Investigator on how to obtain treatment assignment in the event of an emergency unblinding. Any request to unblind a participant for nonemergency purposes should be discussed with the Medical Monitor prior to unblinding.

- The Investigator has the sole responsibility for determining if the unblinding of a participant's treatment assignment is warranted to provide appropriate medical care. Participant safety must always be the first consideration in making such a determination.
- The Investigator should contact the Medical Monitor promptly in case of any treatment unblinding. If a participant's treatment assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason the blind was broken must be recorded in the source documentation and eCRF, as applicable.
- If a participant is unblinded for any reason, they may be discontinued from study treatment following discussion with the Medical Monitor. The primary reason for discontinuation (the event or condition which led to the unblinding) should be recorded.

Sponsor staff or designees not directly involved in the conduct of the study may have access to unblinded information through their work in processing information related to the clinical study (e.g., pharmacovigilance cases, PK and PD data). A record of these individuals will be maintained.

For SUSARs, the Sponsor's Pharmacovigilance designee responsible for managing SAEs, will access the IRT system to obtain the participant's treatment assignment for the purpose of safety regulatory reporting.

6.5. Study Treatment Compliance

When participants are dosed at the site, they will receive study treatment directly from the Investigator or designee, under medical supervision. Study treatment tablets and injections may be administered in any order. The date and time of each dose of study treatment tablet and injection administered in the clinic will be recorded in the source documents and eCRF.

The Investigator is responsible for ensuring that participants are correctly instructed on how to take the study treatment (including both administration of study treatment tablets and injections) and that each participant is fully compliant with the assigned treatment regimen. Participants should be instructed to bring all dispensed bottles of study treatment tablets (including empty bottles) and, for participants randomized to receive semaglutide, bring all dispensed injection supplies (including used supplies) with them to their next visit to determine whether participants are taking study treatment according to the prescribed dosage regimen.

At every visit, the Investigator or qualified staff will review a participant's adherence to the prescribed dosage regimen by counting returned tablets (per bottle) and evaluating the returned injector pens, which should be documented in the source documents. For participants who are consistently not adhering to the prescribed dosage regimen, the Medical Monitor should be consulted to determine whether such participants should be withdrawn from the study.

A record of the quantity of study treatment dispensed to and administered by each participant must be maintained and reconciled with study treatment and compliance records. Treatment start and stop dates, including dates for treatment delays and/or dose interruptions will also be recorded.

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6.6. Dose Modification

There is no provision for dose modification of study treatment tablets.

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If a participant interrupts treatment due to an AE, study treatment can be restarted in consultation with the Medical Monitor.

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

Participants will no longer have access to the study treatment after they complete the study, unless otherwise required by law. The Investigator should ensure that participants continue to receive appropriate standard of care to treat the condition under study.

The Sponsor has the right to terminate this study at any time; refer to Section [10.9.2](#).

6.8. Treatment of Overdose

Study treatment overdose is defined as any accidental or intentional use of study treatment (tablets or injections) in an amount higher than the dose indicated per protocol for a given participant. CCI

Overdoses have been reported with GLP-1 receptor agonists other than semaglutide. Effects have included severe nausea, severe vomiting, and severe hypoglycemia. In the event of overdose, appropriate supportive treatment should be initiated according to the patient's clinical signs and symptoms. A prolonged period of observation and treatment for these symptoms may be necessary, taking into account the long half-life of semaglutide of approximately 1 week.

In the event of an overdose, the Investigator should:

- Evaluate the participant to determine, in consultation with the Medical Monitor, if possible, whether study treatment should be interrupted.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities (as medically appropriate and at least until the next scheduled follow-up) and follow the AE/SAE reporting process.
- Obtain a plasma sample within 4 days from the date of the last dose of study treatment if requested by the Medical Monitor (determined on a case-by-case basis) for PK analysis.
- The start and end dates of the overdose, bottle number(s) or injection pen numbers, number of tablets or injections taken per overdose day, and any AEs related to the overdose should be recorded in the Overdose eCRF. Any AEs associated with the overdose should also be recorded on the AE eCRF.

6.9. Concomitant Therapy

Participants who start prohibited medications or therapies during the treatment period may be withdrawn from study treatment for this protocol deviation (Section 7).

6.9.1. Prohibited Concomitant Therapy and Procedures

The following therapies are prohibited during the treatment period, unless otherwise specified. Required washout periods prior to study participation are listed in the Exclusion Criteria (Section 5.2).

- Investigational drugs or therapies other than the study treatment.
- Semaglutide-containing products or other GLP-1 receptor agonist medicines unless administered as a part of assigned study treatment in this study.
- Medication, nutritional supplement, or over the counter product for weight loss, unless administered as a part of assigned study treatment in this study.

- CCI [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]

A horizontal bar chart titled "Percentage of respondents who have used..." The y-axis lists seven categories: "Used at least one service", "Used all three services", "Used none of the services", "Used two services", "Used no services except the library", "Used only the library", and "Used only the internet". The x-axis represents percentages from 0% to 100%. The bars show the following approximate values: "Used at least one service" (98%), "Used all three services" (12%), "Used none of the services" (2%), "Used two services" (7%), "Used no services except the library" (86%), "Used only the library" (88%), and "Used only the internet" (48%).

Service Usage Category	Percentage of Respondents
Used at least one service	98%
Used all three services	12%
Used none of the services	2%
Used two services	7%
Used no services except the library	86%
Used only the library	88%
Used only the internet	48%

- Prohibited concomitant procedures:
 - Participants should not undergo major elective surgery while on study treatment.
 - Surgical treatment for obesity or placement of endoscopic and/or device-based therapy for obesity.
 - Participants may not donate blood during the study and for 90 days after the last dose of study treatment.
 - Participants may not donate sperm during the study and for 90 days after the last dose of study treatment.
 - Participants may not donate oocytes during the study and for 90 days after the last dose of study treatment.

6.9.2. Allowed Concomitant Therapy and Procedures

Concomitant medications or treatments (including over-the-counter or prescription medicines, vitamins, supplements, or holistic products) for chronic medical conditions other than obesity are permitted as clinically indicated, provided the following criteria are met:

- Dosages of concomitant medications or treatments are stable; dose adjustments of these medications/treatments are permitted as clinically indicated but should be avoided during the study. If a dose adjustment should occur, they must be recorded on the applicable eCRF page.
- Neither the medications/treatments nor the medical conditions meet the exclusion criteria in Section 5.2.
- The medications/treatments are not expected to interfere with the evaluation of or interact with the investigational drug.
- For prescription medications, the medications are approved in the country where they will be administered.

The Investigator should instruct the participant to notify the study site about any new treatments they take after the start of the study treatment. New treatments and dose adjustments of concomitant medications must be recorded on the applicable eCRF page.

The Medical Monitor should be contacted if there are any questions regarding concomitant medications.

7. DISCONTINUATION/INTERRUPTION OF STUDY TREATMENT AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

Discontinuation of specific sites or of the study as a whole are detailed in Section 10.9.2.

7.1. Discontinuation of Study Treatment

Study treatment may be discontinued for any of the following reasons:

- AE/SAE
- AE of interest (refer to Section 8.4.6 for a list of qualifying events)
- Physician decision
- Protocol deviation/noncompliance with the study protocol that, in the judgement of the Investigator and/or Medical Monitor, the participant should not continue study treatment.
- Liver chemistry discontinuation criteria; refer to Section 8.3.4.1.
- CCI [REDACTED]
- Receipt of a prohibited concomitant therapy or procedure.
- CCI [REDACTED]
- [REDACTED]
- Other

Study treatment must be permanently discontinued in the following instances:

- Calcitonin ≥ 100 ng/L (elevated serum calcitonin value may indicate MTC and appropriate clinical follow-up should be initiated. Participants with thyroid nodules noted on physical examination or neck imaging should also be further evaluated; refer to Section 8.3.4.2).
- Study termination by Sponsor
- Withdrawal by participant
- Pregnancy
- Lost to follow-up

Participants may discontinue from study treatment at any time and for any reason without prejudice to their future medical care by the Investigator or at the study site. Every effort should be made to keep participants who have discontinued study treatment in the study, provided that the participant has not withdrawn consent. Participants should be informed about the continued scientific importance of their data, even if they discontinue study treatment.

The Medical Monitor should be notified when a participant is discontinued from study treatment. If study treatment is discontinued prior to the participant's completion of the study, the reason for the discontinuation must be documented in the participant's medical records and entered on the appropriate eCRF page.

7.2. Interruption of Study Treatment

A participant's study treatment may be interrupted if:

- The participant develops an AE (including SAEs and AEs of interest [Section 8.4.6]) which, in the opinion of the Investigator, indicates that it is in the participant's best interest that the study treatment be placed on hold. Study treatment in this situation should be stopped until the AE is medically treated and has resolved per principal Investigator's judgment.

A participant's study treatment must be interrupted for any of the following reasons:

- Confirmed QTcF interval prolongation of > 450 msec in males or > 470 msec in females; refer to Section 8.3.3.1 for guidance on the management of events of QTcF interval prolongation.

- CCI [REDACTED]
[REDACTED]
[REDACTED]
- [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

For study treatment tablets, any study treatment interruption of ≥ 2 consecutive doses must be documented on the corresponding eCRF, with the start date, end date, and reason for interruption (if known) specified. For study treatment injections, any study treatment interruption (i.e., any missed dose) must be documented on the corresponding eCRF, with the start date, end date, and reason for interruption (if known) specified.

- If the interruption was caused by an AE, only the primary AE leading to interruption of the study treatment, per the judgement of the Investigator, should have an action taken of study treatment interrupted.
- If study treatment interruption greater than 2 doses is required for a medical reason during any treatment period, the Investigator must contact the Medical Monitor as soon as this is anticipated.

7.3. Discontinuation from the Study

Participants may be discontinued from the study at any time for any of the following reasons:

- Study termination by Sponsor
- Withdrawal by participant
- Lost to follow-up
- Physician decision
- AE/SAE/AE of interest
- Death
- Deviation/noncompliance with the study protocol that, in the judgement of the Investigator and/or Medical Monitor, the participant should not continue
- Other

A participant may elect to discontinue study participation at any time for any reason without prejudice to their future medical care by the physician or at the institution. Participants who permanently discontinue from the study prematurely, regardless of the reason, should be instructed to return for ET and Follow-Up Visits, unless reason for discontinuation from study treatment is withdrawal of consent, death, or lost to follow-up (Sections 8.1.7 and 8.1.8). Refer to the SoA (Section 1.3) for data to be collected at the ET and Follow-Up Visits.

If a participant withdraws consent for all study procedures including post-treatment study follow-up, no further evaluation(s) should be performed, and no additional data should be collected.

Even if the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

Replacement of participants who withdraw from the study is not permitted.

7.4. Lost to Follow-Up

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

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant (where possible, telephone

calls, and if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, the participant will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the SoA (Section 1.3). Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

Protocol waivers or exemptions are not allowed.

All screening evaluations must be completed and reviewed by the Investigator or designated staff to confirm that potential participants meet all eligibility criteria before randomization. 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 (excluding laboratory assessments) conducted as part of the participant's routine clinical management and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the timeframe defined in the SoA (Section 1.3).

In the event of a significant study-continuity issue (e.g., caused by a pandemic, war, natural disaster), alternate strategies for participant visits, assessments, medication distribution, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.

For several assessments, appropriate training will be provided to investigators and designated study/site staff. Only those individuals trained and certified or licensed to perform these assessments will be performing them during the study.

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

8.1. Administrative and General Procedures

8.1.1. Screening and Eligibility

The Investigator or designee will obtain written informed consent from each participant before any study-specific activity is performed (refer to Section 10.3 for additional detail).

Eligibility will be assessed based on protocol inclusion and exclusion criteria. All screening evaluations must be completed and reviewed by the Investigator or designated staff to confirm potential participants meet all eligibility criteria. Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

Screening procedures must be completed within 30 days (i.e., 4 weeks) prior to receiving the first dose of study treatment. The 30-Day Screening Period may also be extended on a case-by-case basis to accommodate reasonable delays in specific screening assessments due to availability of testing. In each case, the Medical Monitor must be consulted prior to the extension. Safety assessments to be conducted at screening are specified in the SoA, Section 1.3.

For hematology and chemistry laboratory assessments, only those collected during the Screening Period should be used to determine participant eligibility; such results must be obtained and reviewed by the Investigator or designated staff prior to randomization. Results of hematology and chemistry laboratory assessments collected predose as a part of the Day 1 Visit are not considered exclusionary.

Refer to Section 5.4 for information regarding rescreening for participants who fail screening.

For instructions on the determination of body weight (Section 8.2.1) and safety criteria (Section 8.3) to determine eligibility, refer to the applicable subsection.

8.1.2. Sequence of Procedures at Study Visits

Participants are required to fast (at least 10 hours) prior to each study visit for consistency in blood sample assessments.

If assessments are scheduled for the same nominal time, then the assessments should occur in the following order: 1) Vital signs; 2) 12-lead ECG; 3) Blood draws.

At study visits, it is recommended that procedures are performed in a consistent order and at approximately the same time of day for each visit. CCI [REDACTED], assessment of liver parameters by MRI, and dietary and lifestyle/exercise counseling may be scheduled as described per the SoA Section 1.3. The recommended sequence of events during post-screening study visits is as follows:

- Confirm the participant's fasting status.
- Prior and concomitant medications and procedures review
- AE review
- CCI [REDACTED]
- Vital signs
- 12-lead ECG (as required per the SoA Section 1.3)
- CCI [REDACTED]
[REDACTED]
- Body weight, CCI [REDACTED] (Section 8.2.1)
- CCI [REDACTED]
[REDACTED]
- Physical examination

- Blood sample collection for laboratory tests (CCI [REDACTED] and predose PK sampling (as required per the SoA Section 1.3).
- Return study treatment and review compliance
- Dispense/Redispense study treatment.
- Administer study treatment (tablets and injection) at clinic; tablets and injections may be administered in any order.
- Postdose blood sample collection for PK on Week 0/Day 1 and Week 2/Day 15.

8.1.3. Demographic and Social History

Demographics including year of birth and age, sex assigned at birth, and Hispanic ethnicity and race as described by the participant will be collected at screening. In addition, the Investigator will determine the participant's reproductive potential (as defined in [Appendix 1](#)); refer to Section 8.3.5.

At screening, the amount and duration of tobacco, alcohol, and caffeine usage will be collected.

8.1.4. Prior and Ongoing Therapies

Prior therapies are defined as all procedures conducted or therapies taken prior to first intake of study treatment. A concomitant (i.e., ongoing) medication is defined as any medication administered between the first dose of study treatment (i.e., taken on and/or after the first dose) and the last follow-up. Prior therapies that continue after the first dose of the study treatment will also be considered as concomitant therapies.

Any therapy (including over-the-counter or prescription medicines, blood products, vaccines, vitamins, holistic products, and radiotherapy) that the participant is receiving, including those for a study-related AEs, and all procedures that are performed during the Screening Period through the last follow-up must be recorded.

To check eligibility, the use of restricted therapies and procedures will be reviewed against the exclusion criteria at screening. Details of prior therapies related to inclusion or exclusion criteria will be collected in the participant's eCRF. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapies.

Medication history for therapies and procedures not related to the treatment of obesity should include therapies and procedures taken or used by the participant for at least the 30 days prior to screening and should include the reason for use, start and stop dates (month and year), and dosage information (including dose and frequency). Updates to medications or procedures prior to dosing at the Week 0/Day 1 Visit should be made as needed.

Use of any prior medications or conduct of any prior procedures related to the treatment of obesity (i.e., all time/any prior use) should be recorded and include the following information:

- Name of therapy
- Dosage
- Dosing frequency

- Route of administration
- Start and stop dates (month and year)
- Reason for discontinuation

In addition, source documentation for therapies related to obesity should also include any known rationale for prior treatment nonresponse.

Concomitant therapies prohibited and permitted during the study are described in Section 6.9.

8.1.5. Medical History and Disease-Specific History

A complete medical history of each participant will be collected and documented during screening to determine participant eligibility. The history should include recent blood donations (within 90 days), illnesses, and participation in other investigational drug studies.

8.1.6. Drug Screen

A standard urine drug screen will be performed (refer to Table 5). If a participant has a positive result on a urine drug screen, it is not required to exclude the participant from the study. Participants with positive urine drug results at screening will be assessed for eligibility on a case-by-case basis by the Investigator after discussion with the Medical Monitor.

Consumption of poppy seeds within 48 hours prior to drug screening may cause a positive result during drug screening. Participants should be instructed not to consume food items that contain poppy seeds for 48 hours prior to the Screening Visit. Participants who report that they have consumed poppy seeds within 48 hours of the Screening Visit should not be screened. They may return 48 hours after the last poppy seed consumption for screening.

8.1.7. Early Termination

All participants who discontinue from the study prematurely will be asked to return to the clinic for an ET Visit within 1 week of the decision to withdraw from the study (refer to Section 7.3). The ET Visit may occur on the same day as another scheduled study visit.

Assessments for the ET Visit will be conducted per the SoA (Section 1.3).

8.1.8. Follow-Up

A Follow-Up Visit will be conducted 30 days (window + 5 days) after the last dose of study treatment to obtain safety information and additional information on the stability of weight after discontinuation of study treatment. The assessments to be obtained at the Follow-Up Visit are listed in the SoA, Section 1.3.

The required safety Follow-Up Period is ≥ 30 days following the last dose of study treatment (Section 8.4.2.3). Participants should be instructed to report any new AEs (including SAEs and AEs of interest) through 30 days after the last dose of study treatment. The Investigator is responsible for monitoring of AEs that may be ongoing at the time of the participant's last contact, as well as appropriate follow-up of any clinically significant abnormal laboratory results according to local standard of care (Section 8.3.4). If the Investigator determines additional visits are clinically indicated (e.g., for follow-up of AEs or clinically significant abnormal laboratory results), such visits will be captured as unscheduled visits.

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8.2.3. Assessment of Liver Fat, Volume, and Inflammation

MRI will be acquired at Week 0/Day 1 (i.e., baseline) in all participants. CCI

Details for the imaging procedures are provided in the Imaging Acquisition Manual.

CCI

8.3. Safety Assessments

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

8.3.1. Physical Examinations

Complete and symptom-directed (i.e., brief) physical examinations will be performed at timepoints specified in the SoA (Section 1.3).

A complete physical examination will include, at a minimum, assessment of the following:

- General inspection
- Head/ears/eyes/nose/throat examination
- Neck and thyroid
- Lymph nodes
- Cardiac examination
- Auscultation of lungs

- Skin and nails
- Abdominal examination (liver, spleen, and lower abdomen)
- Musculoskeletal assessment to include lower extremity edema evaluation
- Neurological examination

For visits where a complete physical examination is not required, a symptom-directed physical examination may be performed to assess any clinically significant signs and/or symptoms or changes from prior study visits including the baseline physical examination. Symptom-directed physical examinations may be performed at the Investigator's discretion at any time during the study.

8.3.2. Vital Signs

Body temperature, pulse rate, respiratory rate, and BP will be recorded before collection of ECG, and before any blood collection that occurs at an overlapping timepoint with the participant in the seated position.

BP and pulse rate measurements should be preceded by at least 5 minutes of rest (where possible) for the participant in a quiet setting without distractions (e.g., television, cell phones) and collected with the participant in the seated position.

BP and pulse rate will be assessed with a calibrated automated device. Manual techniques will be used only if an automated device is not available. Proper technique should be utilized during the measurement of BP to include the following:

- The participant's arm should be bare and supported at heart level.
- An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be utilized. Participant's legs should not be crossed during the evaluation.
- When obtaining the pulse and BP, the participant should rest in the sitting position for at least 5 minutes before measurement to establish an accurate baseline measurement. After the participant has been sitting for at least 5 minutes, pulse and BP will be measured using an automated validated device (if available).

At screening/prerandomization, up to 3 BP readings may be recorded at intervals of at least 1 minute to confirm abnormal results.

Both screening vital signs and prerandomization vital signs collected predose as a part of the Day 1 Visit are considered when determining participant eligibility for the study; such results must be obtained and reviewed prior to randomization and study treatment administration.

Vital signs will be collected at timepoints specified in the SoA (Section 1.3); if scheduled for the same nominal time, vital signs should be collected prior to ECG and any blood draws.

8.3.3. Electrocardiograms

ECG(s) will be obtained from a 12-lead ECG machine at timepoints specified in the SoA (Section 1.3; if scheduled for the same nominal time, ECG should be collected after collection of vital signs, but prior to any blood draws) and if clinically indicated at any time during the

treatment period at the Investigator's discretion. Every attempt should be made to ensure the participant ECG readings are obtained using the same machine throughout the study.

When the study treatment is to be administered at the study site, ECG will be obtained predose. The 12-lead ECGs should be obtained after vital signs collection but prior to predose blood sample collection. All ECGs will be recorded with the participant in a supine position.

- Parameters to be provided on the confirmed read for each safety ECG are HR and the following intervals: RR, PR, QRS, QT, and QTcF.
- The Investigator will be responsible for review and interpretation of ECGs onsite and assessing whether the ECG is normal, abnormal not clinically significant, or abnormal clinically significant.
 - In the event of an abnormal reading, the ECG should be completed in triplicate regardless of Investigator's assessment of clinical significance; 3 individual ECG tracings should be obtained as closely as possible in succession, if possible, no more than 2 minutes apart. In some cases, it may be appropriate to repeat abnormal ECGs to rule out improper lead placement as contributing to the ECG abnormality.
 - Abnormal clinically significant findings will be documented in the eCRF and evaluated further, as clinically warranted.
- All 12-lead ECG recordings will be transferred to a central reader for analysis. In addition, Paper versions of all ECG tracings will be printed and kept at the site as source documentation. All ECGs performed should be available for collection upon request.
- Participants with a confirmed event of QTcF interval prolongation of > 450 msec in males and > 470 msec in females must have study treatment interrupted; refer to Section 8.3.3.1 for guidance on the management of events of QTcF interval prolongation.

Both screening ECGs and prerandomization ECGs collected predose as a part of the Day 1 Visit are considered when determining participant eligibility for the study; such results must be obtained and reviewed by the Investigator prior to randomization to determine a participant's eligibility.

8.3.3.1. QTcF Criteria Requiring Treatment Interruption

If an ECG shows a new onset QTcF interval > 450 msec in males or > 470 msec in females during any treatment period, a repeat ECG is required. If this abnormal finding is confirmed upon repeat assessment, study treatment must be interrupted, and effective diagnostic and therapeutic strategies should be employed.

Reversible causes of prolonged QTcF interval (e.g., electrolyte abnormalities or hypomagnesemia) should be corrected as clinically indicated. When evaluating a participant with new onset QTcF interval > 500 msec, referral to a cardiologist experienced in treating cardiac conduction disorders should be considered.

Reinitiation of study treatment can be considered only after all of the following have occurred:

- The QTcF interval is < 450 msec (males) or < 470 msec (females),
- The QTcF prolongation is considered by the Investigator and confirmed by the cardiologist as not related to study treatment and likely caused by other factors,
- Individual risk-benefit is favorable (as determined by the Investigator, in agreement with the cardiologist), AND
- After discussion with the Medical Monitor.

Guidance on the documentation requirements when a participant interrupts study treatment is provided in Section 7.2.

8.3.4. Clinical Laboratory Tests

Participants must be in a fasted state at the time of clinical laboratory blood draws throughout the study. Participants must be instructed to fast (no food or drink aside from water) for at least 10 hours before collection of clinical laboratory samples. CCI

Details regarding clinical laboratory sample collection, preparation, and shipment are provided in the Laboratory Manual.

- See Table 5 for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) for the timing and frequency. Additional tests may be performed at any time during the study as determined necessary by the Investigator (i.e., as clinically indicated or to follow-up on an AE).
- If, for any reason, clinical laboratory samples are considered indeterminate for the evaluation of safety or of the study endpoints, additional samples should be collected during the study as determined necessary by the Investigator or Medical Monitor.
- The tests detailed in Table 5 will be performed by the central laboratory. Local laboratory results are only permitted if the central laboratory results are not available in time for either study treatment administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study treatment decision or response evaluation, the results must be entered into the eCRF.
- All laboratory samples should be collected prior to the administration of study treatment and with the participant in a seated or supine position during blood collection.
- The Investigator must review the laboratory results, document their review of each laboratory safety report, and record any clinically significant changes occurring during the study as an AE. The laboratory results must be retained with source documents.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or during the Follow-Up Period after the last dose of study

treatment should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator.

- If clinically significant 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 tests, as defined in [Table 5](#), must be conducted in accordance with the Laboratory Manual and the SoA (Section [1.3](#)).
- If laboratory values from non-protocol-specified laboratory tests 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 interruption), then the results must be recorded.
- Results from tests for exploratory blood and urine biomarkers will not be provided to the Investigator, as these results will not be used for any clinical evaluation during the study.
- Guidance on hepatic monitoring, including study treatment stopping criteria due to elevations in liver enzymes, is provided in Section [8.3.4.1](#).
- Guidance on the monitoring of calcitonin during the study, including study treatment stopping criteria, is provided in Section [8.3.4.2](#).

Table 5: Protocol-Required Laboratory Tests via Central Laboratory Assessment

Laboratory Tests	Parameters	
Hematology	Platelet count	
	Red blood cell count	
	Red blood cell indices	Erythrocyte sedimentation rate ^a Mean corpuscular volume Mean corpuscular hemoglobin Mean corpuscular hemoglobin concentration
	White blood cell count with differential (absolute and %)	Neutrophils Lymphocytes Monocytes Eosinophils Basophils
	Hemoglobin A1C	
	Hemoglobin	
	Hematocrit	

Table 5: Protocol-Required Laboratory Tests via Central Laboratory Assessment (Continued)

[illegible]

Table 5: Protocol-Required Laboratory Tests via Central Laboratory Assessment (Continued)

Laboratory Tests	Parameters
Urinalysis	Specific gravity, color, appearance pH, glucose, protein, ketones, bilirubin, urobilinogen, nitrite, occult blood by dipstick Microscopic examination of sediment (if blood or protein is abnormal)
CCI [REDACTED] [REDACTED]	[REDACTED] [REDACTED] [REDACTED] [REDACTED]
Pregnancy testing	Highly sensitive serum β -hCG pregnancy test (as needed for females of childbearing potential) Follicle-stimulating hormone (as needed in females to confirm postmenopausal status)
Coagulation	Activated partial thromboplastin time International normalized ratio Prothrombin time
Other screening tests	Urine drug screen (CCI [REDACTED]) [REDACTED] [REDACTED] [REDACTED] Serology: HIV antigen/antibody, HBsAg or HBcAb, HCV antibody QuantiFERON [®] -TB

β -hCG, beta-human chorionic gonadotropin; eGFR, estimated glomerular filtration rate; CCI [REDACTED]
[REDACTED] HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDL, high-density lipoprotein; HIV, human immunodeficiency virus; CCI [REDACTED]
[REDACTED] hs-CRP, high-sensitivity C-reactive protein; LDL, low-density lipoprotein; TB, tuberculosis; CCI [REDACTED] TSH, thyroid-stimulating hormone; VLDL, very low-density lipoprotein.

^a Sample may be assessed via local laboratory.

^b Details of liver chemistry stopping criteria and required actions and follow-up are given in Section 8.3.4.1.

^c Details of calcitonin stopping criteria and required actions and follow-up are given in Section 8.3.4.2.

^d Calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

^e CCI [REDACTED]
[REDACTED]

^f CCI [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]

8.3.4.1. Liver Chemistry Monitoring Guidance and Stopping Criteria

The following guidance is supplemental to the general guidance for clinical laboratory tests described in Section 8.3.4.

Liver Chemistry Monitoring Guidance

Recommended follow-up in the event of an increase of serum AST or ALT to $> 3 \times \text{ULN}$ for participants with normal baseline values or, for participants with elevated baseline values, 2-fold increases above baseline:

- Follow-up with repeat testing (within 72 hours) of serum ALT, AST, ALP, and total bilirubin to confirm the abnormalities and to determine if they are increasing or decreasing.
- Coagulation panel should be performed at an unscheduled visit in case of elevated ALT and/or AST.
- Consult the participant to determine whether there are any associated symptoms.
- Record clinically significant abnormalities, symptoms, or medical diagnosis (if known) on the Adverse Events eCRF.
- If symptoms persist or repeat testing shows AST or ALT $> 3 \times \text{ULN}$ for participants with normal baseline measures or 2-fold increases above baseline values for participants with elevated baseline values, monitor to determine whether the abnormalities are improving or worsening (e.g., repeat liver enzyme and serum bilirubin tests 2 or 3 times weekly). Decrease the frequency of testing to once a week or less if abnormalities stabilize or study treatment has been discontinued and the participant is asymptomatic.

All events of ALT or AST $> 3 \times \text{ULN}$ and total bilirubin $> 2 \times \text{ULN}$, or ALT or AST $> 3 \times \text{ULN}$ and INR > 1.5 , if INR measured, which may indicate severe liver injury (possible Hy's Law), must be reported as an SAE. Refer to Section 8.4 for follow-up and reporting of SAEs.

It is important to observe the time course of the AST or ALT elevation, and to seek alternative causes of the liver injury, such as acute viral hepatitis A, B, C, D, or E; concomitant use of a hepatotoxic drug or exposure to hepatotoxins; autoimmune or alcoholic hepatitis; biliary tract disorders; and circulatory problems of hypotension or right heart congestive failure that may cause ischemic or hypoxic hepatopathy.

As appropriate, obtain additional tests to evaluate liver function (e.g., INR). It is also prudent to assess the participant for previously existing liver disease, such as chronic hepatitis C or MASH, which may not have been recognized before exposure to study treatment.

Liver Chemistry Stopping Criteria

Discontinuation of study treatment for abnormal liver function should be considered by the Investigator when a participant meets any of the following conditions:

- The Investigator believes that it is in the best interest of the participant to discontinue.
- ALT or AST $> 8 \times \text{ULN}$.
- ALT or AST $> 5 \times \text{ULN}$ for > 2 weeks.

- ALT or AST $> 3 \times$ ULN and total bilirubin $> 2 \times$ ULN or INR > 1.5 .
- ALT or AST $> 3 \times$ ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia ($> 5\%$).

Because transient fluctuations of ALT or AST are common, and progression to severe drug-induced liver injury or acute liver failure is uncommon, automatic discontinuation of study treatment upon finding a greater than $3 \times$ ULN elevation of ALT or AST may be unnecessary.

8.3.4.2. Calcitonin Monitoring Guidance and Stopping Criteria

Background

Treatment with GLP-1 receptor agonists has been shown to be associated with thyroid C-cell changes in rodents but not in nonhuman primates. The human relevance of this finding is unknown. However, based on the warnings and precautions noted in the product label for semaglutide, monitoring of serum calcitonin (a sensitive biomarker for C-cell activation), will be performed in this study.

While there is general agreement on the clinical interpretation of substantially elevated calcitonin levels (> 100 ng/L) as likely indicative of C-cell neoplasia, the interpretation of values between upper normal range (5.0 and 8.4 ng/L for females and males, respectively) and 100 ng/L is less clear with regards to indication of disease.

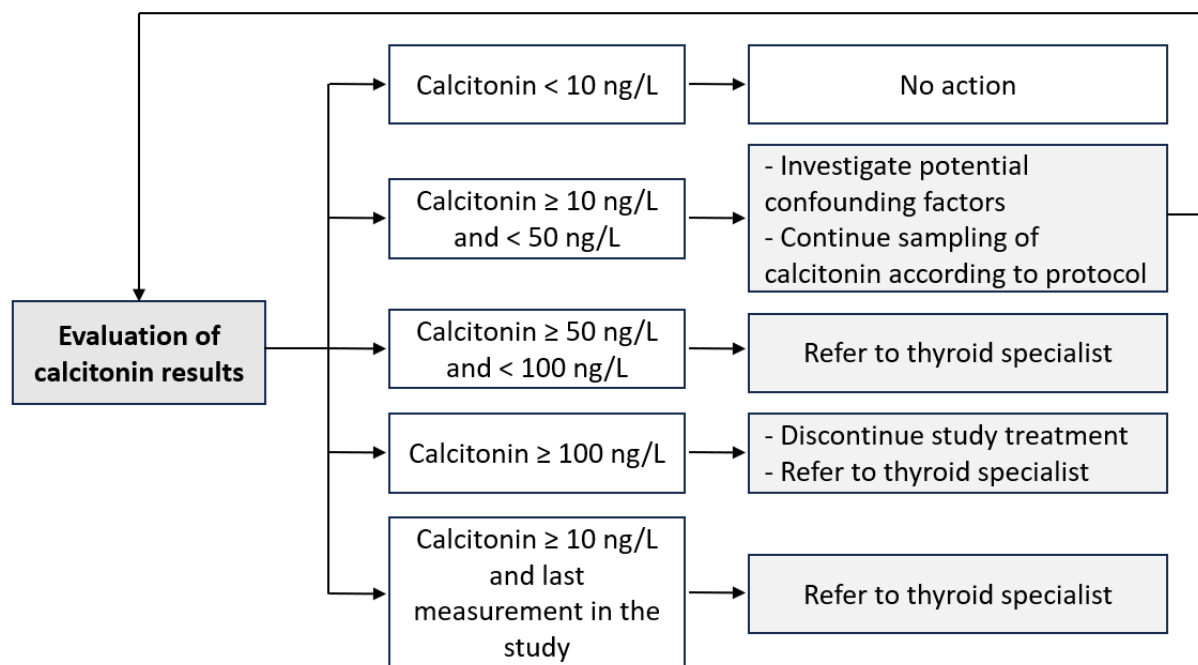
There are several known confounding factors affecting calcitonin levels, including:

- Renal dysfunction
- Tobacco use
- Autoimmune thyroiditis
- Several drug classes (e.g., proton pump inhibitors, beta-blockers, h2-blockers and glucocorticoids)

Physiology of C-cell activation in various clinical conditions and in different patient populations (i.e., with various comorbidities) is poorly understood. There may be various clinical conditions not identified so far which mildly or moderately affect calcitonin secretion by C-cells.

Calcitonin Monitoring

A blood sample will be drawn for measurement of calcitonin at study visits specified in the SoA (Section 1.3). If a participant has a calcitonin value ≥ 10 ng/L, the algorithm outlined in [Figure 2](#) and described below should be followed. The algorithm applies for all calcitonin values in the study.

Figure 2: Flow of Calcitonin Monitoring**Calcitonin ≥ 100 ng/L**

Action: The participant (even if a screen failure) must immediately be referred to a thyroid specialist for further evaluation and study treatment must be discontinued (refer to Section 7.1). The participant should remain in the study; however, all medications suspected to relate to this condition must be discontinued until a diagnosis is established.

Background: These values were found in 9 (0.15%) of a population of 5817 patients with thyroid nodular disease (39). All of these patients were diagnosed with MTC, resulting in a positive predictive value of 100%.

Diagnostic evaluation should include:

- Thyroid ultrasound examination
- Fine needle aspiration of any nodules > 1 cm
- Potentially, surgery with neck dissection

If a participant is diagnosed with MTC, it is common clinical practice to explore the family history of MTC or MEN2 and perform a genetic test for RET proto-oncogene mutation.

Calcitonin ≥ 50 and < 100 ng/L

Action: The participant (even if a screen failure) should be referred to a thyroid specialist for further evaluation. The participant should remain in the study and can continue on study treatment.

Background: These values were found in 8 (0.14%) of the population of 5817 patients with thyroid nodular disease (39). Two of these participants were diagnosed with MTC and 2 were

diagnosed with C-cell hyperplasia, resulting in a positive predictive value of a C-cell anomaly of 50%.

Diagnostic evaluation should include:

- Thyroid ultrasound examination
- If available, and if there are no contraindications, a pentagastrin stimulation test should be done. For participants with positive pentagastrin stimulation test, surgery should be considered.
- If pentagastrin stimulation test is not available, thyroid ultrasound and fine needle aspiration biopsy may add important clinical information about the need for surgery.

Calcitonin ≥ 10 and < 50 ng/L

Action: The participant can continue in the study and on study treatment. Continue sampling of calcitonin according to the protocol.

If the participant is a screen failure, or if the value is from the last sample taken in the study, the subject should be referred to a thyroid specialist for further evaluation.

Background: Calcitonin values from 20 to 50 ng/L were found in up to 1% of subjects of the population of 5817 patients with thyroid nodular disease (39). The predictive value of a C-cell anomaly for this calcitonin level was 8.3%. However, the likelihood of having a medullary carcinoma > 1 cm with calcitonin in this range is extremely low.

For calcitonin values between 10 and 20 ng/L, Costante et al. (39) identified 216 (3.7%) patients. One patient out of the 216 had a subsequent basal (unstimulated) calcitonin value of 33 ng/L and had C-cell hyperplasia at surgery. Two other studies used a cut-off of calcitonin > 10 ng/L to screen for C-cell disease, but they do not provide sufficient information on patients with basal CT > 10 and < 20 ng/L to allow conclusions (40, 41).

8.3.5. Pregnancy Testing and Contraception

Eligibility

During the screening period, the Investigator will determine the participant's reproductive potential as defined in [Appendix 1](#). The Investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a female with an early undetected pregnancy.

Females: Female participants who are biologically capable of having children must agree to use contraception as described in [Appendix 1](#) during treatment. For female participants of childbearing potential receiving study treatment tablets only, a highly effective contraceptive method with a failure rate of $< 1\%$ per year must also be used for at least 30 days after the last dose of study treatment. For female participants of childbearing potential receiving both study treatment tablets and semaglutide injections, a highly effective contraceptive method with a failure rate of $< 1\%$ per year must be used for at least 60 days following the last dose of study treatment. The Investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of study treatment.

A serum pregnancy test for β -hCG will be performed for FOCBP to determine eligibility and is evaluated by the central laboratory; results of the serum test are required to determine eligibility prior to randomization in addition to the results of the urine dipstick pregnancy test on Day 1.

For females not using hormonal contraception or hormonal replacement therapy and with no menses for ≥ 12 months without alternative medical cause, an FSH test is conducted at screening to confirm the participant's postmenopausal status.

Refer to inclusion criteria in Section 5.1 and the SoA (Section 1.3).

Males: Male participants with partners who are of childbearing potential must agree to use a male condom with a FOCBP during the study treatment period and for at least 90 days after the last dose of study treatment. Female partners of male participants should be instructed to use an additional highly effective contraceptive method with a failure rate of $< 1\%$ per year (as listed in Appendix 1).

Testing During Treatment Periods for FOCBP Study Participants

The Investigator must document that the participant has selected an appropriate method of contraception from the permitted list of contraception methods in Appendix 1. At subsequent visits where urine pregnancy tests are performed, the Investigator will instruct the participant on the need to use the agreed contraception method consistently and correctly and will document the conversation and the participant's affirmation in source data. Participants should be instructed to immediately call the Investigator if the agreed upon contraception method is discontinued, changed, or if pregnancy is known or suspected for the female participant or male participant's partner.

Post-screening-pregnancy tests are β -hCG tests performed using a urine dipstick pregnancy test and should be performed at the site or at home, as indicated in the SoA (Section 1.3). All negative pregnancy test results must be documented prior to dosing for applicable study visits. For the Day 1 Visit, results of the urine dipstick pregnancy test are required to determine eligibility prior to randomization.

Participants should be instructed to immediately contact the Investigator in the event of any positive pregnancy test result. If home pregnancy testing is not allowed per local regulations, pregnancy testing will be performed onsite during an unscheduled visit.

If at any time a study participant cannot come into the study site for a visit where pregnancy testing is scheduled as indicated in the SoA (Section 1.3), a home pregnancy test must be performed; the participant should be instructed to immediately report any positive result to the Investigator.

Positive Pregnancy Tests in FOCBP Study Participants

If at any point there is a case of a positive urine β -hCG test in a female study participant, study treatment must be interrupted, and the Investigator should inform the Sponsor or their designee within 24 hours of learning of the pregnancy. In addition, a serum sample will be collected and submitted to the central laboratory for β -hCG testing.

Negative serum test: The participant may resume study treatment if the serum test is negative; refer to Section 7.2 for instructions on resumption of study treatment following dose interruption.

Positive serum test: The participant will be permanently discontinued from study treatment if the serum test is positive; refer to Section 7.1 for instructions regarding permanent discontinuation of study treatment.

For additional instructions on reporting procedures and data collection for events of pregnancies in female study participants, refer to Section 8.4.5.

Positive Pregnancy Tests in Female Partners of Male Study Participants

If at any point there is a case of a positive pregnancy test in the female partner of a male study participant, the Investigator should inform the Sponsor or their designee within 24 hours of learning of the pregnancy. Participants should be instructed to immediately contact the Investigator in the event of any positive pregnancy test result in the female partner of a male study participant.

For instructions on reporting procedures for events of pregnancies in the female partners of male study participants, refer to Section 8.4.5.

The male study participant may continue with study treatment without interruption.

CCI

[REDACTED]

CCI

8.4. Adverse Events, Serious Adverse Events, and Other Safety Reporting

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE and remain responsible for following all AEs according to the reporting time period in Section 8.4.2.3. This includes events reported by the participant or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative. The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided herein.

8.4.1. Definitions

8.4.1.1. Definition of AE

AE Definition

An AE is any untoward medical occurrence in a clinical study participant, temporally associated with the use of study treatment, whether or not considered related to the study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.

Events Meeting the AE Definition

Any abnormal laboratory test results (i.e., hematology, clinical chemistry, coagulation, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease, or more severe than expected for the participant's condition).

Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or severity of the condition.

New condition detected or diagnosed after study treatment administration even though it may have been present before the start of the study.

Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.

Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE term unless it is an intentional overdose taken with possible CCI. Such overdoses should be reported regardless of sequelae.

Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.

The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.

Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.

Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

8.4.1.2. Definition of SAE

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

a. Results in death

b. Is life-threatening

- The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at immediate risk of death at the time of the event. It does not

refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

d. Results in persistent or significant disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

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

8.4.2. Recording and Follow-Up of AE and/or SAE

8.4.2.1. Method of Detecting AEs and SAEs

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a participant. Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.4.2.2. AE and SAE Recording

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

The Investigator will then record all relevant AE/SAE information in the appropriate CRF. Each event must be recorded separately.

It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or their designee in lieu of completion of the appropriate AE eCRF page.

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

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

The following information should be recorded on the AE eCRF:

- Description including onset and resolution dates
- Whether it met SAE criteria
- Severity
- Relationship to study treatment(s) or other causality
- Outcome

For SAEs, events occurring secondary to the primary event should be described in the narrative description of the event. The following should be considered when recording SAEs:

- Death is an outcome of an event. The event that resulted in the death should be recorded and reported on the eCRF. Death with an unknown cause should always be reported as a SAE and documented in the eCRF.
- For hospitalizations, surgical, or diagnostic procedures, the illness leading to the surgical or diagnostic procedure should be recorded as the SAE, not the procedure itself. The procedure should be captured in the narrative as part of the action taken in response to the illness.

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

All AEs (including SAEs and AEs of interest) will be collected from the date the participant signs the ICF until 30 days after the last dose of study treatment is administered or until the participant's last follow-up if such follow-up occurs > 30 days after the last dose of study treatment. For AEs that are serious, considered related to study treatment or procedures, or that caused the participant to discontinue the study or study treatment, such events should be followed until such time that the event has resolved, stabilized, returned to baseline status, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.4), which may be beyond 30 days after the last dose of study treatment. If a nonserious AE has not

resolved or stabilized by this time, the Sponsor, in consultation with the Investigator, will decide whether to continue to monitor the AE or to close out the event in the database when no further follow-up is required.

Investigators and study personnel will record all AEs on the CRF as appropriate, whether received through an unsolicited report by a participant, elicited during participant questioning, discovered during physical examination, laboratory testing, and/or other means.

For participants who fail screening, the active collection period ends when a screen failure status is determined.

All SAEs that occur from the date the participant first signs the Informed Consent (including SAEs that occur during screening in participants who fail screening, pretreatment SAEs occurring in participants who are randomized to study treatment, and treatment-emergent SAEs) **must be recorded and reported to the Sponsor or their designee immediately** in accordance with the instructions provided in Section 8.4.3 and under no circumstance should this exceed **24 hours of awareness**. The Investigator will immediately submit any updated SAE data to the Sponsor or their designee **within 24 hours** of it being available.

Investigators are not obligated to actively seek information on AEs or SAEs that begin after conclusion of the safety reporting period. However, if the Investigator learns of any SAE (including a death) at any time after a participant has been discharged from the study, and the Investigator considers the event to be reasonably related to the study treatment or study participation, the Investigator must promptly notify the Sponsor irrespective of the time elapsed since the last study treatment administration.

8.4.2.4. Assessment of Severity

The Investigator will make an assessment of severity for each AE and SAE reported during the study and assign it to one of the following categories according to the CTCAE v5.0:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling, limiting self-care ADL.**

Grade 4: Life-threatening consequences, urgent intervention indicated.

Grade 5: Death related to AE.

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Note: Severity and Seriousness are not synonymous. Severity is used to describe the intensity (severity) of a specific event. Seriousness as defined in Section 8.4.1.2 (not severity) is based on patient/event outcome or action criteria and serves as a guide for defining regulatory reporting obligations.

8.4.2.5. Assessment of Causality

The Investigator is obligated to assess the relationship between the study treatments and each occurrence of each AE/SAE. The Investigator is to provide a separate causality for each study treatment – semaglutide and blinded VTX3232.

The Investigator will use their clinical judgment and consider all relevant factors (e.g., temporal relationship of the event to study treatment administration, the participant's relevant medical history, concomitant therapies, underlying disease(s)/concurrent conditions, other risk factors, and dechallenge/rechallenge [if applicable]) to determine the causal relationship of the AE/SAE to the study treatments.

The Investigator will define the causal relationship of an AE/SAE to each of the study treatments by selecting one of the following categories:

Related:

- There is a reasonable possibility that there is a causal relationship between the study treatment and the AE.

Not Related:

- There is not a reasonable possibility that there is a causal relationship between the study treatment and the AE.

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

For causality assessments, the Investigator should also consult the VTX3232 IB as well as the WEGOVY® Prescribing Information.

The Investigator must review and provide a separate assessment of causality for each study treatment for each AE/SAE and document this in the medical notes. There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or their designee.

The Investigator may change their opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessments.

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

8.4.2.6. 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 during the course of the study and through the post-treatment safety reporting period as described in Section 8.4.2.3).

The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or their designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may

include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

If a participant dies during participation in the study or during a recognized Follow-Up Period, the Investigator will provide the Sponsor or their designee with a copy of any postmortem findings, including histopathology.

New or updated information (including changes in severity or relationship to study treatment) will be recorded in the originally submitted documents or CRF and submitted to the Sponsor or their designee within 24 hours of receipt of the information.

8.4.3. Reporting of SAEs

All SAEs, whether or not considered related to study treatment, must be immediately reported to the Sponsor or their designee **and under no circumstances should the time to report exceed 24 hours of becoming aware of the event.**

The Contact for SAE reporting:



SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or their designee will be the electronic data collection tool.
- The site will enter the SAE data (initial and follow-up information for any previously reported SAEs) into the electronic system within 24 hours of awareness.
 - If requested, additional pertinent information (e.g., hospital records) should be provided directly to the Sponsor or designated Sponsor Contact.
- In the event of EDC connectivity issues, the site should report the SAE on a Paper SAE Form to the Sponsor or their designee. Once EDC connectivity has been restored, the site is to immediately enter the SAE information directly into EDC.
- After the study is completed, the clinical study database will be locked to prevent the inadvertent entry of new data or changes to existing data.
 - If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been locked, the site can report this information on a Paper SAE Form to the Sponsor or their designee.

8.4.4. Regulatory Reporting Requirements for SAEs, SUSARs, and Periodic Reports

Prompt notification of an SAE by the Investigator to the Sponsor or their designee is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of study treatment(s) under clinical investigation are met.

The Sponsor has a legal responsibility to notify the local regulatory authority, other regulatory agencies (including the IRBs/IECs), and the Investigator sites about the safety of study treatment(s) under clinical investigation, including notification within the required timeframes of all Suspected Unexpected Serious Adverse Reactions (SUSARs), as applicable per local requirements. The term SUSAR refers to an AE that occurs in a participant and which is assessed by the Sponsor and/or Investigator as being unexpected (i.e., not listed in the IB or Prescribing Information, or not listed at the specificity or severity that has been observed), serious, and as having a reasonable possibility of a causal relationship with the study drug (i.e., related to the study drug as per causality assessment in Section 8.4.2.5). The Sponsor will assess whether an event is unexpected. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and Investigators.

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 or their designee will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.

8.4.5. Pregnancy Data Collection and Reporting

- Pregnancies in female participants will be collected after the start of study treatment (i.e., baseline [Day 1]) and through 30 days after the last dose of study treatment. The Investigator will attempt to collect pregnancy information on a male participant's female partner who becomes pregnant after the male participant's start of study treatment and through 30 days after the last dose of study treatment.
- If a pregnancy is reported, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor or their designee **within 24 hours** of learning of the pregnancy of the female participant or female partner of male participant (after obtaining the necessary signed informed consent from the female partner).
 - Any female participant with a confirmed positive serum pregnancy test will be permanently discontinued from study treatment (refer to Section 7.1).
- Pregnant female participants or pregnant female partners will be followed to determine the outcome of the pregnancy; in the event of a delivery, the case will be **followed for 12 months after delivery**. The Investigator will collect follow-up information on the participant or, where possible, pregnant female partner and the neonate; the information will be forwarded to the Sponsor or their designee.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs and will be reported as such even if outside the SAE reporting period.

- Any poststudy pregnancy-related SAE considered reasonably related to the study treatment by the Investigator will be reported to the Sponsor or their designee. While the Investigator is not obligated to actively seek this information in former study participants or pregnant female partners, they may learn of an SAE through spontaneous reporting.

8.4.6. Adverse Events of Interest

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AEs of interest will be monitored on an ongoing basis at each study visit (refer to AE collection timepoints provided in the SoA [Section 1.3] that is inclusive of AEs of interest). Supplementary information on AEs of interest may be collected via the AE narrative form to support further characterization of these events. If the Investigator determines that a participant has an AE of interest, consideration may be given to interruption or permanent discontinuation of study treatment (refer to Section 7) for these events, as appropriate. For select events listed in Section 7.2, study treatment interruption or discontinuation is required.

- Acute gallbladder disease
 - Events of symptomatic acute gallbladder disease (including gallstones and cholecystitis).
- Acute pancreatitis
 - The diagnosis of acute pancreatitis requires two of the following 3 features:
 - Abdominal pain consistent with acute pancreatitis (acute onset of a persistent, severe, epigastric pain often radiating to the back).
 - Serum lipase activity (and/or amylase activity) at least 3 times greater than the ULN.
 - Characteristic findings of acute pancreatitis on imaging.
- Thyroid C-cell tumors
 - Monitoring of serum calcitonin (a sensitive biomarker for C-cell activation) will be performed in this study. If a participant has a calcitonin value ≥ 10 ng/L, the algorithm described in Section 8.3.4.2 should be followed.
- Hypoglycemia
- Acute kidney injury
- Hypersensitivity reactions
- CCI

- CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

8.5. Pharmacokinetics and Pharmacodynamics

Blood samples will be collected in this study to evaluate the PK and PD effects of VTX3232. Samples will be collected according to the SoA (Section 1.3). Detailed procedures for blood sample collection, preparation, and shipping will be provided in a separate Laboratory Manual. Samples will be analyzed using a validated analytical method in compliance with the Sponsor's standard operating procedures and may be analyzed by a central or specialty laboratory.

CCI [REDACTED]

[REDACTED]

Pharmacokinetics

PK samples should be collected for measurement of plasma concentrations of VTX3232, as specified in the SoA (Section 1.3). CCI [REDACTED]

[REDACTED]

On study visit days when samples for PK are collected, participants should take their assigned dose (study treatment tablets and, if applicable, injections) at the study site after predose assessments and procedures have been completed. However, on Week 0/Day 1 and Week 2/Day 15, CCI [REDACTED].

CCI [REDACTED]

[REDACTED]

The time of study treatment tablets and injection administration should be recorded in the source and eCRF along with the time of collection of each PK sample.

All efforts should be made to obtain the PK samples at the exact nominal time relative to dosing of study treatment tablets (i.e., 24 hours after the administration of last tablet dose). The actual time of PK sample collection should be noted in the eCRF. Participants should be instructed to document the date and time of their last dose of study treatment prior to the study visit and that date and time must be recorded in the eCRF.

CCI [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

CCI

9. STATISTICAL CONSIDERATIONS

The analysis and reporting will be done on all data from all participants at the time the study ends.

The SAP will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including the primary endpoint.

9.1. Analysis Sets

Analysis sets in this study are defined in [Table 6](#).

Table 6: Analysis Sets

Population	Description
Full Analysis Set	The FAS consists of all participants who received at least 1 dose of study treatment. For this analysis set, participants are analyzed according to the treatment group to which they were randomized, regardless of the treatment they received during the study. The FAS will be used for all demographics, disposition, and efficacy analyses.
Safety Set	The Safety Set consists of all participants who received at least 1 dose of study treatment. For this analysis set, participants are analyzed according to the treatment they received, regardless of randomization. The Safety Set will be used for all safety and tolerability analyses. The primary safety analysis will be completed based on the Safety Set.
Pharmacokinetic Set	The Pharmacokinetic Set consists of all participants in the Safety Set who have at least 1 quantifiable postdose PK measurement for VTX3232. The Pharmacokinetic Set will be used for all PK analyses.
Pharmacodynamic Set	The Pharmacodynamic Set consists of all participants in the Safety Set who have at least 1 measured PD assessment value at a scheduled timepoint after the first dose of study treatment. The Pharmacodynamic Set will be used for all pharmacodynamic analyses.

FAS, Full Analysis Set; PK, pharmacokinetic.

9.2. Statistical Analyses

9.2.1. General Considerations

Descriptive statistics will be used for categorical or discrete measures, as appropriate. For continuous measures, the longitudinal analysis and change from baseline analyses will be performed. Categorical variables will be presented in tables as frequencies and percentages.

Continuous variables will be summarized in tables and will include the number of participants, mean, SD, median, first quartile, third quartile, min, and max.

Unless otherwise specified, longitudinal continuous endpoints (e.g., change from baseline in hs-CRP, change from baseline in weight, change from baseline in BMI) will be analyzed at scheduled visits up to Week 12 using a MMRM. The MMRM model will include treatment group, visit, interaction of treatment-by-visit, CCI

An unstructured covariance matrix will be specified for the MMRM model. LS means at visit and LS mean differences between treatment groups with p-values and corresponding 95% CIs will be reported. In addition, as sensitivity analyses, these continuous endpoints may be analyzed using an ANCOVA model. CCI

Unless otherwise specified, continuous endpoints that are collected only at screening/baseline and Week 12 will be analyzed using covariance (ANCOVA) model. ANCOVA model will include treatment group CCI

Unless otherwise specified, proportion-based endpoints (e.g., proportion of participants achieving at least 5% and at least 10% weight reduction by Week 12) will be analyzed using Cochran-Mantel-Haenszel test, CCI Results will be expressed as the number and percentage of participants meeting the endpoint criteria, difference percentages and 95% CI and p-value, odds ratio and 95% CI.

Where statistical assumptions (e.g., normality) are not met, alternative approaches will be evaluated (e.g., nonparametric analysis, log transformation).

All statistical tests will be 2-sided and will be performed with a nominal significance (alpha) level of 0.05, unless otherwise specified in the SAP.

For analytical purposes, a detailed SAP will be created. The SAP may modify what is outlined in the protocol, where appropriate, and the SAP will supersede the protocol for outcome measures analyses; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

9.2.2. Safety and Tolerability Analysis

All safety data will be listed and summarized by treatment actually received using the Safety Set. Detailed descriptions of all safety analyses will be provided in the SAP.

A primary endpoint of the study is the incidence and severity of AEs, SAEs, and AEs leading to study treatment discontinuation from the first dose through the end of the Follow-Up Period. Additional safety endpoints are provided in [Table 1](#).

9.2.2.1. Adverse Events

Adverse events will be coded using the MedDRA and tabulated by System Organ Class and Preferred Term.

For each treatment group, the proportion of participants with TEAEs will be summarized overall, by severity, and by relationship to study treatment. A TEAE is defined as:

- An AE that occurs after initiation of study treatment that was not present at the time of treatment start, or
- An AE that increases in severity after the initiation of study treatment, if the event was present at the time of treatment start.

AEs occurring before the first dose of study treatment will be summarized separately.

9.2.2.2. Serious Adverse Events, Adverse Events Leading to Study Treatment Discontinuation, and Adverse Events Leading to Death

All AEs will be coded using the MedDRA and tabulated by System Organ Class and Preferred Term. Proportions of participants with treatment-emergent SAEs, AEs leading to study treatment discontinuation, AEs of interest, and AEs leading to death will be summarized and presented in descending order of frequency.

9.2.2.3. Extent of Exposure

The duration of time on study treatment and time on study will be summarized for each treatment group using descriptive statistics. The number of participants on treatment for certain time intervals may also be summarized.

9.2.2.4. Clinical Laboratory Parameters

Laboratory parameters will be summarized by treatment group at each scheduled assessment timepoint using descriptive statistics. Associated laboratory parameters such as hematology, clinical chemistry, and urinalysis (e.g., coagulation, hepatic enzymes, renal function) values may be grouped and presented together. Individual participant values will be listed and values outside of the standard reference range will be flagged. Shift tables and analyses of changes from baseline may be produced.

9.2.2.5. Electrocardiograms

Individual ECG values will be listed by visit and summarized using descriptive statistics. Along with HR, intervals to be provided for each ECG are RR, PR, QRS, QT, and QTcF. Post-baseline ECGs for each participant will be compared with the baseline ECG and summarized. Any clinically significant change from baseline may be recorded as an AE if deemed appropriate by the Investigator, or Investigator in consultation with the Medical Monitor.

9.2.2.6. Vital Signs

Descriptive statistics for vital signs (BP [systolic, diastolic], pulse rate, respiratory rate, body temperature) will be presented by treatment group. The change from baseline for each of the vital signs will be summarized and the incidence of abnormal vital signs parameters will be tabulated.

9.2.2.7. Physical Examination

Clinically significant physical examination abnormalities will be included in medical history or recorded and summarized as an AE.

CCI [REDACTED]

CCI [REDACTED]

9.2.2.10. Other Safety Assessment(s)

For other safety assessments (e.g., pregnancy tests, serology tests), individual participant values will be listed and values outside of the standard reference range will be flagged. Descriptive statistics for these other safety assessments will be presented by treatment group.

9.2.3. Pharmacodynamic/Biomarker Analyses

A secondary objective of the study is to evaluate the effect of active treatment on hs-CRP compared with placebo ([Table 1](#)). The secondary endpoint change from baseline in hs-CRP will be analyzed at scheduled visits through Week 12 and will be summarized by treatment group.

CCI [REDACTED]

inferential analyses, if warranted by the data.

CCI [REDACTED]

9.2.5. Pharmacokinetic Analysis

PK endpoints are provided in [Table 1](#). Plasma concentrations of VTX3232, and if warranted, other metabolite(s) of interest and semaglutide, will be assessed from PK samples collected predose (trough) during Double-Blind Treatment Period and at a single postdose timepoint as specified in the SoA ([Section 1.3](#)).

PK concentrations will be listed and summarized by treatment and timepoint using descriptive statistics (i.e., n, mean, SD, CV%, median, min, max, and geometric mean) for VTX3232 in plasma. The number of values BLQ per timepoint will also be presented. Geometric statistics will not be calculated for Day 1/baseline predose concentrations in plasma.

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Full details of PK analysis will be provided in the SAP or other analysis documents.

9.2.6. Subgroup Analyses

Subgroup analyses may be performed in primary, secondary, and selected exploratory endpoints for the following baseline demographics and disease characteristics:

- Sex (male or female)
- Race (white or non-white)
- Ethnicity (Hispanic/Latino or Not Hispanic/Not Latino)
- Age ($\leq$ or $>$ median)
- CCI
- Baseline hs-CRP by central laboratory assessment ($\leq$ or $>$ median)

Additional subgroups may be assessed, if deemed necessary, and will be provided in the SAP. If any subgroup includes less than 5% of all participants, no inferential statistics will be generated.

9.3. Interim Analysis

No formal interim analysis is planned for this study.

9.4. Sample Size Determination

No formal sample size or power calculations were performed. For this initial study in participants with obesity, it is planned to treat and complete safety, tolerability, PK, and PD assessments in approximately 160 participants (approximately 40 per treatment group), which is reasonable to assess the primary, secondary, and exploratory study objectives. It is expected that this number of participants will provide guidance for the assessment of tolerability in this patient population.

10. REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1. Regulatory and Ethical Considerations

10.1.1. Good Clinical Practice

This study will be conducted in accordance with the protocol and with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences international ethical guidelines that are consistent with ICH GCP guidelines and other applicable laws and regulations.

The Investigator is responsible for protecting the rights, safety, and welfare of participants under the Investigator's care, and for the control of drugs under investigation. The Investigator must ensure the investigation is conducted according to applicable regulations, the signed Investigator statement, the protocol, or investigational plan as agreed to by the Sponsor and Regulatory Authorities (if applicable) and that was approved by the IRB/IEC. The Investigator/institution and the Sponsor should sign the protocol, or an alternative contract, to confirm this agreement.

If there are any conflicts between the terms of a written agreement (such as a CTA), this protocol will control as to any issue regarding treatment of study participants, and the CTA will control as to all other issues.

The Investigator should not implement any deviation from, or changes to, the protocol without agreement by the Sponsor and without prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate immediate hazard(s) to study participants or when the change involves only logistical or administrative aspects of the study (e.g., change of telephone number).

When an important deviation from the protocol is deemed necessary for an individual participant, the Investigator or site delegate should:

- Contact the Medical Monitor for the study. Such contact must be made as soon as possible to permit a review by the Sponsor to determine the impact of the deviation on the participant's participation and/or the assessment of safety or efficacy in the study. An important deviation to eliminate immediate hazard(s) to study participants does not require approval from the Sponsor prior to implementation.
- Report to the IRB/IEC and regulatory authorities, as applicable (in line with country/region requirements), any significant protocol deviations affecting participant eligibility and/or safety.
- Document and explain any deviation from the approved protocol.

The Sponsor will notify the authorities as applicable (in line with country/region requirements) about serious breaches of regulations, ICH GCP, or the version of the protocol applicable at the time of the breach. A 'serious breach' means a breach likely to affect to a significant degree the safety and rights of a participant or the reliability and robustness of the data generated in the clinical study.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation (as per country/region requirements) except for changes necessary to eliminate an immediate hazard to study participants (e.g., urgent safety measures). For the latter cases, the relevant authorities will have to be informed as early as possible after implementation, in accordance with the applicable local or regional legislative requirements.

10.1.2. Training of Site Personnel

The Sponsor or their designee will train study site personnel on the protocol and applicable procedures prior to study activities being initiated at the study site; training must be documented.

If new study site personnel are assigned after the initial training, study sites must contact the study monitor to coordinate and document this training. Qualified study personnel may conduct training, as appropriate.

10.1.3. Institutional Review Board/Independent Ethics Committee

The Investigator must:

- Obtain and maintain written and dated IRB/IEC approval for the investigational materials including the protocol, protocol amendments, ICF, and other relevant documents (e.g., participant recruitment materials and procedures) before the study is initiated. The Investigator should also provide a copy of the IB, and any updates, to the IRB/IEC.
 - Initial IRB approval, and all materials approved by the IRB for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.
 - Submit documentation of the written approval from the IRB/IEC to the Sponsor before the Investigator can enroll any participant into the study. Such documentation should specify the protocol number, protocol version, documents reviewed, and the date on which the IRB/IEC met and granted the approval.
- Inform the IRB or IEC of any amendments to the protocol in accordance with local requirements. Before implementation of an amendment, the protocol must be reapproved by the IRB/IEC upon receipt of amendments, and annually as required by local regulation, excluding implementation of changes necessary to eliminate an immediate hazard to study participants.
- Provide 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.
- Notify the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures.
- Provide 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, and all other applicable local regulations.

10.1.4. Sponsor Responsibilities

The Sponsor is responsible for compliance with applicable sections of ICH E6(R2) and 21 CFR Part 312, Subpart D (Responsibilities of Sponsors). The Sponsor is responsible for selecting qualified Investigators, providing them with the information they need to investigate properly, and ensuring proper monitoring of the investigation(s). Sponsors are also responsible for ensuring the investigation(s) is conducted in accordance with the general investigational plan and protocols contained in the IND application (or equivalent), maintaining an effective IND (or equivalent) with respect to the investigations, and ensuring the FDA (and/or other regulatory authorities as applicable), and all participating Investigators are promptly informed of significant new adverse effects or risks with respect to the drug.

10.2. Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements per 21 CFR Part 54 (Financial Disclosure by Clinical Investigators) or to other regulatory authorities that have similar requirements. Investigators are responsible for providing information on financial interests, including if any relevant changes occur, during the study and for 1 year after completion of the study.

10.3. Informed Consent Process

The participant's signed and dated informed consent must be obtained before conducting any study activities or procedures. Prior to the Investigator obtaining the informed consent, the Investigator or designee at each center will:

- Explain (by providing adequate oral and written information) the nature and purpose of the study, including the risks and benefits as well as the approval of the study by the IRB/IEC, to the potential participant. If a participant is unable to read, an impartial witness will be present during the entire informed consent discussion.
- Answer all the participant's questions about the study and give the participant time to consider the information provided. Potential participants must be informed that their participation is voluntary and that they are free to discontinue from the study at any time.

10.3.1. Documentation

The Investigator or designee at each center will:

- Document consent via the IRB/IEC approved ICF, which must be signed and dated by the participant and by the person who conducted the informed consent discussion, prior to a participant's participation in the study. The informed consent must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, and privacy and data protection requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written

consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

- The Investigator(s) must maintain the original, signed ICF; a copy of the ICF(s) must be provided to the participant.

10.3.2. Revisions to the ICF or Other Written Information Provided to Participants

Whenever important new information becomes available that may be relevant to the participant's consent, the written ICF and any other written information intended for participants should be revised.

- Participants should be informed in a timely manner if new information becomes available that may be relevant to their willingness to continue participation in the study. The communication of this information should be documented.
- Revised written ICF or other applicable study materials for participants should receive approval from the regulatory authority and IRB/IEC, as required, in advance of use.
- Updated versions of the approved, signed, and dated consent document, as applicable, and any updates to the approved written information should be provided to participants.

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

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.4. Recruitment Strategy

Recruitment will be performed in multiple ways. Sites will search their database to identify participants that potentially qualify for the study and those participants will be contacted to assess their interest in participation. Recruitment materials may be created that can be displayed in public areas after approval by the IRB/IEC and where locally permitted. Participant materials will be developed to support the understanding of the study and procedure. These will be distributed to prospective participants after IRB/IEC approval and permitted by local law.

Participants will receive compensation for time and travel as permitted by the IRB/IEC and local regulations.

10.5. Data Protection

Measures will be implemented to preserve the confidentiality of records containing personal data of participants. In particular, the personnel of the site, Sponsor, CRO, and any other vendors involved in data processing by the Sponsor are bound by obligations of confidentiality.

Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Sponsor will identify the participant by this unique identifier only; participant names or any information which can re-identify the participant will not be transferred. It should be noted that the collection, use, and transfer of the participant's demographics (e.g., age, sex, ethnicity, and race), which are considered identifying data, shall be allowed.

The participant will be informed that their personal study-related data will be used by the Sponsor in accordance with local data protection law. Such information will be provided as part of the ICF or as a standalone document added to the ICF.

The participant will be informed that their medical records containing personal data may be examined by clinical quality assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. The participants shall be informed if remote monitoring that implies remote access to medical data for source data verification is envisaged.

The contract between Sponsor and study sites, as well as those between the CRO, the Sponsor, and/or other vendors, specifies responsibilities of the parties regarding data protection, including handling of data security breaches and respective communication and cooperation of the parties.

In the event of a personal data breach, the party that became aware of the breach will be obliged to notify the Sponsor and/or CRO thereof without undue delay. The Sponsor will assess the nature of the personal data breach and the corrective measures already undertaken and will instruct the parties, as appropriate, on additional measures, if necessary. The Sponsor/Sponsor's designee will also consider if the obligation to notify the data protection authorities applies.

Organizational and technical arrangements will be implemented to avoid unauthorized access, disclosure, dissemination, alteration, or loss of personal data. Information technology systems used to collect, process, and store study-related data are secured through the implementation of such technical and organizational security measures designed to secure the study-related data. The appropriate processes and safeguards depend on the activity and related information system used in the study. These arrangements are described in the study documents; examples include, but are not limited to, the User Access Management Plan, Data Management Plan, Monitoring Plan, TMF Plan and Targeted Source Data Verification Plan. Any additional guidelines that may be issued during the conduct of the study and have impact on the processing of personal data, shall be developed with the consideration of data protection principles of data minimization, confidentiality and integrity, as well as with the application of pseudonymization, access control and encryption as may be appropriate and/or necessary. The Sponsor will ensure that instructions regarding data handling are communicated to the personnel of the involved parties.

Where required by the national law and/or clinical research-related regulations, the Sponsor shall carry out a data protection impact assessment.

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Case Report Forms

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

The Investigator or designee will maintain accurate and up-to-date study documentation for each study participant, including source documentation to support the information entered in the CRF.

The Investigator or designee will correct the CRF, as appropriate. All changed information, including the date and person performing the corrections, should be available via the audit trail, which will be part of the EDC system. For any correction, a reason for the alteration should be provided.

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

The Sponsor will maintain documentation related to the validation of the eCRFs in the TMF, which is maintained by the CRO and the Sponsor.

Guidance on completion of CRFs will be provided in CRF completion guidelines.

Monitoring

The Sponsor or their designee is responsible for the data management of this study and assumes accountability for actions delegated to other individuals (e.g., CROs).

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to all study-related sites, source documents, and reports or records relevant to study conduct. The Investigator should contact the Sponsor immediately if contacted by a regulatory authority about an inspection.

Monitoring details describing strategy, including definition of study critical data items and processes (e.g., risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan, the Risk Management Plan, and the Targeted Source Data Verification Plan.

Retention and Maintenance of Records

The Investigator and study staff have the responsibility of maintaining a comprehensive and centralized filing system containing all study-related documentation for a period of 2 years after the last marketing application approval, or if not approved, 2 years after the appropriate regulatory authorities have been notified of the discontinuance of the test article for investigation. No records may be destroyed during the retention period without the written approval of the Sponsor. Records may be retained for a longer period of time if required by the applicable regulations.

During the record retention period, the Investigator or designee must inform the Sponsor or their designee (e.g., CRO), of the following:

- Location of study documentation
- If the custody of documentation will be transferred or moved to another location
- If the Investigator is unable to retain documentation for the specified period

The Sponsor retains the right to use a document storage location/facility other than that suggested by the Investigator.

If the Investigator withdraws from the study (e.g., relocation, retirement), the records shall be transferred to a mutually agreed upon designee (e.g., another investigator, study site, IRB). Notice of such transfer must be given in writing to the Sponsor or their designee.

If it becomes necessary for the Sponsor or a regulatory authority to review any study documentation, the Investigator must permit access to such records.

10.9. Study and Site Start and Closure

10.9.1. First Act of Recruitment

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

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

10.9.2. Study/Site Termination

The Sponsor or their designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRB/IECs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should ensure appropriate participant treatment and/or follow-up.

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

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

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

- For study termination:
 - Discontinuation of further study treatment development.
 - Changes to the benefit/risk assessment indicating that the risks to participants may outweigh the potential benefits.

- For site termination:
 - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines.
 - Inadequate or no recruitment (evaluated after a reasonable amount of time) of participants by the Investigator.
 - Total number of participants enrolled earlier than expected.

10.10. Publication Policy

Data collected during this study are confidential and proprietary to the Sponsor. Any publications or abstracts arising from this study should adhere to any publication requirements set forth by the Sponsor governing study site or investigator participation, which may be described in a written agreement (e.g., CTA). At a minimum, these requirements include:

- The Investigator's agreement to provide all manuscripts or abstracts to the Sponsor before submission to scientific meetings, journals, or other forums. This allows the Sponsor to protect proprietary information and to provide comments before it is submitted or otherwise disclosed. The Investigator will, on request, remove any confidential information before submission or disclosure, excluding any study or product-related information necessary to the appropriate scientific presentation or understanding of the study results.
- The Sponsor's agreement to comply with standard editorial and ethical practice on the publication requirements of study results; the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

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APPENDIX 1. CONTRACEPTIVE AND BARRIER GUIDANCE

Definitions

Female of Childbearing Potential

Females in the following categories are considered females of childbearing potential (FOCBP; i.e., fertile):

1. Following menarche
2. From the time of menarche until becoming postmenopausal unless permanently sterile (see below)

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 females not using hormonal contraception or hormonal replacement therapy.
- Females on hormonal replacement therapy and whose menopausal status is in doubt (at the judgement of the Investigator) will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their hormonal replacement therapy during the study. Otherwise, they must discontinue hormonal replacement therapy to allow confirmation of postmenopausal status before study enrollment.

Permanent sterilization methods (for the purpose of this study) include:

- 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, gonadal dysgenesis), investigator discretion should be applied to determining study entry.

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

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

Definition of Male Fertility

A participant assigned male at birth is considered fertile after the initiation of puberty unless permanently sterilized by bilateral orchidectomy or has medical documentation of permanent male infertility.

Contraception Guidance

Highly effective contraceptive methods (i.e., methods with a failure rate of < 1% per year when used consistently and correctly) that are permitted in the study are described in [Table 7](#).

Contraceptive use by males and females should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies. If locally required, in accordance with Clinical Trial Facilitation Group (CTFG) guidelines, acceptable contraceptive methods are limited to those which inhibit ovulation as the primary mode of action.

Spermicides only and lactational amenorrhea method are not acceptable methods of contraception. Male condom and female condom should not be used together (due to risk of failure from friction).

Table 7: Allowed Contraception During the Study

Intrauterine device (IUD)
Intrauterine hormone-releasing system (IUS)
Bilateral tubal occlusion or ligation
Azoospermic partner (vasectomized or due to a medical cause) Azoospermia is a highly effective contraceptive method provided that the partner is the sole sexual partner of the female of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation initiated at least 30 days prior to baseline (Day 1) • Oral • Intravaginal • Transdermal • Injectable
Progestogen-only hormone contraception associated with inhibition of ovulation initiated at least 30 days prior to baseline (Day 1) • Oral • Injectable • Implantable
Sexual abstinence^a Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

^a Periodic abstinence (calendar, symptothermal, postovulation methods) and withdrawal (coitus interruptus) are not acceptable methods of contraception.

APPENDIX 2. SUMMARY OF CHANGES

This VTX3232-204 Protocol Amendment is updated from Version 1.0 to Version 2.0.

An overview of the substantive changes between versions is provided below. Minor editorial and formatting revisions made for consistency and clarity are not captured in the table.

Sections Impacted	Change
Throughout	Updated document header, document date, and version number according to Version 2.0.
Title page	Updated document date and version number. Updated confidentiality statement.
Version History	New section.
Section 1.3 Schedule of Activities: Footnote “g” 8.3.2 Vital Signs	The following clarifications in <i>italics</i> and strike through text were made in the second sentence of Footnote “g”, that at screening/ <i>prerandomization, up to 3 BP readings will</i> may be recorded at intervals of at least 1 minute <i>to confirm abnormal results</i> . These edits are consistent with protocol Section 8.3.2 and Exclusion Criterion 5c. In addition, the clarification that the purpose of these triplicate readings is to confirm abnormal results was added to Section 8.3.2.
Section 1.3 Schedule of Activities: Footnote “h” 8.3.3 Electrocardiograms	The following clarifications in <i>italics</i> were made to Footnote “h” and in Section 8.3.3: In the event of an abnormal reading, the ECG should be completed in triplicate, <i>regardless of Investigator’s assessment of clinical significance</i> .
Section 1.3 Schedule of Activities: Footnote “j” and Footnote “k”	CCI [REDACTED] [REDACTED] [REDACTED]
Section 1.3 Schedule of Activities: Footnote “k” 8.2.3 Assessment of Liver Fat, Volume, and Inflammation	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]
5.1 Inclusion Criteria 8.3.5. Pregnancy Testing and Contraception	In criterion 9, updated the time through which female study participants must use contraception to 60 days in accordance with the WEGOVY® Prescribing Information. Corresponding edits were made in Section 8.3.5.
5.2 Exclusion Criteria	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]
8.1.2. Sequence of Procedures at Study Visits	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]

Sections Impacted	Change
	CCI [REDACTED] [REDACTED]
8.3.3. Electrocardiograms 9.2.2.5. Electrocardiograms	Removed the erroneous inclusion of additional QTc from parameters collected on ECG.
8.3.4. Clinical Laboratory Tests Table 5, Hematology	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]
8.3.4. Clinical Laboratory Tests Table 5, Blood for central lab biomarkers	Updated Table 5 to state that blood samples collected for evaluation of central laboratory biomarkers will be analyzed for levels of CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
8.3.4. Clinical Laboratory Tests Table 5, Notes	CCI [REDACTED] [REDACTED] [REDACTED]
8.4.2.4 Assessment of Severity	Revised the definition of Grade 3 to align with Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Added definitions of Instrumental Activities of Daily Living (ADL) and Self-care ADL.
Appendix 2. Summary of Changes	New section.
Appendix 3. Sponsor's Signature Page	Changed the Sponsor's signatory to align with the Sponsor's business process.

APPENDIX 3. SPONSOR'S SIGNATURE PAGE

I have read this protocol in its entirety and agree to conduct the study accordingly.

Sponsor Signatory:

Signature manifest appears after final page of document

PPD

PPD, Clinical Development
Zomagen Biosciences Ltd.

Date

APPENDIX 4. INVESTIGATOR SIGNATURE PAGE

This protocol is a confidential communication of Zomagen Biosciences Ltd. I confirm that I have read this protocol, I understand it, and I will work according to this protocol. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice (GCP) and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from the Sponsor.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Investigator Signature

Investigator signature

Date

Printed name and title

Study center

Document Approvals for VV-QUAL-01918v1.0
VTX3232-204 Protocol V2.0

Approval Task Verdict: Approve	PPD
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