

Statistical Analysis Plan 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

NCT06771115

Approval Date: 25 Sep 2025



STATISTICAL ANALYSIS PLAN

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

Protocol Number: VTX3232-204

Protocol Version/Date: 2.0 / 14 March 2025

Investigational Product: VTX3232

Sponsor: Zomagen Biosciences Ltd., a wholly owned subsidiary of Ventyx Biosciences, Inc.
12790 El Camino Real, Suite 200
San Diego, CA 92130
United States

SAP Version/Date: 1.0 / 25 Sep 2025

CONFIDENTIAL

The information in this document is confidential and is not to be disclosed without the written consent of Zomagen Biosciences Ltd., a wholly owned subsidiary of Ventyx Biosciences, Inc. except to the extent that disclosure would be required by law and for the purpose of evaluating and/or conducting a clinical study for Zomagen Biosciences Ltd., a wholly owned subsidiary of Ventyx Biosciences, Inc. Review Board and study personnel directly involved with conducting this Protocol. Persons to whom the information is disclosed must be informed that the information is confidential and proprietary to Zomagen Biosciences Ltd., a wholly owned subsidiary of Ventyx Biosciences, Inc. and that it may not be further disclosed to third parties.

SIGNATURE PAGE

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

Protocol Number: VTX3232-204

SAP Version/Date: 1.0 / 25 Sep 2025

We, the undersigned, have reviewed and approved of this Statistical Analysis Plan:

Signature	Date
PPD 	
<i>Biostatistician, Biostatistics</i>	
CCI PPD 	
<i>Associate Director, Biostatistics</i>	
CCI PPD 	
<i>Sr. Director, Biostatistics</i> <i>Ventyx Biosciences, Inc.</i>	

VERSION HISTORY

Version	Version Date	Description
1.0	25 Sep 2025	Original signed version

TABLE OF CONTENTS

1	Introduction	8
2	Study Overview	8
2.1	Study Objectives and Endpoints	8
2.1.1	Primary Objective and Endpoints	8
2.1.2	Secondary Objective and Endpoints	8
2.1.3	Exploratory Objective and Endpoints	8
2.1.4	Pharmacokinetic (PK) Objective and Endpoints	10
2.1.5	Pharmacodynamic (PD) Objective and Endpoints	10
2.1.6	Safety Objective and Endpoints	10
2.2	Study Design	10
2.2.1	Overview	10
2.2.2	Randomization and Blinding	11
2.2.3	Study Treatment	12
2.2.4	Sample Size Determination	12
3	Statistical Methodology	12
3.1	General Considerations	12
3.1.1	Analysis Day	12
3.1.2	Definition of Baseline	13
3.1.3	Analysis Visits	13
3.1.4	Summary Statistics	13
3.1.5	Statistical Analyses	13
3.1.6	Handling of Dropouts and Missing Data	14
3.2	Analysis Sets	14
3.2.1	Full Analysis Set	14
3.2.2	Safety Set	15
3.2.3	Pharmacokinetic Set	15
3.2.4	Pharmacodynamic Set	15
3.3	Participant Data and Study Conduct	15
3.3.1	Participant Disposition	15
3.3.2	Protocol Deviations	15
3.3.3	Analysis Sets	15
3.3.4	Demographic and Baseline Characteristics	15
3.3.5	Medical History	16
3.3.6	Prior and Concomitant Medications	16
3.3.7	Study Treatment Exposure and Compliance	16
3.4	Efficacy Assessment	18
3.4.1	Secondary Efficacy Endpoints	18
3.4.2	Exploratory Efficacy Endpoints	19
3.4.3	Subgroups	21

3.5	Pharmacokinetic Assessment	21
3.5.1	Sample Collections for Pharmacokinetic Analysis.....	21
3.5.2	Handling Missing or Below the Lower Limit of Quantification Data.....	21
3.5.3	Pharmacokinetic Concentration	22
3.5.4	Additional PK Analyses	22
3.6	Pharmacodynamic/Biomarker Assessment	22
3.7	Safety Assessment	23
3.7.1	Adverse Events (AEs)	23
3.7.2	Clinical Laboratory Tests.....	24
3.7.3	Vital Signs	24
CCI		
3.7.5	Electrocardiograms (ECGs)	25
3.7.6	Physical Examinations.....	25
CCI		
		
3.7.9	Other Safety Assessment(s)	26
		
5	Changes from Protocol-Specified Statistical Analyses	27
6	Programming Specifications.....	27
	Appendix A: References	28

LIST OF ABBREVIATIONS

Abbreviation	Definition
ADaM	Analysis Data Model
AE	Adverse event
AESI	Adverse events of Special Interest
ALD	above the limit of detection
ALQ	above the limit of quantification
ANCOVA	Analysis of Covariance
AR1	autoregressive of order 1
ATC	Anatomical therapeutic chemical
BLD	below the limit of detection
BLQ	below the limit of quantification
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CRF	Case report form
CS	Compound Symmetry
CSR	Clinical Study Report
CCI	
CTCAE	Common Terminology Criteria for Adverse Events
DBL	Database Lock
DBP	Diastolic Blood Pressure
CCI	
ECG	Electrocardiogram
FAS	Full Analysis Set
FOCBP	Female of childbearing potential
FOCBP	Female of childbearing potential
HbA1C	hemoglobin A1C
HDL	high-density lipoprotein
CCI	
HR	Heart Rate
hs-CRP	high-sensitivity C-reactive protein
IL	interleukin
IMP	Investigational Medicinal Product
IQR	Interquartile Range
CCI	
LDL	low-density lipoprotein
LOCF	last observation carry forward

LS	Least Square
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed effect model with repeated measure
MRI	magnetic resonance imaging
NLRP3	nucleotide-binding domain and leucine-rich repeat family, pyrin domain containing 3
PD	Pharmacodynamic
CCI	
PK	Pharmacokinetic
PR	Pulse Rate
PT	Preferred Term
QD	Once daily
QTc	Corrected QT interval
QTcF	QT Interval Corrected by the Fridericia Correction Formula
RR	Respiratory Rate
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
TFLs	Tables, Figures, and Listings
VLDL	very low-density lipoprotein
WHO	World Health Organization

1 INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to provide a description of the statistical methods to be implemented for the analysis of data from the study with protocol number VTX3232-204. The SAP will be finalized prior to database lock. Any deviations from the SAP after database lock will be documented in the final Clinical Study Report (CSR).

2 STUDY OVERVIEW

2.1 Study Objectives and Endpoints

This section provides information on the study objectives and the corresponding endpoints.

2.1.1 Primary Objective and Endpoints

Primary Objectives	Primary Endpoints
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

2.1.2 Secondary Objective and Endpoints

Secondary Objective	Secondary Endpoint
To evaluate the effect of active treatment on hs-CRP compared with placebo	Change from baseline in hs-CRP over time through Week 12

2.1.3 Exploratory Objective and Endpoints

Exploratory Objectives	Exploratory Endpoints
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]
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]
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]
To evaluate the effect of active treatment on liver parameters compared with placebo	- CCI [REDACTED] - Change from baseline in liver fat as measured by MRI-PDFF at Week 12 among participants with $\geq 5\%$ liver fat at baseline [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]
CCI [REDACTED]	[REDACTED]
CCI [REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

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

2.1.4 Pharmacokinetic (PK) Objective and Endpoints

Pharmacokinetic Objective	Pharmacokinetic Endpoint
To investigate the pharmacokinetics of VTX3232 (and metabolites, as appropriate) in plasma	• CCI [REDACTED] [REDACTED]

2.1.5 Pharmacodynamic (PD) Objective and Endpoints

Pharmacodynamic Objective	Pharmacodynamic Endpoint
CCI [REDACTED] [REDACTED]	• [REDACTED] [REDACTED]

2.1.6 Safety Objective and Endpoints

Safety Objective	Safety Endpoints
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]

Note: For “change from baseline” type of efficacy and PD endpoints, both absolute and relative (percent) change will be analyzed except for BMI, waist circumference, hip circumference, waist:hip circumference ratio, CCI [REDACTED] and vital sign parameters.

2.2 Study Design

2.2.1 Overview

VTX3232 is a brain-penetrant small molecule inhibitor of the NLRP3 inflammasome being evaluated by Zomagen Biosciences Ltd. as a potential oral treatment for participants with obesity. 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). Results from nonclinical studies suggest that combination therapy with VTX3232 and semaglutide may have complementary effects in the improvement of inflammatory and cardiometabolic markers of disease.

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.

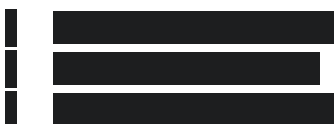
The study design schema is presented in Figure 1. The maximum duration of study participation for an individual participant will be up to approximately 20 weeks, including:

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

Approximately 160 participants are planned to be enrolled and randomized in 4 treatment groups of approximately 40 participants each. Participants will be randomly assigned (1:1:1:1 allocation ratio) to one of the following treatment groups:

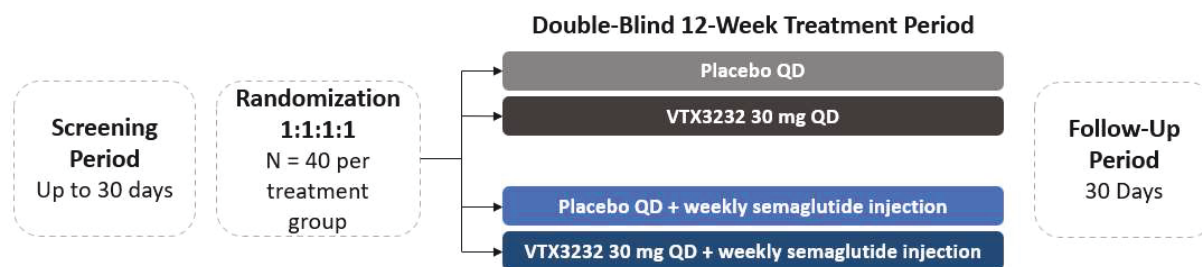
- Placebo QD
- VTX3232 30 mg QD
- Placebo QD and weekly semaglutide injection
- VTX3232 30 mg QD and weekly semaglutide injection

CCI
CCI VTX3232 or placebo will be administered as an oral tablet once daily (QD) alone or in combination with semaglutide (CCI



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). CCI

Figure 1: Schematic Diagram of Study Design



QD, once daily;

CCI

2.2.2 Randomization and Blinding

CCI
CCI

The assignment of study treatment tablets (i.e., VTX3232 or placebo) will be blinded for all treatment groups, in a double-blind fashion, from the time of randomization until after database lock, unless that knowledge is necessary to determine emergency medical care for a participant. However, whether the

participant has been assigned to receive semaglutide injections plus study treatment tablets, or study treatment tablets alone will not be blinded.

2.2.3 Study Treatment

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 groups are outlined in Table 1.

Table 1: Treatment Group(s)

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

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

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®, with a CCI [REDACTED]

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

2.2.4 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 pharmacodynamic (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.

3 STATISTICAL METHODOLOGY

3.1 General Considerations

3.1.1 Analysis Day

Analysis day will be calculated from the date of first dose of study treatment. The day of the first dose of study treatment will be Day 1, and the day immediately before Day 1 will be Day -1. There will be no Day 0.

3.1.2 Definition of Baseline

Baseline is defined as the last non-missing measurement prior to the first dose of study treatment. When there are multiple measurements available at the same visit for vital signs and ECG:

- For continuous or derived categorical parameters, the baseline value will be determined as the average of all available measurements collected prior to the first dose on the same day.
- For collected categorical parameters, the baseline value will be defined as the last recorded measurement prior to the first dose.

3.1.3 Analysis Visits

Analysis Visits will be assigned to the observed values collected at all visits using the corresponding Analysis Day per the Analysis Visit Window in Table 2. In the situation when there are multiple observations falling into the same analysis visit window, the one closest to the Target Analysis Day in the table will be used in the analysis. If two observations are of equal distance to the Target Analysis Day but one before and one after, the one after the Target Analysis Day will be used. If two observations occur at the same time, the observation labeled as scheduled visit will be selected for analysis.

Table 2: Analysis Windows

Scheduled Visit	Target Visit Day	Analysis Visit Window
Baseline	Day 1	Definition in 3.1.2
Week 1	Day 8	Day 1 (post-dose) - Day 11
Week 2	Day 15	Day 12 – Day 22
Week 4	Day 29	Day 23 – Day 43
Week 8	Day 57	Day 44 – Day 71
Week 12	Day 85	Day 72 – Day 99
Follow-up	Last treatment day + 30	Nominal Follow-up Visit

3.1.4 Summary Statistics

Categorical data will generally be summarized with frequencies and percentages of participants. The denominator used for the percentage calculation will be clearly defined.

Continuous data will generally be summarized with descriptive statistics including n (number of non-missing values), mean, standard deviation (SD), median, first quartile, third quartile, minimum, and maximum.

The summary statistics will be provided for all analysis visits specified in Table 2.

3.1.5 Statistical Analyses

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. If the MMRM model with unstructured covariance matrix does not converge, it will be replaced with firstly an Autoregressive of order 1 (AR1) covariance matrix, secondly a Toeplitz covariance matrix, thirdly by a Compound Symmetry (CS) covariance matrix. Least square (LS) means at each visit and the LS mean differences between treatment groups (VTX3232 30 mg QD vs. Placebo QD, Placebo QD and Weekly Semaglutide vs. Placebo QD, VTX3232 30 mg QD and Weekly Semaglutide vs. Placebo QD, VTX3232 30 mg QD

and Weekly Semaglutide vs. Placebo QD and Weekly Semaglutide) with p-values and corresponding 95% confidence intervals (CIs) will be reported. In addition, as sensitivity analyses, these continuous endpoints may be analyzed using an analysis of covariance (ANCOVA) model. The ANCOVA model will include treatment group and sex as factors and baseline BMI and baseline measure as covariates. Unless otherwise specified, continuous endpoints that are collected only at screening/baseline and Week 12 will be analyzed using ANCOVA model.

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 by visit using Cochran-Mantel-Haenszel (CMH) test, CCI [REDACTED] Results will be expressed as the number and percentage of participants meeting the endpoint criteria with number of contributing participants (baseline and post-baseline assessment at visit not missing). The CMH chi-square p-value, stratified risk difference ("common" risk difference) between treatment groups (VTX3232 30 mg QD vs. Placebo QD, Placebo QD and Weekly Semaglutide vs. Placebo QD, VTX3232 30 mg QD and Weekly Semaglutide vs. Placebo QD, VTX3232 30 mg QD and Weekly Semaglutide vs. Placebo QD and Weekly Semaglutide) with 95% CI using the Mantel-Haenszel method, Mantel-Haenszel odds ratio, 95% CI for the Mantel-Haenszel odds ratio and Clopper-Pearson exact 95% confidence intervals will be reported.

All statistical tests will be 2-sided and will be performed with a nominal significance (alpha) level of 0.05.

3.1.6 Handling of Dropouts and Missing Data

3.1.6.1 Efficacy Endpoints

For the primary analysis of the secondary and exploratory efficacy endpoints, missing data for any reasons will not be imputed. For the sensitivity analysis of change from baseline in hs-CRP and body weight and percent change from baseline in body weight over time through Week 12, a last observation carry forward (LOCF) approach will be applied, under which a missing post-baseline value through Week 12 is imputed by the last non-missing post-baseline assessment collected prior to the missing assessment.

3.1.6.1 Safety Endpoints

If there are incomplete start or stop dates for medications (both prior and concomitant medications), dates will be imputed to determine whether medication should be considered prior or concomitant. If a medication start date is incomplete, the first day of the month will be imputed for the missing day and January will be imputed for a missing month. If a medication stop date is incomplete, the last day of the month will be imputed for a missing day and December will be imputed for a missing month. If the imputed end date falls after the database lock (DBL) date, the data cut date will be assigned as the end date. Incomplete start and stop dates will be listed as collected without imputation.

3.2 Analysis Sets

3.2.1 Full Analysis Set

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.

3.2.2 *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.

3.2.3 *Pharmacokinetic Set*

The Pharmacokinetic (PK) Set consists of all participants in the Safety Set who have at least 1 quantifiable postdose PK measurement for VTX3232. The PK Set will be used for all PK analyses.

3.2.4 *Pharmacodynamic Set*

The Pharmacodynamic (PD) 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 PD Set will be used for all pharmacodynamic analyses.

3.3 Participant Data and Study Conduct

3.3.1 *Participant Disposition*

Counts and percentages of participants who were screened (signed informed consent), discontinued early during screening (screen failures), and randomized will be summarized in total based on all screened participants. Reasons for screen failures will also be summarized.

Counts and percentages of participants who were randomized, discontinued early from the study, and completed the study will be summarized by treatment group and in total based on FAS. Reasons for early discontinuation will also be summarized.

A listing of participants who were screen failures will be provided with the demographic information (age, sex, race, ethnicity, height, weight, BMI, CCI).

The disposition of each participant and the analysis sets for which they qualify will be listed for all randomized participants. Inclusion criteria not met and exclusion criteria met will be listed in participant listings.

3.3.2 *Protocol Deviations*

All protocol deviations will be categorized and listed by participant, and major protocol deviations, which are CSR-reportable protocol deviations, will be summarized. Counts and percentages of participants with at least one major protocol deviation by deviation category will be summarized by treatment and overall (all treatment groups) based on all randomized participants.

3.3.3 *Analysis Sets*

Counts and percentages of participants in each analysis set will be summarized by treatment and in total. Analysis sets by participants will be listed.

3.3.4 *Demographic and Baseline Characteristics*

The following demographic and baseline characteristics will be summarized:

- Age (years) and age categories (18-64 years, 65-74 years, 75-84 years; 18-44 years, 45-65 years; > 65 years, ≥ 65 years, ≥ 75 years)
- Sex assigned at birth (male or female)

- Female of childbearing potential (FOCBP), reasons if not
- Race and Race categories (Asian, American Indian or Alaska Native, Black or African American, Native Hawaiian or Other Pacific Islander, White, Multiple)
- Ethnicity (Hispanic/Latino or Not Hispanic/Not Latino)
- Height (cm)
- Weight (kg)
- BMI (kg/m^2) and BMI categories at Baseline ($< 35 \text{ kg}/\text{m}^2$, $\geq 35 \text{ kg}/\text{m}^2$)
- hs-CRP by central laboratory assessment CCI (≤ or > median)
- Usage of tobacco
- Usage of alcohol
- Usage of caffeine

Demographic and baseline characteristics will be summarized with descriptive statistics as appropriate by treatment and in total for Full Analysis Set. “Missing” category will be presented if there are subjects with missing value for the variables.

Listings of demographics and baseline characteristics will be created.

3.3.5 Medical History

Medical history will be coded to system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.1. Counts and percentages of participants with medical history by system organ class and preferred term will be summarized by treatment and in total based on Full Analysis Set.

Medical history data, including details for medical history, will be listed by participants for the FAS.

3.3.6 Prior and Concomitant Medications and Medical Procedures

Concomitant medications will be coded to anatomical therapeutic chemical (ATC) class and preferred term using the WHO Drug Dictionary version Global B3 September 2024. For summary purposes, medications will be considered prior medications if they stopped prior to the first dose of study treatment and concomitant medications if they were taken at any time after the first dose of study treatment (i.e., started prior to the first dose of study treatment and were ongoing or started after the first dose of study treatment).

If a medication (prior and concomitant medication) has incomplete start or stop dates, missing dates will be imputed for the summary table, incomplete start and stop dates will be listed as collected without imputation.

Counts and percentages of participants taking prior and concomitant medications by ATC class and preferred term will be summarized by treatment and in total based on the Safety Set. Listings (separately) for all prior and concomitant medications and concomitant medical procedures will be provided for the Safety Set.

3.3.7 Study Treatment Exposure and Compliance

Days of exposure to VTX3232 will be calculated as date of last dose of study treatment – date of first dose of study treatment + 1. Days of exposure to semaglutide will be calculated as date of last dose of study treatment – date of first dose of study treatment + 7. CCI

Percent compliance with VTX3232 or placebo regimen will be calculated as $100 \times \text{number of actual tablets taken} / \text{number of expected tablets taken}$. The number of actual tablets taken will be calculated as number of tablets dispensed – number of tablets returned. CCI

. The number of tablets expected will be calculated as the earliest date of the end of treatment or end of study date – date of randomization (i.e., the number of days study treatment was expected to be taken x 1 tablets per day).

Percent compliance to semaglutide regimen will be calculated as $100 \times \text{number of actual injector pens used} / \text{number of expected injector pens used}$. The number of actual injector pens used will be calculated as number of injector pens dispensed – number of injector pens returned. If injector pens are not returned, the number of injector pens returned will be considered 0 for the compliance calculation. The number of injector pens expected will be the number of injections that the subject would have taken if all scheduled visits occurred and injections were administered at all scheduled visits prior to discontinuation. CCI

Percent compliance with the study treatment regimen will be summarized by treatment group based on the Safety Set with descriptive statistics and with counts and percentages of participants with compliance in the following categories:

- < 80%
- 80-120%
- > 120%



The percent compliance of placebo or VTX3232 and semaglutide injection in the treatment groups below, respectively, will be provided.

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

A listing of study treatment exposure and compliance will be created for both study treatment injections and study treatment tablets and will include treatment duration (days) = end of treatment date – randomization date +1, study duration (days) = end of study date – randomization date +1, number of days study treatment (injections and tablets) was taken, and total treatment exposure (mg).

Product accountability will be listed (for both injections and tablets) and will include the date dispensed and returned, the bottle ID or injector pen ID dispensed and returned, the amount dispensed and returned, whether the participant had any interruptions 2 consecutive doses during the study, and the reason for interruption.

3.4 Efficacy Assessment

The secondary efficacy endpoint and all exploratory efficacy endpoints will be summarized by treatment groups using the FAS.

CCI

Except for the time points specified in the efficacy endpoints (e.g. Week 12) specified in the protocol, all other scheduled timepoints prior to the endpoint timepoint will be included in the corresponding MMRM/ANCOVA/CMH analyses and presented in output.

The efficacy data at Follow-up visit will be descriptively summarized.

CCI

3.4.1 Secondary Efficacy Endpoints

Primary Analysis

For the secondary endpoint analysis, the change and percent change in hs-CRP from Baseline over time through Week 12 will be compared between the following treatments using an MMRM at scheduled visits through Week 12 (VTX3232 30 mg QD vs. Placebo QD, Placebo QD and Weekly Semaglutide vs. Placebo QD, VTX3232 30 mg QD and Weekly Semaglutide vs. Placebo QD, VTX3232 30 mg QD and Weekly Semaglutide vs. Placebo QD and Weekly Semaglutide).

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, if the MMRM model with unstructured covariance matrix does not converge, it will be replaced with firstly an AR1 covariance matrix, secondly a Toeplitz covariance matrix, thirdly by a CS covariance matrix. LS means at each visit and the LS mean differences between treatment groups with p-values and corresponding 95% CIs will be reported.

CCI

The descriptive summary for hs-CRP will be provided at scheduled visits through Follow-up.

The longitudinal mean plot (also known as mean profile plot) will be provided to illustrate the primary analysis results from the MMRM model for change from baseline (mean $\pm$ 95% CI) in hs-CRP.

The plot of median with interquartile range (IQR) percent change from baseline in hs-CRP overtime through Week 12 will also be provided.

Data for hs-CRP will be listed by participant, date, and visit within randomized treatment for the FAS.

Sensitivity Analyses

In addition, as sensitivity analyses, the change in hs-CRP from Baseline over time through Week 12 will be compared between VTX3232 30 mg QD treatment group and placebo QD treatment group, between VTX3232 30 mg QD plus weekly semaglutide injection treatment group and placebo QD plus weekly semaglutide injection treatment group using an ANCOVA model. ANCOVA model will include treatment group and CCI. LS means along with 95% two-sided confidence intervals and the associated p-value from this ANCOVA model will be presented. Another sensitivity analysis based on LOCF approach (Section 3.1.6) will also be conducted.

CCI

[Redacted text block containing multiple lines of blacked-out content]

3.4.2 Exploratory Efficacy Endpoints

The following exploratory longitudinal continuous endpoints will be analyzed at scheduled visits up to Week 12 using a MMRM. MMRM as described in Section 3.1.5 will be used to analyze the following exploratory endpoints.

- Change and percent change from baseline in body weight over time through Week 12
- Change from baseline in BMI over time through Week 12
- CCI
- 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
- Change and percent change from baseline in measures of fasting lipid levels (total cholesterol, HDL, LDL, VLDL, triglycerides, free fatty acids) over time through Week 12
- CCI
- [Redacted text]
- [Redacted text]

- Change and percent change from baseline in fasting glucose and fasting insulin over time through Week 12
- CCI [REDACTED]
- CCI [REDACTED]
- [REDACTED]
- [REDACTED]

The longitudinal mean plot will be provided to illustrate the analysis results from the MMRM model for change from baseline (mean $\pm$ 95% CI) in change from body weight and percent change from body weight.

The following exploratory continuous endpoints that are collected only at screening/baseline and Week 12 will be analyzed using an ANCOVA model. The ANCOVA model will include treatment group and CCI [REDACTED]

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

CCI
CCI

Results will be expressed as the number and percentage of participants meeting the endpoint criteria with number of contributing participants. The CMH chi-square p-value, stratified risk difference (“common” risk difference) with 95% CI using the Mantel-Haenszel method, Mantel-Haenszel odds ratio, 95% CI for the Mantel-Haenszel odds ratio and Clopper-Pearson exact 95% confidence intervals will be reported.

- Proportion of participants achieving at least 5% body weight reduction at Week 12
- Proportion of participants achieving at least 10% body weight reduction at Week 12

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

A listing for the exploratory efficacy endpoints will be provided for FAS or Pharmacodynamic Set.

3.4.3 Subgroups

Subgroup analyses will be performed for change in hs-CRP and weight by the following baseline demographics and disease characteristics:

- Sex (male or female)
- Race (white, black, other, non-white (black and other combined))
- Age ($\leq$ or $>$ median)
- CCI
- Baseline hs-CRP by central laboratory assessment ($\leq$ or $>$ median)

CCI

If any subgroup includes less than 5% of all participants, no inferential statistics will be generated.

3.5 Pharmacokinetic Assessment

3.5.1 Sample Collections for Pharmacokinetic Analysis

Plasma samples for VTX3232 PK will be collected pre-dose on Week 0/Day 1, Week 1/Day 8, Week 2/Day 15, Week 4/Day 29, Week 8/Day 57 and Week 12/Day 85. At the Week 0/Day 1 and Week 2/Day 15 visits, PK samples will also be collected at 2 hours ($\pm$ 15 minutes) post-dose. An additional PK sample may be taken, if possible, at the time of any SAE, AE leading to study treatment discontinuation (Early Termination), or AE of interest (Unscheduled).

Samples obtained for the VTX3232 PK assessment may also be used for an evaluation of semaglutide PK, where applicable.

3.5.2 Handling Missing or Below the Lower Limit of Quantification Data

For PK concentration data, if the actual sampling time is missing, but a valid concentration value has been measured, the concentration value will be flagged, and the scheduled time point will be used for the calculation of PK parameters.

For missing concentrations for any collection timepoints, the missing data will not be imputed.

For the individual concentration of each treatment group, the following rules will be applied:

- If BLQ values occur after the last measurable concentration in a treatment period, the BLQ should be omitted (set to missing). Otherwise BLQ will be set to zero.

For the concentration summary and mean concentration plot preparation of each treatment group, the following rules will be applied:

- Mean concentration at any individual time point will only be calculated if at least half of the participants have valid values (i.e. quantifiable, not missing and not outside collection window) at this time point for each treatment.
- In cases where a mean value is not calculated due to the above criterion not being met, the value will be set to "NC".
- BLQ values will be set to zero.

3.5.3 Pharmacokinetic Concentration

Individual plasma concentrations of VTX3232 will be summarized by visit and treatment at each nominal time point for the PK Set using descriptive statistics (i.e., n, mean, SD, coefficient of variation [CV%], median, min, max, geometric mean, and geometric CV%). The percentage of PK samples that were BLQ per time point will also be presented. Individual plasma concentrations of VTX3232 will also be listed by treatment group, visit, and time for the PK Set. Geometric statistics will not be calculated for pre-dose concentrations obtained prior to the first VTX3232 dose.

For each treatment group within PK Set, Box and Whisker plots of VTX3232 concentrations against study visit will be generated and overlayed with individual values. Box and Whisker plots of VTX3232 concentrations will be plotted against time and overlayed with individual values for sampling days where post-dose samples are also collected (Week 0/Day 1 and Week 2/Day 15). LLOQ will be plotted as a reference line.

Actual sampling times that are outside the sampling time windows will be excluded from concentration summary and concentration plotting.

Individual values for PK concentration data will be reported to the same level of precision as received from bioanalytical laboratory. For PK summary statistics, N will be reported as integer, CV% and geometric CV% will be reported with 1 decimal place, and all other summary statistics will be reported with 3 significant digits. Geometric mean and geometric CV% will be calculated excluding 0 values.

3.5.4 Additional PK Analyses

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

3.6 Pharmacodynamic/Biomarker Assessment

The biomarker analysis will be the assessment of exploratory pharmacodynamic biomarkers in plasma, serum or urine. The data from the specialty biomarkers IL-1 β singleplex and IL-6 at selected visits (Day 1, Week 12, and Follow-up) will be available for the analysis.

Observed biomarker results, change from baseline results, and percent change from baseline results will be summarized using descriptive statistics (i.e. N, arithmetic mean, standard deviation, median, Q1, Q3, Min, and Max) by visit and time point, where appropriate, for the Pharmacodynamic Set. Geometric statistics (mean, standard deviation, and CV%) will be calculated for the observed non-zero results for the parameter of interest and type of results for the associated visit and time point.

Values below the limit of quantification (BLQ) or below the limit of detection (BLD) will be imputed as 1/2 BLQ and used in summary statistics. Values above the limit of quantification (ALQ) or above the limit of detection (ALD) will be imputed as ALQ and used in summary statistics. The specialty biomarkers that are collected only at screening/baseline and Week 12 will be analyzed using an ANCOVA model and all visits will be descriptively summarized. The ANCOVA model will include treatment group and sex as factors and baseline BMI and baseline measure as covariates, all factors and covariates will be treated as fixed effect in ANCOVA model.

Pharmacodynamic and biomarker results will be listed for the Pharmacodynamic Set.

Analysis of specialty biomarkers will include values available by the time of database lock. After the database lock, if additional samples are assayed, the analysis will be updated to include all samples analyzed.

3.7 Safety Assessment

Analyses of safety will be performed based on the treatment actually received using the Safety Set and consist of descriptive analysis for each safety variable.

3.7.1 Adverse Events (AEs)

AEs will be captured from the date of informed consent through study completion. All AEs will be coded to system organ class (SOC) and preferred term (PT) using MedDRA version 27.1 or higher. Relationship to study treatment will be assessed as not related or related. AEs will be graded by the investigator according to the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. If CTCAE grade is missing, it will be assumed to be Grade 3. If relationship is missing, it will be assumed to be related. If seriousness is missing, the AE will be assumed to be serious. AEs with a missing onset date and non-missing end date will be considered as TEAE unless the end date is prior to the first treatment administration.

A Treatment-emergent adverse events (TEAEs) 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.

An overview of TEAEs, summarized by treatment group, will be provided including counts and percentages of participants with the following:

- Any TEAEs (overall and by maximum severity)
- Any treatment-emergent serious AEs (TESAEs)
- Non-serious TEAEs; non-serious TEAEs related to study treatment
- TEAE and SAE related to study treatment
- TEAE by maximum CTCAE grade; TEAE related to study treatment by maximum CTCAE grade
- TEAEs of CTCAE grade 3 or higher; TEAEs related to study treatment of CTCAE grade 3 or higher
- Any TEAEs leading to study treatment discontinuation; TEAEs related to study treatment leading to study treatment discontinuation
- Any TEAEs leading to discontinuation of study; TEAEs related to study treatment leading to discontinuation from study
- TEAEs leading to study treatment interruption; TEAEs related to study treatment leading to study treatment interruption
- Adverse events of Special Interest (AESI); AESI related to study treatment

- Any AEs leading to death

Counts and percentages of participants will also be presented by SOC and PT for each of the categories in the overview. When the table is displayed by maximum CTCAE grade, the order should be by SOC, PT, and maximum CTCAE grade. In output, SOC is sorted by total number of participants descending and PT within SOC is sorted by total number of participants descending.

A participant experiencing multiple TEAEs under the same SOC / PT will be counted only once for that SOC / PT by worst severity. If a participant experiences the same AE more than once with more than one relationship to study treatment, the worst causal relationship to study treatment will be given precedence.

Separate listings will be presented for all AEs, SAEs, TEAEs leading to study treatment discontinuation, TEAEs leading to study treatment interruption, TEAEs leading to discontinuation of study, and TEAEs of special interest, with flags for TEAE (Y/N) and information regarding onset, end date, duration, severity, seriousness, relationship, outcome, and countermeasures taken. Duration of AEs will be derived and presented in listings. It is calculated as AE stop date minus AE start date +1. Both start and stop dates need to be present to calculate a duration.

3.7.2 Clinical Laboratory Tests

Participants must be in a fasted state at the time of clinical laboratory blood draws throughout the study. Clinical laboratory tests (hematology, clinical chemistry, blood for central lab biomarkers, urinalysis, urine for central lab biomarkers, and coagulation) will be performed at visits specified in the Schedule of Activities, see Section 1.3 in the Protocol. See Table 5: Protocol-Required Laboratory Tests via Central Laboratory Assessment in the Protocol for a complete list of laboratory analytes.

Values reported as the lower limits or upper limits of quantification for clinical laboratory results will be presented as the cutoff value if they contain “=”. Otherwise, they will be presented as one unit lower (for lower limits) or one unit higher (for upper limits) than the cutoff value to the same precision as the original values (e.g., 5.0 would be presented as 5.0 for calculations and < 3.00 would be presented as 2.99 for calculations).

Values and changes from Baseline will be presented at each scheduled visit and Baseline by laboratory test based on the Safety Set.

The incidence of abnormalities (as defined by normal ranges) not present at Baseline and present after the first dose of study treatment will be summarized with counts and percentages of participants using the Safety Set.

A by-participant listing will be provided for each laboratory parameter.

3.7.3 Vital Signs

Vital signs (systolic blood pressure (SBP) [mmHg], diastolic blood pressure (DBP) [mmHg], pulse rate (PR) [beats/min], temperature [C], respiratory rate (RR) [breaths/min]) will be performed at visits specified in the Schedule of Activities (Appendix B). Descriptive statistics for vital signs values and the change from Baseline will be presented by the treatment arm for each scheduled visit based on the Safety Set.

Vital sign assessments will be presented in a by-participant listing with flags for values outside the normal ranges.

CCI

3.7.5 *Electrocardiograms (ECGs)*

ECGs (12-lead) will be performed at visits specified in the Schedule of Activities (Section 1.3 in the Protocol). 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 heart rate (HR) and the following intervals: RR, PR, QRS, QT, and QTcF.

Descriptive statistics for ECG values and the change from Baseline will be presented by treatment arm for each scheduled visit. If there are multiple measurements at the same visit, the last record will be utilized in analysis.

A listing of participants with ECG values with clinically significant abnormalities will be produced.

3.7.6 *Physical Examinations*

Full and brief physical examinations will be performed at visits specified in the Schedule of Activities (Section 1.3 in the Protocol). 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. Clinically significant physical examination abnormalities will be included in medical history or recorded and summarized as an AE.

A listing of physical examinations by participant will be provided.

CCI

-
-
-

- CCI [REDACTED]
- [REDACTED]

[REDACTED]

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

[REDACTED]
[REDACTED]

[REDACTED]
[REDACTED]

[REDACTED] [REDACTED]

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

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

[REDACTED]

3.7.9 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, where appropriate.

4 CCI [REDACTED]

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

[REDACTED]
[REDACTED]
[REDACTED]

CCI

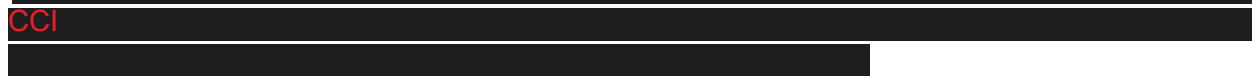
A large rectangular area of the document is redacted with a solid black box. The redaction covers approximately four lines of text.

5 CHANGES FROM PROTOCOL-SPECIFIED STATISTICAL ANALYSES

CCI

A large rectangular area of the document is redacted with a solid black box. The redaction covers approximately six lines of text. The letters "CCI" are visible in large red font on the first line of the redacted area.

CCI

A rectangular area of the document is redacted with a solid black box, covering approximately two lines of text.

6 PROGRAMMING SPECIFICATIONS

Analyses will be performed using SAS® version 9.4 or higher. All available data will be presented in participant data listings which will be sorted by participant and visit date as applicable. Detailed

Tables, Figures and Listings Mock Shell Programming Specifications will be provided in a separate document.

APPENDIX A: REFERENCES

1. CCI [REDACTED]