Protocol Title: **Study OB-409: A Multicenter, Randomized, Double-Blind Study to Compare the Effects of VI-0521, Phentermine, and Placebo on Ambulatory Blood Pressure in Overweight or Obese Subjects**

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Statistical Analysis Plan

Protocol OB-409

VIVUS LLC

A MULTICENTER, RANDOMIZED, DOUBLE-BLIND STUDY TO COMPARE THE EFFECTS OF VI-0521, PHENTERMINE, AND PLACEBO ON AMBULATORY BLOOD PRESSURE IN OVERWEIGHT OR OBESE SUBJECTS

Phase 4

Original Protocol: March 9, 2021

Amendment 1 Protocol: October 15, 2021

Prepared by [redacted]

[redacted]

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Statistical Analysis Plan

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This Statistical Analysis Plan has been reviewed and approved by:

[redacted]

Apr-27-2023

Date

Vivus LLC

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LIST OF ABBREVIATION

ABPM	Ambulatory blood pressure monitoring
AE	Adverse Events
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
ATC	Anatomic therapeutic chemistry
BMI	Body mass index
BP	Blood pressure
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CSR	Clinical study report
DBP	Diastolic blood pressure
ECG	Electrocardiogram
EOS	End of Study
GGT	Gamma-glutamyl transpeptidase
HbA_{1c}	Hemoglobin A_{1c}
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
ICH	International Conference on Harmonization
ITT	Intent-to-treat
LDL-C	Low-density lipoprotein cholesterol
LSM	Least square mean
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities
MI	Multiple imputation
MNAR	Missing not at random
PHEN	Phentermine
PP	Per protocol
PR	Pulse rate
PT	Preferred term
QD	Once per day

RR	Respiration rate
RTSM	Randomization and Trial Management System
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis software
SBP	Systolic blood pressure
SD	Standard Deviation
SE	Standard Error
SOC	System organ class
TEAE	Treatment-emergent adverse event
TPM	Topiramate
TSH	Thyroid-stimulating hormone
T2DM	Type 2 diabetes mellitus
USA	United States of America
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of Childbearing Potential

1 INTRODUCTION

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of protocol OB-409. The proposed methods and approaches to the data analysis should be viewed as flexible. If the data suggest and warrant it, deviations from this plan will be considered. However, any deviations from this statistical analysis plan (SAP) must be substantiated by sound statistical rationale and documented in the final clinical study report.

2 STUDY OBJECTIVES

The objective of this study is to evaluate the effect of VI-0521 on blood pressure as measured by 24-hr Ambulatory Blood Pressure Monitoring (ABPM), compared to both placebo and an active control (phentermine 30 mg).

3 STUDY OVERVIEW

3.1 Study Design

This randomized, double-blind, placebo and active comparator-controlled study will be conducted at about 35 sites in the US. Approximately 555 eligible subjects will be randomly assigned with equal probability, to daily treatment with top-dose VI-0521 (phentermine and topiramate extended-release capsules 15 mg/92 mg), phentermine 30 mg, or placebo (1:1:1 ratio; 185 subjects per group). Stratification factors include sex (male; female), age (< 50; ≥ 50 years), and hypertensive status (no medical diagnosis of or treatment for hypertension; medical diagnosis of hypertension treated with 0-2 antihypertensive agents; or medical diagnosis of hypertension treated with 3 or more antihypertensive agents). The duration of treatment will be 8 weeks, and the total duration of participation will be a total of approximately 12 weeks. Subjects will undergo a 4-week titration period using blister cards with dose increases as described in Table 1 until the randomized dose is reached.

Table 1 Dose Strengths by Titration Week

Assigned Doses of PHEN/TPM (mg/mg)	N	Titration Doses (mg/mg) of PHEN/TPM QD			
		Week 1	Week 2	Week 3	Week 4
Placebo	185	0/0	0/0	0/0	0/0
Phentermine 30	185	30/0	30/0	30/0	30/0
VI-0521 Top-Dose 15/92	185	3.75/23	7.5/46	11.25/69	15/92
PHEN = phentermine; TPM = topiramate; QD = daily					

3.2 Study Procedures

A schedule of study activities is presented in Table 2. Following randomization, subjects will receive diet and exercise counseling on maintaining an appropriate healthy diet with a recommended initial caloric deficit of approximately 500 kcal per day and at least 30 minutes of regular physical activity on most days of the week. The total duration of study treatment will be 8 weeks (4 weeks of dose titration and 4 weeks of treatment at the assigned dose) with 24-hr ABPM recordings performed at Baseline/Randomization and again at Week 8/End of Study or Early Termination. Clinic visits will occur at Screening, Baseline/Randomization (2-day outpatient visit), Week 4, and Week 8/End of Study or Early Termination (2-day outpatient visit). The 24-hr ABPM data will be collected and transferred to the data management/biostatics vendor for analysis in a blinded manner prior to study unblinding, using validated software.

In order to minimize the potential confounding of study results by changes in other medications, all concomitant medications, particularly those for management of blood pressure or other weight-related comorbidities, will be fixed in number, dose, and frequency for the duration of the study unless specific "rescue" criteria are met for blood pressure (≥ 160/100 mmHg, or ≤ 100/60 mmHg and symptoms of hypotension). Any changes in concomitant medication will be fully documented.

Table 2 Schedule of Events

	Screening	Baseline/ Randomization[1]		End of Titration	End of Study or Early Termination	
Study Week	**Week -4**	**Week 0**		**Week 4**	**Week 8**	
Visit # (window in days)	**1**	**2A[2] (+3)**	**2B[2]**	**3(± 3)**	**4A[2](± 3)**	**4B[2]**
Informed Consent	X					
Demographics	X					
Medical History	X					
Inclusion/Exclusion	X	X				
Weight	X	X		X	X	
Height, BMI	X					
Physical Exam	X					X
Vital Signs	X	X[3]		X	X[3]	X
Prior/Concomitant Medications[4]	X	X	X	X	X	X
Adverse Events[5]		X	X	X	X	X
Chemistry (Full Panel)	X					X
Chemistry (Limited Panel)				X		
Hematology/Lipids/HbA1c	X					X
TSH	X					
HIV, HCV, HBsAg	X					
Urinalysis	X					X
Urine Cotinine and Urine Drug Screen	X					
PK trough sample (prior to dosing)					X	
Urine pregnancy (WOCBP) / Contraception Reminder	X	X		X	X	

24-hr ABPM Recording - Begin		X			X	
24-hr ABPM Recording – End & Removal			X			X
ABPM Device Instruction		X			X	
12-Lead ECG	X					X
Lifestyle counseling			X	X		
Contact RTSM	X		X	X		
Randomization			X			
Dispense Study Drug			X	X		
Study Drug Accountability				X	X	X
Schedule Next Visit	X	X	X	X	X	

1. Baseline can occur up to 4 weeks from Screening
2. Outpatient visits
3. Done prior to ABPM hook up. Blood pressure should be the average of three successive BP readings, collected at least 2 minutes apart. The mean of the three values will be recorded as the subject's blood pressure.
4. Prior medications will be recorded only at Screening
5. Through 28 days post last day of study drug

3.3 Randomization Schedule and Blinding Procedures

Eligible subjects will be randomly assigned with equal probability, to daily treatment with top-dose VI-0521, phentermine 30 mg, or placebo (1:1:1 ratio). Subjects will be assigned to study treatment via a Randomization and Trial Supply Management (RTSM) system. Randomization will be stratified by sex (male; female), age (< 50; ≥ 50 years), and hypertensive status (no medical diagnosis of or treatment for hypertension; medical diagnosis of hypertension treated with 0-2 antihypertensive agents; or medical diagnosis of hypertension treated with 3 or more antihypertensive agents). For hypertensive patients who are being treated with fixed-dose combinations, these will be counted as 2 antihypertensive agents. Both the subject and the study site will be blinded as to subject randomization.

Study drug will not be unblinded during the study unless it is considered necessary by the investigator for the management of an adverse event or other medical emergency. In the event of such medical emergency, the site will contact the study designated medical monitor. The identity of the study treatment will be obtained through the RTSM and VIVUS or designee will be notified of the unblinding. Any subject whose treatment assignment has been unblinded must be discontinued from the study.

4 STUDY ENDPOINTS

4.1 Primary Endpoint

The primary endpoint of the study is the change from baseline to Week 8 in mean systolic blood pressure (SBP) as measured by 24-hr ABPM.

4.2 Secondary Endpoints

The secondary endpoints of the study are:

- Change from baseline to Week 8 in mean diastolic blood pressure (DBP) as measured by 24-hr ABPM;
- Mean change in SBP and DBP from baseline to Week 8 as measured in clinic.

4.3 Exploratory Endpoints

The exploratory endpoints of the study are:

- Mean hourly changes in SBP and DBP from baseline to Week 8, defined as the mean change from baseline at each hour;
- Change in mean daytime and nighttime SBP as measured by 24-hr ABPM from baseline to Week 8;

- Change from baseline to Week 8 in nighttime "dipping" of SBP, and the percentage of subjects with a normal SBP "dipping" pattern at Week 8. A normal "dipping" pattern of SBP will be defined as a reduction of mean nighttime SBP of ≥ 10% relative to mean daytime SBP during the same 24-hr recording;
    - SBP dipping is calculated as: 100 x [(mean daytime SBP – mean nighttime SBP)/ mean daytime SBP]
- Change from baseline to Week 8 in nighttime "dipping" of DBP, and the percentage of subjects with a normal DBP "dipping" pattern at Week 8. A normal "dipping" pattern of DBP will be defined as a reduction of mean nighttime DBP of ≥ 10% relative to mean daytime SBP during the same 24-hr recording;
    - DBP dipping is calculated as: 100 x [(mean daytime DBP – mean nighttime DBP)/ mean daytime DBP]
- Percentage of subjects meeting the following BP thresholds at baseline and Week 8 as measured by 24-hr ABPM;
    - SBP: ≥ 160 mmHg for 2 consecutive readings; ≥ 180 mmHg for 2 consecutive readings;
    - DBP: ≥ 100 mmHg for 2 consecutive readings; ≥ 110 mmHg for 2 consecutive readings;
- Percentage of subjects with the average of three successive BP meeting the following thresholds at baseline and each post-baseline visit as measured in clinic;
    - SBP: ≥ 160 mmHg; ≥ 180 mmHg; ≥ 20 mmHg increase from baseline;
    - DBP: ≥ 100 mmHg; ≥ 110 mmHg; ≥ 15 mmHg increase from baseline;
- Change from baseline to Week 8 in mean 24-hr heart rate, mean daytime heart rate, mean nighttime heart rate, and mean hourly heart rate;
- Percentage of subjects meeting the following heart rate thresholds at baseline and Week 8 as measured by 24-hr ABPM;
    - > 100 bpm for 2 consecutive readings; > 100 bpm for at least 1 hour; > 100 bpm for at least 2 hours; > 100 bpm for at least 3 hours; > 100 bpm for at least 4 hours; mean daytime heart rate > 100 bpm;
- Percentage of subjects meeting the following heart rate thresholds at baseline and each post-baseline visit as measured in clinic;
    - > 100 bpm;
    - ≥ 10 bpm increase from baseline; ≥ 20 bpm increase from baseline
    - ≥ 80 bpm at baseline and ≥ 10 bpm increase from baseline; ≥ 90 bpm at baseline and ≥ 10 bpm increase from baseline; ≥ 100 bpm at baseline and ≥ 10 bpm increase from baseline;
- Mean percent change in body weight from baseline to Week 8.

4.4 Safety Endpoints

The safety endpoints include evaluation of the following:

- Adverse events (AEs)
- Changes in laboratory parameters
- Changes in Electrocardiograms (ECG)
- Physical exam findings
- Vital signs
- Requirement for rescue therapy for blood pressure and type 2 diabetes mellitus (T2DM)

5 ANALYSIS POPULATIONS

The following analysis populations will be defined for study summaries and analyses.

5.1 Enrolled Population

Enrolled Population will be comprised of all enrolled subjects (non-screen failures), regardless of randomization. The Enrolled Population will be used for by-subject listings when appropriate.

5.2 Intent-to-Treat (ITT) Population

ITT Population will be comprised of all randomized subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment group they are allocated to by randomization, regardless of early dropout or being exposed to wrong study medication. The ITT population will be used for summaries of subject disposition, demographic and baseline subject characteristics, medical history, concomitant medication, protocol deviations and efficacy evaluations.

5.3 Safety Population

Safety Population will be comprised of all randomized subjects who received at least one dose of study drug. Subjects will be analyzed according to the treatment received. The Safety Population will be used for safety evaluations.

5.4 Per Protocol (PP) Population

PP Population will be comprised of ITT subjects who met all of the following criteria:

- Compliant to study treatment (defined as ≥ 80% treatment compliance as specified in Section 6.5);
- Last daily dose of study drug administered on the same date that ABPM was initiated at Visit 4A (first day of Week 8/End of Study or Early Termination);
- Had at least 23.5 hours of ABPM data (i.e. blood pressure and heart rate data) at baseline and at Week 8/End of Study or Early Termination, and at least 75% of 24-hr ABPM readings (or equivalently 48 readings during the 24-hr period) are not missing;
- Subjects with any major protocol deviation that had impact on ABPM readings will be excluded from the PP Population.

The PP population will be used to assess the primary and secondary endpoints as primary analyses. Subject inclusion in the PP population will be determined and documented prior to database lock and treatment unblinding.

6 STUDY SUBJECTS

6.1 Subject Disposition

Counts and percentages of subjects who were screened, enrolled, randomized, randomized and not treated, completed or were discontinued from the study, as well as the reason for discontinuation, will be summarized by treatment group.

6.2 Demographic and Baseline Characteristics

Demographic and baseline characteristic data, including but not limited to, age, sex, race, ethnicity, hypertensive status, SBP, DBP, diabetic status (Yes/No for T2DM), height, weight, and body mass index (BMI) will be summarized by treatment group for subjects in the ITT population.

If a subject meets one of the following criteria, the subject will be counted as “Yes” for T2DM:

- Has a medical history of T2DM
- Uses concomitant antidiabetic medications (see Section 6.6 for concomitant medications)
- Has baseline lab fasting glucose ≥126 mg/dL (see Section 7.1.3 for the definition of baseline)

6.3 Medical History

Medical history will be listed and summarized descriptively with count and percentage by coded term and treatment group for the ITT population. Coded terms will be defined using a current version of the Medical Dictionary for Regulatory Activities (MedDRA).

6.4 Inclusion/Exclusion Criteria and Subject Eligibility

Subject eligibility, e.g., inclusion and exclusion criteria failures will be listed for all screened subjects.

6.5 Study Drug Exposure and Treatment Compliance

The extent of exposure to study drug will be presented by duration of treatment and will be summarized with descriptive statistics by treatment group. Duration of exposure (in days) will be defined as (last dose date – first dose date + 1).

Treatment compliance, e.g., based on difference between actual capsule consumption and the expected capsule consumption of subjects, will be summarized by treatment group for the ITT population. Percent study drug compliance for the overall treatment period is calculated as: 100 × [(total number of capsules consumed)/(planned number of capsules the subject should have consumed while still actively enrolled)]. The total number of capsules consumed will be calculated from the total capsules dispensed minus unused capsules returned for each subject.

Study drug exposure and accountability will be presented in listings.

6.6 Concomitant Medications

The latest World Health Organization Drug Dictionary (WHO-DD) will be used to categorize verbatim descriptions of non-study medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), preferred term, and trade name (if appropriate).

Concomitant medications are referred to non-study medications that have been used on or after receiving the first randomized study medication. Medications will be categorized into 3 types:

Pre-treatment medications: any non-study medications that started and stopped prior to receiving the first randomized study dose.

Prior concomitant medications: any non-study medications taken before the first randomized study dose date and continued beyond the first randomized study dose date.

New concomitant medications: any new non-study medications that started on or after receiving the first randomized study medication.

Counts and percentages of subjects receiving concomitant medications, prior concomitant medications, and new concomitant medications will be summarized by treatment group and ATC classification level 4 and preferred term for the ITT population. Additionally, concomitant medications used for management of blood pressure or diabetes, if any, will be summarized separately.

Pre-treatment medications will be provided in a listing.

6.7 Protocol Deviations

Protocol deviations may include deviations from informed consent, study procedure, study medication administration, study restrictions, etc. All protocol deviations will be reviewed by clinical and statistical personnel to identify major deviations (those anticipated to have an impact on efficacy or safety findings) prior to database lock and unblinding. The ICH guideline on protocol deviation classification will be followed. The major protocol deviations will be used as one of the criteria to determine the subject's eligibility for inclusion in the PP population. Major protocol deviations will be summarized by treatment group and deviation category for the ITT population. All protocol deviations will be presented in a listing.

7 STATISTICAL METHODS OF ANALYSIS

7.1 General Considerations

Efficacy data will be summarized "as-randomized," meaning the subjects will be summarized under the treatment they were randomized to, regardless of what treatment was actually received. The PP population will be the primary analysis population for all efficacy analyses while the ITT population will be used to support efficacy analyses, if appropriate. The Safety Population will be the primary analysis population for all safety analyses.

Estimand and its estimator(s) and estimate(s) for primary and secondary efficacy endpoints will be defined, where inferential statistical comparison and hypothesis testing related to a treatment effect are of interest. When analyzing the efficacy endpoints, effort will be made to distinguish intercurrent events from non-informative withdrawals, as well as applying various sensitivity analyses to assess the robustness of the estimate(s) for the pre-specified estimands. Details on estimands, estimators, estimates, and intercurrent events are discussed in individual endpoint analysis section.

7.1.1 Statistical Notation and Presentation

For descriptive statistical summaries, the sample size (n), mean, standard deviation (SD), standard error (SE), median, minimum and maximum will be calculated for continuous variables. For categorical variables, frequency and percentage in each category will be provided. Inferential statistical analyses will be performed using either parametric method (e.g., assessing continuous variables) or non-parametric method (e.g., assessing categorical variables). All tabulations of analysis results will include summaries for the three treatment groups: VI-0521 PHEN 15 mg/TPM 92 mg, Phentermine 30mg and Placebo.

Minimum and maximum values will be rounded to the precision of the original value. Means and medians will be rounded to one decimal place greater than the precision of the original value. SDs, SEs, and 95% confidence intervals (CIs) will be rounded to two decimal places greater than the precision of the original value. Percentages for summarizing categorical data will be rounded to one decimal place. P-values, if needed, will be presented with 4 decimal places and values less than 0.0001 will be presented as <0.0001.

The by-subject listings, including data at scheduled and unscheduled visits, will be sorted by treatment group, subject number, and then by date/time of the records.

7.1.2 Hypothesis Testing

All hypothesis testing will be based on two-sided test at a significance level of 0.05. The primary hypothesis is that VI-0521 does not have deleterious effect on SBP as measured by mean 24-hr ABPM in overweight or obese subjects compared to placebo.

For non-inferiority tests, the null hypothesis (H_0) to be tested is that the upper bound of the two-sided 95% confidence interval for the between-treatment group difference (VI-0521 minus placebo or phentermine) in change from baseline in 24-hr mean SBP is equal to or more than 3 mmHg. The alternative hypothesis (H_a) is that the upper bound of the two-sided 95% confidence interval for the between-treatment comparison with placebo (or phentermine) is less than 3 mmHg. Thus:

$$H_0: \Delta_U \geq 3 \text{ mmHg}$$

$$H_a: \Delta_U < 3 \text{ mmHg}$$

For superiority tests, the null hypothesis (H_0) to be tested is that the upper bound of the two-sided 95% confidence interval for the between-treatment group difference (VI-0521 minus placebo or phentermine) in change from baseline in 24-hr mean SBP is equal to or more than 0 mmHg. The alternative hypothesis (H_a) is that the upper bound of the two-sided 95% confidence interval for the between-treatment comparison with placebo (or phentermine) is less than 0 mmHg. Thus:

$$H_0: \Delta_U \geq 0 \text{ mmHg}$$

$$H_a: \Delta_U < 0 \text{ mmHg}$$

7.1.2.1 Multiplicity Adjustment

This study is designed to maintain an overall study-wise type I error rate of α=0.05. A hierarchical gatekeeping approach will be used to control the family-wise type 1 error of the primary and secondary endpoints. The order of the hypothesis testing will be:

(1) The comparison between VI-0521 and placebo for non-inferiority,

(2) The comparison between VI-0521 and phentermine for non-inferiority,

(3) The comparison between VI-0521 and placebo for superiority, and

(4) The comparison between VI-0521 and phentermine for superiority.

If the superiority of top-dose VI-0521 versus phentermine is achieved for the primary endpoint, the same testing order and hypothesis tests will be applied to the secondary endpoints: change from baseline to Week 8 in mean DBP as measured by 24-hr ABPM, and then mean change in SBP and DBP from baseline to Week 8 as measured in clinic, respectively.

In this hierarchical testing procedure, only when testing of a given hypothesis is successful, the subsequent hypothesis tests will be evaluated; otherwise, the subsequent hypothesis tests will be considered exploratory.

7.1.3 Baseline and Change from Baseline

In general, the baseline value for each variable is defined as the last non-missing observation obtained prior to the dispense of the first study drug. The actual first randomized dose date/time will be compared to the date/time of data collection to define the baseline for each parameter. In the case where the last non-missing measurement (except AE and concomitant medications) and the first dose coincide at the same time, or the same date if time of the measurement is not collected, that measurement will be considered as baseline value. The change from baseline value is defined as post-baseline value minus baseline value. The percent change from baseline value is defined as (post-baseline value minus baseline value) / baseline value × 100.

7.1.4 Handling of Ambulatory Blood Pressure Monitoring Data

For the 24-hr ABPM, blood pressure and heart rate will be measured every 20 minutes from 6:00 to 22:00 hours, and every 30 minutes from 22:01 to 5:59 hours for 24 consecutive hours. The baseline and post-baseline values for mean ABPM (SBP and DBP) will be calculated by taking the average of ABPM measurements over the given 24-hr time period.

For assessment of daytime and nighttime blood pressure, “night” will be defined as the mean of all systolic or diastolic blood pressure values recorded between 24:00 and 05:00 (inclusive) and “day” will be defined as the mean of all systolic or diastolic blood pressure values recorded between 07:30 and 21:30 (inclusive).

Mean hourly changes in blood pressure and heart rate will be calculated by taking the average of ABPM measurements available at each hour and calculating the change from baseline of the average. The measurements taken in the 60 minute duration prior to each hour will be used to get the average value. For example, the average of blood pressure measurements taken at 6:05, 6:25 and 6:45 will be defined as the mean blood pressure at 7:00.

7.1.5 Handling of Multiple Observations or Out of Window Observations

For efficacy data, if multiple assessments were recorded for the same protocol defined visit (e.g., same nominal visit but different time points or re-assayed), the later one or the re-assayed data will be used for data summary and analysis.

If a subject has a scheduled visit, the assessment obtained at the scheduled visit will be used for data summary and analysis. Otherwise, if no scheduled visit assessment exists but unscheduled visit assessments are available within the visit window, the data from the latest unscheduled visit will be used for statistical analysis.

Regarding the visit windows that will be applied to handle multiple observations and unscheduled visits, Table 7-1 shows the protocol-defined visit windows and the data analysis visit windows. Protocol-defined visit windows are usually more stringent to ensure study better adherence to study schedule; however, it could be too narrow for inclusion of unscheduled visits for data analysis. In order to include study data collected from any unscheduled visits, the analysis time windows will be widened for visit attribution. Note that data collected from an unscheduled visit that is out of the time window will not be included in data analysis, but will be provided in listings.

Table 7-1 Analysis Visit Window

Visit Number	Visit Name	Study Week	Target Study Day[1]	Protocol-Defined Time Window	Time Window to Attribute Unscheduled Visit to Analysis Visit
1	Screening	Week -4	-28	--	--
2A	Baseline/Randomization	Week 0	-1	+3 days	The last measurement prior to receiving the 1st randomized dose

Visit Number	Visit Name	Study Week	Target Study Day[1]	Protocol-Defined Time Window	Time Window to Attribute Unscheduled Visit to Analysis Visit
2B	Baseline/Randomization	Week 0	1	--	--
3	End of Titration	Week 4	28	±3 days	-3 and +6
4A	End of Study or Early Termination	Week 8	56	±3 days	Week 7 to all visits before or on the last study dose date
4B	End of Study or Early Termination	Week 8	57	--	All visits after the last study dose date

[1] Study day 1 is defined as the date of the first dose for each subject.

7.1.6 Handling of Missing or Partial Dates

In cases of incomplete dates for AEs or non-study medications, the missing component(s) will be assumed as the most conservative value(s) possible. For example, the imputation rule is to conservatively capture AEs with missing start dates as treatment-emergent AEs (TEAEs). Actual data values, as they appear in the clinical database, will be shown in the data listings. Rules for partial dates are described in Table 7-2.

Table 7-2 Rules for Missing or Partial Dates

Parameter	Missing	Additional Conditions	Imputation
Start date for AEs	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as M and Y of first dose of study drug	First day of non-missing month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 1 of non-missing year
	M, D and Y	None – date completely missing	Date of first dose of study drug
Stop date for AEs	D only		Last day of non-missing month
	D and M		Use Dec 31 of non-missing year
	M, D and Y	Deceased	Date of death
		Not deceased	Date of the end of trial participation

Parameter	Missing	Additional Conditions	Imputation
Start date for non-study medications	D only	M and Y same as M and Y of first dose of study drug	Date of first dose of study drug
		M and/or Y not same as M and Y of first dose of study drug	First day of non-missing month
	D and M	Y same as Y of first dose of study drug	Date of first dose of study drug
		Y not same as Y of first dose of study drug	Use Jan 1 of non-missing year
	M, D and Y	None – date completely missing	Date prior to date of first dose of study drug
Stop date for non-study medications	D only	M and Y same as M and Y of first dose of study drug	Last day of non-missing month
		M and/or Y not same as M and Y of first dose of study drug	Last day of non-missing month
	D and M	Y same as Y of first dose of study drug	Use Dec 31 of non-missing year
		Y not same as Y of first dose of study drug	Use Dec 31 of non-missing year
	M, D and Y	None – date completely missing	Date will not be imputed

Notes: D=Day, M=Month, Y=Year

7.1.7 Handling of Missing Efficacy Data

Every effort will be made to obtain the protocol-required data for all subjects according to the study schedule. However, subjects may withdraw from the study prior to completion, or discontinue study medication for any reasons. For subjects who discontinue treatment prior to study completion, every attempt will be made to obtain end of study ABPM assessments prior to their discontinuation of treatment or initiation of changes to concomitant antihypertensive medications or prohibited treatments for diabetes or weight loss. Missing data imputation methods and sensitivity analyses are discussed in each of the endpoint analysis section.

To retain as much observed data as possible, the imputation of missing data will proceed after unscheduled visits have been mapped to analysis visits, if applicable. Refer to Section 7.1.5 for handling multiple observations and unscheduled visits.

7.2 Efficacy Analyses

7.2.1 Primary Efficacy Analysis

The primary efficacy endpoint of change in mean SBP obtained from 24-hr ABPM from baseline to Week 8 (or imputed Week 8 values for early termination subjects) will be evaluated on the PP population. An analysis of covariance (ANCOVA) model will be used to evaluate between-group differences in changes from baseline (top-dose VI-0521 vs. placebo and top-dose VI-0521 vs. phentermine) in 24-hr mean SBP. Factors included in the model are

treatment (VI 0521, phentermine, and placebo), sex (male and female), age (< 50; ≥ 50 years), and hypertensive status (no medical diagnosis of or treatment for hypertension; medical diagnosis of hypertension treated with 0-2 antihypertensive agents; or medical diagnosis of hypertension treated with 3 or more antihypertensive agents). Baseline values of 24-hr mean SBP will be adjusted in the model as a covariate. Adjusted means (LS Mean ± standard error) with associated two-sided 95% confidence intervals for the between-treatment comparisons and for the changes from baseline will be reported.

If the upper bound of the two-sided 95% confidence interval for the between-treatment group difference (VI-0521 minus placebo or phentermine) in change from baseline in 24-hr mean SBP is less than 3 mmHg, success for a non-inferiority test will be claimed and the null hypothesis will be rejected. If the upper bound of the two-sided 95% confidence interval is less than 0 mmHg, i.e., with a p-value less than 0.05 significance level, superiority will be claimed.

The estimand, estimator, and estimate of this primary endpoint are defined as follows:

Estimand	Population	Per Protocol
	Endpoint	Changes from Baseline in mean SBP obtained from 24-hr ABPM at Week 8
	How to account for intercurrent events	The treatment policy strategy will be followed, whereby the observed value (if not missing) for the endpoint of interest will be used for analysis.
	Population-level summary	The between-treatment difference in changes from baseline to Week 8 in mean SBP from 24-hr ABPM.
Estimator	Analysis	ANCOVA with treatment, stratification factors (sex, age and hypertensive status) and baseline value of 24-hr mean SBP as a covariate.
Estimates	Primary to support the estimand	Between-group comparison (effect in VI-0521 minus effect in placebo [or phentermine]): ✓ LSM for the between-group difference ✓ 95% CI of the LSM ✓ p-value
	Tributary	Within-treatment group comparison (effect at Week 8 minus the value at baseline): ✓ LSM for the within-group difference ✓ 95% CI of the LSM ✓ p-value

The following SAS programming codes will be applied:

```
PROC MIXED DATA=DATAIN;
      CLASS TREATMENT(REF='Placebo' [or 'Phentermine']) SEX AGE HYPSTATUS;
      MODEL CHG_SBP=TREATMENT SEX AGE HYPSTATUS BASE_SBP/SOLUTION DDFM=KR;
      LSMEANS TREATMENT/ALPHA=0.05 PDIFF CL;
```

```
RUN;
```

For subjects who discontinue from the study but complete Early Termination ABPM assessments, such measurements will be mapped to Week 8/End of Study or Early Termination for analysis. For subjects who have missing 24-hr SBP measurements at baseline or at Week 8 after mapping unscheduled visits, missing data will be imputed using the approach below. If the percentage of missing readings at either visit is ≤ 25% (see Section 5.4), 24-hr mean SBP values will be calculated by taking the average of non-missing and imputed measurements over the 24-hr time period. Imputed measurements will be derived as follows:

1. For any intermediate missing observations between two non-missing readings BP_1 and BP_2, missing observations will be imputed using the formula: $BP = (BP_2 - BP_1)/(t_2 - t_1) \times (t - t_1) + BP_1$; whereas t_1, t, and t_2 are the time of the measurements respectively;
2. If missing observations are at the beginning or at the end, the beginning observations will be imputed as the average of non-missing and step 1 imputed data points from 6:00 to 22:00 hours. The end observations will be imputed similarly using data points from 22:01 to 5:59 hours.

7.2.1.1 Sensitivity Analyses of Primary Endpoint

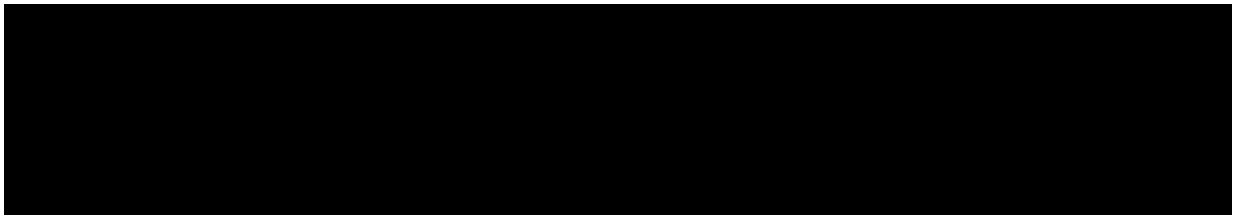
The following sensitivity analyses will be conducted on the ITT Population to evaluate the robustness of the primary analysis results and the effect of missing data for the primary endpoint:

Missing at Random (MAR) based Multiple Imputation (MI)

Step 1: If the percentage of missing 24-hr SBP readings at baseline or at Week 8 is ≤ 25%, such missing subject data will be imputed using the approach specified in Section 7.2.1. The 24-hr mean SBP value will be calculated by taking the average of non-missing and imputed measurements over the 24-hr time period.

Step 2: If the percentage of missing 24-hr SBP readings at baseline or at Week 8 is > 25%, MAR-based MI approach with Fully Conditional Specification (FCS) Regression will be applied to impute the 24-hr mean SBP value using Step 1 calculated 24-hr mean SBP values.

Example SAS programming codes are:



The ANCOVA model will be examined for each set of data. The results from the 50 sets of

data will be combined via Rubin's rule to produce estimated LSMs and 95% CIs that incorporate the uncertainty from missing data. PROC MIANALYZE will be used.

Example SAS programming codes are:

[redacted]

Two-way Tipping Point Analysis

An additional sensitivity analysis using 2-way tipping point strategy[1] will be conducted on Step 2 above to explore the influence of missing data for 1) VI-0521 versus placebo; 2) VI-0521 versus phentermine on the overall conclusion of statistical inference. In this approach, a wide spectrum of assumptions regarding the magnitude of missingness (from less conservative to more conservative) is proposed for replacing missing data. The goal is to find a 'tipping' point from among these assumptions under which the study conclusions shift from being favorable to VI-0521 to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. The tipping point can be identified when the result is no longer statistically significant.

To conduct this analysis, the PROC MI procedure will be used with additional "shift" parameters to account for missing not at random (MNAR). The shift parameters will be added using MNAR ADJUST syntax.

Example SAS codes for this MI procedure are:

SHIFTPARAM1

SHIFTPARAM2), the MI procedure outlined above will be executed. ANCOVA analysis will be run on all imputed datasets. Confidence intervals of the between-treatment comparisons estimated from the PROC MIANALYZE will be reported. The following shift parameters will be identified:

1. For non-inferiority: when the upper bound of the two-sided 95% confidence interval just crosses 3 mmHg;
2. For superiority: when the upper bound of the two-sided 95% confidence interval just crosses 0 mmHg.

Analysis of Missing Data Pattern

Number and percentage of subjects with at least 75% of non-missing 24-hr ABPM readings at baseline and Week 8 will be summarized by the following variables on the ITT Population:

- Baseline mean SBP as measured by 24-hr ABPM (< population median and ≥ population median);
- Baseline mean DBP as measured by 24-hr ABPM (< population median and ≥ population median);
- Sex (male and female);
- Age (< 50 and ≥ 50 years);
- Race (white and not white);
- Hypertensive status (no medical diagnosis of or treatment for hypertension; medical diagnosis of hypertension treated with 0-2 antihypertensive agents; or medical diagnosis of hypertension treated with 3 or more antihypertensive agents).

Number and percentage of subjects with more than two consecutive hours of missing 24-hr ABPM readings will also be summarized by visit on the ITT Population.

7.2.1.2 Supportive Analysis of Primary Endpoint

Observed Case

The primary efficacy analysis will be repeated using only the observed case data for the PP population. The data will include any unscheduled visits that have been mapped to analysis visits using the rules outline in Table 7-1. Data will not be imputed after mapping unscheduled visits. 24-hr mean SBP values will be calculated using the non-imputed data.

7.2.1.3 Subgroup Analyses of Primary Endpoint

The primary efficacy analysis will be performed for the following subgroups for the PP population:

- Sex (male and female);
- Age (< 50 and ≥ 50 years);
- Race (white and not white);
- Hypertensive status (no medical diagnosis of or treatment for hypertension; medical diagnosis of hypertension treated with 0-2 antihypertensive agents; or medical diagnosis of hypertension treated with 3 or more antihypertensive agents).

The primary efficacy analysis for the subgroup medical diagnosis (T2DM and obstructive sleep apnea) may be performed if applicable.

7.2.2 Analyses of Secondary Endpoints

Secondary endpoints including change from baseline to Week 8 in mean DBP as measured by 24-hr ABPM, mean change in SBP and DBP from baseline to Week 8 as measured in clinic will be analyzed for the PP population using a similar ANCOVA model structure as that of the primary analysis. The model will comprise of treatment, stratification factors (sex, age and hypertensive status) and baseline value of the dependent variable as a covariate. Adjusted means (LS Mean ± standard error) with associated two-sided 95% confidence intervals for the between-treatment comparisons and for the changes from baseline will be reported.

The estimand, estimator, and estimate of these secondary endpoints are defined as follows:

Estiman	Population	Per Protocol
t	Endpoint	Changes from Baseline in Variable X at Week 8

	How to account for intercurrent events	The treatment policy strategy will be followed, whereby the observed value (if not missing) for the endpoint of interest will be used for analysis.
	Population-level summary	The between-treatment difference in changes from baseline to Week 8 in Variable X.
Estimator	Analysis	ANCOVA with treatment, stratification factors (sex, age and hypertensive status) and baseline value of variable X as a covariate.
Estimates	Primary to support the estimand	Between-group comparison (effect in VI-0521 minus effect in placebo [or phentermine]): ✓ LSM for the between-group difference ✓ 95% CI of the LSM ✓ p-value
	Tributary	Within-treatment group comparison (effect at Week 8 minus the value at baseline): ✓ LSM for the within-group difference ✓ 95% CI of the LSM ✓ p-value

Similar imputation method as described in Section 7.2.1 will be carried out for missing DBP values from the 24-hr ABPM. For missing clinic SBP and DBP, data will not be imputed after mapping unscheduled visits.

Additionally, supportive analysis of the 24-hr mean DBP endpoint will be carried out similarly as described in Section 7.2.1.2. Supportive analysis of the clinical SBP and DBP endpoint will be performed using the observed case data for the ITT population. Extra sensitivity analyses similar to the primary endpoint may be conducted on the secondary endpoints if applicable.

7.2.3 Analysis of Exploratory Endpoints

Analysis of exploratory endpoints will be performed on the PP population using the observed case data.

All change from baseline exploratory endpoints will be analyzed using ANCOVA models in a similar manner to the primary and secondary endpoints. For the endpoints on percentage of subjects with a normal SBP and DBP 'dipping pattern' at Week 8, a Cochran-Mantel-Haenszel (CMH) $\chi 2$ test that is stratified by sex, age and hypertensive status will be used for analysis. Corresponding estimates of the common Mantel-Haenszel relative risk will be provided along with 95% confidence intervals (CIs). For the endpoints on percentage of subjects meeting the BP or heart rate thresholds, descriptive summary will be provided.

Example SAS codes for CMH test are:

[redacted]

No sensitivity analysis is planned for the exploratory endpoints.

In addition, all 24-hr ABPM measurements including blood pressure and heart rate that are summarized in the endpoints will be presented in a listing.

7.2.4 Pharmacokinetic Analyses

PK blood samples will be collected at the end of the study and will be used to obtain the PK profile of phentermine and topiramate levels. The concentration data will be summarized descriptively by treatment group.

7.3 Safety Analyses

All safety analyses will be performed on the Safety population.

7.3.1 Adverse Events

Adverse events (AEs) are defined as any untoward medical occurrences in subjects administered the study treatment, whether or not they have a causal relationship to the treatment. All reported terms (investigator descriptions) for AEs will be coded using the most recent version of the MedDRA. TEAEs are defined as any AEs that occurred or worsened after the first randomized study medication; regardless of on-treatment or off-treatment periods. All TEAEs will be summarized with frequencies and percentages of subjects by treatment group, system organ class (SOC), and preferred term (PT). The frequencies and percentage of subjects with any AE across all SOCs will be summarized by treatment group. The AEs occurring prior to receiving the first randomized dose are defined as pre-treatment AEs and will be listed only.

TEAEs leading to discontinuation of study drug, TEAEs related to study drug, serious TEAEs, and TEAEs by maximum severity will be summarized and listed. Deaths will be listed if any. An overall summary of the above categories by treatment group will also be provided. All AEs leading to discontinuation from study, serious AEs, and death will be provided in listings.

TEAEs of special interest including AEs that require initiation or modification of antihypertensive therapy will be summarized separately, if applicable.

7.3.2 Clinical Laboratory Evaluations

All hematology, fasting blood chemistry, lipid panel, urinalysis and other lab results will be listed, including scheduled and unscheduled/repeat measurements (if any). Laboratory

assessments that are outside of normal ranges and/or with potential clinical significance will be considered an abnormal value and flagged in the listings.

Baseline values, values at post-baseline visits, and change from baseline values will be summarized descriptively for all laboratory parameters with numerical measures by treatment. Additionally, shift tables will be generated to summarize the normal and abnormal (abnormal high and abnormal low) status change from baseline to post-baseline visits. The frequency and percentage of subjects with laboratory results above or below the normal range and threshold limits at each scheduled assessment or any time during the treatment will be summarized by treatment group. All laboratory measurements that are collected from unscheduled visits will be mapped according to the visit window defined in Section 7.1.5. Data from any unscheduled visits that are not be able to mapped to a scheduled visit will not be summarized in the by-visit descriptive tables, but will be included in the assessment when summarizing the worst case scenario, e.g., abnormality status.

Laboratory tests are shown in the table below.

<table>
<tr><th>Hematology</th><th>Fasting blood full chemistry</th><th>Pregnancy Testing</th></tr>
<tr><td rowspan="15">• hemoglobin
• hematocrit
• red blood cell count
• total white blood cell count
• white blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
• platelet count</td><td rowspan="15">• albumin
• alkaline phosphatase
• ALT
• AST
• blood urea nitrogen
• serum calcium
• serum chloride
• serum sodium
• bicarbonate
• creatinine (and estimated creatinine clearance)
• gamma-glutamyl transpeptidase (GGT)
• glucose
• lactate dehydrogenase
• serum phosphorus
• serum potassium
• total and direct bilirubin
• total protein
• uric acid
• total cholesterol
• triglycerides
• LDL-C
• HDL-C
• TSH (at screening only)
• HbA1c</td><td>• Urine pregnancy test (WOCBP)</td></tr>
<tr><td>Urinalysis</td></tr>
<tr><td>• midstream urinalysis with reflex microscopic evaluation</td></tr>
<tr><td>Urine Drug Screen (Screening Only)</td></tr>
<tr><td>• cannabinoids
• amphetamines
• cocaine
• barbiturates
• benzodiazepine
• opiates</td></tr>
<tr><td>Serology (Screening only)</td></tr>
<tr><td>• HBsAg
• HCV
• HIV</td></tr>
<tr><td>Urine Cotinine (Screening Only)</td></tr>
<tr><td>PK sample (End of Study Only)</td></tr>
<tr><td>• Phentermine
• Topiramate</td></tr>
<tr><td colspan="3">Limited chemistry panel: sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose.</td></tr>
</table>

7.3.3 Vital Signs

Baseline values, values at post-baseline visits, and change from baseline values will be summarized descriptively by treatment group and visit for the Safety Population. Vital signs parameters include systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, temperature. For blood pressure, the average of three successive readings will be used for summary. All vital signs data will be presented in a listing.

7.3.4 Physical Examination

Physical examination will be done at Screening and Week 8/End of Study or Early Termination visits. The results will be provided in a listing. Abnormal physical exam findings will be summarized descriptively by treatment group, if applicable.

7.3.5 Electrocardiogram Findings

ECG will be performed at Screening and Week 8 or early termination visits. ECGs will be evaluated for arrhythmias, conduction disturbances, or other clinically relevant changes during the study period. Changes from baseline of the ECG will be summarized descriptively by treatment group at each visit for heart rate, RR interval, PR interval, QRS interval and QT interval. The number of subjects with clinically significant ECG abnormalities will also be summarized by treatment group and visit. All ECG data will be included in the listing.

7.3.6 Blood pressure and T2DM

Requirement for rescue therapy for blood pressure and T2DM, if any, will be compared across treatment groups.

8 POWER AND SAMPLE SIZE

Approximately 555 subjects (185 per group) will be randomized to top-dose VI-0521, phentermine 30 mg, or placebo. Assuming a standard deviation of 10 mmHg for change in 24-hr mean SBP as measured by ABPM, the intended sample size of 185 subjects per treatment group will provide 80% power to detect superiority of VI-0521 to comparator treatments (placebo or phentermine) if the comparator subtracted change in mean SBP has a value of less than -3.0 mmHg, and will provide 80% power to demonstrate non-inferiority based on a non-inferiority margin of 3 mmHg if the comparator subtracted change in mean SBP is less than 0.0 mmHg. The above-mentioned calculations were based on two-sample equal variance t-test at 2-sided α=0.05 for demonstrating superiority and at 1-sided α=0.025 for demonstrating non-inferiority. This sample size estimate also accounts for a 5% drop-out rate over the course of the study.

9 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS® version 9.4 (or later).

10 REFERENCE

1. Yuan, Yang. "Sensitivity analysis in multiple imputation for missing data." *Proceedings of the SAS Global Forum 2014 Conference:[http://support. sas. com/resources/papers/proceedings14/SAS270-2014. pdf]*. 2014.