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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CLINICAL PROTOCOL

Protocol No. **OB-409**

Title: **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**

Study Phase: 4

US IND No.: 68,651

Version: Original, 9 March 2021
Amendment #1, 15 October 2021

Sponsor: **VIVUS LLC**
900 East Hamilton Avenue, Suite 550
Campbell, CA 95008
Tel: (650) 934-5200

Approval Signatures:

[redacted]

CONFIDENTIAL

INVESTIGATOR AGREEMENT PAGE

VIVUS LLC

OB-409

Protocol Title: 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

Version: Amendment #1, 15 October 2021

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by the Sponsor to the study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the investigational drug and the clinical trial protocol.

I agree to conduct this clinical trial according to the attached protocol, except when mutually agreed to in writing. I also agree to conduct this clinical trial in compliance with all applicable federal, state and local regulations, International Conference on Harmonization Guidelines for Good Clinical Practice, and the Declaration of Helsinki, as well as with the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator Signature: _____

Date: _____

Printed Name: _____

Institution: _____

Address: _____

1.0 TABLE OF CONTENTS

LIST OF TABLES

2.0 PROTOCOL SYNOPSIS

Title of Clinical Trial:	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
Sponsor:	VIVUS LLC (VIVUS)
Phase of Development:	4
Trial Rationale:	Qsymia® (known as VI-0521 in investigational studies) has been approved in the US since 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese) and 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus (T2DM), or dyslipidemia. Clinical data from the VI-0521 phase 2 and 3 studies indicate that VI-0521 is associated with a clinically meaningful decrease in blood pressure in normotensive and hypertensive subjects. Blood pressure changes reached their respective peaks within 4-8 weeks of treatment initiation and remained stable for up to one year. A large body of evidence indicates that blood pressure measured in an ambulatory blood pressure monitoring (ABPM) setting throughout the day has predictive value for major adverse cardiovascular events (MACE) over and above measurements obtained in-clinic. Although blood pressure measurements obtained in-clinic have been utilized in clinical trials demonstrating improved blood pressure control as well as improved outcomes, ABPM can offer a broader assessment of blood pressure responses. Given that blood pressure data collected to date for VI-0521 has been obtained only at clinic visits, assessment of changes in ambulatory blood pressure over a 24-hr period could provide additional insight into the potential implications of this treatment on the risk for MACE. Such blood pressure issues are particularly relevant given the common association of hypertension and borderline blood pressures in overweight and obese patients as well as the improvements seen in blood pressure with weight loss. The effects of VI-0521 would be best placed in the context of comparison to placebo, and to phentermine, which in addition to being a component of VI-0521, is also commonly used alone for the short-term treatment of obesity.
Trial Objectives:	The objective of this study is to evaluate the effect of VI-0521 on blood pressure as measured by 24-hr ABPM, compared to both placebo and an active control (phentermine 30 mg).
Trial Design:	This randomized, double-blind, placebo and active comparator-controlled study will be conducted at about 35 sites in the US.

	Approximately 555 subjects will be randomized, stratified by gender, age, and hypertensive status, to daily treatment with top-dose VI-0521 (phentermine and topiramate extended-release capsules 15 mg/92 mg), phentermine 30 mg, or placebo (185 subjects per group). Subjects will undergo a four-week titration period with dose increases until the randomized dose is reached. 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 (2-day outpatient visit), Week 4, and Week 8/end of study (2-day outpatient visit). The 24-hr ABPM data will be read and analyzed in a blinded manner by a central reader, using validated software.
Study Population:	Key Inclusion Criteria (see Section 8.1 for a complete list): • Overweight or obese adult males and females 18-75 years of age with a BMI ≥ 27 kg/m^2; • Medical diagnosis of at least 1 weight-related comorbidity (i.e., hypertension, dyslipidemia, type 2 diabetes mellitus or prediabetes, or obstructive sleep apnea).
Study Population:	Key exclusions include (see Section 8.2 for a complete list): • Screening blood pressure of > 140/90 mmHg; • Type 1 diabetes; type 2 diabetes mellitus treated with insulin, sulfonylureas (SFUs), GLP-1 receptor agonists, SGLT inhibitors; or not on stable diabetic medications for at least 3 months prior to randomization; • Clinically significant cardiac, hepatic, renal, pulmonary, or thyroid disease; • History of bipolar disorder, psychosis, greater than one lifetime episode of major depressive disorder, or presence or history of suicidal behavior or suicidal ideation with intent to act; • History of glaucoma; • Night shift workers; • Obesity of known genetic or endocrine origin; recent history of weight instability, or recent participation in a formal weight loss program within 3 months prior to screening; and • Smoking cessation within 3 months prior to screening.

Primary Endpoint Evaluation:	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.
Secondary Efficacy 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.
Exploratory Endpoints:	The exploratory endpoints of the study are: • Mean hourly change in SBP and DBP from baseline to Week 8; • 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; o 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 DBP during the same 24-hr recording. o DBP dipping is calculated as: 100 x [(mean daytime DBP – mean nighttime DBP)/ mean daytime DBP] For assessment of daytime and nighttime blood pressure, "night" will be defined as the mean of all systolic and diastolic blood pressure values recorded between 24:00 and 05:00 (inclusive) and "day" will be defined as the mean of all systolic and diastolic blood pressure values recorded between 07:30 and 21:30 (inclusive); • 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; • Mean percent change in body weight from baseline to Week 8.
Safety Evaluation:	Safety will be evaluated by analyses of adverse events, changes in laboratory parameters, changes in ECG, physical exam findings, vital signs, and requirement for rescue therapy for blood pressure and T2DM.

Statistical Considerations	All analyses will be performed on the intent-to-treat (ITT) population. For the primary endpoint, and all other endpoints evaluating continuous variables, an analysis of covariance (ANCOVA) model will be used to evaluate between group differences in changes from baseline (top-dose VI-0521 vs. placebo, top-dose VI-0521 vs. phentermine 30 mg, and phentermine 30 mg vs. placebo) in mean 24-hr SBP. Factors included in the model are treatment (VI-0521, phentermine, and placebo), gender (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). Baseline values of the dependent variable will be adjusted in the model as a covariate. Multiple imputation method will be applied to impute missing Week 8 measurements. 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. To claim success for a non-inferiority test, the upper bound of the two-sided 95% confidence interval for the between-treatment group difference (VI-0521 minus placebo or phentermine) in mean change from baseline in 24-hr SBP should be less than 3 mmHg. If the upper bound of the two-sided 95% confidence interval is less than 0 mmHg (i.e., p-value less than 0.05 significance level), superiority will be claimed. 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 top-dose VI-0521 and placebo for non-inferiority, (2) the comparison between top-dose VI-0521 and placebo for superiority, (3) the comparison between top-dose VI-0521 and phentermine for non-inferiority, and (4) the comparison between top-dose VI-0521 and phentermine for superiority. The comparison between phentermine and placebo will be for assay sensitivity and will not be included in the hierarchical testing procedure. If the superiority of top-dose VI-0521 versus phentermine is achieved for the primary endpoint, the same testing order will be applied in the same manner 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 will the subsequent hypothesis tests will be evaluated; otherwise, the subsequent hypothesis tests will be considered exploratory.

	Subgroup ABPM analyses will be performed on subjects within each baseline stratum for hypertensive status. All analyses will be described in further detail in the statistical analysis plan (SAP).
Sample Size Determination:	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 mean 24-hr 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 alpha=0.05 for demonstrating superiority and at 1-sided alpha=0.025 for demonstrating non-inferiority. This sample size estimate also accounts for a 5% drop-out rate over the course of the study.

3.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
ABPM	Ambulatory blood pressure monitoring
AE	Adverse event
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AST	Aspartate transaminase
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CFR	Code of Federal Regulations
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRF	Case report form
DBP	Diastolic blood pressure
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transpeptidase
GLP-1	Glucagon-like peptide-1
HbA_{1c}	Hemoglobin A_{1c}
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
hr	Hour
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat
LDL-C	Low-density lipoprotein cholesterol

Abbreviation or Term	Definition/Explanation
MACE	Major adverse cardiovascular events
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities
mmHg	millimeters of mercury
NYHA	New York Heart Association
OTC	Over-the-counter
PHEN	Phentermine
PK	Pharmacokinetics
QD	Once per day
RTSM	Randomization and Trial Supply Management
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SGLT	Sodium-glucose cotransporter
SFU	Sulfonylurea
TPM	Topiramate
TSH	Thyroid-stimulating hormone
T2DM	Type 2 diabetes mellitus
ULN	Upper limit of normal
USA	United States of America
WOCBP	Women of Childbearing Potential

4.0 BACKGROUND

4.1 VI-0521

Qsymia® (known as VI-0521 in investigational studies) has been approved in the US since 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese) and 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia.

VI-0521 is a combination product for oral administration that contains VIVUS' proprietary formulations of immediate-release phentermine hydrochloride beads and extended-release topiramate beads in a hard gelatin capsule.

The clinical development program of VI-0521 for the treatment of obesity enrolled more than 5,000 subjects in multiple studies, including two large pivotal studies in which over 3,500 subjects were treated for 1 year, and an extension study in which more than 600 subjects were treated for up to 2 years.[1] Data from these pivotal studies demonstrated that Qsymia® produces significant weight loss averaging approximately 10% at one year in conjunction with improvements in obesity-related co-morbidities such as hypertension, diabetes, and dyslipidemia.[2,3]

Several of the most commonly observed adverse events, notably paresthesia, dry mouth, dysgeusia, and insomnia, are well known and characterized side effects of one or the other individual components and do not represent the new onset of side effects arising from the combined pharmacology of the two component drugs. There was no evidence of any new or unexpected safety issues with Qsymia® relative to phentermine or topiramate monotherapy.

Phentermine, as a sympathomimetic agent, has been a subject of concern for possible cardiovascular adverse reactions such as tachycardia or elevation of blood pressure. Although mechanistically, these effects could be caused by an imbalance of cardiovascular autonomic function due to increased sympathetic nerve tone, it is likely that the selective release of norepinephrine within the hypothalamus with little or no dopamine or 5-hydroxytryptamine activity provides a rational basis for it having minimal cardiovascular effects at therapeutic doses.[4] In a clinical trial evaluating multiple dose levels of phentermine, topiramate, and combinations of these agents, phentermine given at daily doses of 7.5 mg and 15 mg for 6 months produced modest increases in heart rate compared to placebo, but no increases in systolic or diastolic blood pressure.[5] When phentermine was given in combination with topiramate, increases in heart rate were still observed at the top dose level, but clinically meaningful decreases in both systolic and diastolic blood pressure (BP) compared to placebo were achieved.[2,3,5,6]

4.2 Cardiovascular Risk and Blood Pressure Changes

The association between blood pressure and Major Adverse Cardiovascular Events (MACE) has been extensively evaluated, and it is now recognized that in adults of middle age or older, increased blood pressure is associated with an increased risk for MACE.[7,8] This association, along with the benefits of blood pressure-lowering agents for reducing the risk of these events has been acknowledged in FDA guidance documents.[9] Additionally, evidence indicating that blood pressure measured in an ambulatory setting throughout the day has predictive value for

MACE over and above spot measurements obtained in clinic has also been assembled.[10] Given that blood pressure data collected to date for VI-0521 has been obtained only at clinic visits, typically in the morning, assessment of changes in ambulatory blood pressure over a 24-hr period could provide a useful insight to better understand potential implications of this treatment on the risk for MACE.

5.0 TRIAL OBJECTIVES

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

6.0 TRIAL 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 gender (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).

Subjects will undergo a four-week titration period with weekly dose increases until the randomized dose is reached (Section 9.4.1).

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 (2-day outpatient visit), Week 4, and Week 8/end of study (2-day outpatient visit). The 24-hr ABPM data will be read and analyzed in a blinded manner by a central reader, 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.

7.0 STUDY ENDPOINTS

7.1 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.

7.2 Secondary Endpoints

The secondary endpoints of the study are:

- 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.

7.3 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]
- 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;
- Mean percent change in body weight from baseline to Week 8.

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

7.4 Safety Evaluation

Safety will be evaluated by analysis of adverse events, changes in laboratory parameters, changes in ECG, physical exam findings, vital signs, and requirement for rescue therapy for blood pressure and T2DM.

8.0 SELECTION AND WITHDRAWAL OF SUBJECTS

The following eligibility criteria are intended to select subjects for whom protocol treatment is considered appropriate and does not subject participants to undue medical risk. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject.

8.1 Inclusion Criteria

To be eligible for enrollment into this study, subjects must meet all of the following criteria at Screening (unless otherwise specified):

1. Overweight or obese adult males and females 18-75 years of age with a BMI $\geq$ 27 kg/m^2;
2. Medical diagnosis of at least 1 weight-related comorbidity (i.e., hypertension, dyslipidemia, type 2 diabetes mellitus or prediabetes, or obstructive sleep apnea);
3. Must be ambulatory, willing, and able to wear ABPM monitor apparatus for 24 hours during two study measuring visits, at Baseline and Week 8/end of study or early termination;
4. Screening laboratory values that are within the ranges specified below:

    a. Bicarbonate $\geq$ LLN
    b. AST and ALT < 3 x ULN
    c. HbA1c $\leq$ 7.5%
    d. TSH $\leq$ 1.5 x ULN
    e. Triglyceride $\leq$ 400 mg/dL
    f. Creatinine clearance $\geq$ 60 mL/minute (MDRD)

5. Females of childbearing potential must be using adequate contraception, defined as double barrier methods, stable hormonal contraception plus single barrier method, or previously documented bilateral tubal ligation. Women are considered of childbearing potential unless they are $\geq$ 50 years of age with spontaneous amenorrhea for at least 12 months or have had a hysterectomy and/or bilateral oophorectomy;
6. Provide written informed consent; and
7. Willing and able to comply with scheduled study visits, treatment plan, laboratory tests, and other study procedures.

8.2 Exclusion Criteria

To be eligible for enrollment into this study, subjects must not meet any of the following criteria at screening (unless otherwise specified):

1. Screening blood pressure of > 140/90 mmHg;

2. Known allergy or hypersensitivity to phentermine or topiramate, any prior use of a combination of phentermine and topiramate for weight loss or use of phentermine or topiramate for any indication within the past 3 months;
3. Weight gain or loss of greater than 5 kg, use of a very low-calorie diet, or participation in a formal weight loss program (investigational or otherwise) within the past 3 months (this includes: Weight Watchers and related dietary/lifestyle intervention programs; prepared food programs; prescribed or over-the-counter weight loss medications; dietary supplement or herbal preparations, teas, or tinctures intended for weight loss; or any medically-supervised fast or very low calorie diet);
4. Obesity of a known genetic or endocrine origin;
5. Previous bariatric surgery or other non-surgical weight loss procedure;
6. History of any eating disorders (e.g., bulimia, binge eating disorder) within the past year;
7. History or presence of a seizure disorder;
8. History of drug or alcohol abuse within the past year or positive drug test;
9. Smoking cessation within the past 3 months or intent to quit during the study;
10. Use of antihypertensive medications, antidiabetic medications, statins or other lipid lowering agents, or CPAP therapy that has not been stable for at least 3 months prior to randomization;
11. Chronic conditions/diseases associated with a reduced ability to maintain autonomic regulation such as multiple sclerosis or any known autonomic neuropathy;
12. History of glaucoma, increased intraocular pressure, or any past or present use of medications to treat increased intraocular pressure;
13. Clinical evidence of hyperthyroidism, or use of thyroid hormone treatment that has not been stable for at least 3 months prior to randomization;
14. Use of chronic systemic glucocorticoid therapy, or any other steroid hormone therapy that has not been stable for at least 3 months at the time of randomization;
15. Any history of bipolar disorder or psychosis, greater than one lifetime episode of major depressive disorder, or presence or any history of suicidal behavior or suicidal ideation with some intent to act; any use of tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), lithium, levodopa, or dopamine receptor agonists; or allowed antidepressant use that has not been stable for at least 3 months;
16. Need to perform strenuous manual labor or exercise while wearing the ABPM monitor during the 24-hr periods when those measurements are being recorded;
17. Night shift workers who routinely sleep during the daytime and whose work hours include midnight to 4:00 am, or workers who are subject to assignment to different shifts during the study;
18. Diagnosis of type 1 diabetes; type 2 diabetes mellitus with ongoing insulin, sulfonylureas (SFUs), GLP-1 receptor agonist, or SGLT inhibitor therapy;
19. Stroke, myocardial infarction, or coronary revascularization within the past 6 months;

20. Presence of cardiac pacemaker or implantable defibrillator;
21. Presence or history of clinically significant atrial fibrillation or atrial flutter, AV block > 1st degree, ventricular ectopy, or sustained ventricular tachycardia;
22. Unstable angina, congestive heart failure (NYHA Class III or IV), or known or suspected cardiac valvulopathy;
23. Presence of asthma or COPD (chronic obstructive pulmonary disease) requiring routine or rescue treatment with an adrenergic bronchodilator;
24. Any history of malignancy within the past 5 years other than surgically excised basal or squamous cell carcinoma of the skin or cervical cancer;
25. Cholelithiasis within the past 6 months;
26. Any history of nephrolithiasis;
27. Use of any investigational medication or device for any indication within a month prior to randomization;
28. COVID-19 vaccination or treatment for severe COVID-19 infection within a month prior to randomization; or
29. Clinically significant renal, pulmonary, hepatic, psychiatric or other condition by history, physical examination or laboratory studies that, in the opinion of the investigator, would contraindicate the administration of study drugs, affect compliance, interfere with study evaluations or confound the interpretation of study results.

8.3 Discontinuation of Study Drug and Subject Withdrawal

The Sponsor reserves the right to discontinue this trial at any time. The investigator must discontinue subjects from the study should any of the following occur:

- Any medical condition or circumstance that exposes the subject to substantial risk and/or does not allow the subject to adhere to the requirements of the protocol;
- Any serious adverse event (SAE), clinically significant adverse event (AE), severe laboratory abnormality, intercurrent illness, or other medical condition in which, in the judgment of the investigator, continued participation in the study is not in the best interest of the subject;
- Pregnancy;
- Subject elects to withdraw;
- Requirement for other medical treatment that is excluded by the protocol;
- Subject is unblinded by the investigator;
- Failure of the subject to comply with protocol requirements or study related procedures; or
- Termination of the clinical trial by the Sponsor or by FDA.

Reason(s) for subject withdrawals as well as details relevant to the subject withdrawal will be documented. If a subject is withdrawn from the clinical trial prior to trial completion, the subject will undergo all end of study procedures.

9.0 TREATMENT OF SUBJECTS

9.1 Study Treatment

Eligible subjects will receive either top-dose VI-0521 (phentermine and topiramate extended-release capsules 15 mg/92 mg), phentermine 30 mg capsules, or placebo capsules for daily use. The duration of treatment will be 8 weeks, and the total duration of participation will be a total of approximately 12 weeks.

9.2 Allocation to Treatment

Subjects will be assigned to study treatment via an electronic data capture (EDC)/Randomization and Trial Supply Management (RTSM) System. 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). Randomization will be stratified by gender (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 should be counted as 2 antihypertensive agents.

Sites will be pre-stocked with study drug corresponding to each treatment group. When study subjects qualify for randomization, site personnel will contact the EDC/RTSM through a designated website and provide the requested information about the study subject. The randomization assignment will be made, and site personnel will be instructed to dispense a specific titration blister card or treatment bottle corresponding to the treatment assignment to the study subject. Additional study drug will be shipped to sites to replace those dispensed.

9.3 Breaking the Blind

Study drug must 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 should contact the study designated medical monitor. The identity of the study treatment will be obtained through the EDC/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.

Investigators are also required to ensure that any potential serious adverse events (SAEs) are reported according to the requirements outlined in Section 12.4.1 and provide a written report to VIVUS or designee within 7 days to document the reason for unblinding.

9.4 Drug Supply

Clinical supplies will be manufactured for VIVUS by [redacted] in accordance with current Good Manufacturing Practices. All clinical supplies will be labeled with information required by national regulations.

9.4.1 Formulation and Packaging

Study drug will consist of #0 elongated capsules filled with beads containing phentermine and topiramate extended-release, phentermine, or placebo. Doses specified for each treatment group will be achieved by varying the amounts of phentermine beads, topiramate beads, or placebo beads added to each capsule. All study treatments will be administered as a single capsule of medication to be taken in the morning.

Study drug will be packaged into titration blister cards (first 4 weeks) and treatment bottles (last 4 weeks). Each titration blister card will contain 4 columns of 8 capsules each. Each column on the blister card will be labeled with the week number (1 through 4) and will contain capsules with the dose specified for that week of treatment, as outlined in Table 1. Each treatment bottle will contain 35 capsules of study drug at the treatment dosages (top dose VI-0521, phentermine 30 mg, or placebo). Each blister card or bottle will be labeled with the study number, a unique kit number, storage instructions, and spaces for the subject number and initials.

Subjects will undergo a four-week titration period with dose increases as described below 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 = once per day					

9.4.2 Preparation and Dispensing

Clinical supplies provided by the Sponsor are to be dispensed only by or under the direct supervision of qualified investigators to subjects meeting the criteria for study entry and in accordance with this protocol. Assignment of study drug to study subjects will require the use of the EDC/RTSM. No other preparation of clinical supplies is required of the site staff.

9.4.3 Administration

Investigators will instruct subjects to take 1 capsule of study drug every morning with or without food. Capsules must be taken whole, and should not be broken or split apart in any manner. When dispensing titration blister cards, investigators should ensure that subjects understand that each blister card contains a 4-week supply of study drug, and that the capsules must be taken in a specific order (i.e., Week 1 before Week 2, and Week 3 before Week 4).

When dispensing study drug bottles, investigators should ensure that subjects understand that each bottle contains a 4-week supply of study drug and that each bottle contains extra capsules that should only be taken for special circumstances (e.g. capsule is accidently dropped and cannot be retrieved or subject cannot return to the end of study visit within window). Study drug will not be dispensed until the morning of Day 2 after the ABPM device is removed following the baseline 24-hr recording and data has been confirmed to be compliant.

Subjects will be instructed to withhold dosing of study drug on study visit days until after certain procedures are completed.

9.4.4 Compliance

Subject compliance with dosing of study drug will be assessed by counting capsules that are returned by subjects at each study visit. Subjects whose actual medication consumption differs from their expected capsule consumption should be queried by site personnel about reasons for not using study drug as directed, and site personnel should implement any corrective action as necessary. Trough blood samples will also be collected at study completion, and may be used to identify subjects with compliance levels that are unacceptable for inclusion in per-protocol analyses.

Study drug must be dispensed and administered according to the procedures described herein. In accordance with applicable regulatory requirements, only subjects who are enrolled in the study may receive study drug, and only authorized members of the site staff may supply or administer the study drug.

9.4.5 Drug Storage and Drug Accountability

All unused study drug must be stored in its packaging at room temperature, 15 to 25°C (59 to 77°F), in a dry, secure area. Access to drug storage areas should be limited to the investigator and designated staff involved with the study. All used and unused drug must be maintained at the study site and made available for audits by VIVUS personnel or their designee.

It should be noted that phentermine and VI-0521 are Schedule IV controlled substances. The investigator should take all appropriate measures to control access to and dispensing of study drug.

The investigator must maintain records documenting the amount, condition and date of delivery of all study drug received from the sponsor. In addition, all drug dispensed to study subjects during the course of the study must be recorded on the appropriate accountability forms. Subjects must be instructed to return all study drug (blister cards and the bottle, even if empty) in its original packaging at each study visit and sites must make an accounting of drug use by each subject. No study drug or packaging, used or unused, may be discarded. All packaging and used and unused study drug must be returned to the sponsor upon completion of the study.

9.5 Lifestyle Counseling Guidelines

All randomized subjects will receive diet and exercise counseling at the baseline visit with support and reinforcement provided at follow-up visits. Guidelines should include advice 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. On days when ABPM is attached, subjects should refrain from heavy exercise.

9.6 Concomitant Medications

9.6.1 Excluded Medications

Use of any of the following medications during participation in this study is prohibited:

- Tricyclic antidepressants, MAOIs, lithium, levodopa, and dopamine receptor agonists;
- Insulin, sulfonylureas (SFUs), GLP-1 receptor agonists, SGLT inhibitors for subjects with type 2 diabetes mellitus; or

- OTC, prescription medications, herbal agents and dietary supplements used to lose body weight.

9.6.2 Management of Blood Pressure

Concomitant medications used for management of blood pressure, must be fixed in number, dose, and frequency for the duration of the study unless specific "rescue" criteria are met for blood pressure.

Rescue criteria are defined as:

- Blood pressure ≥ 160/100 mmHg, or;
- Blood pressure ≤ 100/60 mmHg, and subjects exhibiting symptoms associated with low blood pressure, concomitant antihypertensive medications should be withdrawn or doses should be reduced.

As this study has a short (8-week) duration, and as the first post-randomization evaluation occurs after 4 weeks of treatment (half way through the study), if rescue criteria for blood pressure are met at the Week 4 visit, sites should make all reasonable efforts to keep the subject on the study, to continue taking study drug, and to have them return within 1-2 weeks for re-evaluation of their blood pressure. If rescue criteria are still met at the repeat visit, then sites should complete the final ABPM evaluation and end of study procedures. Once the final ABPM evaluation and end of study procedures have been completed, rescue therapy should be initiated, and the subject discontinued from the study.

Adverse events that require initiation or modification of antihypertensive therapy are considered events of special interest and should be clearly documented and explained to enable narratives.

9.6.3 Management of Diabetes Medication

If subjects require addition of therapy with insulin, SFUs, GLP-1 receptor agonists, or SGLT inhibitors during the study, investigators should discontinue these subjects from the study, making all reasonable attempts to collect ABPM and assessments that are scheduled to occur at study completion prior to stopping study drug and changing these concurrent therapies.

9.6.4 Documentation of Concomitant Medication Use

All concomitant medications, including OTC products and nutritional/herbal supplements, must be listed on the appropriate case report form (CRF) at study entry. Any changes in concomitant medication use during the course of the study must also be noted on the appropriate CRF.

10.0 STUDY PROCEDURES

A schedule of study activities by visit are presented in Appendix 1. For baseline and end of study ABPM visits, when possible, subjects should come in on the same day of the week to minimize within-subject variability. A detailed list of these activities is provided below.

10.1 Screening (Visit 1)

A schedule of study activities by visit is presented in Appendix 1. A detailed list of these activities is provided below.

The following activities will take place at Screening (within 4 weeks of Baseline):

- Obtain written informed consent;
- Obtain demographics (including age, gender, race, and ethnicity) and medical history;
- Assess inclusion/exclusion criteria;
- Obtain body weight and height and calculate BMI. If a subject does not meet the BMI criterion for inclusion into the study, no further screening procedures should be undertaken;
- Perform a physical examination;
- Obtain vital signs (blood pressure, heart rate, respiration rate and temperature);
- Record prior and concomitant medications;
- Obtain blood sample for chemistry (full panel), hematology, lipids, HbA1c, TSH, HIV, HIV, and HBsAg; and urine sample for cotinine, urinalysis, and onsite urine drug screen. Refer to Appendix 1 and Table 2 for a listing of specific tests;
- Perform urine pregnancy test (women of childbearing potential [WOCBP] only) and remind subject about contraception. If the subject is pregnant, no further screening procedures should be performed;
- Perform 12-lead electrocardiogram (ECG);
- Enter screened subject into EDC/RTSM; and
- Schedule the Randomization visit within 4 weeks (+3 days).

10.2 Baseline/Randomization (Visit 2, Week 0/Beginning of Titration)

The following activities will take place at Visit 2A (first day of 2-day visit):

- Assess inclusion/exclusion criteria (applicable criteria referencing the baseline visit);
- Obtain body weight;
- Obtain vital signs (blood pressure, heart rate, respiration rate and temperature);
- Record any adverse events reported or observed;
- Record any changes in concomitant medications;
- Perform a urine pregnancy test (WOCBP only) and remind subject about contraception. If the subject is pregnant, she will not qualify for the study;
- Set up 24-hr ABPM monitoring equipment, and initiate monitoring;
- Provide subject with instructions for proper handling of ABPM device and remind the subject to return to the clinic in 24 hours to complete evaluation.

The following activities will take place at Visit 2B (second day of 2-day visit):

- Record any adverse events reported or observed;
- Record any changes in concomitant medications;

- End 24-hr ABPM monitoring, disconnect devices, and upload data;
- Contact EDC/RTSM to obtain randomization assignment for subject upon verifying successful ABPM; if verification of successful ABPM cannot be made, repeat 24-hr ABPM setup as described for Visit 2A and bring subject back in 24 hours to complete evaluation;
- Dispense study drug and instruct the subject to take one capsule every morning (with or without food) in the order indicated on the blister card (Section 9.4.3) and advise on lifestyle counseling. Subject should also be instructed to withhold dosing on the morning of the next scheduled study visit; and
- Schedule the next study visit in 4 weeks (28 ± 3 days).

10.3 Week 4 (Visit 3, End of Titration)

The following activities will take place at Week 4:

- Obtain body weight;
- Obtain vital signs (blood pressure, heart rate, respiration rate and temperature);
- Record any adverse events reported or observed;
- Record any changes in concomitant medications;
- Collect blood sample for limited chemistry panel;
- Perform a urine pregnancy test (WOCBP only) and remind subject about contraception. If the subject is pregnant, she will be withdrawn from study;
- Administer the final dose of study drug from the previous visit, collect previously dispensed drug, assess treatment compliance, and perform drug accountability (do not administer study drug if subject has taken a dose prior to coming in for this visit, and instruct the subject that for the next visit, they must not take their study drug until they arrive at the clinic);
- Contact EDC/RTSM to dispense study drug and instruct the subject on the proper use of the study drug (including withholding dosing on the morning of the next scheduled visit), and advise on lifestyle counseling;
- Schedule the next study visit in 4 weeks (28 ± 3 days).

10.4 Week 8/End of Study or Early Termination (Visit 4)

The following activities will take place at Visit 4A (first day of 2-day visit):

- Obtain body weight;
- Obtain vital signs (blood pressure, heart rate, respiration rate and temperature);
- Collect PK blood sample for assessment of phentermine and topiramate levels (prior to dosing);
- Record any adverse events reported or observed;

- Record any changes in concomitant medications;
- Perform a urine pregnancy test (WOCBP only) and remind subject about contraception;
- Set up 24-hr ABPM monitoring equipment;
- Collect study drug from previous visit, assess treatment compliance, and perform drug accountability;
- Administer last daily dose of study drug, record time of dosing, then initiate ABPM monitoring; and
- Provide subject with instructions for proper handling of ABPM device and remind the subject to return to the clinic in 24 hours to complete study.

The following activities will take place at Visit 4B (second day of 2-day visit):

- Record any adverse events reported or observed (note that as described in Section 12.3 adverse events known to the investigator and occurring within 28 days after the last dose of study drug must be reported);
- Record any changes in concomitant medications;
- Perform a physical examination;
- End 24-hr ABPM monitoring, disconnect devices, and upload data upon verifying successful ABPM; if verification of successful ABPM cannot be made, repeat 24-hr ABPM setup as described for Visit 4A and bring subject back in 24 hours to complete evaluation;
- Perform 12-lead electrocardiogram (ECG);
- Obtain full blood chemistry, hematology, and urinalysis for laboratory testing;
- Obtain vital signs (blood pressure, heart rate, respiration rate and temperature); and
- Discontinue subject's study participation.

11.0 ASSESSMENTS

11.1 Weight Measurement

Subject's weight will be obtained at each study visit. Subjects should be weighed using a calibrated scale. The same scale should be used for each measurement, and measurements should be evaluated by the same site personnel at each visit, whenever possible. Subject weights should be obtained, whenever possible, under the same conditions (no shoes, clothing of similar weight) that were employed at the first (Screening) weigh-in. Subjects should be encouraged to complete their weigh-in visits in the morning.

11.2 Height and BMI

Height measurements (cm) and BMI will be determined by the site at Screening only (see BMI chart in Appendix 2). Height measurements should be made without shoes and should be recorded to the nearest centimeter.

If a subject does not meet the BMI criterion for inclusion into the study, no further screening procedures should be undertaken.

11.3 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, temperature) will be assessed at Screening, Randomization, Week 4, and Week 8/end of study or early termination. Subjects should be seated comfortably for at least 10 minutes prior to assessing vital signs. Heart rate and respiratory rate measurements should be made by counting events (heartbeats or breaths) for a period of 30 seconds and multiplying these values by 2 to obtain the rates per minute. A calibrated blood pressure monitor should be employed for blood pressure measurements. The same cuff should be used for the same subject across multiple visits when blood pressure is performed. The same person should perform all assessments for a given subject.

Clinic blood pressure for determining hypertension 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.

11.4 24-hr Ambulatory Blood Pressure Monitoring (24-hr ABPM)

At Baseline and at Week 8/end of study or early termination, 24-hr ABPM will be performed non-invasively using a validated oscillometric monitor provided by a central vendor. 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, while subjects continue normal routine activities. The monitor will be attached in the morning and removed after at least 24 hours. Data will be uploaded to a computer at the end of the recording session and prior to discharging the subject from the study visit, site staff will review the data to assure that: (1) at least 80% of the readings are valid, (2) there are at least 24 hours of data, and (3) there are no more than two consecutive hours of missing data. If any of these criteria are not satisfied, subjects will be asked to repeat the assessment for an additional 24 hours. ABPM hook up will be done by qualified staff.

The accuracy of ABPM reading is highly dependent upon proper use of the equipment. Using a correct cuff is vital to the accuracy of monitoring data. Site staff must ensure at the Screening visit that the ABPM cuff size used is appropriate for the patient's upper arm circumference, and the same size cuff must be used for both the screening, and end of study visits. The cuff will be placed on the subject's non-dominant upper arm. Fresh batteries should be installed prior to hooking up the ABPM monitor.

With reference to the ABPM operating manuals, clinical site personnel will ensure appropriate hook-up and safe use of the monitor by explaining the following instructions to the subjects, including but not limited to:

- The importance of proper cuff fitting and data quality;
- Wear loose fitting clothes on days when ABPM is performed;
- Keep their arm steady during measurement;
- Keep the cuff at heart level during measurement;

- Maintain normal activities between measurements;
- Avoid swimming, showering, or bathing during monitoring;
- The frequency of inflation and deflation as per protocol;
- Avoid strenuous activities, or operating heavy equipment or power tools, as vibrations may functionally disrupt the monitor;
- Keep the monitor attached at night; and
- Place the monitor under a pillow or on the bed at night, making sure the hose connecting the cuff to the monitor is not kinked.

Diurnal and nocturnal blood pressure variation will be assessed during the study; therefore subjects should be reminded to go to bed and rise about the same time during the study.

A central 24-hr ABPM reading laboratory will perform data collection, reading, quality evaluation and data analyses. Software for the ABPM device will use default settings for exclusion of outliers (including failed inflations) from the overall averaged statistics on the final ABPM report for each recording. Additionally, readings that are not acceptable will contain error codes associated with failed inflations specifying what happened (i.e., too much movement, kinked hose, etc.). Data transfers will include all data, including data excluded from analyses for errors. Excluded data will be labeled with error codes.

All readers will be blinded to treatment. Quality control will be monitored by the central reader.

11.5 Laboratory Tests

Safety laboratory tests will be performed at a licensed, certified central testing laboratory approved by the Sponsor. Testing will be conducted according to the schedule of study activities (Appendix 1). Clinical laboratory tests will be used to determine eligibility for study participation, for safety monitoring and to determine which subjects may progress to later phases of the study.

Subjects should be fasting for at least 8 hours prior to obtaining blood samples for analyses.

For WOCBP, a urine pregnancy test will be performed locally at in-clinic study visit per Appendix 1.

A blood sample for trough pharmacokinetic evaluations will be collected at the end of study to assess treatment compliance.

Table 2 summarizes the clinical laboratory testing for the study.

Table 2 Clinical Laboratory Tests

Hematology	**Blood Chemistry (Full)**	**Urine Pregnancy Test** (WOCBP; Done Onsite)
• hemoglobin • hematocrit • red blood cell count • total white blood cell count • white blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) • platelet count	• albumin • alkaline phosphatase • ALT • AST • GGT • blood urea nitrogen • serum calcium • serum chloride • serum sodium • bicarbonate • creatinine (and estimated creatinine clearance) • glucose • lactate dehydrogenase • serum phosphorus • serum potassium • total and direct bilirubin • total protein • uric acid	**Urinalysis** • midstream urinalysis with reflex microscopic evaluation
Blood Chemistry (Limited) • blood urea nitrogen • serum chloride • serum sodium • bicarbonate • creatinine (and estimated creatinine clearance) • glucose • serum potassium		**Urine Drug Screen (Screening Only; Done Onsite)** • cannabinoids • amphetamines • cocaine • barbiturates • benzodiazepine • opiates
Lipid Panel • total cholesterol • triglycerides • LDL-C • HDL-C	**Glycemic Testing** • HbA1c	**Serology (Screening only)** • HBsAg • HCV • HIV **Other (Screening Only)** • thyroid stimulating hormone **Urine Cotinine (Screening Only)** **PK Sample (End of Study Only)** • Phentermine • Topiramate

11.6 Physical Examination

A complete physical examination will be performed at screening, and end of study or early termination visits. The physical examination will consist of an examination of the following systems: general appearance, skin, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart (including any auscultated cardiac murmurs), abdomen, extremities, and neurologic.

11.7 Electrocardiograms

Twelve-lead ECG assessments will be performed at screening, and end of study or early termination visits. ECGs will be evaluated for clinically significant abnormalities that would prevent entry into the study, and for arrhythmias, conduction disturbances, or other clinically relevant changes between randomization and each of the subsequent evaluations. Parameters including heart rate, R-R, P-R, QT intervals, and QRS duration will be recorded.

12.0 ADVERSE EVENT REPORTING

12.1 Adverse Events

Adverse events are defined as any untoward medical occurrences in subjects administered study treatment, whether or not they have a causal relationship to the treatment. All observed or volunteered adverse events regardless of suspected causal relationship to the investigational product must be reported as described in the following sections.

Investigators must pursue and obtain information adequate to describe adverse events, their severity, relationship to study treatment, and their outcomes. For adverse events with a causal relationship to the investigational product, follow-up by the investigator is required for up to 28 calendar days after the last dose of study drug or until the events or their sequelae resolve or stabilize at a level acceptable to the investigator, and VIVUS concurs with that assessment. Investigators must also assess whether any adverse events meet the criteria for classification as an SAE (see Section 12.1.4), which requires immediate notification to VIVUS or its designated representative.

12.1.1 Severity Assessment

Investigators will assess the severity of all adverse events using the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of each adverse event. For purposes of consistency, these intensity grades are defined as follows:

- MILD: Does not interfere with the subject's usual function;
- MODERATE: Interferes to some extent with the subject's usual function; or
- SEVERE: Interferes significantly with the subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's daily function) but would not be classified as serious unless it met one of the criteria for SAEs (see Section 12.1.4).

12.1.2 Causality Assessment

Investigators are required to provide an assessment of causality, for all adverse events (serious and non-serious) observed during this study. This assessment will provide a determination of whether, in the investigator's judgment, there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. For this assessment, investigators must categorize the causality as either "related" or "not related." For an adverse event to be considered "related" to the study treatment, there should be evidence that the event follows a reasonable temporal sequence from the administration of study treatment, or that the event follows a known response pattern to the drug. Causality would be further confirmed by improvement in an adverse event upon stopping the study treatment, and reappearance of the event upon rechallenge.

12.1.3 Abnormal Test Findings

Merely repeating an abnormal test, in the absence of any of the conditions described below, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms;
- Test result requires additional diagnostic testing or medical/surgical intervention;
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or
- Test result is considered by the investigator or Sponsor to represent a clinically significant finding.

12.1.4 Serious Adverse Events or Serious Suspected Adverse Reactions

As defined in the Code of Federal Regulations (21 CFR 312.32), an adverse event or suspected adverse drug reaction is considered "serious" if, in the view of either the investigator or the Sponsor, it results in any of the following outcomes:

- Death;
- A life-threatening adverse event (Note: An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator or Sponsor, its occurrence places the subject in immediate risk of death. It does not include an adverse event or suspected adverse event that, had it occurred in more severe form, might have caused death. The determination of whether an adverse event is life-threatening can be based on the opinion of either the investigator or Sponsor.);
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions; or
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

For this study, blood pressure values that exceed 180 mmHg (systolic) or 110 mmHg (diastolic) should be reported as serious adverse events.

If either the Sponsor or investigator believes that the event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.1.5 Definition of Hospitalization

Adverse events reported from clinical trials that result in hospitalization or prolong an existing hospitalization are considered serious. Any initial admission (even if less than 24 hours) to a healthcare facility meets this definition.

Outpatient ambulatory surgical procedures (same-day surgeries) and routine emergency room treatment do not qualify as hospitalizations. Additionally, hospitalization in the absence of a precipitating clinical adverse event is not in itself an SAE. Examples include, but are not limited to, the following:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment abnormality);
- Administrative admission (e.g., for yearly physical examination);
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery); and
- Pre-planned treatments or surgical procedures should be noted in the baseline documentation for the entire protocol and/or for the individual subject.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse event, and the resulting appendectomy should be recorded as treatment of the adverse event.

12.2 Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject. In addition, study subjects should be questioned by site personnel about adverse events at each scheduled in-clinic and scheduled telephone study visit using a standard non-leading question, such as "*Have you experienced anything new or different since your previous study visit?*"

Certain adverse events require prompt and specific action by the investigator in any clinical trial.

12.3 Reporting Period

The reporting period for adverse events begins when the subject provides written informed consent and extends until 28 calendar days after the last dose of the investigational product is administered. All adverse events that occur during this period and are known to the investigator must be reported according to the requirements outlined in Section 12.4.

12.4 Reporting Requirements

All adverse events will be reported on the adverse event page of the CRF. In addition, serious adverse events information must also be reported on a designated section of the AE Form. For cases in which the same data are collected, the forms must be completed in a consistent manner. For example, the same adverse event term should be used on both forms. Adverse events should

be reported using concise medical terminology on the CRFs as well as on the form for collection of serious adverse events or suspected adverse reactions information.

12.4.1 Serious Adverse Event Reporting Requirements

If an SAE occurs, VIVUS or designee is to be notified within 1 business day of awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to VIVUS or designee must be made immediately, irrespective of the extent of available adverse event information. This timeframe also applies to additional new information (follow-up) on previously reported SAEs.

In the event that the investigator does not become aware of the occurrence of an SAE immediately (e.g., if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 1 business day after learning of it and document the time of his/her first awareness of the adverse event.

For all SAEs, the investigator is obligated to pursue and provide information to VIVUS or designee in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by VIVUS or designee to obtain specific additional follow-up information in an expedited fashion. This information may be more detailed than that captured on the adverse event CRF. In general, this will include a description of the SAE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to VIVUS or designee.

12.4.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events meeting the reporting requirements described above (Section 12.4) are to be reported on the Adverse Event CRFs, which are to be submitted to VIVUS or designee.

12.4.3 Pregnancy

If any study subject becomes or is found to be pregnant while receiving the investigational product, the investigator must immediately discontinue study treatment and report the pregnancy to VIVUS or designee within 1 business day of learning of the pregnancy.

The investigator will follow the pregnancy until completion or until pregnancy termination (i.e., elective pregnancy termination) and then notify VIVUS or designee of the outcome. The investigator will provide this information as a follow-up to the initial pregnancy report.

For reported pregnancies that result in a live birth, the status of the newborn should be assessed at the time of birth. The status of an aborted fetus should be assessed by gross visual inspection, unless pre-abortion test findings are suggestive of a congenital anomaly.

If pregnancy outcomes meet the criteria for classification as SAEs (i.e., stillbirth, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Similarly, any pregnancy outcomes that are considered to be adverse events should be reported as such on the appropriate CRF. However, pregnancy in itself need not be reported as an adverse event if there is no associated adverse outcome.

For reporting purposes, ectopic pregnancies should be reported as SAEs, but because the fetus is not potentially viable, they need not be reported as a pregnancy.

13.0 STATISTICAL CONSIDERATIONS

13.1 Statistical Analysis and Methods

All analyses will be performed on the intent-to-treat (ITT) population (all randomized subjects who received at least one dose of study drug). Analyses of a per-protocol population may also be utilized to confirm the presence or absence of a pressor signal. Subject demographic data and baseline characteristics will be summarized for all subjects enrolled in the study.

Detailed methodology for summary and statistical analyses of the data collected in this clinical trial will be documented in a prospectively developed Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment. Additional statistical analyses other than those described in this section may be performed if deemed appropriate and included in the plan.

13.1.1 Analysis of Primary Endpoint

The primary endpoint of the study is change from baseline to Week 8 (or imputed Week 8 values for early termination subjects) in mean SBP obtained from 24-hr ABPM. The primary hypothesis is that VI-0521 does not have deleterious effects on SBP as measured by mean 24-hr ABPM in overweight or obese subjects. A deleterious effect of study treatment may be ruled out if the upper bound of the two-sided 95% confidence interval for the between-treatment comparison with placebo is less than 3 mmHg. This study will also attempt to demonstrate differences between the top-dose of VI-0521 and phentermine 30 mg with respect to changes from baseline to Week 8 in mean 24-hr SBP.

The analysis of the primary endpoint will be based on the intent-to-treat (ITT) 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, top-dose VI-0521 vs. phentermine, and phentermine vs. placebo) in mean 24-hr SBP. Factors included in the model are treatment (VI 0521, phentermine, and placebo), gender (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 the dependent variable will be adjusted in the model as a covariate. Multiple imputation method will be applied to impute missing Week 8 measurements. 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.

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

Subgroup ABPM analyses will be performed on subjects within each baseline stratum for hypertensive status. Details will be described in the SAP.

13.1.2 Method for Prevention and Treatment of Missing Values

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.

Several sensitivity analyses will be considered to explore any deviations from statistical assumptions and the impact of missing data on the conclusion of the primary analysis. The details of the sensitivity analyses will be included in the SAP.

13.1.3 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed using the same methods as described above for the primary endpoints.

The secondary endpoints will be:

- 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.

13.1.4 Multiplicity Adjustment to Control Family-wise Type 1 Error Rate

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 top-dose VI-0521 and placebo for non-inferiority, (2) the comparison between top-dose VI-0521 and placebo for superiority, (3) the comparison between top-dose VI-0521 and phentermine for non-inferiority, and (4) the comparison between top-dose VI-0521 and phentermine for superiority. The comparison between phentermine and placebo will be for assay sensitivity and will not be included in the hierarchical testing procedure.

If the superiority of top-dose VI-0521 versus phentermine is achieved for the primary endpoint, the same testing order will be applied in the same manner 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 will the subsequent hypothesis tests will be evaluated; otherwise, the subsequent hypothesis tests will be considered exploratory.

13.1.5 Analysis of Exploratory Endpoints

Exploratory endpoints that are continuous measurements will be analyzed using the same methods as described above for the primary endpoint. For categorical outcomes, differences between treatments will be evaluated using a non-parametric method. Details will be provided in the SAP.

The exploratory endpoints will be the difference between treatment groups (top-dose VI-0521 vs. placebo, top-dose VI-0521 vs. phentermine, and phentermine vs. placebo) in the change from baseline in:

- 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 nighttime 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 nighttime 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].
- 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;
- Mean percent change in body weight from baseline to Week 8.

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

13.1.6 Safety Analyses

Safety analyses will be performed on the ITT population (all randomized subjects who received at least one dose of study drug).

The incidence of adverse events will be summarized. The summary will be repeated for events considered related to study drug and for any serious adverse events. Laboratory results and vital signs will be summarized by timepoint and change from baseline. Changes to physical exam and ECG and requirement for rescue therapy for blood pressure and T2DM will be compared across treatment groups. The number of subjects taking concomitant medications will be summarized by medication. The primary reason for any early discontinuation will be summarized. The results of laboratory tests will be included in the safety analysis.

Adverse events will be coded according to MedDRA and summarized for each treatment group. The number and percentage of subjects experiencing adverse events in each treatment group will be tabulated by MedDRA system organ class and preferred term.

13.2 Sample Size Determination

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 mean

24-hr 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 alpha=0.05 for demonstrating superiority and at 1-sided alpha=0.025 for demonstrating non-inferiority. This sample size estimate also accounts for a 5% drop-out rate over the course of the study.

14.0 TRIAL TERMINATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, or drug safety problems. In addition, VIVUS retains the right to discontinue this trial at any time.

If a clinical trial is prematurely terminated or discontinued, VIVUS will promptly notify the investigators. After notification, the investigator must contact all participating subjects within 2 - 3 days. As directed by VIVUS or designee, all study materials must be collected and all CRFs completed to the greatest extent possible.

15.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

Data generated by this clinical trial must be available for inspection by the FDA, by the Sponsor or a designate acting on behalf of the Sponsor, by applicable foreign health authorities, and by the IRB or IEC as appropriate. At a subject's request, medical information may be given to their personal physician or other appropriate medical personnel responsible for their welfare.

Subject medical information obtained during the course of this study is confidential and disclosure to third parties other than those noted above is prohibited.

16.0 QUALITY CONTROL AND QUALITY ASSURANCE

During trial conduct, VIVUS or its designee will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practice (GCP) guidelines are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow VIVUS monitors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site and trial-related documents may be subject to review by the IRB/IEC, and/or to quality assurance audits performed by VIVUS or its agents, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

17.0 ETHICAL CONSIDERATIONS

17.1 Institutional Review Board /Independent Ethics Committee

Regulations require that an IRB/IEC oversee all investigational drug clinical trials. This board or committee, the makeup of which must conform to local and regional regulations, will approve all aspects of the trial, including the protocol, advertising and written informed consent form to be used prior to initiation of the trial. It is the responsibility of the investigator to have prospective approval of the clinical trial protocol, protocol amendments, informed consent forms, and other relevant documents, e.g., advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the investigator file. Copies of IRB/IEC approvals should be forwarded to VIVUS or its designee.

Amendments to the protocol must be reviewed and approved by VIVUS and the IRB/IEC prior to implementation. The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/IEC and VIVUS or designee in writing within 5 working days after the implementation.

The investigator is responsible for keeping the IRB/IEC advised of the progress of the study and of any changes made to the protocol as deemed appropriate.

17.2 Ethical Conduct of the Clinical Trial

The clinical trial will be performed in accordance with the protocol, International Conference on Harmonization Good Clinical Practice (ICH GCP) guidelines, and applicable local regulatory requirements and laws.

17.3 Subject Information and Consent

The informed consent form and any changes to the informed consent form during the course of the trial must be agreed to by VIVUS or designee, and the IRB/IEC and must be in compliance with ICH, GCP, local regulatory requirements, and legal requirements.

The investigator or designee(s) must ensure that each clinical trial subject is fully informed about the nature and objectives of the clinical trial and possible risks associated with participation. The investigator or designee(s) will obtain written informed consent from each subject before any trial-specific activity is performed. The informed consent form used in this clinical trial, and any changes made during the course of the trial, must be prospectively approved by both the IRB/IEC and VIVUS or designee before use. The original signed copy of the informed consent form must be maintained by the investigator and is subject to inspection by a representative of VIVUS, their representatives, auditors, the IRB/IEC and/or regulatory agencies. A copy of the signed informed consent form will be given to the subject.

18.0 DATA HANDLING AND RECORD KEEPING

18.1 Case Report Forms/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this clinical trial.

A CRF is required and should be completed for each subject. The completed original CRFs are the sole property of VIVUS and should not be made available in any form to third parties, except for authorized representatives of VIVUS or appropriate regulatory authorities, without written permission from VIVUS.

It is the investigator's responsibility to ensure completion and to review and approve all CRFs. CRFs must be signed by the investigator or by an authorized staff member. These signatures serve to attest that the information contained on the CRFs is true. At all times, the investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs. Subject source documents are the physician's subject records maintained at the study site. In most cases, the source documents will be the hospital's or the physician's chart. In cases where the source documents are the hospital or the physician's chart, the information collected on the CRFs must match those charts.

In some cases, the CRF may also serve as the source document. In these cases, VIVUS and the investigator must prospectively document which items will be recorded in the source documents and for which items the CRF will stand as the source document.

18.2 Record Retention

To enable evaluations and/or audits from regulatory authorities or VIVUS, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, SAE forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to ICH, local regulations, or as specified in the Clinical Trial Agreement, whichever is longer.

If the investigator relocates, retires, or for any reason withdraws from the study, VIVUS should be prospectively notified. The study records must be transferred to an acceptable designee, such as another investigator, another institution, or to VIVUS. The investigator must obtain written VIVUS' written permission before disposing of any records prior to completion of the required/stipulated retention period.

19.0 PUBLICATION PLAN

Publication of study results is addressed in the Clinical Trial Agreement with each site.

All information and data, including the terms of this protocol, and all data, clinical results, and research conducted hereunder concerning VIVUS's products and operations including VIVUS patent applications, formulas, manufacturing processes, basic scientific data, and formulation information that has been supplied by VIVUS and not previously published are considered confidential by VIVUS and will remain the sole property of VIVUS. The investigator understands and agrees that said proprietary and/or confidential information disclosed to or produced by him/her there under is highly valuable to VIVUS and will be used exclusively by the Investigator in accomplishing this clinical trial and will not be used for any other purposes.

20.0 REFERENCES

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APPENDIX 1: 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[6]	X					
PK Trough Sample (Prior to Dosing)					X	
Urine Pregnancy Test (WOCBP)[6] / 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 EDC/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
6. Urine drug screen and urine pregnancy test will be done onsite.

APPENDIX 2: BMI CONVERSION CHART

Weight	(lb)	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210	215	220	225
	(kg)	56.8	59.1	61.4	63.6	65.9	68.2	70.5	72.7	75.0	77.3	79.5	81.8	84.1	86.4	88.6	90.9	93.2	95.5	97.7	100.0	102.3
Height																						
(in)	(cm)																					
58	147.3	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45	46	47
59	149.9	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43	44	45	46
60	152.4	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44
61	154.9	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
62	157.5	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38	39	40	41
63	160.0	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37	38	39	40
64	162.6	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36	37	38	39
65	165.1	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35	36	37	38
66	167.6	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34	35	36	36
67	170.2	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33	34	35	35
68	172.7	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	34	34
69	175.3	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32	33	33
70	177.8	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	32	32
71	180.3	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31	31
72	182.9	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30	31
73	185.4	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28	28	29	30
74	188.0	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28	29
75	190.5	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27	28	28
76	193.0	15	16	16	17	18	18	19	20	20	21	21	22	23	23	24	24	25	26	26	27	27

APPENDIX 3: SUMMARY OF CHANGES IN AMENDMENT #1

Amendment #1 (15 October 2021)

Rationale:

This protocol amendment is being implemented to clarify or revise several inconsistencies that had been noted in the original version. This amendment does not involve substantive changes to the subject population or additional study procedures, and is not expected to have any impact on the safety of study subjects. Specific changes are noted by section in the following table.

Section and/ or Item	Changes Effected
Throughout	***Revised***: VIVUS Inc. to VIVUS LLC and other administrative wording edits
Header	***Updated*** protocol version and version date.
Title Page	***Added*** new line for Amendment 1 and version date.
Investigator Signature Page	***Updated*** protocol version and version date.
Table of Contents	***Updated*** Table of Contents
Protocol Synopsis (Study Population Key Exclusions)	***Text revised***: "Screening blood pressure of ≧ > 140/90 mmHg"
Section 8.2, Exclusion #8	***Text added***: "History of drug or alcohol abuse within the past year *or positive drug test*;"
Section 8.2, Exclusion #9	***Text added***: "Smoking cessation within the past 3 months *or intent to quit during the study*;"
Section 8.2, Exclusion #15	***Text added***: "Any history of bipolar disorder or psychosis, greater than one lifetime episode of major depressive disorder, or presence or any history of suicidal behavior or suicidal ideation with some intent to act; *any use of tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), lithium, levodopa, or dopamine receptor agonists; or allowed antidepressant use that has not been stable for at least 3 months*;"
Section 8.2, Exclusion #23	***Text removed***: "~~Left ventricular ejection fraction (LVEF) ≤ 40% based on available medical records;~~"
Section 9.6.1 Excluded Medications	***Text added:*** "Tricyclic antidepressants, MAOIs, lithium, levodopa, and dopamine receptor agonists;"
Section 9.6.2 Management of Blood Pressure	***Text added:*** "As this study has a short (8-week) duration, and as the first post-randomization evaluation …. subject on the study, *to continue taking study drug*, and to have …. the subject discontinued from the study.
Section 10.1 Screening (Visit 1)	***Text revised:*** "Obtain blood ~~and urine~~ sample~~s~~ for chemistry (full panel), hematology, lip*id*s, HbA1c, TSH, HIV, HIV, and HBsAg; *and urine sample for cotinine, urinalysis, and onsite urine drug screen*. Refer to Appendix 1 and Table 2 for a listing of specific tests;

Section and/ or Item	Changes Effected
Section 10.2 Baseline/Randomization Section 10.4 Week 8/End of Study	***Text added:*** "Contact *EDC*/RTSM to obtain randomization assignment for subject *upon verifying successful ABPM; if verification of successful ABPM cannot be made, repeat 24-hr ABPM setup as described for Visit 2A and bring subject back in 24 hours to complete evaluation;*
Section 11.5 Laboratory Tests, Table 2	***Text revised:*** "*Urine* Pregnancy Test~~ing Urine pregnancy test~~ (WOCBP; *Done Onsite*)" ***Text added:*** "Urine Drug Screen (Screening Only*; Done Onsite*)"
Section 20.0 Reference #1	***Text revised:*** "Qsymia® (VI-0521) Investigator Brochure. *13*~~2~~ (*8*~~5~~ Oct 2021~~18~~) ed. ~~Mountain View~~ *Campbell*, CA: VIVUS *LLC*~~, Inc.~~; 2021~~18~~.
Appendix 1: Schedule of Events	***Added*** Footnote #6 and additional texts for clarification