Protocol

This Protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Aaron S. Kelly, Megan O. Bensignor, Daniel S. Hsia, et al. Phentermine/Topiramate for the Treatment of Adolescent Obesity. NEJM Evidence. DOI: 10.1056/EVIDoa2200014.

This supplement contains the following items:

1. Original protocol and final protocol, including the summary of changes; note that the first amendment to the protocol was implemented prior to trial initiation (page 1)
2. Original, which is also the final, statistical analysis plan; note that an unofficial (unsigned) draft of the statistical analysis plan was submitted to the United States Food and Drug Administration for initial review and comment prior to finalization of the statistical analysis plan and protocol (page 134)

CLINICAL PROTOCOL

Protocol No. OB-403

Title: A Phase IV, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Determine the Safety and Efficacy of VI-0521 in Obese Adolescents

Version: Original, 24 August 2017

Sponsor: VIVUS, Inc.
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, MD — 24 AUG 2017

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24 AUG 2017

Craig Peterson, Sr. Director, Clinical Research — **Date**

CONFIDENTIAL

INVESTIGATOR AGREEMENT PAGE

VIVUS, Inc.

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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 in writing. I also agree to conduct this clinical trial in compliance with all federal, state and local regulations, Good Clinical Practice, and the Declaration of Helsinki, and the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator: _____

Date: _____

Printed Name: _____

Institution: _____

Address: _____

1.0 TABLE OF CONTENTS

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2.0 PROTOCOL SYNOPSIS

Title of Clinical Study:	A Phase IV, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Determine the Safety and Efficacy of VI-0521 in Obese Adolescents
Sponsor:	VIVUS, Inc. (VIVUS)
Phase of Development:	4
Indication:	Weight management in obese adolescents
Study Rationale:	Obesity remains a major problem in pediatrics. National Health and Nutrition Examination Survey (NHANES) data indicate that 17.0% of children and adolescents age 2 to 19 years and 20.5% of adolescents age 12 to 19 years met the definition of obesity in 2011–2014. Obesity in childhood or adolescence increases the risk of adult obesity, type 2 diabetes mellitus, and dyslipidemia. VI-0521 (marketed as Qsymia® in the United States), a fixed dose combination of immediate-release (IR) phentermine (PHEN) and extended-release (ER) topiramate (TPM), was approved in July 2012 by the FDA as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in overweight and obese adults. Topiramate is used as an anticonvulsant in children as young as 2 years, typically beginning at doses of 1–3 mg/kg/day and titrating as needed to 5–9 mg/kg/day. Adequate and well-controlled studies of phentermine have not been conducted in children. Based on a previously completed PK study of obese adolescents (study OB-402), PK parameters in obese adolescent subjects were consistent with those observed in previous Phase 1 to 3 studies conducted in adult obese subjects. This study is being conducted to assess the safety and efficacy of VI-0521, accompanied by a lifestyle modification program, in obese adolescents.
Study Design:	In this multicenter, randomized, double-blind, placebo-controlled, parallel-design study, approximately 200 subjects will be enrolled at approximately 20 sites in the United States. Subjects will be randomly assigned in a 1:1:2 ratio to placebo, N=50; mid-dose (PHEN/TPM 7.5 mg/46 mg), N= 50; or top-dose (PHEN/TPM 15 mg/92 mg), N=100 of VI-0521, to be taken orally once daily in the morning. Randomization will be stratified by age (12-14 vs 15-17 years old) and gender. The study will consist of a screening period of up to 28 days, followed by a 56-week treatment period.

<table>
<tr><td></td><td>Subjects will be instructed to follow a mild hypocaloric diet modification program representing a 500-calorie/day deficit and to implement a family-based lifestyle modification program for adolescents, as tolerated, throughout the study period. The lifestyle program will include physical activity, behavior change, and family support. The same lifestyle modification program, specific to this population, will be implemented across all sites. Study drug doses will be titrated according to the following schema.
<table>
<tr><th rowspan="2">Group</th><th rowspan="2">Treatment Dosage for PHEN/TPM (mg)</th><th colspan="4">Titration Dose for PHEN/TPM (mg)</th></tr>
<tr><th>Weeks 1-2</th><th>Weeks 3-4</th><th>Weeks 13-14</th><th>Weeks 15-16</th></tr>
<tr><td>Placebo</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/0</td></tr>
<tr><td>VI-0521 Mid</td><td>7.5/46</td><td>3.75/23</td><td>7.5/46</td><td>7.5/46</td><td>7.5/46</td></tr>
<tr><td>VI-0521 Top</td><td>15/92</td><td>3.75/23</td><td>7.5/46</td><td>11.25/69</td><td>15/92</td></tr>
</table>
Subjects who are unable to tolerate the assigned dose may be treated at a reduced dose or may take a drug holiday as defined in the protocol.

All subjects will return at approximately 4-week intervals for study assessments. All female subjects will undergo a pregnancy test at each visit. Subjects who discontinue the treatment during the study will be encouraged to remain on study (off study drug) for continued follow-up by attending all remaining visits and have all study-related procedures performed, and to return at the 56-week time point for measurements and evaluations. For those who choose to completely withdraw from the study at any point, the end of study (Week 56) procedures should be completed.</td></tr>
<tr><td>Study Objectives:</td><td>The primary objectives are to evaluate the safety and efficacy of VI-0521 (PHEN/TPM 7.5 mg/46 mg and PHEN/TPM and 15 mg/92 mg doses) for the treatment of obesity in adolescents. The secondary objective is to characterize changes in obesity-related risk factors.</td></tr>
<tr><td>Duration of Treatment:</td><td>The treatment period will be 56 weeks.</td></tr>
<tr><td>Sample Size:</td><td>Approximately 200 subjects</td></tr>
<tr><td>Number of Sites/Locations:</td><td>Approximately 20 sites in the United States</td></tr>
</table>

Study Population:	**Key Inclusion Criteria** (see Section 7.1 for a complete list): • Aged ≥ 12 years and < 17 years at the time of screening; • BMI ≥ the 95th percentile, with documented history of failure to lose sufficient weight or failure to maintain weight loss in a lifestyle modification program; • If female, must be using adequate contraception, defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence.
Study Population:	**Key Exclusion Criteria** (see Section 7.2 for a complete list): • Type 1 diabetes; • Congenital heart disease; clinically significant ECG abnormality; • Physical exam, vital signs, or laboratory abnormality; clinically significant hepatic or renal disease; • Creatinine clearance (Schwartz formula) < 60 mL/minute; • Clinically significant thyroid dysfunction as evidenced by signs, symptoms, or TSH > 1.5 x ULN; • Obesity of known genetic or endocrine origin; • History of bipolar disorder or psychosis, depression of moderate or greater severity, or presence or history of suicidal behavior or active suicidal ideation; • Recent weight instability, or prior bariatric surgery; • History of glaucoma or increased intraocular pressure; • Current smoker or smoking cessation within 3 months of screening; • Currently taking or plan on taking any of following medications during the study: o Anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, GABA analogues, hydantoins, phenyltriazines, succinimides, and other agents (valproic acid and its derivatives, carbamazepine and its derivatives, zonisamide, and felbamate); o Tricyclic antidepressants, MAOIs, lithium, levodopa, and dopamine receptor agonists; o Carbonic anhydrase inhibitors; o Insulin, SFUs, GLP-1 agonists, SGLT-1, and SGLT-2 inhibitors;

	○ Chronic systemic steroids (i.e. glucocorticoids, anabolic steroids) other than oral contraceptives; ○ Treatment for hyperactivity disorder; or ○ OTC, prescription medications, herbal agents and dietary supplements used with the intention to lose body weight.
Study Drug Form and Strength:	• Low-dose (for titration purposes only): One PHEN/TPM 3.75/23 mg capsule administered daily • Mid-dose: One PHEN/TPM 7.5/46 mg capsule administered daily • ¾-dose (for titration purposes only): One PHEN/TPM 11.25/69 mg capsule administered daily • Top-dose: One PHEN/TPM 15/92 mg capsule administered daily Study drug will be packaged into 2 types of kits; titration kits (blister cards) for use during the first 4 weeks of dosing and the first 4 weeks following up-titration for subjects randomized to the top-dose (Weeks 13-16), and treatment kits (bottles), for use once subjects have been titrated to their assigned dosage.
Regimen/Administration:	Each capsule of study drug will be taken orally in the morning, with or without food, and with water.
Primary Efficacy Endpoints:	The primary endpoint is the mean percent change in BMI from baseline to end of study (Week 56)
Second Efficacy Endpoints:	The secondary endpoints are: • Percent of subjects achieving a reduction ≥ 5%, ≥ 10% and ≥ 15% of baseline BMI at Week 56; • Change from baseline in waist circumference at Week 56; • Change from baseline in fasting insulin and Whole Body Insulin Sensitivity Index (Matsuda) at Week 56; • Change from baseline in triglycerides and HDL-C at Week 56; • Change from baseline in blood pressure at Week 56.
Exploratory Endpoints:	Additional exploratory analyses will be conducted to evaluate effects of treatment on IWQOL-Kids questionnaire scores, changes in various glycemic and lipid markers, and change in BMI Z-score.
Safety Evaluations and Oversight:	Safety monitoring and tolerability will be assessed by evaluation of adverse events/serious adverse events, physical exams, vitals, cognitive function tests using the CANTAB, responses to PHQ-9, C-SSRS, bone age (X-ray of the hand and wrist), DXA in a

	subset (approximately 25 subjects each on the placebo and mid-dose, and 50 subjects on the top-dose), and periodic monitoring of laboratory test results. An independent Data Monitoring Committee (DMC) will be established to evaluate accumulating trial data on a periodic basis and to assess the ongoing safety of the study.
Statistical Methods:	Analysis Populations: Randomized: This population will be comprised of all subjects who were initially randomized. This population will be used for summaries of subject disposition and baseline subject characteristics. Intent-to-treat (ITT)/Safety: This population will be comprised of all subjects who were initially randomized and received at least one dose of study drug. This will be the primary population for all summaries of subject disposition and baseline characteristics, efficacy analyses, and safety analyses for purposes of regulatory submissions. Comparisons in the primary endpoint of change from the baseline BMI between treatment groups will be assessed using a mixed effects model with repeated measures (MMRM) with factors of treatment, visit, treatment by visit interaction, baseline BMI value, age stratification, and gender stratification. Appropriate contrast will be applied for treatment comparisons at Week 56. The 3 comparisons of interest are 1) top-dose vs. placebo; 2) mid-dose vs. placebo; and 3) top-dose vs. mid-dose. Sensitivity analyses will be conducted to examine the impact of missing data on the robustness of statistical conclusions. In previous studies in adults, PHEN/TPM 7.5 mg/46 mg dose resulted in a placebo-subtracted BMI reduction of 2.4 units with a standard deviation of 2.9. Assuming a similar effect size, with enrollment of 200 subjects (100 randomized to the top-dose, 50 randomized to the mid-dose, and 50 randomized to the placebo), the present study will have greater than 90% power to detect a significant difference in BMI reduction between the top-dose and the placebo, and approximately 80% power to detect a significant difference between the mid-dose group and the placebo. The above power calculation assumes very conservative differences between the active doses and placebo and a worst case 30% dropout rate.

3.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ACE	Angiotensin converting enzyme
ADHD	Attention-deficit/hyperactivity disorder
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
AST	Aspartate transaminase
ALT	Alanine aminotransferase
AUC	Area under the curve
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
^{o}C	Degrees Celsius
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CL	Apparent clearances
C_{max}	Maximum observed drug concentration
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
ER	Extended-release
^{o}F	Degrees Fahrenheit
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase

Abbreviation or Term	Definition/Explanation
GLP-1	Glucagon-like peptide -1
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
ITT	Intent to treat
IR	Immediate-release
IRB	Institutional Review Board
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
IWRS	Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LSD	Least significant difference
MAOI	Monoamine oxidase inhibitor
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	Modified intent to treat
mmHg	Millimeters of mercury pressure
MMRM	Mixed effect Model with Repeated Measures
MNAR	Missing not at random
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral glucose tolerance test
OTC	Over-the-counter
PA	Posterior-anterior
PHEN	Phentermine

Abbreviation or Term	Definition/Explanation
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
sCr	Serum creatinine
SFU	Sulfonylurea
SGLT	Sodium glucose transporter
TBLH	Total body less head
T_{max}	Time to maximum concentration
TPM	Topiramate
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinedione
ULN	Upper limit of normal
USA	United States of America
Vc/F	Apparent volume of distribution
WHO	World Health Organization

4.0 BACKGROUND

Obesity remains a major problem in pediatrics. National Health and Nutrition Examination Survey (NHANES) data indicate that 17.0% of children and adolescents age 2 to 19 years and 20.5% of adolescents age 12 to 19 years met the definition of obesity in 2011–2014.[1] Obesity in childhood or adolescence increases the risk of adult obesity, type 2 diabetes mellitus, and dyslipidemia.[2,3,4] Although lifestyle changes and behavior modification programs have shown some benefit, these measures have not been widely adopted for the treatment of obesity in children. When intensive lifestyle modification is unsuccessful in reaching weight loss goals, adjunct pharmacotherapy may be warranted. Few weight loss drug therapies have been evaluated in children and currently there is only one FDA approved product (orlistat) to treat adolescent obesity. Additional pharmacotherapy options are needed in order to address pediatric obesity.

VI-0521 (marketed as Qsymia® in the United States), a fixed dose combination of immediate-release (IR) phentermine (PHEN) and extended-release (ER) topiramate (TPM), was approved in July 2012 by the Food and Drug Administration (FDA) as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in overweight and obese adults. Mean weight loss of > 10% was achieved after one year of treatment in obese adults randomized to top-dose (PHEN/TPM 15 mg/92 mg) and > 8% in those randomized to mid-dose (PHEN/TPM 7.5 mg/46 mg) of VI-0521. Weight loss was sustained over two years. In addition to weight loss, VI-0521 also resulted in significant reductions in blood pressure, improved glycemic parameters, increased HDL-C, and reduced triglycerides.[5] The doses employed in this combination represent a fraction of those commonly prescribed as single agents for other indications.

Topiramate is used as an anticonvulsant in children as young as 2 years, typically beginning at doses of 1–3 mg/kg/day and titrating as needed to 5–9 mg/kg/day.[6] The 92 mg of topiramate in the top-dose of VI-0521 falls well within the dose range currently used in children. Adequate and well-controlled studies of phentermine have not been conducted in children. The top-dose of VI-0521 contains roughly ½ of the maximum phentermine dose currently approved for use in adults.

The single- and multiple-dose pharmacokinetics (PK) of topiramate and potential drug interactions between topiramate and phentermine in VI-0521 have been fully investigated in the adult population. The major route of elimination of phentermine and its metabolites is through the urine. Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Previous population PK analyses demonstrated that creatinine clearance and body weight were the most important components describing the PK of phentermine and topiramate in VI-0521, that the PK parameters of phentermine and topiramate were dose proportional, and that no relationship was observed between PK parameters and age, gender, or body mass index (BMI) for either drug.[5]

By the time children reach adolescent age, their kidneys are fully developed and there is little variation in kidney function compared to adults.

Based on the PK study of obese adolescents (study OB-402), plasma concentrations in obese adolescents were consistent with those observed in previous Phase 1 to 3 studies conducted in adult obese subjects.

For phentermine, geometric means of individual posterior Bayes PK parameters (apparent clearance [CL/F] and apparent volume of distribution [Vc/F]) in obese adolescent subjects were within 10% of those previously assessed in obese adult subjects enrolled in Phase 2 and Phase 3

studies, and arithmetic means of area under the curve (AUC) and C_{max} in obese adolescent subjects were within 10% of arithmetic means previously obtained based on rich concentration-time profiles of phentermine under steady-state in obese adults. Medians of T_{max} in adolescent subjects were within 11% of medians of T_{max} observed in obese adults.

For topiramate, geometric means of individual posterior Bayes CL/F were within 30% of those previously assessed in obese adult subjects enrolled in Phase 2 and Phase 3 studies, with higher CL/F values in the adolescent population. Geometric means of posterior Bayes Vc/F of TPM in obese adults and obese adolescents were similar. The higher CL/F values in adolescents are consistent with lower serum creatinine values in this population, but did not result in marked differences in exposure, as arithmetic means of AUC and C_{max} of topiramate were within 12% of arithmetic means previously obtained based on rich concentration-time profiles of topiramate under steady-state in obese adults. Medians of T_{max} in adolescent subjects were within 2% of medians of T_{max} observed in obese adults.

This study is being conducted to assess the safety and efficacy of VI-0521, accompanied by a lifestyle modification program, in obese adolescents.

5.0 STUDY OBJECTIVES

The primary objectives are to evaluate the safety and efficacy of VI-0521 for the treatment of obesity in adolescents. The secondary objective is to characterize changes in obesity-related risk factors.

6.0 STUDY DESIGN

In this multicenter, randomized, double-blind, placebo-controlled, parallel-design study, approximately 200 subjects will be enrolled at approximately 20 sites in the United States. Subjects will be randomly assigned in a 1:1:2 ratio to placebo, N= 50; mid-dose (PHEN/TPM 7.5 mg/46 mg), N= 50; or top-dose (PHEN/TPM 15 mg/92 mg), N =100, of VI-0521, to be taken orally once daily in the morning. Randomization will be stratified by age (12-14 vs 15-17 years old) and gender. The study will consist of a screening period of up to 28 days, followed by a 56-week treatment period.

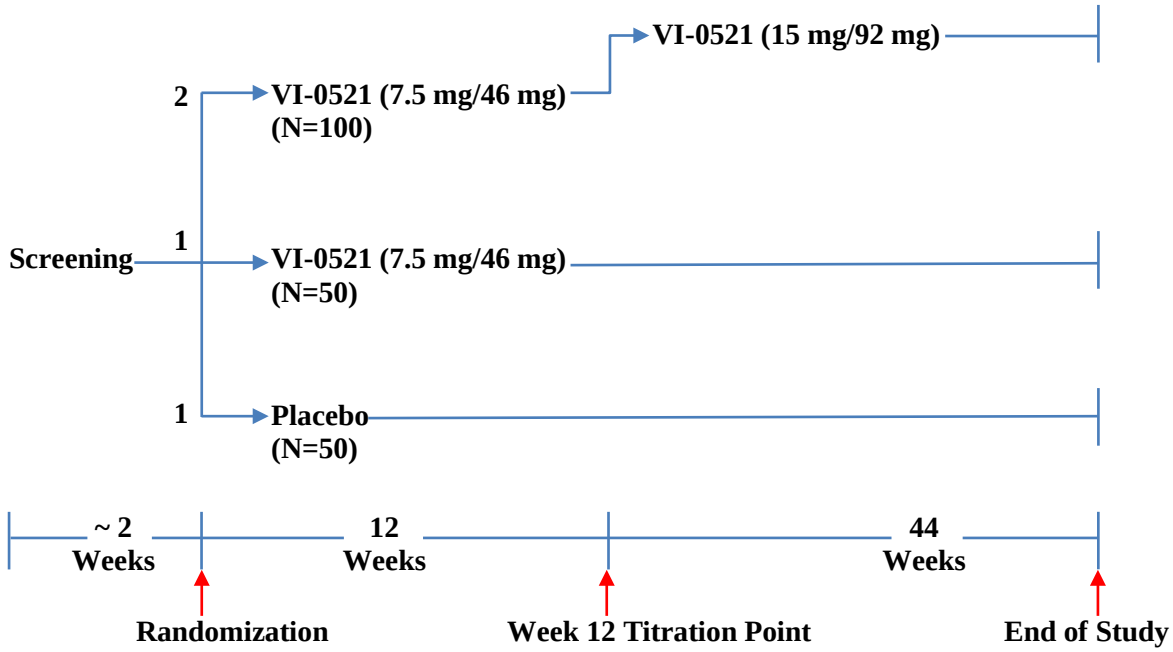
Subjects will be instructed to follow a mild hypocaloric diet modification program representing a 500-calorie/day deficit and to implement a family-based lifestyle modification program for adolescents, as tolerated, throughout the study period. The lifestyle program will include physical activity, behavior change, and family support. The same lifestyle modification program, specific to this population, will be implemented across all sites. Study drug will be titrated as described in Section 8.4.1.

Subjects who are unable to tolerate the assigned dose may be treated at a reduced dose level or may take a drug holiday as defined in Section 8.4.4. In addition, for growth monitoring, investigators will monitor rates of weight loss in treated subjects. For subjects with baseline BMI 95-98th percentile, reduce study drug dosage when BMI is < 85th percentile or when weight loss exceeds an average of 2 lbs (0.9 kg) per week. For subjects with baseline BMI ≥ 99th percentile, reduce study drug when weight loss exceeds an average of 2 lbs (0.9 kg)/week.

All subjects will return at approximately 4-week intervals for study assessments. All female

subjects will undergo a pregnancy test at each visit. Subjects who discontinue study drug during the study will be encouraged to remain on study (off study drug) for continued follow-up by attending all remaining visits and have all study-related procedures performed, and to return at the 56-week time point for measurements and evaluations. For those who choose to completely withdraw from the study at any point, the end of study (Week 56) procedures should be completed.

Figure 1. Schematic Diagram of Study Design



6.1 Primary Efficacy Endpoints

The primary endpoint is the mean percent change in BMI from baseline to end of study (Week 56).

6.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- Percent of subjects achieving a reduction ≥ 5%, ≥ 10% and ≥ 15% of baseline BMI at Week 56;
- Change from baseline in waist circumference at Week 56;
- Change from baseline in fasting insulin and Whole Body Insulin Sensitivity Index (Matsuda) at Week 56;
- Change from baseline in triglycerides and HDL-C at Week 56;
- Change from baseline in blood pressure at Week 56.

6.3 Exploratory Endpoints:

Additional exploratory analyses will be conducted to evaluate effects of treatment on Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire scores, changes in various glycemic and lipid markers, and change in BMI Z-score.

6.4 Safety Endpoints

Safety will be assessed by evaluation adverse events (AEs)/serious adverse events (SAEs); vital signs, laboratory parameters (screening, periodically during the study and end of study); electrocardiograms; physical examinations; cognitive function tests using the Cambridge Neuropsychological Test Automated Battery (CANTAB). All subjects will be screened for the presence and severity of depression using the PHQ-9: Modified for Teens (Appendix 4) and for suicidal/ideation using the Columbia Suicide Severity Rating Scale (C-SSRS) (Appendix 5) and follow up assessments will be done at each visit after treatment has been initiated. Bone age (X-ray of the hand and wrist) will be evaluated at baseline and end of study or early termination. Effect on bone mineral density and bone mineral content, as evaluated by Dual-energy X-Ray Absorptiometry (DXA) will be performed at baseline, end of study or early termination, at selected sites.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

To be eligible for enrollment into this study, each subject must meet all of the following criteria at screening:

1. Provide written informed consent (of a parent or legal guardian) who will accompany the subject to all study visits;
2. Provide written assent (of study subject);
3. Be an adolescent ≥ 12 years and < 17 years of age with Tanner Staging of ≥ 2 at the time of screening;
4. Have a BMI ≥ the 95th percentile of BMI for age and gender (see Appendix 3), with documented history of failure to lose sufficient weight or failure to maintain weight loss in a lifestyle modification program;
5. Be willing and able to comply with scheduled study visits, treatment plan, laboratory tests and other study procedures;
6. If female, must be using adequate contraception, defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence.

7.2 Exclusion Criteria

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

1. Weight gain or weight loss of greater than 5 kg, use of a supervised fast or very low-

calorie diet within the past 3 months;

2. Treatment with phentermine, topiramate, lorcaserin, naltrexone HCl/bupropion HCl, any over-the-counter (OTC) or prescription or herbal agents and dietary supplements, teas or tinctures used with the intention to lose body weight within 3 months of screening;
3. Any stimulants used for treatment of attention-deficit/hyperactivity disorder (ADHD) within 3 months of screening;
4. Condition or disease interfering with metabolism, such as untreated hypothyroidism, Cushing's syndrome;
5. Pulmonary disorders (other than asthma not requiring continuous medication or sleep apnea-related disorders);
6. Type 1 diabetes or any medical treatment with insulin, sulfonylureas (SFUs), glucagon-like peptide-1 (GLP-1) agonists, sodium glucose transporter (SGLT-1) inhibitors, and SGLT-2 inhibitors;
7. Congenital heart disease;
8. Clinically significant arrhythmia or electrocardiogram (ECG) abnormality;
7. Screening laboratory values as specified (tests may be repeated per investigator's discretion):

a.	Bicarbonate	< LLN
b.	AST and ALT	> 3 x ULN
c.	HbA1c	≥ 8.0 %
d.	Fasting glucose	≥ 270 mg/dL
e.	Triglyceride	≥ 400 mg/dL
f.	Creatinine clearance	< 60 mL/minute (Schwartz Formula)[7] (see Appendix 7)
g.	TSH	> 1.5 ULN

8. Clinically significant hepatic or renal disease;
9. Clinically significant thyroid dysfunction as evidenced by signs or symptoms of hypothyroidism, a thyroid stimulating hormone (TSH) > 1.5 x ULN, or use of thyroid hormone treatment that has not been stable for at least 3 months;
10. Systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg or concurrent antihypertensive medication that has not been stable for 3 months;
11. Any history of bipolar disorder or psychosis, major depressive disorder, current depression of moderate or greater severity (PHQ-9 score of 10 or more), presence or history of suicidal behavior or ideation with some intent to act on it; tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), lithium, levodopa, and dopamine receptor agonists; or allowed antidepressant use that has not been stable for at least 3 months;
12. Use of chronic systemic glucocorticoid therapy (i.e. glucocorticoids, anabolic steroids) or any other steroid hormone therapy other than oral contraceptives, that has not been stable for at least 3 months;
13. Pregnancy or breastfeeding;

14. Any history of any eating disorders (e.g. bulimia; binge eating disorder; anorexia);
15. Any history of laxative abuse;
16. History of glaucoma, use of carbonic anhydrase inhibitors, history of increased intraocular pressure or any past or present use of medications to treat increased intraocular pressure;
17. Prior bariatric surgery;
18. Any history of nephrolithiasis;
19. Any history of epilepsy, or requirement for anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, gamma-aminobutyric acid (GABA) analogues, hydantoins, phenyltriazines, succinimides, and other agents (valproic acid and its derivatives, carbamazepine and its derivatives, zonisamide, and felbamate);
20. Positive urine drug screen;
21. Current smoker or smoking cessation within 3 months of screening;
22. Obesity of a known genetic or endocrine origin, such as Prader-Willi Syndrome;
23. Known allergy or hypersensitivity to phentermine or topiramate or history of anaphylaxis to any drug;
24. Use of any investigational medication or device for any indication or participation in a clinical study within 30 days prior to screening; or
25. Other clinically significant medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.

7.3 Subject Withdrawal

Subjects are free to withdraw from the clinical trial or discontinue treatment at any time for any reason.

The sponsor reserves the right to discontinue this trial at any time (see Section 13.0 on clinical trial discontinuation criteria).

Subject participation in this clinical trial may be discontinued for any of the following reasons:

- Occurrence of 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 that indicates to the Investigator that continued participation is not in the best interest of the subject;
- Subject's (or a parent’s or legal guardian’s) decision to withdraw;
- Requires other medical treatment that is excluded by the protocol (see Section 8.5);

- Subject failure to comply with protocol requirements or study related procedures; or
- Termination of the clinical trial by the sponsor, FDA, or other regulatory authorities.

Withdrawn subjects will not be replaced.

Subjects discontinued from treatment should be encouraged to remain in the trial off-treatment and to continue study visits at the scheduled intervals. Subjects who withdraw completely from the trial at any point should complete the end of study (Visit 16, Week 56) procedures. The date of last dose should be recorded.

Every effort should be made to document subject outcome. For subjects who elect to withdraw from the trial without continuing study visits, the investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit (Section 9.1.4) and follow-up with the subject regarding any unresolved adverse events.

At about the 56-week time point, withdrawn subjects who have not continued study visits should be asked to return to the site to obtain weight and height measurements at a minimum and, if possible, all the other tests and procedures (except physical examination and ECG) required for end of study visit.

If a subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8.0 TREATMENT OF SUBJECTS

8.1 Study Treatment

Eligible subjects will receive 56 weeks of treatment with either VI-0521, or matching placebo for daily use.

8.2 Allocation to Treatment

Written informed consent will be obtained prior to the performance of any study-related procedures. Eligible subjects will be randomly assigned in a 1:1:2 ratio to placebo, mid-dose (PHEN/TPM 7.5 mg/46 mg) or top-dose (PHEN/TPM 15 mg/92 mg) of VI-0521. Randomization will be stratified by gender and age (12-14 vs 15-17 years old), and will be implemented using an Interactive Web Response System (IWRS). The sponsor, the subjects, and the study site will be blinded as to subject randomization.

When a subject qualifies for randomization, site personnel will log into the IWRS to obtain a specific titration blister card or bottle number to dispense to the study subject. The subject will return the study drug at every clinic visit for drug accountability and will be dispensed with a new blister card/bottle for the next treatment period.

8.3 Breaking the Blind

Study drug must not be unblinded during the study unless it is considered absolutely necessary

by the investigator for the management of an adverse event or other medical emergency. Under such conditions, investigators will first contact the medical monitor when deciding to unblind a subject and if unblinding is deemed medically necessary the identity of the study treatment may be obtained via the IWRS. Any subject whose treatment assignment has been unblinded must be withdrawn from the study.

Investigators are also required to ensure that any potential SAEs are reported according to the requirements outlined in Section 11.1.5 and provide a written report to VIVUS or designee within 7 days to document the reason for unblinding.

8.4 Drug Supply

Clinical supplies will be manufactured for VIVUS by Catalent Pharma Solutions, LLC in accordance with current Good Manufacturing Practices (cGMP). All clinical supplies will be labeled with information required by national regulations.

8.4.1 Formulation and Packaging

Sufficient quantities of VI-0521, phentermine and topiramate capsules will be supplied by the sponsor in blister cards and bottles and shipped to a designee at the study site. All clinical supplies will be labeled with information required by national and/or international regulations. Study drug will be packaged into 2 types of kits; titration kits (blister cards) for use during the first 4 weeks of study treatment and the first 4 weeks following up-titration for subjects randomized to the top-dose (Weeks 13-16), and treatment kits (bottles), for use once subjects have been titrated to their assigned dose.

Each titration kit contains 1 blister card for use during Weeks 1 through 4 of titration, with each card containing 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. Titration kits will consist of blister cards labeled with the study number, a unique kit number, storage instructions, and spaces for the subject number and initials. Treatment kits will consist of bottles, each containing 35 capsules of study medication at the treatment dosages shown in Table 1. Each kit will contain a single bottle labeled with the study number, a unique kit number, storage instruction, and spaces for the subject number and initials.

Table 1: VI-0521 Dosage Strengths by Titration Week for Each Treatment Group

Group	Treatment Dosage for Phentermine/Topiramate (mg)	Titration Dose for Phentermine/Topiramate (mg)			
		Weeks 1-2	Weeks 3-4	Weeks 13-14	Weeks 15-16
Placebo	0/0	0/0	0/0	0/0	0/0
VI-0521 Mid	7.5/46	3.75/23	7.5/46	7.5/46	7.5/46
VI-0521 Top	15/92	3.75/23	7.5/46	11.25/69	15/92

8.4.2 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. Randomization scheme will be followed by site staff for assignment of specific bottle to study subjects. No other preparation of clinical supplies is required of the study staff.

8.4.3 Administration

Subjects will be instructed to take 1 capsule of study drug every morning with or without food, and with water. Subjects should stay hydrated by drinking plenty of water while in the study. Subjects will be reminded not to take study drug to school or work. Capsules are not to be broken or split apart in any manner.

When dispensing titration kits, investigators should ensure that subjects understand that each blister card contains a 4-week supply of medication, 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 the capsules must be taken for the treatment period that the bottle is dispensed for. Instruction should also be provided that each bottle contains extra capsules that should only be taken should the next study visit be scheduled after Week 4. Investigators will also instruct subjects to return all study drug (blister card and the bottle, even if empty) to the site at each study visit.

8.4.4 Dose Reduction and/or Interruption During Trial Participation

Dose reduction is an option for subjects who experience adverse events that are sufficiently severe to cause the subject to consider discontinuation or to cause the investigator concern about the subject's ability to continue in the study.

It should be recognized that caloric restriction resulting in rapid weight loss (independent of any specific drug mechanisms) carries the potential to negatively affect growth. Due to the potential of the study drug to cause significant weight loss which may affect growth in adolescents, investigators should actively monitor the subject's rate of weight loss and growth (using height and weight), and implement a down-titration of study drug should rates of weight loss in a given subject exceed rates that are deemed safe. For subjects with baseline BMI 95-98th percentile, reduce study drug dosage when BMI is < 85th percentile or when weight loss exceeds an average

of 2 lbs (0.9 kg) per week. For subjects with baseline BMI $\geq 99^{th}$ percentile, reduce study drug when weight loss exceeds an average of 2 lbs (0.9 kg)/week.

Dose reduction is implemented through the IWRS, and will be done without breaking the blind. Subjects assigned to the mid-dose may be reduced down to the low-dose and those assigned to the top-dose may be reduced down to the mid-dose, and if necessary, the low-dose in a blinded manner. Dose reduction is not an option for subjects who experience intolerable adverse events related to study medication during the first week of titration (Week 1) during the initial randomization; these subjects will be withdrawn from treatment.

When dose reduction is not appropriate or when dose interruption may be required due to events unrelated to study treatment, subjects may temporarily discontinue from treatment (up to 7 days) on one or more occasions. Dose interruptions longer than 7 days are possible with agreement from the medical monitor. All subjects undergoing dose interruptions for any duration may be titrated back up to the original dose level based on discretion of the investigator. If study drug has been discontinued for 2 weeks or more, a new titration kit should be ordered through IWRS to resume treatment. Subjects who have a drug holiday following dose reduction due to study medication intolerance will be retitrated to the dose specified for use after dose reduction. For subjects having a drug holiday due to events unrelated to treatment, attempts should be made to retitrate to the initial randomized dose. For treatment interruptions of less than 2 weeks, subjects may resume treatment by dosing every other day for the first week that treatment is resumed.

If symptoms remain intolerable after dose reduction and drug holidays, subjects may be discontinued from treatment. Subjects discontinued from treatment will be encouraged to remain in the trial off-treatment and to continue to make study visits at the regularly scheduled intervals. The last date on which the subject is dosed with study medication should be recorded on the case report form (CRF).

If the subject remains in the trial off-treatment, all study procedures should be continued for the duration of subject participation and they should be encouraged to return at the 56- week time point for measurements and evaluations. For those who choose to completely withdraw from the study at any point, the end of study (Week 56) procedures should be completed.

8.4.5 Discontinuing Study Drug

Abrupt withdrawal of topiramate, a component of VI-0521, has been associated with seizures in individuals without a history of seizures or epilepsy. Subjects discontinuing VI-0521 should be gradually tapered by taking a dose every other day for 1 week prior to stopping treatment altogether.

8.4.6 Compliance

Subject compliance with study drug will be assessed by counting capsules that are returned at each study visit. Subjects whose actual capsule consumption differs from their expected capsule consumption by more than 20% should be queried by site personnel about reasons for not using study drug as directed, and site personnel should plan any corrective action as necessary. Subjects who remain noncompliant with study drug dosing despite corrective action by site personnel may be withdrawn from the study.

8.4.7 Drug Storage and Drug Accountability

All unused study drug must be stored in its packaging at controlled room temperature, 15 to 25°C (59 to 77°F) with excursion to 30°C (86°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, one component of the VI-0521 combination is a Schedule IV controlled substance. 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 empty containers and all unused medication in its original packaging, and sites must make an accounting of drug use by each subject. No study drug, used or unused, may be discarded. All used and unused drug must be returned to the sponsor or designated representative upon completion of the study.

8.5 Concomitant Medications

8.5.1 Excluded Medications

Subjects may not use any of the following medications during participation in this study. Subjects who develop a need for any of these medications must be discontinued from the study:

- Anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, GABA analogues, hydantoins, phenyltriazines, succinimides, and other agents (valproic acid and its derivatives, carbamazepine and its derivatives, zonisamide, and felbamate);
- Tricyclic antidepressants, MAOIs, lithium, levodopa, and dopamine receptor agonists;
- Carbonic anhydrase inhibitors;
- Insulin, sulfonylureas (SFUs), GLP-1 agonists, SGLT-1 inhibitors, and SGLT-2 inhibitors;
- Chronic systemic steroids (i.e. glucocorticoids, anabolic steroids) other than oral contraceptives;
- Treatment for hyperactivity disorder; or
- OTC, prescription medications, herbal agents and dietary supplements used with the intention to lose body weight.

8.5.2 Other Restricted Medications

Subjects using hormone replacement therapy (estrogen, thyroid, or other) or allowed antidepressants must be on doses that have been stable for at least 3 months prior to screening. Subjects who develop symptoms indicative of hypothyroidism during the course of the study need not withdraw but should be evaluated and managed as indicated.

Benzodiazepine and non-benzodiazepine sleep medications are permitted, provided that the dosage has been stable for at least 1 month prior to screening, and the frequency of use does not exceed twice a week.

Subjects may not initiate any other organized weight loss program during their participation in this study.

8.5.3 Documentation of Concomitant Medication Use

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

8.6 Treatment of Diabetes

Subjects who develop type 2 diabetes during the course of the study will be provided with blood glucose meters and supplies and will be provided appropriate usage instructions. They will be instructed to measure a fasting morning glucose daily and to record the results in the blood glucose and hypoglycemic event log. Diabetic subjects will bring their meters and logs to each visit.

If concomitant antidiabetic therapy is determined necessary, metformin is suggested as the initial therapy for newly-emergent type 2 diabetes unless contraindicated in a specific subject. Insulin secretagogues, including SFUs and meglitinides, either alone or in combination with other medications, should be reserved for subjects who cannot achieve adequate control with other modes of treatment. Insulins and incretins are prohibited, and subjects requiring treatment with these medications must be discontinued from the trial. Subjects whose blood glucose cannot be adequately controlled with the concomitant treatments allowed in this trial should be maintained in the study but discontinued from treatment, and referred back to their primary healthcare provider for more intensive treatment (see Section 7.3).

During treatment, subjects whose fasting blood glucose is less than 72 mg/dL on 2 or more occasions, or who experience any signs or symptoms associated with hypoglycemia, should have their antidiabetic therapy reevaluated.

8.7 Treatment of Elevated Blood Pressure

For subjects whose blood pressure requires management, antihypertensive therapy should be initiated with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). If these medications are already present, calcium channel blockers, beta-blockers, or thiazide diuretics may be added.

Subjects whose blood pressure exceeds 140/90 mmHg on 3 consecutive visits and who have undergone dose increases or the addition of antihypertensive medications over each of 3 visits, should be discontinued from study drug and referred back to their primary healthcare provider for more intensive management. Subjects may continue attending study visits off study drug, and if blood pressure control is re-established without requiring excluded medications, subjects may be restarted on study drug.

Subjects whose blood pressure drops below 110/70 mmHg, or who exhibit symptoms associated

with low blood pressure during the trial should have their antihypertensive medications reevaluated.

8.8 Treatment of Hypothyroidism

Individuals who experience rapid weight loss sometimes develop signs and/or symptoms of hypothyroidism with or without elevation of TSH. Subjects who develop symptoms of hypothyroidism need not be discontinued from study drug. These subjects should be assessed clinically and with appropriate laboratory testing (TSH, free T3, free T4). Subjects found to be hypothyroid may be considered for thyroid replacement therapy, as appropriate.

9.0 STUDY PROCEDURES

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

9.1 Schedule of Visits

9.1.1 Screening Visit (Visit 1, Up to – 4 Weeks)

Activities at the Screening visit are:

- Obtain written parental informed consent and subject assent;
- Obtain written parental informed consent and subject assent for DXA (at selected sites);
- Obtain demographics (including age, gender, race, and ethnicity);
- Obtain medical history (including contraception methods);
- Assess inclusion/exclusion criteria;
- Record concomitant medications;
- Administer PHQ-9 and C-SSRS questionnaires;
- Obtain vital signs (blood pressure, heart rate, respiration rate, and temperature);
- Obtain weight and waist circumference measurements;
- Measure 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;
- Obtain serum samples for blood chemistry panel, hematology panel, lipid panel, HbA1c, HIV, HCV, HBsAg, TSH;
- Obtain urine sample for routine urinalysis, drug screen, and pregnancy test (female subjects);
- Provide contraception/pregnancy counseling (female subjects); and
- Schedule the Randomization visit within 4 weeks (± 3 days).

9.1.2 Baseline/Randomization (Visit 2, Week 0)

Subjects eligible for treatment will be randomized and have study drug dispensed at visit 2. If a subject is found to be ineligible for participation due to laboratory values, the subject may be notified prior to visit 2. Activities at baseline are:

- Confirm inclusion/exclusion criteria (Section 7.0);
- Administer PHQ-9, C-SSRS, and IWQOL-Kids questionnaires;
- Administer neurocognitive battery (CANTAB);
- Obtain vital signs (blood pressure, heart rate, respiration rate, and temperature);
- Obtain weight and waist circumference measurements;
- Measure height and calculate BMI;
- Record any changes in concomitant medications;
- Record any adverse events reported or observed;
- Perform complete physical examination (include Tanner Staging);
- Perform and evaluate 12-lead ECG;
- Perform urine pregnancy test (female only);
- Perform OGTT for all subjects eligible for participation by results of Visit 1 screening tests (a separate visit may be scheduled for the OGTT) and obtain blood sample for glucose and insulin at 2 hours following oral glucose load;
- Conduct hand and wrist X-ray;
- Conduct DXA measurement (if applicable);
- Contact IWRS to randomize the subject. Dispense study drug and instruct the subject on the proper use of the study drug (Section 8.4.3);
- Provide diet (a 500-calorie/day deficit), lifestyle modification and contraception/pregnancy counseling (female subjects); and
- Schedule the next study visit in 4 weeks (± 7 days).

9.1.3 Treatment Week 4 Through Week 52 (Visits 3 Through 15)

- Obtain weight and waist circumference measurements;
- Administer PHQ-9 and C-SSRS questionnaires;
- Administer neurocognitive battery (CANTAB), Visit 3 only;
- Obtain vital signs;
- Measure height and calculate BMI;
- Record any changes in concomitant medications;
- Record any adverse events reported or observed;

- Perform urine pregnancy test;
- Collect study drug from previous visit, assess treatment compliance, and perform drug accountability; and dispense study medication and instruct the subject in the proper use of the study drug;
- Obtain blood sample for chemistry panel (Visits 3, 4, and 9 only);
- Obtain blood sample for hematology and lipids panel (Visit 9 only);
- Obtain blood sample for HbA1c (Visits 5 and 11 only);
- Provide diet (a 500-calorie/day deficit), lifestyle modification and contraception/pregnancy counseling (female subjects); and
- Schedule the next study visit in 4 weeks (± 7 days).

9.1.4 Treatment Week 56, End of Study; Early Termination (Visit 16)

The end of study visit will be performed for subjects completing the study or for subjects who are withdrawn from the study prior to completion of the study at the time of their treatment termination. For subjects who withdraw from the study prior to completion, the site will also attempt to contact the subject at or about the 56-week time point to obtain end of study assessments.

Activities at the end of study visit include:

- Administer PHQ-9, C-SSRS, and IWQOL-Kids questionnaires;
- Administer neurocognitive battery (CANTAB);
- Obtain vital signs;
- Obtain weight and waist circumference measurements;
- Measure height and calculate BMI;
- Collect study drug from previous visit, assess treatment compliance, and perform drug accountability;
- Obtain blood sample for chemistry, hematology, and lipids, panel;
- Obtain blood sample for HbA1c;
- Obtain urine sample for routine urinalysis and urine pregnancy test (female only);
- Administer glucose load for OGTT and obtain blood sample for glucose and insulin at 2 hours following oral glucose load (Section 10.10);
- Perform complete physical examination (include Tanner Staging);
- Perform and evaluate 12-lead electrocardiogram (ECG);
- Conduct hand and wrist X-ray;
- Conduct DXA measurement (if applicable);
- Record any changes in concomitant medications;

- Record any adverse events reported or observed;
- Discontinue subject's study participation.

9.2 Study Period

The study period for each subject will begin when written informed consent is provided and will continue until Week 56 or early termination is completed. Sites should link the scheduling of visits to the randomization visit (Visit 2, Day 0). Visit windows are provided to allow subject and site scheduling convenience. However, every effort should be made to ensure that visits occur within these windows so that the overall treatment duration is 56 days for subjects who complete all visits. In certain instances, adverse event information may be required for events occurring after the study period (Section 11.3).

10.0 ASSESSMENT

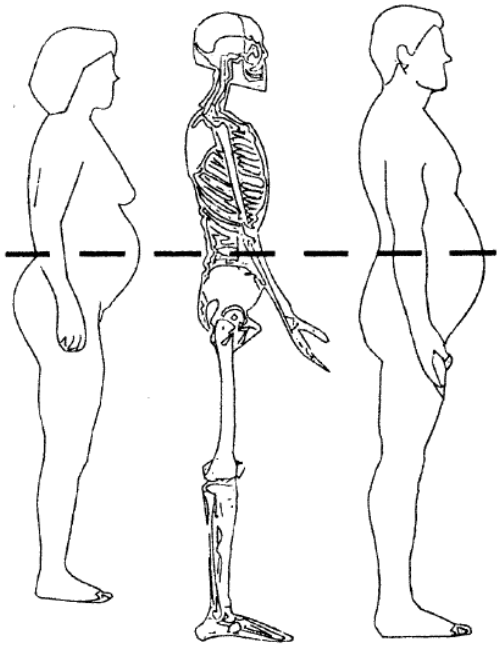
10.1 Weight Measurement

Subject weight will be obtained at every 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.

10.2 Waist Circumference Measurement

Waist circumference measurements will be taken using a measuring tape provided by the sponsor or designee, and should be obtained by the same individual, whenever possible, at every study visit. To measure the waist circumference, locate the top of the right iliac crest. Place the measuring tape in a horizontal plane (parallel to the floor) around the abdomen at the level of the top of the iliac crest as shown in Figure 2.

Figure 2. Measuring Tape Position for Waist Circumference Assessments



Ensure that the subject is relaxed. Ensure that the tape is snug but does not indent or compress the skin, and make the measurement (in centimeters) at the end of a normal expiration.

10.3 Height and BMI

Height measurements (cm) and BMI will be determined by the site at every visit (see BMI Chart in Appendix 2). Height measurements should be made using a calibrated stadiometer without shoes, socks, or hats. At each study visit, 3 independent measurements of height should be made, and the median value from these measurements recorded on the eCRF. Height should be recorded to the nearest centimeter. The same stadiometer should be used for all visits for any given subject. Stadiometer should be calibrated, at least daily, if used, following the equipment's manufacturer instructions and/or site SOP.

If a subject does not meet the BMI criterion for inclusion into the study (see CDC Clinical Growth Chart[8] in Appendix 3), no further screening procedures should be undertaken.

10.4 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, temperature) will be assessed at each study visit. 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 cuff should be employed for blood pressure measurements. Site staff should ensure at the Screening visit that the cuff size used is appropriate for the patient's arm circumference. Overweight and obese subjects often require a larger cuff than is typically used for adults of normal size and weight.

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.

10.5 Physical Examinations and Tanner Staging

A complete physical examination will be performed at baseline, 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. Puberty maturation will be assessed using the Tanner Staging (also known as the Sexual Maturity Rating (SMR), a gender specific 5-point scale of secondary sexual characteristics. Boys are rated for genital development and pubic hair growth, and girls are rated for breast development and pubic hair growth. Tanner Staging should be conducted by site personnel who have been trained on the proper technique for these assessments, and sites should ensure that the same observer conducts all Tanner Staging evaluations for any given subject.

10.6 Electrocardiograms

Twelve-lead ECG studies will be performed at baseline, 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.

10.7 X-Ray of the Hand and Wrist

An X-ray of the hand and wrist will be performed at baseline, and end of study or early termination visit to assess bone growth. Equipment and procedures used to obtain hand and wrist X-ray data will be standardized as described in a separate document. X-rays will be read at a central facility and the reader will be blinded.

10.8 DXA (Sub Study)

A bone health sub-study will be conducted at selected sites in approximately 100 subjects (25 each on placebo and mid-dose, and 50 on top-dose) to assess the effect of Qsymia administration on bone health using Dual X-ray Absorptiometry (DXA). DXA scans of the posterior-anterior (PA) spine (lumbar), and total body less head (TBLH) will be performed at baseline and at the end of study or early termination. Equipment and procedures used to obtain DXA data will be standardized as described in a separate document. Sites involved in DXA measurement will be trained on these procedures prior to performing scans on study subjects. Scans will be read at a central facility and the reader will be blinded.

The following enrollment criteria will apply:

1) Both male and female will be eligible to participate;
2) Subjects with a history of any non-traumatic fracture will not be eligible;
3) Subjects with juvenile osteoporosis at baseline will not be eligible; and

4) Subjects must meet manufacturer equipment specifications with regard to height and weight limitations.

10.9 Laboratory Tests

Laboratory tests will be performed at a licensed, certified central testing laboratory identified by the sponsor. 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. Table 2 summarizes the clinical laboratory testing for the study. Laboratory tests required at each study visit are detailed in Section 9.0 and Appendix 1.

Table 2: Clinical Laboratory Tests

Fasting blood chemistry	**Hematology**	**Other**
• albumin • alkaline phosphatase • ALT • AST • GGT • bicarbonate • blood urea nitrogen • serum calcium • serum chloride • serum sodium • carbon dioxide • creatinine (and estimated creatinine clearance) • glucose • lactate dehydrogenase • serum phosphorus • serum potassium • total and direct bilirubin • total protein • uric acid	• hemoglobin • hematocrit • red blood cell count • red blood cell indices • total white blood cell count • white blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) • platelet count	• thyroid stimulating hormone
	Lipid panel	**Urinalysis**
	• total cholesterol • LDL-C • HDL-C • triglycerides	• midstream urinalysis with reflex microscopic evaluation • pregnancy test (all female subjects)
		Urine Drug Screen
		• cannabinoids • amphetamines • cocaine • barbiturates • benzodiazepine • opiates
	Glycemic testing	**Serology**
	• HbA1c • insulin • glucose	• HBsAg • HCV • HIV

10.10 Oral Glucose Tolerance Test

An oral glucose tolerance test (OGTT) will be obtained at Visit 2 (after results from Visit 1 indicate the subject may be eligible for participation), and at end of study or early termination for all subjects.

The OGTT will use a 75 g oral glucose load; blood samples will be obtained at baseline and at 2 hours post glucose load for evaluation of both glucose and insulin levels.

10.11 CANTAB (Cambridge Neuropsychological Test Automated Battery)

Cognitive function will be assessed using selected tests from the CANTAB including paired associates learning, pattern recognition memory, and spatial span. The CANTAB will be assessed at baseline, Week 4, and end of study or early termination.

10.12 IWQOL-Kids

The Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire (Appendix 6) is a 27-item, self-administered instrument that will be completed at baseline (Visit 2), Visit 9 (Week 28) and end of study (Visit 16 at Week 56 or early termination).

The IWQOL-Kids is validated for use in adolescents aged 11-19 years old. This questionnaire is designed to evaluate the impact of excess weight on quality of life domains including physical mobility and comfort (Physical Comfort), how an individual feels about themselves and their body (Body Esteem), how an individual is treated in their social environment (Social Life), and the individual's perception of what family members may think and feel about them (Family Relations).[9] Because this instrument is intended to be completed directly by study subjects, it is important that site personnel remain neutral and do not influence subject answers on this questionnaire in any way. Should subjects ask questions to site personnel regarding the meaning of specific items, site personnel should not interpret items for the subjects, rather, they should repeat items back to subjects as they are worded on the instrument.

Site personnel must also recognize that the subject's answers to this questionnaire reflect their perceptions and attitudes at the time the questionnaire is completed, and that missing answers cannot be queried at a later date. It is critical, therefore, that site personnel review questionnaires for completeness at the time they are initially filled out, and that any missing answers are completed before the subject leaves the office.

10.13 PHQ-9: Modified for Teens

The Patient Health Questionnaire for Adolescents (PHQ-9: Modified for Teens) (Appendix 4) is a 9-item, self-administered instrument for the assessment of depression in adolescents.

Because this instrument is intended to be completed directly by study subjects, it is important that site personnel remain neutral and do not influence subject answers on this questionnaire in any way. Should subjects ask questions to site personnel regarding the meaning of specific items, site personnel should not interpret items for subjects, rather, they should repeat items back to subjects as they are worded on the instrument. Because this questionnaire assesses the subject's level of depression over a specific time frame (the past 2 weeks), answers not completed by subjects at a given visit cannot be queried or filled in at a later date. Site personnel, therefore, must carefully review questionnaires for completeness before subjects leave the clinic, and assure that questionnaires are properly completed.

The PHQ-9 questionnaire is being used to screen for and to assess the severity of any depression in study subjects. This questionnaire will be completed at every visit. Answers to the questionnaire may reveal evidence of significant depression, including the possibility of suicidal thoughts or plans. It is the responsibility of the investigator to evaluate subjects' responses to these questionnaires carefully, and to perform any additional evaluation and management that is indicated, including referral to a mental health professional if necessary. The evaluation by the investigator will be guided by the standardized methods for the PHQ-9 that have been developed to provide information regarding diagnosis of depression, severity of symptoms, and treatment follow-up options. Investigators should document any such problems identified in study source documents using standard diagnostic criteria and terminology as provided in the standardized guidelines. It is expected that any randomized subject presenting with a PHQ-9 score of 15 or

more should be treated and may require referral to a qualified mental health care professional.

10.14 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale is an 11-item clinician-administered assessment of both suicidal behavior (6 items) and suicidal ideation (5 items).[10] Each of the items comprising this scale corresponds to a specific level, or severity of ideation or behavior, and is answered on a yes/no basis. This assessment will be administered to all subjects at screening in order to confirm the absence of suicidal behavior or ideation with at least some intent to act on it, and to document the pre-study status of all subjects included in the treatment program. Subsequently, C-SSRS evaluations may be done at the investigator's discretions to evaluate and aid in diagnosis of reported or suspected events of suicidality. All C-SSRS assessments must be administered by a trained staff member. If any test reveals suicidal behavior or ideation with some intent to act on it, then test results must be confirmed by a physician investigator prior to discharging the subject from the study visit (see Appendix 5).

11.0 ADVERSE EVENT REPORTING

11.1 Adverse Events

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

Investigator must pursue and obtain information adequate to describe adverse events, their severity and 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 adverse events meet the criteria for classification as serious adverse events requiring immediate notification to VIVUS or its designated representative.

11.1.1 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 listed in Section 11.1.5.

11.1.2 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.

11.1.3 Abnormal Test Findings

Merely repeating an abnormal test, in the absence of any of the above conditions, 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; or
- Test result is considered by the investigator or sponsor to represent a clinically significant finding.

11.1.4 Mood or Depression Related Events

All subjects will be screened for the presence and severity of depression at screening using a validated survey instrument (PHQ-9) designed for assessment of depression in a primary care setting. The PHQ-9 is a self-administered, nine-item depression module based directly on the diagnostic criteria for major depressive disorder in DSM-V-TR. This questionnaire may be used at the investigator's discretion at other times during the study to aid in diagnosis and evaluation of reported or suspected events of depression.

Suicidality will also be assessed at each study visit using the C-SSRS (see Appendix 5). The C-SSRS may also be used at the investigator's discretion at unscheduled visits during the study to aid in evaluation and diagnosis of reported or suspected events of suicidality. Should this additional assessment indicate the presence any suicidal behavior, or suicidal ideation with any intent to act on it, study treatment will be stopped, and the investigator must provide appropriate referral to a mental health professional for additional assessment and management. Any such event must be reported to the Medical Monitor and to the sponsor within 24 hours. Subjects must be followed until resolution of these events.

Any mood- or depression-related adverse events must be documented using standard diagnostic criteria and terminology.

11.1.5 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.

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.

11.1.6 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 these criteria.

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 any of 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); or
- 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.

11.2 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 clinic 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.

11.3 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 this protocol.

11.4 Reporting Requirements

All adverse events will be reported on the adverse event page of the CRF. In addition, serious adverse events must also be reported on a separate SAE 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.

11.4.1 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 SAE.

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 its designee.

11.4.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the Adverse Event CRFs, which are to be submitted to VIVUS or its designee.

11.4.3 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.

12.0 STATISTICAL PLAN

12.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this clinical trial will be documented in a Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints 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. The SAP will be finalized and signed prior to the finalization of the database.

12.2 Sample Size Determination

In previous studies in adults, VI-0521 mid-dose (PHEN/TPM 7.5 mg/46 mg) resulted in a placebo-subtracted BMI reduction of 2.4 units with a standard error approximately 0.16 units and a within treatment standard deviation of 2.9. A very conservative estimate of the treatment

difference between the mid-dose and placebo would be 2 units of BMI which represents more than 2 standard errors below what was observed before. If we enroll 200 subjects (50 placebo, 50 mid-dose, and 100 top-dose), we will have at least 90% power to detect a statistically significant difference between the top-dose (PHEN/TPM 15 mg/92 mg) and the placebo because we could assume that the top-dose will have a higher effect size than the mid-dose. This calculation assumes that there will be an approximately 30% dropout rate. This sample size will also provide approximately 80% power to detect a statistically significant difference between the mid-dose and placebo.

12.3 Analysis Populations

Three different analysis populations will be used for analysis of data from this study, as described below:

- Randomized: This population will be comprised of all subjects who were initially randomized. This population will be used for summaries of subject disposition and baseline subject characteristics.
- Intent-to-treat (ITT)/Safety: This population will be comprised of all subjects who were initially randomized and received at least one dose of study drug. This will be the primary population for all summaries of subject disposition and baseline characteristics, efficacy analyses, and safety analyses for purposes of regulatory submissions.
- Modified Intent-to Treat (m-ITT): This population will be comprised of all randomized study subjects who receive study treatment and return for at least one post-randomization assessment of height and weight. This population will be used for the analysis of all efficacy variables for all other purposes, including but not limited to publications, presentations, and robustness of sensitivity of analyses.

12.4 Subgroups

BMI change will be tabulated by age and gender. Additionally, further exploratory subgroup analyses of the primary efficacy endpoints may include evaluation by race and/or other subgroups deemed medically and/or scientifically important.

12.5 Statistical Methods

12.5.1 Analysis of the Primary Endpoint

The primary endpoint for this study is the mean % change in BMI from baseline to end of study (Week 56).

Comparisons in the primary endpoint of change from the baseline BMI between treatment groups be assessed for the ITT population using a mixed effects model with repeated measures (MMRM) with factors of treatment, visit, treatment by visit interaction, baseline BMI value, age stratification, and gender stratification. Appropriate contrast will be applied for treatment comparisons at Week 56. The pairwise comparisons of interest are top-dose vs. placebo, and mid-dose vs. placebo, and top-dose vs. mid-dose. The primary null hypothesis will be that there is no treatment difference between any VI-0521 treatment groups and the placebo in the percent change from baseline to Week 56 in BMI. An appropriate contrast will be used for the

comparisons at Week 56. The family-wise type 1 error for the comparisons will be controlled by Fisher's protected least significant difference (LSD) method at the 0.05 significance level: placebo, mid-dose, and top-dose will be first compared for overall difference in the percent change from baseline in BMI. Once the overall difference is significant at the 0.05 significance level, the above 3 pairwise comparisons will be conducted using Fisher's LSD method at the 0.05 significance levels. The order for comparisons of interest is top-dose vs. placebo, mid-dose vs. placebo, and top-dose vs. mid-dose. Due to the fact that only three treatments are compared, the above procedure strongly controls the family-wise type 1 error.[11]

12.5.2 Method for Prevention and Treatment of Missing Values

For subjects who discontinue treatment prior to trial completion, every attempt will be made to have them continue with clinic visits and study assessments. Particular attention will be given to collecting Week 56 assessments of weight and height, regardless of when subjects discontinued treatment.

The above MMRM method used for the analysis of the primary endpoint has an inherent mechanism for imputing missing data. Therefore, MMRM is applied to the m-ITT population with the observed data without imputation. The following sensitivity analyses may be considered to explore the impact of missing data on the conclusion of the primary analysis. The details of the sensitivity analyses will be included in the statistical analysis plan.

The first sensitivity analysis is using a multiple imputation method based on the monotonic missing pattern under the assumption of missing at random (MAR). The intermittent missing data will be imputed using multiple imputation MCMC (Markov chain Monte Carlo) procedure.

The second sensitivity analysis is also using multiple imputation, however, under the assumption of missing not at random (MNAR) to explore the validity of MAR using pattern-mixture model:

1) For subjects who discontinue study participation prior to Week 56 and do not have follow-up visit, the missing data will be imputed using the observed data from the subjects in the same arm who discontinue the study treatment but have the primary endpoint measurement in the follow up visit using a regression method. The intermittent missing data will be imputed using multiple imputation MCMC procedure. an ANCOVA model using a similar mixed procedure (without the repeated measures) as the primary analysis will be applied to these multiple-imputed % change in BMI at Week 56 with treatment, baseline BMI value as a covariate, and age and gender as stratification factors. The results of ANCOVA analysis on the multiple imputed datasets will be combined and summarized.
2) Tipping point analyses: Subjects from the treatment arm who drop out the study will have their unobserved efficacy data imputed by the observed data from completers in the same arm using the multiple imputation method based on the monotonic missing pattern under the assumption of missing at random (MAR) with the resulting imputed values further worsened by an amount δ. Subjects who drop out the study from the control arm will be assumed to exhibit the same evolution of the disease as the completers in control arms and their values will be imputed by the multiple imputation method based on the monotonic missing pattern under the assumption of missing at random (MAR) above without the addition of δ. Sensitivity analysis may be performed for a range of δ to find a "tipping point" value of δ at which study conclusions start to change. When $\delta=0$ the

missing data are assumed to be MAR. When $\delta > 0$, the missing data are assumed to be MNAR.

The third sensitivity analysis is the last observation carried forward (LOCF). For those subjects who discontinue study participation prior to Week 56, the last observed weight and height will be used to derive the change in BMI.

Similar analyses will be performed for the primary endpoint for the m-ITT population.

12.5.3 Analysis of the Secondary Endpoints

If both the mid- and top-doses are shown to be statistically significantly better than placebo for the primary endpoint using the Fisher's LSD procedure, then the secondary endpoints will be tested in a stepwise way to preserve the familywise type 1 errors. Details of the stepwise testing procedure for secondary efficacy endpoints will be described in a prospective SAP.

Percent of subjects achieving a reduction $\geq 5\%$ from baseline in BMI at Week 56 will be analyzed using a logistic regression, with treatment, age and gender stratification as the main effect and baseline BMI value as a covariate at the 0.05 significance level. The adjusted odds ratios between the top-dose and placebo and between the mid-dose and placebo will be calculated together with their 95% confidence intervals. The p-values for the comparisons will also be generated.

The percent of subjects achieving a reduction $\geq 10\%$ and $\geq 15\%$ from baseline in BMI at Week 56 will be analyzed similarly.

Secondary efficacy endpoints that are continuous variables will be analyzed by a similar MMRM model as for the primary endpoint where the baseline BMI value will be replaced by the baseline value of the corresponding endpoint as a covariate.

The above analyses will be conducted for both the ITT and m-ITT populations.

12.6 Safety Analysis

All safety analyses will be done for the ITT population. Safety data will be summarized for all treatment groups.

Safety will be assessed by an evaluation of adverse events (each study visit); laboratory parameters (screening, periodically during the study and end of study); electrocardiograms; physical examinations (screening, end of study); PHQ-9: Modified for Teens (see Appendix 4), C-SSRS, and vital signs, at each study visit). Descriptive statistics will be generated for the questionnaire data.

12.6.1 Analysis of CANTAB

CANTAB will be scored according to its instructions. The scores will be summarized by treatment descriptively.

12.6.2 Analysis of Hand and Wrist X-Ray

Changes from baseline to Week 56 in hand and wrist X-ray will be evaluated. Differences between treatment groups will be evaluated using methods similar to those used to evaluate other

continuous variables.

12.6.3 Analysis of DXA

In the subset of subjects treated at sites where DXA scans are being done, mean changes from baseline to Week 56 in bone mineral density (BMD) and bone mineral content (BMC)-Z scores will be evaluated. The mean change in BMD and BMC will be summarized descriptively as a continuous variable.

12.6.4 Adverse Events

Adverse events will be coded using a MedDRA coding dictionary. The number and percentage of subjects who reported at least one adverse event in each system organ class and preferred term category, and the total number and percentage of subjects with any AE over all system organ classes will be summarized by treatment group.

Subsets of AEs that are considered serious or required discontinuation of the study medication will be summarized separately and listed by subject.

12.6.5 Clinical Laboratory Tests

A summary of observed values and change from baseline will be presented for all laboratory parameters with numerical measures using descriptive statistics. Shift tables displaying low-normal-high at baseline versus low-normal-high at end of study in a 3-by-3 contingency table will be provided. For selected laboratory parameters, scatter plots of baseline versus Week 56 results, will be produced by treatment group.

A laboratory value that is above or below normal range will be considered an abnormal value. For selected laboratory parameters, threshold limits of clinical concern will be defined as multiplicative factors of the normal ranges. The list of multiplicative factors for each laboratory parameter will be included in the Statistical Analysis Plan. The frequency and percentage of subjects with laboratory results above or below the normal range and threshold limits at each scheduled assessment or any time during the treatment will be summarized by treatment group.

12.6.6 Vital Signs and Other Safety Evaluations

Mean blood pressures, heart rate, respiration, rate and temperature, obtained at each visit, will be summarized and plotted by treatment group. Medications, other than study medication, taken during the study will be considered as concomitant medications. They will be summarized by treatment group according to the preferred terms, using the World Health Organization (WHO) Drug Dictionary.

12.7 Interim Analysis

No interim analysis is planned.

12.8 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) with multidisciplinary representation will be established to evaluate accumulating trial data on a periodic basis and to assess the ongoing

safety of the study for the subjects enrolled and to be enrolled. As a result, following each data review, the DMC will make a recommendation to the sponsor regarding continuation, revision, or termination of the study. Details related to DMC responsibilities, authorities, and procedures will be documented in the DMC charter, which will be finalized by the DMC prior to the first DMC data review meeting.

13.0 TRIAL TERMINATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the institutional review board (IRB)/independent ethics committee (IEC), drug safety problems, or at the discretion of VIVUS. In addition, VIVUS retains the right to discontinue this study at any time.

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

14.0 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.

15.0 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) 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 study-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.

16.0 ETHICAL CONSIDERATIONS

16.1 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 (ICF) 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 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.

16.2 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.

16.3 Subject Information and Consent/Assent

The informed consent form and any changes to the informed consent form during the course of the trial must be agreed to by VIVUS 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 study 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 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.

Parental consent and/or subject assent will be obtained according to IRB/IEC guidelines.

17.0 DATA HANDLING AND RECORD KEEPING

17.1 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 included 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. A CRF is required and should be completed for each randomized 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.

17.2 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 VIVUS' written permission from VIVUS before disposing of any records prior to completion of the required/stipulated retention period.

18.0 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.

19.0 REFERENCES

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APPENDIX 1: SCHEDULE OF EVENTS

	Screening	Baseline (± 3 days)	Treatment (± 1 Week)													
Study Weeks→	**Screen[a]**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56/ET**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Informed Consent/Assent	X															
Demographics and Medical History	X															
Review Inclusion/Exclusion	X	X														
Weight, Waist Circumference, Height, and BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (include Tanner Staging)		X														X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-9/C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram		X														X
DXA (selected sites only)		X														X
Chemistry (Fasting)	X		X	X					X							X
Hematology/Lipids	X								X							X
TSH, HIV, HCV, HBsAg	X															
HbA1c	X				X						X					X
Urinalysis	X															X
Urine Drug Screen	X															
Urine Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand and Wrist X-ray (bone age assessment)		X														X
OGTT[b]		X														X
Cognitive Battery (CANTAB)		X	X													X
IWQOL-Kids		X														X
Diet/Lifestyle Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contraception Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization		X														
Dispense Study Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X

[a] Up to – 4 weeks
[b] Blood sample at 2 hours post glucose load

APPENDIX 2: BMI CONVERSION CHART

Weight	(lb)	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210
	(kg)	49.9	52.2	54.5	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
Height																						
(in)	(cm)																					
55	139.7	26	27	28	29	30	31	33	34	35	36	37	38	40	41	42	43	44	45	46	48	49
56	142.2	25	26	27	28	29	30	31	33	34	35	36	37	38	39	40	41	43	44	45	46	47
57	144.8	24	25	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45
58	147.3	23	24	25	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44
59	149.9	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43
60	152.4	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
61	154.9	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40
62	157.5	20	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38
63	160.0	19	20	21	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37
64	162.6	19	20	21	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36
65	165.1	18	19	20	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35
66	167.6	18	19	19	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34
67	170.2	17	18	19	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33
68	172.7	17	17	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32
69	175.3	16	17	18	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31
70	177.8	16	16	17	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30
71	180.3	15	16	17	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29
72	182.9	15	16	16	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29
73	185.4	15	15	16	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28
74	188.0	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27
75	190.5	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26

APPENDIX 3: CDC CLINICAL GROWTH CHARTS[8]

	Male	Female
Age (in months)	**95th Percentile BMI Value**	**95th Percentile BMI Value**
143.5	24.1	25.2
144.5	24.2	25.3
145.5	24.3	25.3
146.5	24.4	25.4
147.5	24.5	25.5
148.5	24.6	25.6
149.5	24.6	25.7
150.5	24.7	25.8
151.5	24.8	25.9
152.5	24.9	26.0
153.5	24.9	26.0
154.5	25.0	26.1
155.5	25.1	26.2
156.5	25.2	26.3
157.5	25.3	26.4
158.5	25.3	26.5
159.5	25.4	26.5
160.5	25.5	26.6
161.5	25.5	26.7
162.5	25.6	26.8
163.5	25.7	26.9
164.5	25.8	26.9
165.5	25.8	27.0
166.5	25.9	27.1
167.5	26.0	27.2
168.5	26.0	27.3
169.5	26.1	27.3
170.5	26.2	27.4
171.5	26.3	27.5
172.5	26.3	27.6
173.5	26.4	27.6
174.5	26.5	27.7
175.5	26.5	27.8
176.5	26.6	27.8
177.5	26.6	27.9
178.5	26.7	28.0
179.5	26.8	28.1
180.5	26.8	28.1
181.5	26.9	28.2

	Male	Female
Age (in months)	**95th Percentile BMI Value**	**95th Percentile BMI Value**
182.5	27.0	28.3
183.5	27.0	28.3
184.5	27.1	28.4
185.5	27.1	28.5
186.5	27.2	28.5
187.5	27.3	28.6
188.5	27.3	28.7
189.5	27.4	28.7
190.5	27.4	28.8
191.5	27.5	28.8
192.5	27.6	28.9
193.5	27.6	29.0
194.5	27.7	29.0
195.5	27.7	29.1
196.5	27.8	29.2
197.5	27.9	29.2
198.5	27.9	29.3
199.5	28.0	29.3
200.5	28.0	29.4
201.5	28.1	29.5
202.5	28.1	29.5
203.5	28.2	29.6
204.5	28.3	29.6
205.5	28.3	29.7
206.5	28.4	29.8
207.5	28.4	29.8
208.5	28.5	29.9
209.5	28.5	29.9
210.5	28.6	30.0
211.5	28.7	30.0
212.5	28.7	30.1
213.5	28.8	30.2
214.5	28.8	30.2
215.5	28.9	30.3
216.5	29.0	30.3
217.5	29.0	30.4
218.5	29.1	30.4
219.5	29.1	30.5
220.5	29.2	30.6

APPENDIX 4: PHQ-9: MODIFIED FOR TEENS

PHQ-9: Modified for Teens

Name: _____ **Clinician:** _____ **Date:** _____

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an **"X"** in the box beneath the answer that best describes how you have been feeling.

	(0) Not At All	(1) Several Days	(2) More Than Half the Days	(3) Nearly Every Day
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				
9. Thoughts that you would be better off dead, or of hurting yourself in some way?				

In the **past year** have you felt depressed or sad most days, even if you felt okay sometimes?
[ ] Yes [ ] No

If you are experiencing any of the problems on this form, how **difficult** have these problems made it for you to do your work, take care of things at home or get along with other people?
[ ] Not difficult at all [ ] Somewhat difficult [ ] Very difficult [ ] Extremely difficult

Has there been a time in the **past month** when you have had serious thoughts about ending your life?
[ ] Yes [ ] No

Have you **EVER**, in your WHOLE LIFE, tried to kill yourself or made a suicide attempt?
[ ] Yes [ ] No

***If you have had thoughts that you would be better off dead or of hurting yourself in some way, please discuss this with your Health Care Clinician, go to a hospital emergency room or call 911.*

Office use only **Severity score:** _____

Modified with permission by the GLAD-PC team from the PHQ-9 (Spitzer, Williams, & Kroenke, 1999), Revised PHQ-A (Johnson, 2002), and the CDS (DISC Development Group, 2000)

APPENDIX 5: SAMPLE COLUMBIA SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M.A., Halberstam B. & Mann J. J, Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", answer questions 3, 4 and 5.	**Lifetime - Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself?*** ***Do you intend to carry out this plan?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION		
Ideation Type *Type # (1-5)* *Description of Ideation* *Baseline* *Most Common Ideation: _____ _____* *Most Severe Ideation: _____ _____*	**Lifetime – Time He/She Felt Most Suicidal**	
The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.	Most Common	Most Severe
Frequency ***How many times have you had these thoughts?*** 1. Less than once a week 2. Once a week 3. 2-5 times in week 4. Daily or almost daily 5. Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** 1. Fleeting - few seconds or minutes 2. Less than 1 hour/some of the time 3. 1-4 hours/a lot of time 4. 4-8 hours/most of day 5. More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** 1. Easily able to control thoughts 2. Can control thoughts with little difficulty 3. Can control thoughts with some difficulty 4. Can control thoughts with a lot of difficulty 5. Unable to control thoughts 0. Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** 1. Deterrents definitely stopped you from attempting suicide 2. Deterrents probably stopped you 3. Uncertain that deterrents stopped you 4. Deterrents most likely did not stop you 5. Deterrents definitely did not stop you 0. Does not apply; wish to die only	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** 1. Completely to get attention, revenge or a reaction from others. 2. Mostly to get attention, revenge or a reaction from others. 3. Equally to get attention, revenge or a reaction from others and to end/stop the pain. 4. Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). 5. Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself*** ***(like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ **Total # of attempts** ____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted ____

Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐	**No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐	**No** ☐
Completed Suicide:	**Yes** ☐	**No** ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Worst/Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M.A., Halberstam B. & Mann J. J, Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," answer questions 3, 4 and 5.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it".* ***Have you been thinking about how you might do this?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself?*** ***Do you intend to carry out this plan?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION		
Ideation Type Type # (1-5) Description of Ideation *Most Common Ideation: _____ _____* *Most Severe Ideation: _____ _____*	**Since Last Visit**	
The following features should be rated with respect to both most common and most severe types of ideation experienced since last visit. Only rate most common if most severe and most common are different.	Most Common	Most Severe
Frequency ***How many times have you had these thoughts?*** 1. Less than once a week 2. Once a week 3. 2-5 times in week 4. Daily or almost daily 5. Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** 1. Fleeting - few seconds or minutes 2. Less than 1 hour/some of the time 3. 1-4 hours/a lot of time 4. 4-8 hours/most of day 5. More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** 1. Easily able to control thoughts 2. Can control thoughts with little difficulty 3. Can control thoughts with some difficulty 4. Can control thoughts with a lot of difficulty 5. Unable to control thoughts 0. Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from taking your life or acting on thoughts of committing suicide?*** 1. Deterrents definitely stopped you from attempting suicide 2. Deterrents probably stopped you 3. Uncertain that deterrents stopped you 4. Deterrents most likely did not stop you 5. Deterrents definitely did not stop you 0. Does not apply; wish to die only	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** 1. Completely to get attention, revenge or a reaction from others. 2. Mostly to get attention, revenge or a reaction from others. 3. Equally to get attention, revenge or a reaction from others and to end/stop the pain 4. Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). 5. Completely to end or stop the pain (you couldn't go on living with the pain or how you were	____	____

feeling).		

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ **Total # of attempts** ____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else.	**Yes** ☐ **No** ☐ Total # of aborted

Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything? If yes, describe:	____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Completed Suicide:	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Worst/Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX 6: IWQOL-KIDS

The subject will answer questions based on what best applies to them in the past seven days. Each question contains five response options: “always true”, “usually true”, “sometimes true”, “rarely true”, and “never true”, scaled from 1 to 5, respectively.

Physical Comfort

1. Because of my weight I avoid using stairs whenever possible.
2. Because of my weight it is hard for me to bend over to tie my shoes or to pick something up off the floor.
3. Because of my weight it is hard for me to move around.
4. Because of my weight it is hard for me to fit into seats in public places (e.g. movie theaters, desks at school, and booths in restaurants).
5. Because of my weight my knees or ankles hurt.
6. Because of my weight it is hard for me to cross my legs.

Body Esteem

7. Because of my weight I am ashamed of my body.
8. Because of my weight I don’t like myself very much.
9. Because of my weight I try not to look at myself in mirrors or in photographs.
10. Because of my weight I have a hard time believing compliments that I receive from others.
11. Because of my weight I am lacking in self-confidence.
12. Because of my weight I avoid activities that involve wearing shorts or a bathing suit.
13. Because of my weight it is very difficult for me to buy clothing.
14. Because of my weight I don’t like to change my clothes or undress in front of others.
15. Because of my weight I am embarrassed to try out for activities at school.

Social Life

16. Because of my weight people tease me or make fun of me.
17. Because of my weight people talk about me behind my back.
18. Because of my weight people avoid spending time with me.
19. Because of my weight people stare at me.
20. Because of my weight I have trouble making or keeping friends.
21. Because of my weight people don’t think I’m very smart.

Family Relations

22. Because of my weight family members treat me differently from the way they treat other people.
23. Because of my weight family members talk about me behind my back.
24. Because of my weight one or more people in my family reject me.
25. Because of my weight my parents aren’t proud of me.
26. Because of my weight family members make fun of me.
27. Because of my weight family members don’t want to be seen with me.

APPENDIX 7: FORMULAS FOR ESTIMATING CREATININE CLEARANCE

Creatinine clearance in adolescent boys and girls should be calculated based on height (HT) and serum creatinine (sCr) using the Schwartz formula (refs) as noted below.[7]

$$CrCl_{adolescent\ boy} = \frac{[0.70 \times Ht(cm)]}{sCr\ (\frac{mg}{dL})}$$

$$CrCl_{adolescent\ girl} = \frac{[0.55 \times Ht(cm)]}{sCr\ (\frac{mg}{dL})}$$

CLINICAL PROTOCOL

Protocol No.	OB-403
Title:	A Phase IV, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Determine the Safety and Efficacy of VI-0521 in Obese Adolescents
Current Version:	Amendment #2, 21 June 2019
Previous Version:	Original, 24 August 2017 Amendment #1, 05 October 2018
Sponsor:	VIVUS, Inc. 900 E. Hamilton Ave, Suite 550 Campbell, CA 95008 Tel: (650) 934-5200

Approval Signatures:

MD 21 JUN 2019

Santosh Varghese, MD, Chief Medical Officer **Date**

21 Jun 2019

Craig Peterson, Sr. Director, Clinical Research **Date**

INVESTIGATOR AGREEMENT PAGE

VIVUS, Inc.

Protocol Title: A Phase IV, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Determine the Safety and Efficacy of VI-0521 in Obese Adolescents

Version: Amendment #2, 21 June 2019

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 in writing. I also agree to conduct this clinical trial in compliance with all federal, state and local regulations, Good Clinical Practice, and the Declaration of Helsinki, and the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

Principal Investigator: _____

Date: _____

Printed Name: _____

Institution: _____

Address: _____

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2.0 PROTOCOL SYNOPSIS

Title of Clinical Study:	A Phase IV, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Determine the Safety and Efficacy of VI-0521 in Obese Adolescents
Sponsor:	VIVUS, Inc. (VIVUS)
Phase of Development:	4
Indication:	Weight management in obese adolescents
Study Rationale:	Obesity remains a major problem in pediatrics. National Health and Nutrition Examination Survey (NHANES) data indicate that 18.5% of children and adolescents age 2 to 19 years and 20.6% of adolescents age 12 to 19 years met the definition of obesity in 2015-2016. Obesity in childhood or adolescence increases the risk of adult obesity, type 2 diabetes mellitus, and dyslipidemia. VI-0521 (marketed as Qsymia® in the United States), a fixed dose combination of immediate-release (IR) phentermine (PHEN) and extended-release (ER) topiramate (TPM), was approved in July 2012 by the FDA as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in overweight and obese adults. Topiramate is used as an anticonvulsant in children as young as 2 years, typically beginning at doses of 1–3 mg/kg/day and titrating as needed to 5–9 mg/kg/day. Adequate and well-controlled studies of phentermine have not been conducted in children. Based on a previously completed PK study of obese adolescents (study OB-402), PK parameters in obese adolescent subjects were consistent with those observed in previous Phase 1 to 3 studies conducted in adult obese subjects. This study is being conducted to assess the safety and efficacy of VI-0521, accompanied by a lifestyle modification program, in obese adolescents.
Study Design:	In this multicenter, randomized, double-blind, placebo-controlled, parallel-design study, approximately 200 subjects will be enrolled at approximately 20 sites in the United States. Subjects will be randomly assigned in a 1:1:2 ratio to placebo, N=50; mid-dose (PHEN/TPM 7.5 mg/46 mg), N= 50; or top-dose (PHEN/TPM 15 mg/92 mg), N=100 of VI-0521, to be taken orally once daily in the morning. Randomization will be stratified by age (12-14 vs 15-16 years old) and gender. The study will consist of a screening period of up to 28 days, followed by a 56-week treatment period.

<table>
<tr><td></td><td>Subjects will be instructed to follow a mild hypocaloric diet modification program representing a 500-calorie/day deficit and to implement a family-based lifestyle modification program for adolescents, as tolerated, throughout the study period. The lifestyle program will include physical activity, behavior change, and family support. The same lifestyle modification program, specific to this population, will be implemented across all sites. Study drug doses will be titrated according to the following schema.
<table>
<tr><th rowspan="2">Group</th><th rowspan="2">Treatment Dosage for PHEN/TPM (mg)</th><th colspan="4">Titration Dose for PHEN/TPM (mg)</th></tr>
<tr><th>Weeks 1-2</th><th>Weeks 3-4</th><th>Weeks 13-14</th><th>Weeks 15-16</th></tr>
<tr><td>Placebo</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/0</td><td>0/0</td></tr>
<tr><td>VI-0521 Mid</td><td>7.5/46</td><td>3.75/23</td><td>7.5/46</td><td>7.5/46</td><td>7.5/46</td></tr>
<tr><td>VI-0521 Top</td><td>15/92</td><td>3.75/23</td><td>7.5/46</td><td>11.25/69</td><td>15/92</td></tr>
</table>
Subjects who are unable to tolerate the assigned dose may be treated at a reduced dose or may take a drug holiday as defined in the protocol.

All subjects will return at approximately 4-week intervals for study assessments. All female subjects will undergo a pregnancy test at each visit. Subjects who discontinue the treatment during the study will be encouraged to remain on study (off study drug) for continued follow-up by attending all remaining visits and have all study-related procedures performed, and to return at the 56-week time point for measurements and evaluations. For those who choose to completely withdraw from the study at any point, the end of study (Week 56) procedures should be completed.</td></tr>
<tr><td>Study Objectives:</td><td>The primary objectives are to evaluate the safety and efficacy of VI-0521 (PHEN/TPM 7.5 mg/46 mg and PHEN/TPM 15 mg/92 mg doses) for the treatment of obesity in adolescents. The secondary objective is to characterize changes in obesity-related risk factors.</td></tr>
<tr><td>Duration of Treatment:</td><td>The treatment period will be 56 weeks.</td></tr>
<tr><td>Sample Size:</td><td>Approximately 200 subjects</td></tr>
<tr><td>Number of Sites/Locations:</td><td>Approximately 20 sites in the United States</td></tr>
</table>

Study Population:	**Key Inclusion Criteria** (see Section 7.1 for a complete list): • Aged ≥ 12 years and < 17 years at the time of screening; • BMI ≥ the 95th percentile, with documented history of failure to lose sufficient weight or failure to maintain weight loss in a lifestyle modification program; • If female, must be using adequate contraception, defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence.
Study Population:	**Key Exclusion Criteria** (see Section 7.2 for a complete list): • Type 1 diabetes; • Congenital heart disease; clinically significant ECG abnormality; • Physical exam, vital signs, or laboratory abnormality; clinically significant hepatic or renal disease; • Creatinine clearance (Schwartz formula) < 60 mL/minute; • Clinically significant thyroid dysfunction as evidenced by signs, symptoms, or TSH > 1.5 x ULN; • Obesity of known genetic or endocrine origin; • History of bipolar disorder or psychosis, greater than one lifetime episode of major depressive disorder, depression of moderate or greater severity, or presence or history of suicidal behavior or active suicidal ideation; • Recent weight instability, or prior bariatric surgery; • History of glaucoma or increased intraocular pressure; • Current smoker or smoking cessation within 3 months of screening; • Currently taking or plan on taking any of following medications during the study: o Anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, GABA analogues, hydantoins, phenyltriazines, succinimides, and other agents (valproic acid and its derivatives, carbamazepine and its derivatives, zonisamide, and felbamate); o Tricyclic antidepressants, MAOIs, lithium, levodopa, and dopamine receptor agonists; o Carbonic anhydrase inhibitors; o Insulin, SFUs, GLP-1 agonists, SGLT-1, and SGLT-2 inhibitors;

	○ Chronic systemic steroids (i.e. glucocorticoids, anabolic steroids) other than oral contraceptives; ○ Treatment for hyperactivity disorder; or ○ OTC, prescription medications, herbal agents and dietary supplements used with the intention to lose body weight.
Study Drug Form and Strength:	• Low-dose (for titration purposes only): One PHEN/TPM 3.75/23 mg capsule administered daily • Mid-dose: One PHEN/TPM 7.5/46 mg capsule administered daily • ¾-dose (for titration purposes only): One PHEN/TPM 11.25/69 mg capsule administered daily • Top-dose: One PHEN/TPM 15/92 mg capsule administered daily Study drug will be packaged into 2 types of kits; titration kits (blister cards) for use during the first 4 weeks of dosing and the first 4 weeks following up-titration for subjects randomized to the top-dose (Weeks 13-16), and treatment kits (bottles), for use once subjects have been titrated to their assigned dosage.
Regimen/Administration:	Each capsule of study drug will be taken orally in the morning, with or without food, and with water.
Primary Efficacy Endpoints:	The primary endpoint is the mean percent change in BMI from baseline to end of study (Week 56)
Second Efficacy Endpoints:	The secondary endpoints are: • Percent of subjects achieving a reduction ≥ 5%, ≥ 10% and ≥ 15% of baseline BMI at Week 56; • Change from baseline in waist circumference at Week 56; • Change from baseline in fasting insulin and Whole Body Insulin Sensitivity Index (Matsuda) at Week 56; • Change from baseline in triglycerides and HDL-C at Week 56; • Change from baseline in blood pressure at Week 56.
Exploratory Endpoints:	Additional exploratory analyses will be conducted to evaluate effects of treatment on IWQOL-Kids questionnaire scores, changes in various glycemic and lipid markers, and change in BMI Z-score.
Safety Evaluations and Oversight:	Safety monitoring and tolerability will be assessed by evaluation of adverse events/serious adverse events, physical exams, vitals, cognitive function tests using the CANTAB, responses to PHQ-9, C-SSRS, bone age (X-ray of the hand and wrist), DXA in a

	subset (approximately 25 subjects each on the placebo and mid-dose, and 50 subjects on the top-dose), and periodic monitoring of laboratory test results. An independent Data Monitoring Committee (DMC) will be established to evaluate accumulating trial data on a periodic basis and to assess the ongoing safety of the study.
Statistical Methods:	<u>Analysis Populations:</u> Randomized: This population will be comprised of all subjects who were initially randomized. This population will be used for summaries of subject disposition and baseline subject characteristics. Intent-to-treat (ITT)/Safety: This population will be comprised of all subjects who were initially randomized and received at least one dose of study drug. This will be the primary population for all summaries of subject disposition and baseline characteristics, efficacy analyses, and safety analyses for purposes of regulatory submissions. Comparisons in the primary endpoint of change from the baseline BMI between treatment groups will be assessed using a mixed effects model with repeated measures (MMRM) with factors of treatment, visit, treatment by visit interaction, baseline BMI value, age stratification, and gender stratification. Appropriate contrast will be applied for treatment comparisons at Week 56. The 3 comparisons of interest are 1) top-dose vs. placebo; 2) mid-dose vs. placebo; and 3) top-dose vs. mid-dose. Sensitivity analyses will be conducted to examine the impact of missing data on the robustness of statistical conclusions. In previous studies in adults, PHEN/TPM 7.5 mg/46 mg dose resulted in a placebo-subtracted BMI reduction of 2.4 units with a standard deviation of 2.9. Assuming a similar effect size, with enrollment of 200 subjects (100 randomized to the top-dose, 50 randomized to the mid-dose, and 50 randomized to the placebo), the present study will have greater than 90% power to detect a significant difference in BMI reduction between the top-dose and the placebo, and approximately 80% power to detect a significant difference between the mid-dose group and the placebo. The above power calculation assumes very conservative differences between the active doses and placebo and a worst case 30% dropout rate.

3.0 LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
AE	Adverse event
ACE	Angiotensin converting enzyme
ADHD	Attention-deficit/hyperactivity disorder
ANCOVA	Analysis of covariance
ARB	Angiotensin receptor blocker
AST	Aspartate transaminase
ALT	Alanine aminotransferase
AUC	Area under the curve
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
^{o}C	Degrees Celsius
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CL	Apparent clearances
C_{max}	Maximum observed drug concentration
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DMC	Data Monitoring Committee
DXA	Dual-energy X-ray absorptiometry
ECG	Electrocardiogram
ER	Extended-release
^{o}F	Degrees Fahrenheit
FDA	Food and Drug Administration
GABA	Gamma-aminobutyric acid
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase

Abbreviation or Term	Definition/Explanation
GLP-1	Glucagon-like peptide -1
HbA1c	Hemoglobin A1c
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
ITT	Intent to treat
IR	Immediate-release
IRB	Institutional Review Board
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
IWRS	Interactive Web Response System
LDL-C	Low-density lipoprotein cholesterol
LOCF	Last observation carried forward
LSD	Least significant difference
MAOI	Monoamine oxidase inhibitor
MAR	Missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
m-ITT	Modified intent to treat
mmHg	Millimeters of mercury pressure
MMRM	Mixed effect Model with Repeated Measures
MNAR	Missing not at random
NHANES	National Health and Nutrition Examination Survey
OGTT	Oral glucose tolerance test
OTC	Over-the-counter
PA	Posterior-anterior
PHEN	Phentermine

Abbreviation or Term	Definition/Explanation
PHQ	Patient Health Questionnaire
PI	Principal Investigator
PK	Pharmacokinetics
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Standard deviation
sCr	Serum creatinine
SFU	Sulfonylurea
SGLT	Sodium glucose transporter
TBLH	Total body less head
T_{max}	Time to maximum concentration
TPM	Topiramate
TSH	Thyroid Stimulating Hormone
TZD	Thiazolidinedione
ULN	Upper limit of normal
USA	United States of America
Vc/F	Apparent volume of distribution
WHO	World Health Organization

4.0 BACKGROUND

Obesity remains a major problem in pediatrics. National Health and Nutrition Examination Survey (NHANES) data indicate that 18.5% of children and adolescents age 2 to 19 years and 20.6% of adolescents age 12 to 19 years met the definition of obesity in2015-2016.[1] Obesity in childhood or adolescence increases the risk of adult obesity, type 2 diabetes mellitus, and dyslipidemia.[2,3,4] Although lifestyle changes and behavior modification programs have shown some benefit, these measures have not been widely adopted for the treatment of obesity in children. When intensive lifestyle modification is unsuccessful in reaching weight loss goals, adjunct pharmacotherapy may be warranted. Few weight loss drug therapies have been evaluated in children and currently there is only one FDA approved product (orlistat) to treat adolescent obesity. Additional pharmacotherapy options are needed in order to address pediatric obesity.

VI-0521 (marketed as Qsymia® in the United States), a fixed dose combination of immediate-release (IR) phentermine (PHEN) and extended-release (ER) topiramate (TPM), was approved in July 2012 by the Food and Drug Administration (FDA) as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in overweight and obese adults. Mean weight loss of > 10% was achieved after one year of treatment in obese adults randomized to top-dose (PHEN/TPM 15 mg/92 mg) and > 8% in those randomized to mid-dose (PHEN/TPM 7.5 mg/46 mg) of VI-0521. Weight loss was sustained over two years. In addition to weight loss, VI-0521 also resulted in significant reductions in blood pressure, improved glycemic parameters, increased HDL-C, and reduced triglycerides.[5] The doses employed in this combination represent a fraction of those commonly prescribed as single agents for other indications.

Topiramate is used as an anticonvulsant in children as young as 2 years, typically beginning at doses of 1–3 mg/kg/day and titrating as needed to 5–9 mg/kg/day.[6] The 92 mg of topiramate in the top-dose of VI-0521 falls well within the dose range currently used in children. Adequate and well-controlled studies of phentermine have not been conducted in children. The top-dose of VI-0521 contains roughly ½ of the maximum phentermine dose currently approved for use in adults.

The single- and multiple-dose pharmacokinetics (PK) of topiramate and potential drug interactions between topiramate and phentermine in VI-0521 have been fully investigated in the adult population. The major route of elimination of phentermine and its metabolites is through the urine. Topiramate is not extensively metabolized and is primarily eliminated unchanged in the urine (approximately 70% of an administered dose). Previous population PK analyses demonstrated that creatinine clearance and body weight were the most important components describing the PK of phentermine and topiramate in VI-0521, that the PK parameters of phentermine and topiramate were dose proportional, and that no relationship was observed between PK parameters and age, gender, or body mass index (BMI) for either drug.

By the time children reach adolescent age, their kidneys are fully developed and there is little variation in kidney function compared to adults.

Based on the PK study of obese adolescents (study OB-402), plasma concentrations in obese adolescents were consistent with those observed in previous Phase 1 to 3 studies conducted in adult obese subjects.

For phentermine, geometric means of individual posterior Bayes PK parameters (apparent clearance [CL/F] and apparent volume of distribution [Vc/F]) in obese adolescent subjects were within 10% of those previously assessed in obese adult subjects enrolled in Phase 2 and Phase 3

studies, and arithmetic means of area under the curve (AUC) and C_{max} in obese adolescent subjects were within 10% of arithmetic means previously obtained based on rich concentration-time profiles of phentermine under steady-state in obese adults. Medians of T_{max} in adolescent subjects were within 11% of medians of T_{max} observed in obese adults.

For topiramate, geometric means of individual posterior Bayes CL/F were within 30% of those previously assessed in obese adult subjects enrolled in Phase 2 and Phase 3 studies, with higher CL/F values in the adolescent population. Geometric means of posterior Bayes Vc/F of TPM in obese adults and obese adolescents were similar. The higher CL/F values in adolescents are consistent with lower serum creatinine values in this population, but did not result in marked differences in exposure, as arithmetic means of AUC and C_{max} of topiramate were within 12% of arithmetic means previously obtained based on rich concentration-time profiles of topiramate under steady-state in obese adults. Medians of T_{max} in adolescent subjects were within 2% of medians of T_{max} observed in obese adults.

This study is being conducted to assess the safety and efficacy of VI-0521, accompanied by a lifestyle modification program, in obese adolescents.

5.0 STUDY OBJECTIVES

The primary objectives are to evaluate the safety and efficacy of VI-0521 for the treatment of obesity in adolescents. The secondary objective is to characterize changes in obesity-related risk factors.

6.0 STUDY DESIGN

In this multicenter, randomized, double-blind, placebo-controlled, parallel-design study, approximately 200 subjects will be enrolled at approximately 20 sites in the United States. Subjects will be randomly assigned in a 1:1:2 ratio to placebo, N= 50; mid-dose (PHEN/TPM 7.5 mg/46 mg), N= 50; or top-dose (PHEN/TPM 15 mg/92 mg), N =100, of VI-0521, to be taken orally once daily in the morning. Randomization will be stratified by age (12-14 vs 15-16 years old) and gender. The study will consist of a screening period of up to 28 days, followed by a 56-week treatment period.

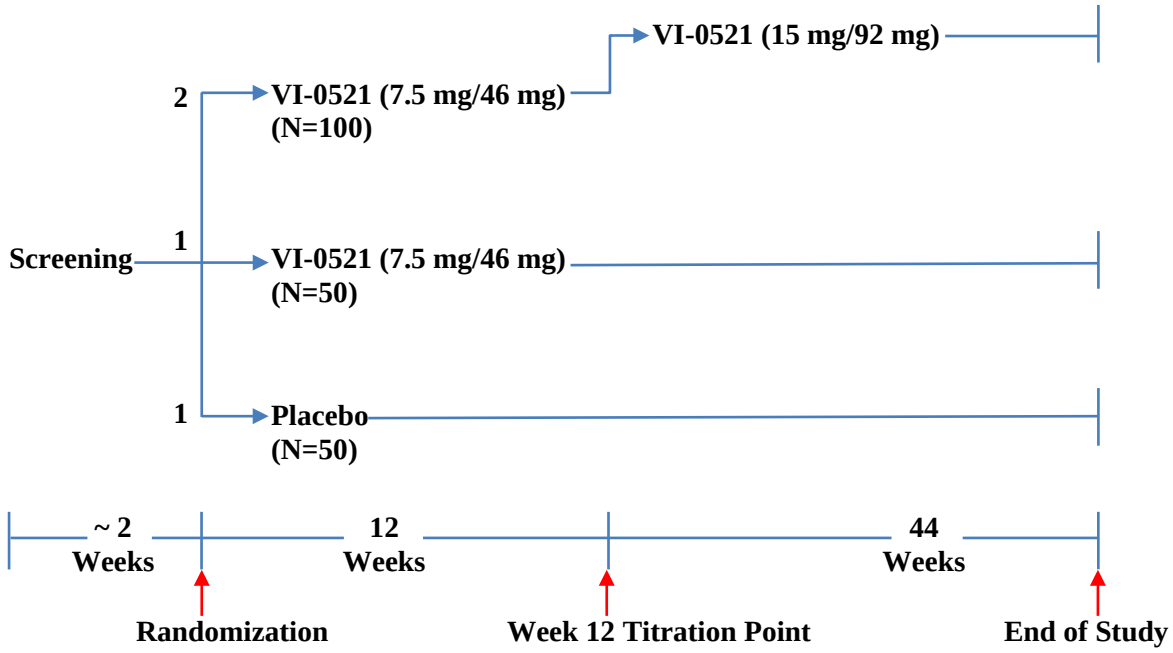
Subjects will be instructed to follow a mild hypocaloric diet modification program representing a 500-calorie/day deficit and to implement a family-based lifestyle modification program for adolescents, as tolerated, throughout the study period. The lifestyle program will include physical activity, behavior change, and family support. The same lifestyle modification program, specific to this population, will be implemented across all sites. Study drug will be titrated as described in Section 8.4.1.

Subjects who are unable to tolerate the assigned dose may be treated at a reduced dose level or may take a drug holiday as defined in Section 8.4.4. In addition, for growth monitoring, investigators will monitor rates of weight loss in treated subjects. For subjects with baseline BMI 95-98th percentile, reduce study drug dosage when BMI is < 85th percentile or when weight loss exceeds an average of 2 lbs (0.9 kg) per week. For subjects with baseline BMI ≥ 99th percentile, reduce study drug when weight loss exceeds an average of 2 lbs (0.9 kg)/week.

All subjects will return at approximately 4-week intervals for study assessments. All female

subjects will undergo a pregnancy test at each visit. Subjects who discontinue study drug during the study will be encouraged to remain on study (off study drug) for continued follow-up by attending all remaining visits and have all study-related procedures performed, and to return at the 56-week time point for measurements and evaluations. For those who choose to completely withdraw from the study at any point, the end of study (Week 56) procedures should be completed.

Figure 1. Schematic Diagram of Study Design



6.1 Primary Efficacy Endpoints

The primary endpoint is the mean percent change in BMI from baseline to end of study (Week 56).

6.2 Secondary Efficacy Endpoints

The secondary endpoints are:

- Percent of subjects achieving a reduction ≥ 5%, ≥ 10% and ≥ 15% of baseline BMI at Week 56;
- Change from baseline in waist circumference at Week 56;
- Change from baseline in fasting insulin and Whole Body Insulin Sensitivity Index (Matsuda) at Week 56;
- Change from baseline in triglycerides and HDL-C at Week 56;
- Change from baseline in blood pressure at Week 56.

6.3 Exploratory Endpoints:

Additional exploratory analyses will be conducted to evaluate effects of treatment on Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire scores, changes in various glycemic and lipid markers, and change in BMI Z-score.

6.4 Safety Endpoints

Safety will be assessed by evaluation adverse events (AEs)/serious adverse events (SAEs); vital signs, laboratory parameters (screening, periodically during the study and end of study); electrocardiograms; physical examinations; cognitive function tests using the Cambridge Neuropsychological Test Automated Battery (CANTAB). All subjects will be screened for the presence and severity of depression using the PHQ-9: Modified for Teens (Appendix 4) and for suicidal/ideation using the Columbia Suicide Severity Rating Scale (C-SSRS) (Appendix 5: Sample Columbia Suicide Severity Rating Scale) and follow up assessments will be done at each visit after treatment has been initiated. Bone age (X-ray of the hand and wrist) will be evaluated at baseline and end of study or early termination. Effect on bone mineral density and bone mineral content, as evaluated by Dual-energy X-Ray Absorptiometry (DXA) will be performed at baseline, end of study or early termination, at selected sites.

7.0 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

To be eligible for enrollment into this study, each subject must meet all of the following criteria at screening:

1. Provide written informed consent (of a parent or legal guardian) who will accompany the subject to all study visits;
2. Provide written assent (of study subject);
3. Be an adolescent ≥ 12 years and < 17 years of age with Tanner Staging of ≥ 2 at the time of screening;
4. Have a BMI ≥ the 95th percentile of BMI for age and gender (see Appendix 3: CDC Clinical Growth Charts8), with documented history of failure to lose sufficient weight or failure to maintain weight loss in a lifestyle modification program;
5. Be willing and able to comply with scheduled study visits, treatment plan, laboratory tests and other study procedures;
6. If female, must be using adequate contraception, defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence.

7.2 Exclusion Criteria

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

1. Weight gain or weight loss of greater than 5 kg, use of a supervised fast or very low-

calorie diet within the past 3 months;

2. Treatment with phentermine, topiramate, lorcaserin, naltrexone HCl/bupropion HCl, any over-the-counter (OTC) or prescription or herbal agents and dietary supplements, teas or tinctures used with the intention to lose body weight within 3 months of screening;
3. Any stimulants used for treatment of attention-deficit/hyperactivity disorder (ADHD) within 3 months of screening;
4. Condition or disease interfering with metabolism, such as untreated hypothyroidism, Cushing's syndrome;
5. Pulmonary disorders (other than asthma not requiring continuous medication or sleep apnea-related disorders);
6. Type 1 diabetes or any medical treatment with insulin, sulfonylureas (SFUs), glucagon-like peptide-1 (GLP-1) agonists, sodium glucose transporter (SGLT-1) inhibitors, and SGLT-2 inhibitors;
7. Congenital heart disease;
8. Clinically significant arrhythmia or electrocardiogram (ECG) abnormality;
9. Screening laboratory values as specified (tests may be repeated per investigator's discretion):

a. Bicarbonate	< LLN
b. AST and ALT	> 3 x ULN
c. HbA1c	≥ 8.0 %
d. Fasting glucose	≥ 270 mg/dL
e. Triglyceride	≥ 400 mg/dL
f. Creatinine clearance	< 60 mL/minute (Schwartz Formula)[7] (see Appendix 7: Formulas for Estimating Creatinine Clearance)
g. TSH	> 1.5 ULN

10. Clinically significant hepatic or renal disease;
11. Clinically significant thyroid dysfunction as evidenced by signs or symptoms of hypothyroidism, a thyroid stimulating hormone (TSH) > 1.5 x ULN, or use of thyroid hormone treatment that has not been stable for at least 3 months;
12. Systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg or concurrent antihypertensive medication that has not been stable for 3 months;
13. Any history of bipolar disorder or psychosis, greater than one lifetime episode of major depressive disorder, current depression of moderate or greater severity (PHQ-9 score of 10 or more), presence or history of suicidal behavior or ideation with some intent to act on it; tricyclic antidepressants, monoamine oxidase inhibitors (MAOIs), lithium, levodopa, and dopamine receptor agonists; or allowed antidepressant use that has not been stable for at least 3 months;
14. Use of chronic systemic glucocorticoid therapy (i.e. glucocorticoids, anabolic steroids) or any other steroid hormone therapy other than oral contraceptives, that has not been stable for at least 3 months;

15. Pregnancy or breastfeeding;
16. Any history of eating disorders (e.g. bulimia; binge eating disorder; anorexia);
17. Any history of laxative abuse;
18. History of glaucoma, use of carbonic anhydrase inhibitors, history of increased intraocular pressure or any past or present use of medications to treat increased intraocular pressure;
19. Prior bariatric surgery;
20. Any history of nephrolithiasis;
21. Any history of epilepsy, or requirement for anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, gamma-aminobutyric acid (GABA) analogues, hydantoins, phenyltriazines, succinimides, and other agents (valproic acid and its derivatives, carbamazepine and its derivatives, zonisamide, and felbamate);
22. Positive urine drug screen;
23. Current smoker or smoking cessation within 3 months of screening;
24. Obesity of a known genetic or endocrine origin, such as Prader-Willi Syndrome;
25. Known allergy or hypersensitivity to phentermine or topiramate or history of anaphylaxis to any drug;
26. Use of any investigational medication or device for any indication or participation in a clinical study within 30 days prior to screening; or
27. Other clinically significant medical or psychiatric condition or laboratory abnormality that may increase the risk associated with trial participation or investigational product administration or may interfere with the interpretation of trial results and, in the judgment of the investigator, would make the subject inappropriate for entry into this trial.

7.3 Subject Withdrawal

Subjects are free to withdraw from the clinical trial or discontinue treatment at any time for any reason.

The sponsor reserves the right to discontinue this trial at any time (see Section 13.0 on clinical trial discontinuation criteria).

Subject participation in this clinical trial may be discontinued for any of the following reasons:

- Occurrence of 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 that indicates to the Investigator that continued participation is not in the best interest of the subject;
- Subject's (or a parent’s or legal guardian’s) decision to withdraw;
- Requires other medical treatment that is excluded by the protocol (see Section 8.5);

- Subject failure to comply with protocol requirements or study related procedures; or
- Termination of the clinical trial by the sponsor, FDA, or other regulatory authorities.

Withdrawn subjects will not be replaced.

Subjects discontinued from treatment should be encouraged to remain in the trial off-treatment and to continue study visits at the scheduled intervals. Subjects who withdraw completely from the trial at any point should complete the end of study (Visit 16, Week 56) procedures. The date of last dose should be recorded.

Every effort should be made to document subject outcome. For subjects who elect to withdraw from the trial without continuing study visits, the investigator should inquire about the reason for withdrawal, request that the subject return all unused investigational product(s), request that the subject return for a final visit (Section 9.1.4) and follow-up with the subject regarding any unresolved adverse events.

At about the 56-week time point, withdrawn subjects who have not continued study visits should be asked to return to the site to obtain weight and height measurements at a minimum and, if possible, all the other tests and procedures (except physical examination and ECG) required for end of study visit.

If a subject withdraws from the trial and also withdraws consent for disclosure of future information, no further evaluations will be performed and no additional data will be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8.0 TREATMENT OF SUBJECTS

8.1 Study Treatment

Eligible subjects will receive 56 weeks of treatment with either VI-0521, or matching placebo for daily use.

8.2 Allocation to Treatment

Written informed consent will be obtained prior to the performance of any study-related procedures. Eligible subjects will be randomly assigned in a 1:1:2 ratio to placebo, mid-dose (PHEN/TPM 7.5 mg/46 mg) or top-dose (PHEN/TPM 15 mg/92 mg) of VI-0521. Randomization will be stratified by gender and age (12-14 vs 15-16 years old), and will be implemented using an Interactive Web Response System (IWRS). The sponsor, the subjects, and the study site will be blinded as to subject randomization.

When a subject qualifies for randomization, site personnel will log into the IWRS to obtain a specific titration blister card or bottle number to dispense to the study subject. The subject will return the study drug at every clinic visit for drug accountability and will be dispensed with a new blister card/bottle for the next treatment period.

8.3 Breaking the Blind

Study drug must not be unblinded during the study unless it is considered absolutely necessary

by the investigator for the management of an adverse event or other medical emergency. Under such conditions, investigators will first contact the medical monitor when deciding to unblind a subject and if unblinding is deemed medically necessary the identity of the study treatment may be obtained via the IWRS. Any subject whose treatment assignment has been unblinded must be withdrawn from the study.

Investigators are also required to ensure that any potential SAEs are reported according to the requirements outlined in Section 11.1.5 and provide a written report to VIVUS or designee within 7 days to document the reason for unblinding.

8.4 Drug Supply

Clinical supplies will be manufactured for VIVUS by Catalent Pharma Solutions, LLC in accordance with current Good Manufacturing Practices (cGMP). All clinical supplies will be labeled with information required by national regulations.

8.4.1 Formulation and Packaging

Sufficient quantities of VI-0521, phentermine and topiramate capsules will be supplied by the sponsor in blister cards and bottles and shipped to a designee at the study site. All clinical supplies will be labeled with information required by national and/or international regulations. Study drug will be packaged into 2 types of kits; titration kits (blister cards) for use during the first 4 weeks of study treatment and the titration period during study Weeks 13-16, and treatment kits (bottles), for use once subjects have been titrated to their assigned dose.

Each titration kit contains 1 blister card for use during Weeks 1 through 4 of titration, with each card containing 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. Titration kits will consist of blister cards labeled with the study number, a unique kit number, storage instructions, and spaces for the subject number and initials. Treatment kits will consist of bottles, each containing 35 capsules of study medication at the treatment dosages shown in Table 1. Each kit will contain a single bottle labeled with the study number, a unique kit number, storage instruction, and spaces for the subject number and initials.

Table 1: VI-0521 Dosage Strengths by Titration Week for Each Treatment Group

Group	Treatment Dosage for Phentermine/Topiramate (mg)	Titration Dose for Phentermine/Topiramate (mg)			
		Weeks 1-2	Weeks 3-4	Weeks 13-14	Weeks 15-16
Placebo	0/0	0/0	0/0	0/0	0/0
VI-0521 Mid	7.5/46	3.75/23	7.5/46	7.5/46	7.5/46
VI-0521 Top	15/92	3.75/23	7.5/46	11.25/69	15/92

8.4.2 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. Randomization scheme will be followed by site staff for assignment of specific bottle to study subjects. No other preparation of clinical supplies is required of the study staff.

8.4.3 Administration

Subjects will be instructed to take 1 capsule of study drug every morning with or without food, and with water. Subjects should stay hydrated by drinking plenty of water while in the study. Subjects will be reminded not to take study drug to school or work. Capsules are not to be broken or split apart in any manner.

When dispensing titration kits, investigators should ensure that subjects understand that each blister card contains a 4-week supply of medication, 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 the capsules must be taken for the treatment period that the bottle is dispensed for. Instruction should also be provided that each bottle contains extra capsules that should only be taken should the next study visit be scheduled beyond 4 weeks after the previous visit. Investigators will also instruct subjects to return all study drug (blister card and the bottle, even if empty) to the site at each study visit.

8.4.4 Dose Reduction and/or Interruption During Trial Participation

Dose reduction is an option for subjects who experience adverse events that are sufficiently severe to cause the subject to consider discontinuation or to cause the investigator concern about the subject's ability to continue in the study.

It should be recognized that caloric restriction resulting in rapid weight loss (independent of any specific drug mechanisms) carries the potential to negatively affect growth. Due to the potential of the study drug to cause significant weight loss which may affect growth in adolescents, investigators should actively monitor the subject's rate of weight loss and growth (using height and weight), and implement a down-titration of study drug should rates of weight loss in a given subject exceed rates that are deemed safe. For subjects with baseline BMI 95-98th percentile, reduce study drug dosage when BMI is < 85th percentile or when weight loss exceeds an average of 2 lbs (0.9 kg) per week. For subjects with baseline BMI ≥ 99th percentile, reduce study drug when weight loss exceeds an average of 2 lbs (0.9 kg)/week.

Dose reduction is implemented through the IWRS, and will be done without breaking the blind. Subjects assigned to the mid-dose may be reduced down to the low-dose and those assigned to the top-dose may be reduced down to the mid-dose, and if necessary, the low-dose in a blinded manner. Dose reduction is not an option for subjects who experience intolerable adverse events related to study medication during the first week of titration (Week 1) during the initial randomization; these subjects will be withdrawn from treatment.

When dose reduction is not appropriate or when dose interruption may be required due to events unrelated to study treatment, subjects may temporarily discontinue from treatment (up to 7 days)

on one or more occasions. Dose interruptions longer than 7 days are possible with agreement from the medical monitor. All subjects undergoing dose interruptions for any duration may be titrated back up to the original dose level based on discretion of the investigator. If study drug has been discontinued for 2 weeks or more, a new titration kit should be ordered through IWRS to resume treatment. Subjects who have a drug holiday following dose reduction due to study medication intolerance will be retitrated to the dose specified for use after dose reduction. For subjects having a drug holiday due to events unrelated to treatment, attempts should be made to retitrate to the initial randomized dose. For treatment interruptions of less than 2 weeks, subjects may resume treatment by dosing every other day for the first week that treatment is resumed.

If symptoms remain intolerable after dose reduction and drug holidays, subjects may be discontinued from treatment. Subjects discontinued from treatment will be encouraged to remain in the trial off-treatment and to continue to make study visits at the regularly scheduled intervals. The last date on which the subject is dosed with study medication should be recorded on the case report form (CRF).

If the subject remains in the trial off-treatment, all study procedures should be continued for the duration of subject participation and they should be encouraged to return at the 56- week time point for measurements and evaluations. For those who choose to completely withdraw from the study at any point, the end of study (Week 56) procedures should be completed.

8.4.5 Discontinuing Study Drug

Abrupt withdrawal of topiramate, a component of VI-0521, has been associated with seizures in individuals without a history of seizures or epilepsy. Subjects discontinuing VI-0521 should be gradually tapered by taking a dose every other day for 1 week prior to stopping treatment altogether.

8.4.6 Compliance

Subject compliance with study drug will be assessed by counting capsules that are returned at each study visit. Subjects whose actual capsule consumption differs from their expected capsule consumption by more than 20% should be queried by site personnel about reasons for not using study drug as directed, and site personnel should plan any corrective action as necessary. Subjects who remain noncompliant with study drug dosing despite corrective action by site personnel may be withdrawn from the study.

8.4.7 Drug Storage and Drug Accountability

All unused study drug must be stored in its packaging at controlled room temperature, 15 to 25°C (59 to 77°F) with excursion to 30°C (86°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, one component of the VI-0521 combination is a Schedule IV controlled substance. 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 empty containers and all unused medication in its original packaging, and sites must make an accounting of drug use by each subject. No study drug, used or unused, may be discarded. All used and unused drug must be returned to the sponsor or designated representative upon completion of the study.

8.5 Concomitant Medications

8.5.1 Excluded Medications

Subjects may not use any of the following medications during participation in this study. Subjects who develop a need for any of these medications must be discontinued from the study:

- Anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, GABA analogues, hydantoins, phenyltriazines, succinimides, and other agents (valproic acid and its derivatives, carbamazepine and its derivatives, zonisamide, and felbamate);
- Tricyclic antidepressants, MAOIs, lithium, levodopa, and dopamine receptor agonists;
- Carbonic anhydrase inhibitors;
- Insulin, sulfonylureas (SFUs), GLP-1 agonists, SGLT-1 inhibitors, and SGLT-2 inhibitors;
- Chronic systemic steroids (i.e. glucocorticoids, anabolic steroids) other than oral contraceptives;
- Treatment for hyperactivity disorder; or
- OTC, prescription medications, herbal agents and dietary supplements used with the intention to lose body weight.

8.5.2 Other Restricted Medications

Subjects using hormone replacement therapy (estrogen, thyroid, or other) or allowed antidepressants must be on doses that have been stable for at least 3 months prior to screening. Subjects who develop symptoms indicative of hypothyroidism during the course of the study need not withdraw but should be evaluated and managed as indicated.

Benzodiazepine and non-benzodiazepine sleep medications are permitted, provided that the dosage has been stable for at least 1 month prior to screening, and the frequency of use does not exceed twice a week.

Subjects may not initiate any other organized weight loss program during their participation in this study.

8.5.3 Documentation of Concomitant Medication Use

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

8.6 Treatment of Diabetes

Subjects who develop type 2 diabetes during the course of the study will be provided with blood glucose meters and supplies and will be provided appropriate usage instructions. They will be instructed to measure a fasting morning glucose daily and to record the results in the blood glucose and hypoglycemic event log. Diabetic subjects will bring their meters and logs to each visit.

If concomitant antidiabetic therapy is determined necessary, metformin is suggested as the initial therapy for newly-emergent type 2 diabetes unless contraindicated in a specific subject. Insulin secretagogues, including SFUs and meglitinides, either alone or in combination with other medications, should be reserved for subjects who cannot achieve adequate control with other modes of treatment. Insulins and incretins are prohibited, and subjects requiring treatment with these medications must be discontinued from the trial. Subjects whose blood glucose cannot be adequately controlled with the concomitant treatments allowed in this trial should be maintained in the study but discontinued from treatment, and referred back to their primary healthcare provider for more intensive treatment (see Section 7.3).

During treatment, subjects whose fasting blood glucose is less than 72 mg/dL on 2 or more occasions, or who experience any signs or symptoms associated with hypoglycemia, should have their antidiabetic therapy reevaluated.

8.7 Treatment of Elevated Blood Pressure

For subjects whose blood pressure requires management, antihypertensive therapy should be initiated with angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB). If these medications are already present, calcium channel blockers, beta-blockers, or thiazide diuretics may be added.

Subjects whose blood pressure exceeds 140/90 mmHg on 3 consecutive visits and who have undergone dose increases or the addition of antihypertensive medications over each of 3 visits, should be discontinued from study drug and referred back to their primary healthcare provider for more intensive management. Subjects may continue attending study visits off study drug, and if blood pressure control is re-established without requiring excluded medications, subjects may be restarted on study drug.

Subjects whose blood pressure drops below 110/70 mmHg, or who exhibit symptoms associated with low blood pressure during the trial should have their antihypertensive medications reevaluated.

8.8 Treatment of Hypothyroidism

Individuals who experience rapid weight loss sometimes develop signs and/or symptoms of hypothyroidism with or without elevation of TSH. Subjects who develop symptoms of hypothyroidism need not be discontinued from study drug. These subjects should be assessed clinically and with appropriate laboratory testing (TSH, free T3, free T4). Subjects found to be hypothyroid may be considered for thyroid replacement therapy, as appropriate.

9.0 STUDY PROCEDURES

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

9.1 Schedule of Visits

9.1.1 Screening Visit (Visit 1, Up to – 4 Weeks)

Activities at the Screening visit are:

- Obtain written parental informed consent and subject assent;
- Obtain written parental informed consent and subject assent for DXA (at selected sites);
- Obtain demographics (including age, gender, race, and ethnicity);
- Obtain medical history (including contraception methods);
- Assess inclusion/exclusion criteria;
- Record concomitant medications;
- Administer PHQ-9 and C-SSRS questionnaires;
- Administer neurocognitive battery (CANTAB) familiarization session;
- Obtain vital signs (blood pressure, heart rate, respiration rate, and temperature);
- Obtain weight and waist circumference measurements;
- Measure 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;
- Obtain serum samples for blood chemistry panel, hematology panel, lipid panel, HbA1c, HIV, HCV, HBsAg, TSH;
- Obtain urine sample for routine urinalysis, drug screen, and pregnancy test (female subjects);
- Provide contraception/pregnancy counseling (female subjects); and
- Schedule the Randomization visit within 4 weeks (± 3 days).

9.1.2 Baseline/Randomization (Visit 2, Week 0)

Subjects eligible for treatment will be randomized and have study drug dispensed at visit 2. If a subject is found to be ineligible for participation due to laboratory values, the subject may be notified prior to visit 2. Activities at baseline are:

- Confirm inclusion/exclusion criteria (Section 7.0);
- Administer PHQ-9, C-SSRS, and IWQOL-Kids questionnaires;
- Administer neurocognitive battery (CANTAB);
- Obtain vital signs (blood pressure, heart rate, respiration rate, and temperature);

- Obtain weight and waist circumference measurements;
- Measure height and calculate BMI;
- Record any changes in concomitant medications;
- Record any adverse events reported or observed;
- Perform complete physical examination (include Tanner Staging);
- Perform and evaluate 12-lead ECG;
- Perform urine pregnancy test (female only);
- Perform OGTT for all subjects eligible for participation by results of Visit 1 screening tests (a separate visit may be scheduled for the OGTT) and obtain blood sample for glucose and insulin at 2 hours following oral glucose load;
- Conduct hand and wrist X-ray;
- Conduct DXA measurement (if applicable);
- Contact IWRS to randomize the subject. Dispense study drug and instruct the subject on the proper use of the study drug (Section 8.4.3);
- Provide diet (a 500-calorie/day deficit)/lifestyle modification and contraception/pregnancy counseling (female subjects); and
- Schedule the next study visit in 4 weeks (± 7 days).

9.1.3 Treatment Week 4 Through Week 52 (Visits 3 Through 15)

- Obtain weight and waist circumference measurements;
- Administer PHQ-9 and C-SSRS questionnaires;
- Administer neurocognitive battery (CANTAB), Visit 6 only;
- Obtain vital signs;
- Measure height and calculate BMI;
- Record any changes in concomitant medications;
- Record any adverse events reported or observed;
- Perform urine pregnancy test;
- Collect study drug from previous visit, assess treatment compliance, and perform drug accountability; and dispense study medication and instruct the subject in the proper use of the study drug;
- Obtain blood sample for chemistry panel (Visits 3, 4, and 9 only);
- Obtain blood sample for hematology and lipids panel (Visit 9 only);
- Obtain blood sample for HbA1c (Visits 5 and 11 only);
- Provide diet (a 500-calorie/day deficit)/lifestyle modification and

contraception/pregnancy counseling (female subjects); and

- Schedule the next study visit in 4 weeks (± 7 days).

9.1.4 Treatment Week 56, End of Study; Early Termination (Visit 16)

The end of study visit will be performed for subjects completing the study or for subjects who are withdrawn from the study prior to completion of the study at the time of their treatment termination. For subjects who withdraw from the study prior to completion, the site will also attempt to contact the subject at or about the 56-week time point to obtain end of study assessments.

Activities at the end of study visit include:

- Administer PHQ-9, C-SSRS, and IWQOL-Kids questionnaires;
- Administer neurocognitive battery (CANTAB);
- Obtain vital signs;
- Obtain weight and waist circumference measurements;
- Measure height and calculate BMI;
- Collect study drug from previous visit, assess treatment compliance, and perform drug accountability;
- Obtain blood sample for chemistry, hematology, and lipids, panel;
- Obtain blood sample for HbA1c;
- Obtain urine sample for routine urinalysis and urine pregnancy test (female only);
- Administer glucose load for OGTT and obtain blood sample for glucose and insulin at 2 hours following oral glucose load (Section 10.10);
- Perform complete physical examination (include Tanner Staging);
- Perform and evaluate 12-lead electrocardiogram (ECG);
- Conduct hand and wrist X-ray;
- Conduct DXA measurement (if applicable);
- Record any changes in concomitant medications;
- Record any adverse events reported or observed;
- Discontinue subject's study participation.

9.2 Study Period

The study period for each subject will begin when written informed consent is provided and will continue until Week 56 or early termination is completed. Sites should link the scheduling of visits to the baseline/randomization visit (Visit 2, Day 0). Visit windows are provided to allow subject and site scheduling convenience. However, every effort should be made to ensure that visits occur within these windows so that the overall treatment duration is 56 weeks for subjects

who complete all visits. In certain instances, adverse event information may be required for events occurring after the study period (Section 11.3).

10.0 ASSESSMENT

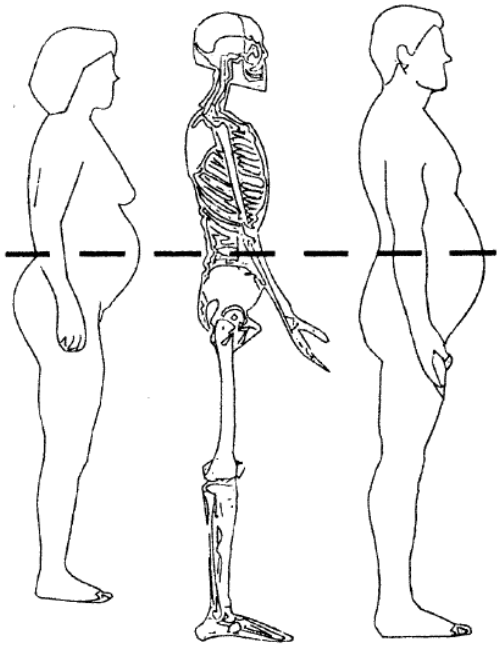
10.1 Weight Measurement

Subject weight will be obtained at every 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.

10.2 Waist Circumference Measurement

Waist circumference measurements will be taken using a measuring tape provided by the sponsor or designee, and should be obtained by the same individual, whenever possible, at every study visit. To measure the waist circumference, locate the top of the right iliac crest. Place the measuring tape in a horizontal plane (parallel to the floor) around the abdomen at the level of the top of the iliac crest as shown in Figure 2.

Figure 2. Measuring Tape Position for Waist Circumference Assessments



Ensure that the subject is relaxed. Ensure that the tape is snug but does not indent or compress the skin, and make the measurement (in centimeters) at the end of a normal expiration.

10.3 Height and BMI

Height measurements (cm) and BMI will be determined by the site at every visit (see BMI Chart in Appendix 2). Height measurements should be made using a calibrated stadiometer without shoes, socks, or hats. At each study visit, 3 independent measurements of height should be made, and the median value from these measurements recorded on the eCRF. Height should be recorded to the nearest centimeter. The same stadiometer should be used for all visits for any given subject. Stadiometer should be calibrated, at least daily, if used, following the equipment's manufacturer instructions and/or site SOP.

If a subject does not meet the BMI criterion for inclusion into the study (see CDC Clinical Growth Chart[8] in Appendix 3), no further screening procedures should be undertaken.

10.4 Vital Signs

Vital signs (systolic blood pressure, diastolic blood pressure, heart rate, respiration rate, temperature) will be assessed at each study visit. 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 cuff should be employed for blood pressure measurements. Site staff should ensure at the Screening visit that the cuff size used is appropriate for the patient's arm circumference. Overweight and obese subjects often require a larger cuff than is typically used for adults of normal size and weight. 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.

10.5 Physical Examinations and Tanner Staging

A complete physical examination will be performed at baseline, 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. Puberty maturation will be assessed using the Tanner Staging (also known as the Sexual Maturity Rating (SMR), a gender specific 5-point scale of secondary sexual characteristics. Boys are rated for genital development and pubic hair growth, and girls are rated for breast development and pubic hair growth. Tanner Staging should be conducted by site personnel who have been trained on the proper technique for these assessments, and sites should ensure that the same observer conducts all Tanner Staging evaluations for any given subject.

10.6 Electrocardiograms

Twelve-lead ECG studies will be performed at baseline, 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.

10.7 X-Ray of the Hand and Wrist

An X-ray of the hand and wrist will be performed at baseline, and end of study or early termination visit to assess bone growth. Equipment and procedures used to obtain hand and wrist X-ray data will be standardized as described in a separate document. X-rays will be read at a central facility and the reader will be blinded.

10.8 DXA (Sub Study)

A bone health sub-study will be conducted at selected sites in approximately 100 subjects (25 each on placebo and mid-dose, and 50 on top-dose) to assess the effect of Qsymia administration on bone health using Dual X-ray Absorptiometry (DXA). DXA scans of the posterior-anterior (PA) spine (lumbar), and total body less head (TBLH) will be performed at baseline and at the end of study or early termination. Equipment and procedures used to obtain DXA data will be standardized as described in a separate document. Sites involved in DXA measurement will be trained on these procedures prior to performing scans on study subjects. Scans will be read at a central facility and the reader will be blinded.

The following enrollment criteria will apply:

1) Both male and female will be eligible to participate;
2) Subjects with a history of any non-traumatic fracture will not be eligible;
3) Subjects with juvenile osteoporosis at baseline will not be eligible; and
4) Subjects must meet manufacturer equipment specifications with regard to height and weight limitations.

10.9 Laboratory Tests

Laboratory tests will be performed at a licensed, certified central testing laboratory identified by the sponsor. 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. Table 2 summarizes the clinical laboratory testing for the study. Laboratory tests required at each study visit are detailed in Section 9.0 and Appendix 1.

Table 2: Clinical Laboratory Tests

Fasting blood chemistry	**Hematology**	**Other**
• albumin • alkaline phosphatase • ALT • AST • GGT • bicarbonate • blood urea nitrogen • serum calcium • serum chloride • serum sodium • carbon dioxide • creatinine (and estimated creatinine clearance) • glucose • lactate dehydrogenase • serum phosphorus • serum potassium • total and direct bilirubin • total protein • uric acid	• hemoglobin • hematocrit • red blood cell count • red blood cell indices • total white blood cell count • white blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils) • platelet count	• thyroid stimulating hormone
	Lipid panel	**Urinalysis**
	• total cholesterol • LDL-C • HDL-C • triglycerides	• midstream urinalysis with reflex microscopic evaluation • pregnancy test (all female subjects)
		Urine Drug Screen
		• cannabinoids • amphetamines • cocaine • barbiturates • benzodiazepine • opiates
	Glycemic testing	**Serology**
	• HbA1c • insulin • glucose	• HBsAg • HCV • HIV

10.10 Oral Glucose Tolerance Test

An oral glucose tolerance test (OGTT) will be obtained at baseline (after results from screening visit indicate the subject may be eligible for participation), and at end of study or early termination for all subjects.

The OGTT will use a 75 g oral glucose load; blood samples will be obtained at baseline and at 2 hours post glucose load for evaluation of both glucose and insulin levels.

10.11 CANTAB (Cambridge Neuropsychological Test Automated Battery)

Cognitive function will be assessed using selected tests from the CANTAB including paired associates learning, pattern recognition memory, and spatial span. The CANTAB will be assessed at screening (familiarization session only), baseline, Week 16 (Visit 6), and end of study or early termination.

10.12 IWQOL-Kids

The Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire (Appendix 6) is a 27-item, self-administered instrument that will be completed at baseline, and end of study or early termination.

The IWQOL-Kids is validated for use in adolescents aged 11-19 years old. This questionnaire is designed to evaluate the impact of excess weight on quality of life domains including physical mobility and comfort (Physical Comfort), how an individual feels about themselves and their body (Body Esteem), how an individual is treated in their social environment (Social Life), and the individual's perception of what family members may think and feel about them (Family

Relations).[9] Because this instrument is intended to be completed directly by study subjects, it is important that site personnel remain neutral and do not influence subject answers on this questionnaire in any way. Should subjects ask questions to site personnel regarding the meaning of specific items, site personnel should not interpret items for the subjects, rather, they should repeat items back to subjects as they are worded on the instrument.

Site personnel must also recognize that the subject's answers to this questionnaire reflect their perceptions and attitudes at the time the questionnaire is completed, and that missing answers cannot be queried at a later date. It is critical, therefore, that site personnel review questionnaires for completeness at the time they are initially filled out, and that any missing answers are completed before the subject leaves the office.

10.13 PHQ-9: Modified for Teens

The Patient Health Questionnaire for Adolescents (PHQ-9: Modified for Teens) (Appendix 4) is a 9-item, self-administered instrument for the assessment of depression in adolescents.

Because this instrument is intended to be completed directly by study subjects, it is important that site personnel remain neutral and do not influence subject answers on this questionnaire in any way. Should subjects ask questions to site personnel regarding the meaning of specific items, site personnel should not interpret items for subjects, rather, they should repeat items back to subjects as they are worded on the instrument. Because this questionnaire assesses the subject's level of depression over a specific time frame (the past 2 weeks), answers not completed by subjects at a given visit cannot be queried or filled in at a later date. Site personnel, therefore, must carefully review questionnaires for completeness before subjects leave the clinic, and assure that questionnaires are properly completed.

The PHQ-9 questionnaire is being used to screen for and to assess the severity of any depression in study subjects. This questionnaire will be completed at every visit. Answers to the questionnaire may reveal evidence of significant depression, including the possibility of suicidal thoughts or plans. It is the responsibility of the investigator to evaluate subjects' responses to these questionnaires carefully, and to perform any additional evaluation and management that is indicated, including referral to a mental health professional if necessary. The evaluation by the investigator will be guided by the standardized methods for the PHQ-9 that have been developed to provide information regarding diagnosis of depression, severity of symptoms, and treatment follow-up options. Investigators should document any such problems identified in study source documents using standard diagnostic criteria and terminology as provided in the standardized guidelines. It is expected that any randomized subject presenting with a PHQ-9 score of 15 or more should be treated and may require referral to a qualified mental health care professional.

10.14 Columbia Suicide Severity Rating Scale (C-SSRS)

The Columbia Suicide Severity Rating Scale is an 11-item clinician-administered assessment of both suicidal behavior (6 items) and suicidal ideation (5 items).[10] Each of the items comprising this scale corresponds to a specific level, or severity of ideation or behavior, and is answered on a yes/no basis. This assessment will be administered to all subjects at screening in order to confirm the absence of suicidal behavior or ideation with at least some intent to act on it, and to document the pre-study status of all subjects included in the treatment program. Subsequently,

C-SSRS evaluations may be done at the investigator's discretions to evaluate and aid in diagnosis of reported or suspected events of suicidality. All C-SSRS assessments must be administered by a trained staff member. If any test reveals suicidal behavior or ideation with some intent to act on it, then test results must be confirmed by a physician investigator prior to discharging the subject from the study visit (see Appendix 5).

11.0 ADVERSE EVENT REPORTING

11.1 Adverse Events

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

Investigator must pursue and obtain information adequate to describe adverse events, their severity and 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 adverse events meet the criteria for classification as serious adverse events requiring immediate notification to VIVUS or its designated representative.

11.1.1 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 listed in Section 11.1.5.

11.1.2 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.

11.1.3 Abnormal Test Findings

Merely repeating an abnormal test, in the absence of any of the above conditions, 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; or
- Test result is considered by the investigator or sponsor to represent a clinically significant finding.

11.1.4 Mood or Depression Related Events

All subjects will be screened for the presence and severity of depression at screening using a validated survey instrument (PHQ-9) designed for assessment of depression in a primary care setting. The PHQ-9 is a self-administered, nine-item depression module based directly on the diagnostic criteria for major depressive disorder in DSM-V-TR. This questionnaire may be used at the investigator's discretion at other times during the study to aid in diagnosis and evaluation of reported or suspected events of depression.

Suicidality will also be assessed at each study visit using the C-SSRS (see Appendix 5). The C-SSRS may also be used at the investigator's discretion at unscheduled visits during the study to aid in evaluation and diagnosis of reported or suspected events of suicidality. Should this additional assessment indicate the presence any suicidal behavior, or suicidal ideation with any intent to act on it, study treatment will be stopped, and the investigator must provide appropriate referral to a mental health professional for additional assessment and management. Any such event must be reported to the Medical Monitor and to the sponsor within 24 hours. Subjects must be followed until resolution of these events.

Any mood- or depression-related adverse events must be documented using standard diagnostic criteria and terminology.

11.1.5 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.

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.

11.1.6 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 these criteria.

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 any of 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); or
- 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.

11.2 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 clinic 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.

11.3 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 day of study participation. All adverse events that occur during this period and are known to the investigator must be reported according to the requirements outlined in this protocol.

11.4 Reporting Requirements

All adverse events will be reported on the adverse event page of the CRF. In addition, serious adverse events must also be reported on a separate SAE 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.

11.4.1 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 SAE.

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 its designee.

11.4.2 Non-Serious Adverse Event Reporting Requirements

Non-serious adverse events are to be reported on the Adverse Event CRFs, which are to be submitted to VIVUS or its designee.

11.4.3 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.

12.0 STATISTICAL PLAN

12.1 Statistical Analysis

Detailed methodology for summary and statistical analyses of the data collected in this clinical trial will be documented in a Statistical Analysis Plan (SAP). This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoints 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. The SAP will be finalized and signed prior to the finalization of the database.

12.2 Sample Size Determination

In previous studies in adults, VI-0521 mid-dose (PHEN/TPM 7.5 mg/46 mg) resulted in a placebo-subtracted BMI reduction of 2.4 units with a standard error approximately 0.16 units and a within treatment standard deviation of 2.9. A very conservative estimate of the treatment difference between the mid-dose and placebo would be 2 units of BMI which represents more than 2 standard errors below what was observed before. If we enroll 200 subjects (50 placebo, 50 mid-dose, and 100 top-dose), we will have at least 90% power to detect a statistically significant difference between the top-dose (PHEN/TPM 15 mg/92 mg) and the placebo because we could assume that the top-dose will have a higher effect size than the mid-dose. This

calculation assumes that there will be an approximately 30% dropout rate. This sample size will also provide approximately 80% power to detect a statistically significant difference between the mid-dose and placebo.

12.3 Analysis Populations

Three different analysis populations will be used for analysis of data from this study, as described below:

- Randomized: This population will be comprised of all subjects who were initially randomized. This population will be used for summaries of subject disposition and baseline subject characteristics.
- Intent-to-treat (ITT)/Safety: This population will be comprised of all subjects who were initially randomized and received at least one dose of study drug. This will be the primary population for all summaries of subject disposition and baseline characteristics, efficacy analyses, and safety analyses for purposes of regulatory submissions.
- Modified Intent-to Treat (m-ITT): This population will be comprised of all randomized study subjects who receive study treatment and return for at least one post-randomization assessment of height and weight. This population will be used for the analysis of all efficacy variables for all other purposes, including but not limited to publications, presentations, and robustness of sensitivity of analyses.

12.4 Subgroups

BMI change will be tabulated by age and gender. Additionally, further exploratory subgroup analyses of the primary efficacy endpoints may include evaluation by race and/or other subgroups deemed medically and/or scientifically important.

12.5 Statistical Methods

12.5.1 Analysis of the Primary Endpoint

The primary endpoint for this study is the mean % change in BMI from baseline to end of study (Week 56).

Comparisons in the primary endpoint of change from the baseline BMI between treatment groups be assessed for the ITT population using a mixed effects model with repeated measures (MMRM) with factors of treatment, visit, treatment by visit interaction, baseline BMI value, age stratification, and gender stratification. Appropriate contrast will be applied for treatment comparisons at Week 56. The pairwise comparisons of interest are top-dose vs. placebo, and mid-dose vs. placebo, and top-dose vs. mid-dose. The primary null hypothesis will be that there is no treatment difference between any VI-0521 treatment groups and the placebo in the percent change from baseline to Week 56 in BMI. An appropriate contrast will be used for the comparisons at Week 56. The family-wise type 1 error for the comparisons will be controlled by Fisher's protected least significant difference (LSD) method at the 0.05 significance level: placebo, mid-dose, and top-dose will be first compared for overall difference in the percent change from baseline in BMI. Once the overall difference is significant at the 0.05 significance level, the above 3 pairwise comparisons will be conducted using Fisher's LSD method at the

0.05 significance levels. The order for comparisons of interest is top-dose vs. placebo, mid-dose vs. placebo, and top-dose vs. mid-dose. Due to the fact that only three treatments are compared, the above procedure strongly controls the family-wise type 1 error.[11]

12.5.2 Method for Prevention and Treatment of Missing Values

For subjects who discontinue treatment prior to trial completion, every attempt will be made to have them continue with clinic visits and study assessments. Particular attention will be given to collecting Week 56 assessments of weight and height, regardless of when subjects discontinued treatment.

The above MMRM method used for the analysis of the primary endpoint has an inherent mechanism for imputing missing data. Therefore, MMRM is applied to the m-ITT population with the observed data without imputation. The following sensitivity analyses may be considered to explore the impact of missing data on the conclusion of the primary analysis. The details of the sensitivity analyses will be included in the statistical analysis plan.

The first sensitivity analysis is using a multiple imputation method based on the monotonic missing pattern under the assumption of missing at random (MAR). The intermittent missing data will be imputed using multiple imputation MCMC (Markov chain Monte Carlo) procedure.

The second sensitivity analysis is also using multiple imputation, however, under the assumption of missing not at random (MNAR) to explore the validity of MAR using pattern-mixture model:

1) For subjects who discontinue study participation prior to Week 56 and do not have follow-up visit, the missing data will be imputed using the observed data from the subjects in the same arm who discontinue the study treatment but have the primary endpoint measurement in the follow up visit using a regression method. The intermittent missing data will be imputed using multiple imputation MCMC procedure. an ANCOVA model using a similar mixed procedure (without the repeated measures) as the primary analysis will be applied to these multiple-imputed % change in BMI at Week 56 with treatment, baseline BMI value as a covariate, and age and gender as stratification factors. The results of ANCOVA analysis on the multiple imputed datasets will be combined and summarized.
2) Tipping point analyses: Subjects from the treatment arm who drop out the study will have their unobserved efficacy data imputed by the observed data from completers in the same arm using the multiple imputation method based on the monotonic missing pattern under the assumption of missing at random (MAR) with the resulting imputed values further worsened by an amount δ. Subjects who drop out the study from the control arm will be assumed to exhibit the same evolution of the disease as the completers in control arms and their values will be imputed by the multiple imputation method based on the monotonic missing pattern under the assumption of missing at random (MAR) above without the addition of δ. Sensitivity analysis may be performed for a range of δ to find a "tipping point" value of δ at which study conclusions start to change. When $\delta=0$ the missing data are assumed to be MAR. When $\delta > 0$, the missing data are assumed to be MNAR.

The third sensitivity analysis is the last observation carried forward (LOCF). For those subjects who discontinue study participation prior to Week 56, the last observed weight and height will be

used to derive the change in BMI.

Similar analyses will be performed for the primary endpoint for the m-ITT population.

12.5.3 Analysis of the Secondary Endpoints

If both the mid- and top-doses are shown to be statistically significantly better than placebo for the primary endpoint using the Fisher's LSD procedure, then the secondary endpoints will be tested in a stepwise way to preserve the familywise type 1 errors. Details of the stepwise testing procedure for secondary efficacy endpoints will be described in a prospective SAP.

Percent of subjects achieving a reduction ≥ 5% from baseline in BMI at Week 56 will be analyzed using a logistic regression, with treatment, age and gender stratification as the main effect and baseline BMI value as a covariate at the 0.05 significance level. The adjusted odds ratios between the top-dose and placebo and between the mid-dose and placebo will be calculated together with their 95% confidence intervals. The p-values for the comparisons will also be generated.

The percent of subjects achieving a reduction ≥ 10% and ≥ 15% from baseline in BMI at Week 56 will be analyzed similarly.

Secondary efficacy endpoints that are continuous variables will be analyzed by a similar MMRM model as for the primary endpoint where the baseline BMI value will be replaced by the baseline value of the corresponding endpoint as a covariate.

The above analyses will be conducted for both the ITT and m-ITT populations.

12.6 Safety Analysis

All safety analyses will be done for the ITT population. Safety data will be summarized for all treatment groups.

Safety will be assessed by an evaluation of adverse events (each study visit); laboratory parameters (screening, periodically during the study and end of study); electrocardiograms; physical examinations (screening, end of study); PHQ-9: Modified for Teens (see Appendix 4), C-SSRS, and vital signs, at each study visit). Descriptive statistics will be generated for the questionnaire data.

12.6.1 Analysis of CANTAB

CANTAB will be scored according to its instructions. The scores will be summarized by treatment descriptively.

12.6.2 Analysis of Hand and Wrist X-Ray

Changes from baseline to Week 56 in hand and wrist X-ray will be evaluated. Differences between treatment groups will be evaluated using methods similar to those used to evaluate other continuous variables.

12.6.3 Analysis of DXA

In the subset of subjects treated at sites where DXA scans are being done, mean changes from

baseline to Week 56 in bone mineral density (BMD) and bone mineral content (BMC)-Z scores will be evaluated. The mean change in BMD and BMC will be summarized descriptively as a continuous variable.

12.6.4 Adverse Events

Adverse events will be coded using a MedDRA coding dictionary. The number and percentage of subjects who reported at least one adverse event in each system organ class and preferred term category, and the total number and percentage of subjects with any AE over all system organ classes will be summarized by treatment group.

Subsets of AEs that are considered serious or required discontinuation of the study medication will be summarized separately and listed by subject.

12.6.5 Clinical Laboratory Tests

A summary of observed values and change from baseline will be presented for all laboratory parameters with numerical measures using descriptive statistics. Shift tables displaying low-normal-high at baseline versus low-normal-high at end of study in a 3-by-3 contingency table will be provided. For selected laboratory parameters, scatter plots of baseline versus Week 56 results, will be produced by treatment group.

A laboratory value that is above or below normal range will be considered an abnormal value. For selected laboratory parameters, threshold limits of clinical concern will be defined as multiplicative factors of the normal ranges. The list of multiplicative factors for each laboratory parameter will be included in the Statistical Analysis Plan. The frequency and percentage of subjects with laboratory results above or below the normal range and threshold limits at each scheduled assessment or any time during the treatment will be summarized by treatment group.

12.6.6 Vital Signs and Other Safety Evaluations

Mean blood pressures, heart rate, respiration, rate and temperature, obtained at each visit, will be summarized and plotted by treatment group. Medications, other than study medication, taken during the study will be considered as concomitant medications. They will be summarized by treatment group according to the preferred terms, using the World Health Organization (WHO) Drug Dictionary.

12.7 Interim Analysis

No interim analysis is planned.

12.8 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) with multidisciplinary representation will be established to evaluate accumulating trial data on a periodic basis and to assess the ongoing safety of the study for the subjects enrolled and to be enrolled. As a result, following each data review, the DMC will make a recommendation to the sponsor regarding continuation, revision, or termination of the study. Details related to DMC responsibilities, authorities, and procedures will be documented in the DMC charter, which will be finalized by the DMC prior to the first DMC data review meeting.

13.0 TRIAL TERMINATION CRITERIA

Premature termination of this clinical trial may occur because of a regulatory authority decision, change in opinion of the institutional review board (IRB)/independent ethics committee (IEC), drug safety problems, or at the discretion of VIVUS. In addition, VIVUS retains the right to discontinue this study at any time.

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

14.0 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.

15.0 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) 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 study-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.

16.0 ETHICAL CONSIDERATIONS

16.1 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 (ICF) 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 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.

16.2 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.

16.3 Subject Information and Consent/Assent

The informed consent form and any changes to the informed consent form during the course of the trial must be agreed to by VIVUS 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 study 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 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.

Parental consent and/or subject assent will be obtained according to IRB/IEC guidelines.

17.0 DATA HANDLING AND RECORD KEEPING

17.1 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 included 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. A CRF is required and should be completed for each randomized 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.

17.2 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 VIVUS' written permission from VIVUS before disposing of any records prior to completion of the required/stipulated retention period.

18.0 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.

19.0 REFERENCES

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APPENDIX 1: SCHEDULE OF EVENTS

	Screening	Baseline[a] (+ 3 days)	Treatment (± 1 Week)													
Study Weeks→	**Screen**	**0**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**	**52**	**56/ET**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Informed Consent/Assent	X															
Demographics and Medical History	X															
Review Inclusion/Exclusion	X	X														
Weight, Waist Circumference, Height, and BMI	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam (include Tanner Staging)		X														X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PHQ-9/C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Electrocardiogram		X														X
DXA (selected sites only)		X														X
Chemistry (Fasting)	X		X	X					X							X
Hematology/Lipids	X								X							X
TSH, HIV, HCV, HBsAg	X															
HbA1c	X				X						X					X
Urinalysis	X															X
Urine Drug Screen	X															
Urine Pregnancy Test	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Hand and Wrist X-ray (bone age assessment)		X														X
OGTT[b]		X														X
Cognitive Battery (CANTAB)	X[c]	X				X										X
IWQOL-Kids		X														X
Diet/Lifestyle Counseling		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Contraception/Pregnancy Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Randomization		X														
Dispense Study Drug		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug Accountability			X	X	X	X	X	X	X	X	X	X	X	X	X	X
Schedule Next Visit	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

[a] Baseline can occur up to 4 weeks from Screening.
[b] Blood sample at 2 hours post glucose load
[c] Familiarization session only

APPENDIX 2: BMI CONVERSION CHART

Weight	(lb)	110	115	120	125	130	135	140	145	150	155	160	165	170	175	180	185	190	195	200	205	210
	(kg)	49.9	52.2	54.5	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
Height																						
(in)	(cm)																					
55	139.7	26	27	28	29	30	31	33	34	35	36	37	38	40	41	42	43	44	45	46	48	49
56	142.2	25	26	27	28	29	30	31	33	34	35	36	37	38	39	40	41	43	44	45	46	47
57	144.8	24	25	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44	45
58	147.3	23	24	25	26	27	28	29	30	31	32	34	35	36	37	38	39	40	41	42	43	44
59	149.9	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	43
60	152.4	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41
61	154.9	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	39	40
62	157.5	20	21	22	23	24	25	26	27	27	28	29	30	31	32	33	34	35	36	37	38	38
63	160.0	19	20	21	22	23	24	25	26	27	28	28	29	30	31	32	33	34	35	36	36	37
64	162.6	19	20	21	22	22	23	24	25	26	27	28	28	29	30	31	32	33	34	34	35	36
65	165.1	18	19	20	21	22	23	23	24	25	26	27	28	28	29	30	31	32	33	33	34	35
66	167.6	18	19	19	20	21	22	23	23	24	25	26	27	27	28	29	30	31	32	32	33	34
67	170.2	17	18	19	20	20	21	22	23	24	24	25	26	27	27	28	29	30	31	31	32	33
68	172.7	17	17	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31	32
69	175.3	16	17	18	18	19	20	21	21	22	23	24	24	25	26	27	27	28	29	30	30	31
70	177.8	16	16	17	18	19	19	20	21	22	22	23	24	24	25	26	27	27	28	29	29	30
71	180.3	15	16	17	17	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29	29
72	182.9	15	16	16	17	18	18	19	20	20	21	22	22	23	24	24	25	26	27	27	28	29
73	185.4	15	15	16	17	17	18	19	19	20	20	21	22	22	23	24	24	25	26	26	27	28
74	188.0	14	15	15	16	17	17	18	19	19	20	21	21	22	23	23	24	24	25	26	26	27
75	190.5	14	14	15	16	16	17	18	18	19	19	20	21	21	22	23	23	24	24	25	26	26

APPENDIX 3: CDC CLINICAL GROWTH CHARTS[8]

	Male	Female
Age (in months)	**95th Percentile BMI Value**	**95th Percentile BMI Value**
143.5	24.1	25.2
144.5	24.2	25.3
145.5	24.3	25.3
146.5	24.4	25.4
147.5	24.5	25.5
148.5	24.6	25.6
149.5	24.6	25.7
150.5	24.7	25.8
151.5	24.8	25.9
152.5	24.9	26.0
153.5	24.9	26.0
154.5	25.0	26.1
155.5	25.1	26.2
156.5	25.2	26.3
157.5	25.3	26.4
158.5	25.3	26.5
159.5	25.4	26.5
160.5	25.5	26.6
161.5	25.5	26.7
162.5	25.6	26.8
163.5	25.7	26.9
164.5	25.8	26.9
165.5	25.8	27.0
166.5	25.9	27.1
167.5	26.0	27.2
168.5	26.0	27.3
169.5	26.1	27.3
170.5	26.2	27.4
171.5	26.3	27.5
172.5	26.3	27.6
173.5	26.4	27.6
174.5	26.5	27.7
175.5	26.5	27.8
176.5	26.6	27.8
177.5	26.6	27.9
178.5	26.7	28.0
179.5	26.8	28.1
180.5	26.8	28.1
181.5	26.9	28.2

	Male	Female
Age (in months)	**95th Percentile BMI Value**	**95th Percentile BMI Value**
182.5	27.0	28.3
183.5	27.0	28.3
184.5	27.1	28.4
185.5	27.1	28.5
186.5	27.2	28.5
187.5	27.3	28.6
188.5	27.3	28.7
189.5	27.4	28.7
190.5	27.4	28.8
191.5	27.5	28.8
192.5	27.6	28.9
193.5	27.6	29.0
194.5	27.7	29.0
195.5	27.7	29.1
196.5	27.8	29.2
197.5	27.9	29.2
198.5	27.9	29.3
199.5	28.0	29.3
200.5	28.0	29.4
201.5	28.1	29.5
202.5	28.1	29.5
203.5	28.2	29.6
204.5	28.3	29.6
205.5	28.3	29.7
206.5	28.4	29.8
207.5	28.4	29.8
208.5	28.5	29.9
209.5	28.5	29.9
210.5	28.6	30.0
211.5	28.7	30.0
212.5	28.7	30.1
213.5	28.8	30.2
214.5	28.8	30.2
215.5	28.9	30.3
216.5	29.0	30.3
217.5	29.0	30.4
218.5	29.1	30.4
219.5	29.1	30.5
220.5	29.2	30.6

APPENDIX 4: PHQ-9: MODIFIED FOR TEENS

PHQ-9: Modified for Teens

Name: _____ **Clinician:** _____ **Date:** _____

Instructions: How often have you been bothered by each of the following symptoms during the past **two weeks**? For each symptom put an **"X"** in the box beneath the answer that best describes how you have been feeling.

	(0) Not At All	(1) Several Days	(2) More Than Half the Days	(3) Nearly Every Day
1. Feeling down, depressed, irritable, or hopeless?				
2. Little interest or pleasure in doing things?				
3. Trouble falling asleep, staying asleep, or sleeping too much?				
4. Poor appetite, weight loss, or overeating?				
5. Feeling tired, or having little energy?				
6. Feeling bad about yourself – or feeling that you are a failure, or that you have let yourself or your family down?				
7. Trouble concentrating on things like school work, reading, or watching TV?				
8. Moving or speaking so slowly that other people could have noticed? Or the opposite – being so fidgety or restless that you were moving around a lot more than usual?				
9. Thoughts that you would be better off dead, or of hurting yourself in some way?				

In the **past year** have you felt depressed or sad most days, even if you felt okay sometimes?
[ ] Yes [ ] No

If you are experiencing any of the problems on this form, how **difficult** have these problems made it for you to do your work, take care of things at home or get along with other people?
[ ] Not difficult at all [ ] Somewhat difficult [ ] Very difficult [ ] Extremely difficult

Has there been a time in the **past month** when you have had serious thoughts about ending your life?
[ ] Yes [ ] No

Have you **EVER**, in your WHOLE LIFE, tried to kill yourself or made a suicide attempt?
[ ] Yes [ ] No

***If you have had thoughts that you would be better off dead or of hurting yourself in some way, please discuss this with your Health Care Clinician, go to a hospital emergency room or call 911.*

Office use only **Severity score:** _____

Modified with permission by the GLAD-PC team from the PHQ-9 (Spitzer, Williams, & Kroenke, 1999), Revised PHQ-A (Johnson, 2002), and the CDS (DISC Development Group, 2000)

APPENDIX 5: SAMPLE COLUMBIA SUICIDE SEVERITY RATING SCALE

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Baseline

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M.A., Halberstam B. & Mann J. J, Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", answer questions 3, 4 and 5.	**Lifetime - Time He/She Felt Most Suicidal**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it"*. ***Have you been thinking about how you might do this?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them"*. ***Have you had these thoughts and had some intention of acting on them?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself?*** ***Do you intend to carry out this plan?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION		
Ideation Type *Type # (1-5)* *Description of Ideation* *Baseline* *Most Common Ideation: _____ _____* *Most Severe Ideation: _____ _____*	**Lifetime – Time He/She Felt Most Suicidal**	
The following features should be rated with respect to both most common and most severe types of ideation. Ask about time he/she was feeling the most suicidal. Only rate most common if most severe and most common are different.	Most Common	Most Severe
Frequency ***How many times have you had these thoughts?*** 1. Less than once a week 2. Once a week 3. 2-5 times in week 4. Daily or almost daily 5. Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** 1. Fleeting - few seconds or minutes 2. Less than 1 hour/some of the time 3. 1-4 hours/a lot of time 4. 4-8 hours/most of day 5. More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** 1. Easily able to control thoughts 2. Can control thoughts with little difficulty 3. Can control thoughts with some difficulty 4. Can control thoughts with a lot of difficulty 5. Unable to control thoughts 0. Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** 1. Deterrents definitely stopped you from attempting suicide 2. Deterrents probably stopped you 3. Uncertain that deterrents stopped you 4. Deterrents most likely did not stop you 5. Deterrents definitely did not stop you 0. Does not apply; wish to die only	____	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** 1. Completely to get attention, revenge or a reaction from others. 2. Mostly to get attention, revenge or a reaction from others. 3. Equally to get attention, revenge or a reaction from others and to end/stop the pain. 4. Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). 5. Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	____	____

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Lifetime**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself*** ***(like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ **Total # of attempts** ____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted ____

Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐	**No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐	**No** ☐
Completed Suicide:	**Yes** ☐	**No** ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Worst/Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended for use by trained clinicians. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidality depends on clinical judgment.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M.A., Halberstam B. & Mann J. J, Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.] Standardized Evaluation in Clinical Practice, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries contact posnerk@childpsych.columbia.edu

SUICIDAL IDEATION	
Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes," answer questions 3, 4 and 5.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g. *"I've thought about killing myself"*) without general thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g. thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it…..and I would never go through with it"*. ***Have you been thinking about how you might do this?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having <u>some intent to act on such thoughts</u>, as opposed to *"I have the thoughts but I definitely will not do anything about them"*. ***Have you had these thoughts and had some intention of acting on them?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself?*** ***Do you intend to carry out this plan?*** ***Frequency of Ideation: _____*** If yes, describe:	**Yes** ☐ **No** ☐

INTENSITY OF IDEATION		
Ideation Type *Type # (1-5)* *Description of Ideation* *Most Common Ideation: _____ _____* *Most Severe Ideation: _____ _____*	**Since Last Visit**	
The following features should be rated with respect to both most common and most severe types of ideation experienced since last visit. Only rate most common if most severe and most common are different.	Most Common	Most Severe
Frequency ***How many times have you had these thoughts?*** 1. Less than once a week 2. Once a week 3. 2-5 times in week 4. Daily or almost daily 5. Many times each day	____	____
Duration ***When you have the thoughts how long do they last?*** 1. Fleeting - few seconds or minutes 2. Less than 1 hour/some of the time 3. 1-4 hours/a lot of time 4. 4-8 hours/most of day 5. More than 8 hours/persistent or continuous	____	____
Controllability ***Could /can you stop thinking about killing yourself or wanting to die if you want to?*** 1. Easily able to control thoughts 2. Can control thoughts with little difficulty 3. Can control thoughts with some difficulty 4. Can control thoughts with a lot of difficulty 5. Unable to control thoughts 0. Does not attempt to control thoughts	____	____
Deterrents ***Are there things - anyone or anything (e.g. family, religion, pain of death) - that stopped you from taking your life or acting on thoughts of committing suicide?*** 1. Deterrents definitely stopped you from attempting suicide 2. Deterrents probably stopped you 3. Uncertain that deterrents stopped you 4. Deterrents most likely did not stop you 5. Deterrents definitely did not stop you 0. Does not apply; wish to die only	____	____

Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** 1. Completely to get attention, revenge or a reaction from others. 2. Mostly to get attention, revenge or a reaction from others. 3. Equally to get attention, revenge or a reaction from others and to end/stop the pain 4. Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling). 5. Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling).	___	___

SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act.* Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g. gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____ as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you _____?*** ***Or did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** *(*Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	**Yes** ☐ **No** ☐ **Total # of attempts** ____ **Yes** ☐ **No** ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred).* Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose	**Yes** ☐ **No** ☐

around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Total # of interrupted ____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	**Yes** ☐ **No** ☐ Total # of aborted ____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g. buying pills, purchasing a gun) or preparing for one's death by suicide (e.g. giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	**Yes** ☐ **No** ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	**Yes** ☐ **No** ☐
Completed Suicide:	**Yes** ☐ **No** ☐

Answer for Actual Attempts Only	**Most Recent Attempt Date:**	**Worst/Most Lethal Attempt Date:**	**Initial/First Attempt Date:**
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g. surface scratches). 1. Minor physical damage (e.g. lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g. conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g. comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g. comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____	*Enter Code* _____	*Enter Code* _____

APPENDIX 6: IWQOL-KIDS

The subject will answer questions based on what best applies to them in the past seven days. Each question contains five response options: “always true”, “usually true”, “sometimes true”, “rarely true”, and “never true”, scaled from 1 to 5, respectively.

Physical Comfort

1. Because of my weight I avoid using stairs whenever possible.
2. Because of my weight it is hard for me to bend over to tie my shoes or to pick something up off the floor.
3. Because of my weight it is hard for me to move around.
4. Because of my weight it is hard for me to fit into seats in public places (e.g. movie theaters, desks at school, and booths in restaurants).
5. Because of my weight my knees or ankles hurt.
6. Because of my weight it is hard for me to cross my legs.

Body Esteem

7. Because of my weight I am ashamed of my body.
8. Because of my weight I don’t like myself very much.
9. Because of my weight I try not to look at myself in mirrors or in photographs.
10. Because of my weight I have a hard time believing compliments that I receive from others.
11. Because of my weight I am lacking in self-confidence.
12. Because of my weight I avoid activities that involve wearing shorts or a bathing suit.
13. Because of my weight it is very difficult for me to buy clothing.
14. Because of my weight I don’t like to change my clothes or undress in front of others.
15. Because of my weight I am embarrassed to try out for activities at school.

Social Life

16. Because of my weight people tease me or make fun of me.
17. Because of my weight people talk about me behind my back.
18. Because of my weight people avoid spending time with me.
19. Because of my weight people stare at me.
20. Because of my weight I have trouble making or keeping friends.
21. Because of my weight people don’t think I’m very smart.

Family Relations

22. Because of my weight family members treat me differently from the way they treat other people.
23. Because of my weight family members talk about me behind my back.
24. Because of my weight one or more people in my family reject me.
25. Because of my weight my parents aren’t proud of me.
26. Because of my weight family members make fun of me.
27. Because of my weight family members don’t want to be seen with me.

APPENDIX 7: FORMULAS FOR ESTIMATING CREATININE CLEARANCE

Creatinine clearance in adolescent boys and girls should be calculated based on height (HT) and serum creatinine (sCr) using the Schwartz formula (refs) as noted below.[7]

$$CrCl_{adolescent\ boy} = \frac{[0.70 \times Ht(cm)]}{sCr\ (\frac{mg}{dL})}$$

$$CrCl_{adolescent\ girl} = \frac{[0.55 \times Ht(cm)]}{sCr\ (\frac{mg}{dL})}$$

APPENDIX 8: SUMMARY OF CHANGES IN AMENDMENT #1

Amendment #1 (05 October 2018)

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
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.
Section 1.0: Table of Contents	***Updated*** Table of Contents
Section 2.0: Protocol Synopsis – Study Objectives	***Text deleted***: "…VI-0521 (PHEN/TPM 7.5 mg/46 mg and PHEN/TPM ~~and~~ 15 mg/92 mg doses) for..."
Section 7.2: Exclusion Criteria #14	***Text deleted***: "Any history of ~~any~~ eating disorders (e.g. bulimia; binge eating disorder; anorexia);"
Section 8.4.1: Formulation and Packaging	***Revised***: "…during the first 4 weeks of study treatment ~~and the first 4 weeks following up-titration for subjects randomized to the top-dose (~~*titration period during study* Weeks 13-16~~)~~, and treatment kits (bottles), for use once subjects have been titrated to their assigned dose."
Section 8.4.3: Administration	***Revised***: "…should the next study visit be scheduled ~~after Week 4~~*beyond 4 weeks after the previous visit*. Investigators will…"
Section 9.1: Screening Visit (Visit 1, Up to – 4 Weeks)	***Added***: "Administer neurocognitive battery (CANTAB) familiarization session"
Section 9.1.3: Treatment Week 4 Through Week 52 (Visits 3 Through 15)	***Revised***: "Administer neurocognitive battery (CANTAB), Visit ~~3~~6 only;"
Section 9.2: Study Period	***Revised***: "…Sites should link the scheduling of visits to the *baseline*/randomization visit (Visit 2, Day 0). … so that the overall treatment duration is 56 ~~days~~*weeks* for subjects…
Section 10.10: Oral Glucose Tolerance Test	***Revised***: "An oral glucose tolerance test (OGTT) will be obtained at *baseline*~~Visit 2~~ (after results from ~~Visit 1~~*screening visit* indicate the subject …"

Section and/ or Item	Changes Effected
Section 10.11: CANTAB (Cambridge Neuropsychological Test Automated Battery)	***Revised***: "An oral glucose tolerance test (OGTT) will be obtained at *baseline*~~Visit 2~~ (after results from ~~Visit 1~~*screening visit* indicate the subject …"
Section 10.12: IWQOL-Kids	***Revised***: "… is a 27-item, self-administered instrument that will be completed at baseline ~~(Visit 2)~~, ~~Visit 9 (Week 28)~~ and end of study ~~(Visit 16 at Week 56~~ or early termination~~)~~."
Appendix 1: Schedule of Events	***Updated*** CANTAB test to add familiarization test to Screening and moved test at Week 4 to Week 16. ***Text added*** to "Contraception/*Pregnancy* Counseling" ***Added*** "Schedule Next Visit" ***Added*** footnote c.
Appendix 1: Schedule of Events	***Updated*** CANTAB test to add familiarization test to Screening and moved test at Week 4 to Week 16. ***Text added*** to "Contraception/*Pregnancy* Counseling" ***Added*** "Schedule Next Visit" ***Added*** footnote c.
Section 19.0: References	***Updated*** References #1, #3, #5, #6.
Appendix 1: Schedule of Events	***Updated*** CANTAB test to add familiarization test to Screening and moved test at Week 4 to Week 16. ***Text added*** to "Contraception/*Pregnancy* Counseling" ***Added*** "Schedule Next Visit" ***Added*** footnote c.

APPENDIX 9: SUMMARY OF CHANGES IN AMENDMENT #2

Amendment #2 (21 June 2019)

Rationale:

This protocol amendment is being implemented to clarify or revise several inconsistencies that had been noted in the previous 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
Header	***Updated*** protocol version and version date.
Title Page	***Updated*** current and previous protocol version and version date.
Investigator Signature Page	***Updated*** protocol version and version date.
Section 1.0: Table of Contents	***Updated*** Table of Contents
Section 2.0: Protocol Synopsis – Study Rational	***Text updated***: "Obesity remains a major problem in pediatrics. National Health and Nutrition Examination Survey (NHANES) data indicate that ~~17.0~~*18.5%* of children and adolescents age 2 to 19 years and ~~20.5~~*20.6*% of adolescents age 12 to 19 years met the definition of obesity in ~~2011–2014~~*2015-2016*…."
Section 2.0: Protocol Synopsis – Study Design	***Text revised***: "…Randomization will be stratified by age (12-14 vs 15-~~17~~*16* years old) and gender...."
Section 2.0: Protocol Synopsis – Study Population: Key Exclusion Criteria	***Text added***: "…History of bipolar disorder or psychosis, *greater than one lifetime episode of major depressive disorder,* depression of moderate or greater severity..."
Section 4.0: Background	***Text updated***: "Obesity remains a major problem in pediatrics. National Health and Nutrition Examination Survey (NHANES) data indicate that ~~17.0~~*18.5%* of children and adolescents age 2 to 19 years and ~~20.5~~*20.6*% of adolescents age 12 to 19 years met the definition of obesity in ~~2011–2014~~*2015-2016*…."
Section 6.0: Study Design	***Text revised***: "…Randomization will be stratified by age (12-14 vs 15-~~17~~*16* years old) and gender...."
Section 7.2: Exclusion Criteria #9-27	***Updated*** numbering.
Section 7.2: Exclusion Criteria #13	***Text added***: "Any history of bipolar disorder or psychosis, *greater than one lifetime episode of* major depressive disorder, current depression of moderate or greater severity..."
Section 8.2: Allocation to Treatment	***Text revised***: "…Randomization will be stratified by gender and age (12-14 vs 15-~~17~~*16* years old), and..."
Section 11.3: Reporting Period	***Text revised***: "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~~*day of study participation*...."

Section and/ or Item	Changes Effected
Appendix 1: Schedule of Events	***Revised*** table header and footer.

Statistical Analysis Plan

VIVUS, Inc.

OB-403

Covance Study ID: 000000173988
Document Version: Final 1.1
Document Date: April 01, 2021

Covance Inc. CDCS
Clinical Development Commercialization Services

Table of Contents

Approvals

The undersigned agree that all required reviews of this document are complete, and approve this Statistical Analysis Plan as final. Programming of the tables, figures and listings based upon the specifications within this document can proceed.

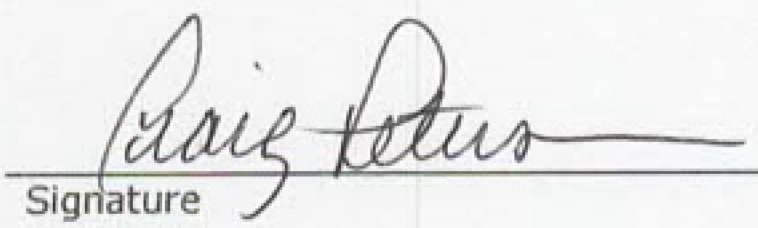
Approved by
Covance Lead Statistician Approval

Jingsong He
Senior Statistician
I authored this document
07 Apr 2021 9:16 PM -04:00

Signature Date

Jingsong He, Senior Statistician
Printed Name/Title

Vivus Approval:



07 APR 2021

Signature Date

Craig Peterson, Senior Director, Clinical Research
Printed Name/Title

Cambridge Cognition Approval:

6th April 2021

Signature Date

Elizabeth Baker, Director of Statistical Sciences
Printed Name/Title

Reviewers

The following reviews of the SAP were conducted:

Name and Title	Role	Version Last Reviewed	Company/ Organization
Jingsong He Senior Statistician	Lead Statistician	Final 1.1	Covance
Cecilia McWhirter Senior Principle Statistician	Peer Review Statistician	Final 1.1	Covance
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Elizabeth Baker Director of Statistical Sciences	Biostatistician	Final 1.1	Cambridge Cognition

Version History

Version #	Description of Changes	Version Date
Final 1.0	Original Version	01Sept2020
1.1	Updates to Sections 5.2 and 6	07Jan2021

Glossary of Abbreviations

Abbreviations pertain to the SAP only (not the TFLs).

Abbreviation	Term
AE	Adverse event
ANCOVA	Analysis of Covariance
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
BP	Blood Pressure
BMD	bone mineral density
BMC	bone mineral content
CANTAB	Cambridge Neuropsychological Test Automated Battery
CI	Confidence Interval
CRF	Case report form
C-SSRS	Columbia Suicide Severity Rating Scale
DXA	Dual-energy X-Ray Absorptiometry
ECG	Electrocardiogram
ET	Early Termination
HR	Heart Rate
LSD	protected Least Significant Difference
ITT	Intention-to-treat
IWQOL-Kids	Impact of Weight on Quality of Life-Kids
LOCF	Last observation carried forward
MAR	missing at random
MCMC	Markov chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-treat
MMRM	Mixed Effects Model with Repeated Measures
MNAR	missing not at random
PHQ-9	Patient Health Questionnaire-9
SAE	Serious Adverse Event
SD	Standard Deviation
SOC	System Organ Class
TEAEs	Treatment–Emergent AEs
TFLs	Tables, Figures and Listings

STATISTICAL ANALYSIS PLAN AMENDMENT 1

Not applicable.

1. Source Documents

The Statistical Analysis Plan (SAP) was written based on the following documentation:

Document	Date	Version
Protocol	24 Aug 2017	Original
Protocol Amendment #1	05 Oct 2018	Amendment # 1
Protocol Amendment #2	21 Jun 2019	Amendment # 2
<e>CRF	17 Sep 2019	3.0
DMC Charter	27 Feb 2020	1.0
DMC Charter Amendment	NA	NA

2. Protocol Details

2.1 Study Objectives

The primary objectives are to evaluate the safety and efficacy of VI-0521 for the treatment of obesity in adolescents. The secondary objective is to characterize changes in obesity-related risk factors.

2.2 Overall Study Design

In this multicenter, randomized, double-blind, placebo-controlled, parallel-design study, approximately 200 subjects will be enrolled at approximately 20 sites in the United States. Subjects will be randomly assigned in a 1:1:2 ratio to placebo, N= 50; mid-dose (PHEN/TPM 7.5 mg/46 mg), N= 50; or top-dose (PHEN/TPM 15 mg/92 mg), N =100, of VI-0521, to be taken orally once daily in the morning. Randomization will be stratified by age (12-14 vs 15-16 years old) and gender. The study will consist of a screening period of up to 28 days, followed by a 56-week treatment period.

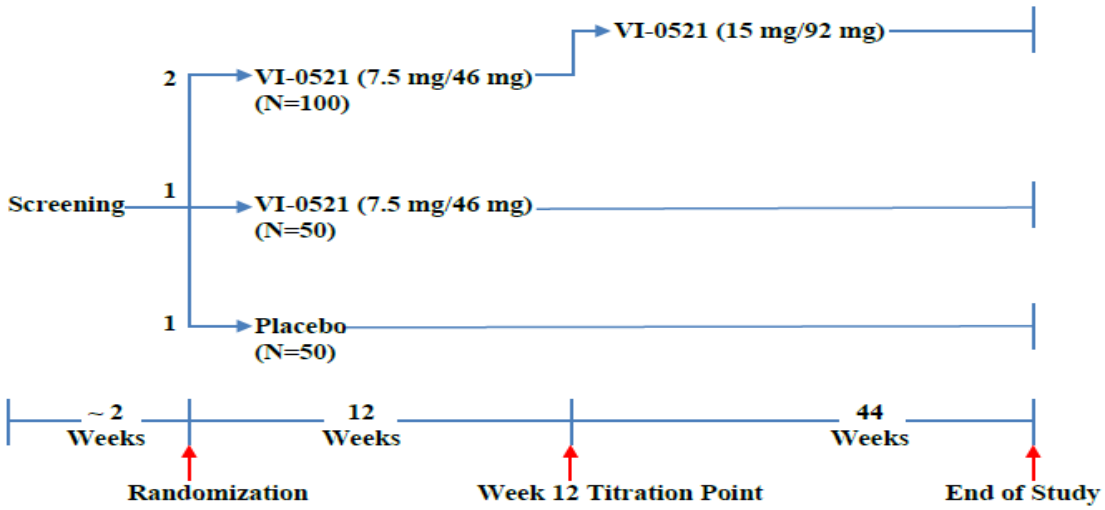
Subjects will be instructed to follow a mild hypocaloric diet modification program representing a 500-calorie/day deficit and to implement a family-based lifestyle modification program for adolescents, as tolerated, throughout the study period. The lifestyle program will include physical activity, behavior change, and family support. The same lifestyle modification program, specific to this population, will be implemented across all sites. Study drug will be titrated according to the following schema.

Group	Treatment Dosage for PHEN/TPM (mg)	Titration Dose for PHEN/TPM (mg)			
		Weeks 1-2	Weeks 3-4	Weeks 13-14	Weeks 15-16
Placebo	0/0	0/0	0/0	0/0	0/0
VI-0521 Mid	7.5/46	3.75/23	7.5/46	7.5/46	7.5/46
VI-0521 Top	15/92	3.75/23	7.5/46	11.25/69	15/92

Subjects who are unable to tolerate the assigned dose may be treated at a reduced dose level or may take a drug holiday as defined in the protocol. In addition, for growth monitoring, investigators will monitor rates of weight loss in treated subjects. For subjects with baseline BMI 95-98th percentile, reduce study drug dosage when BMI is < 85th percentile or when weight loss exceeds an average of 2 lbs (0.9 kg) per week. For subjects with baseline BMI ≥ 99th percentile, reduce study drug when weight loss exceeds an average of 2 lbs (0.9 kg)/week.

All subjects will return at approximately 4-week intervals for study assessments. All female subjects will undergo a pregnancy test at each visit. Subjects who discontinue study drug during the study will be encouraged to remain on study (off study drug) for continued follow-up by attending all remaining visits and have all study-related procedures performed, and to return at the 56-week time point for measurements and evaluations. For those who choose to completely withdraw from the study at any point, the end of study (Week 56) procedures should be completed.

Figure 1. Schematic Diagram of Study Design



2.3 Sample Size and Power

In previous studies in adults, VI-0521 mid-dose (PHEN/TPM 7.5 mg/46 mg) resulted in a placebo-subtracted BMI reduction of 2.4 units with a standard error approximately 0.16 units and a within treatment standard deviation of 2.9. A very conservative estimate of the treatment difference between the mid-dose and placebo would be 2 units of BMI which represents more than 2 standard errors below what was observed before. If we enroll 200 subjects (50 placebo, 50 mid-dose, and 100 top-dose), we will have at least 90% power to detect a statistically significant difference between the top-dose (PHEN/TPM 15 mg/92 mg) and the placebo because we could assume that the top-dose will have a higher effect size than the mid-dose. This calculation assumes that there will be an approximately 30% dropout rate. This sample size will also provide approximately 80% power to detect a statistically significant difference between the mid-dose and placebo.

3. Efficacy and Safety Variables

3.1 Primary Efficacy Endpoints

- The mean percent change in BMI from baseline to end of study (Week 56).

3.2 Secondary Efficacy Endpoints

- Percent of subjects achieving a reduction ≥ 5%, ≥ 10% and ≥ 15% of baseline BMI at Week 56;
- Change from baseline in waist circumference at Week 56;
- Change from baseline in fasting insulin and Whole Body Insulin Sensitivity Index (Matsuda) at Week 56;
- Percent change from baseline in triglycerides and HDL-C at Week 56;
- Change from baseline in blood pressure at Week 56.

3.3 Exploratory Endpoints

- Evaluate effects of treatment on Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire scores.
- Changes in various glycemic and lipid markers.
- Change in BMI Z-score.

3.4 Safety Endpoints

Safety will be assessed by evaluating adverse events (AEs)/serious adverse events (SAEs); vital signs, laboratory parameters (screening, periodically during the study and end of study); electrocardiograms; physical examinations; cognitive function tests using the Cambridge Neuropsychological Test Automated Battery (CANTAB). All subjects will be screened for the presence and severity of depression using the PHQ-

9: Modified for Teens and for suicidal/ideation using the Columbia Suicide Severity Rating Scale (C-SSRS) and follow up assessments will be done at each visit after treatment has been initiated. Bone age (X-ray of the hand and wrist) will be evaluated at baseline and end of study or early termination. Effect on bone mineral density and bone mineral content, as evaluated by Dual-energy X-Ray Absorptiometry (DXA) will be performed at baseline, end of study or early termination, at selected sites.

3.5 DXA (Sub Study)

A bone health sub-study will be conducted at selected sites in approximately 100 subjects (25 each on placebo and mid-dose, and 50 on top-dose) to assess the effect of VI-0521 administration on bone health using Dual X-ray Absorptiometry (DXA). DXA scans of the posterior-anterior (PA) spine (lumbar), and total body less head (TBLH) will be performed at baseline and at the end of study or early termination. Equipment and procedures used to obtain DXA data will be standardized as described in a separate document. Sites involved in DXA measurement will be trained on these procedures prior to performing scans on study subjects. Scans will be read at a central facility and the reader will be blinded.

The following enrollment criteria will apply:

1) Both male and female will be eligible to participate;
2) Subjects with a history of any non-traumatic fracture will not be eligible;
3) Subjects with juvenile osteoporosis at baseline will not be eligible; and
4) Subjects must meet manufacturer equipment specifications with regard to height and weight limitations.

4. Analysis populations

4.1 Randomized

This population will be comprised of all subjects who were initially randomized. This population will be used for summaries of subject disposition and baseline subject characteristics.

4.2 Safety

This population will be comprised of all subjects who were initially randomized and received at least one dose of study drug. This will be the primary population for all summaries of subject disposition and baseline characteristics, and safety analyses for purposes of regulatory submissions. The safety population is based on the treatments actually received.

4.3 Intent-to-treat (ITT)

This population will be comprised of all subjects who were initially randomized and received at least one dose of study drug. This will be the primary population for all summaries of efficacy analyses for purposes of regulatory submissions. The ITT population is based on the randomized treatments.

4.4 Modified Intent-to-treat (mITT)

This population will be comprised of all randomized study subjects who receive study treatment and return for at least one post-randomization assessment of height and weight. This population will be used for the analysis of all efficacy variables for all other purposes, including but not limited to publications, presentations, and robustness of sensitivity of analyses.

4.5 Special Subpopulations

BMI change will be tabulated by age and gender. Additionally, further exploratory subgroup analyses of the primary efficacy endpoints may include evaluation by race and/or other subgroups deemed medically and/or scientifically important.

5. DATA Handling

5.1 Time Points and Visit Windows

Day 0 (Visit 2) is defined as the Baseline/Randomization visit, is also the first day of treatment. Relative days are calculated as (assessment date – Day 1 date). The day prior to Day 0 is Day -1.

The following visit windows defined in Table 1 will be used for the by-visit analyses of the primary endpoint, the secondary and other endpoints. All other analyses will use the nominal study visit as defined in the Study Schedule and eCRF.

If there are multiple visits (scheduled or unscheduled) within a visit window, the measurement closest to the target day of the visit will be used in the analysis. If the measurements are equally distant to the target day, then the later one will be used in the analysis. If both scheduled and unscheduled visits fall within the same visit window, the scheduled visit will be used for analysis.

Table 1 Definition of Visit Windows

Visit	Visit time (Week)	Acceptable visit window	Study Day Analysis Visit Window Range
1 Screening	Screening	-28 days from baseline	NA
2 Baseline[a]	Week 0	±3 days	Day -27 to Day 2
3 Treatment	Week 4	±1 week	Day 3 to Day 41(Week 6)
4 Treatment	Week 8	±1 week	Day 42 to Day 69(Week 10)
5 Treatment	Week 12	±1 week	Day 70 to Day 97(Week 14)
6 Treatment	Week 16	±1 week	Day 98 to Day 125(Week 18)
7 Treatment	Week 20	±1 week	Day 126 to Day 153(Week 22)
8 Treatment	Week 24	±1 week	Day 154 to Day 181(Week 26)
9 Treatment	Week 28	±1 week	Day 182 to Day 209(Week 30)
10 Treatment	Week 32	±1 week	Day 210 to Day 237(Week 34)
11 Treatment	Week 36	±1 week	Day 238 to Day 265(Week 38)
12 Treatment	Week 40	±1 week	Day 266 to Day 293(Week 42)
13 Treatment	Week 44	±1 week	Day 294 to Day 321(Week 46)
14 Treatment	Week 48	±1 week	Day 322 to Day 349(Week 50)
15 Treatment	Week 52	±1 week	Day 350 to Day 377(Week 54)
16 End of Study/ET[b]	Week 56/ET	±1 week	Day 378 to Day 398(Week 57)

[a] Baseline Visit (Visit 2) can be scheduled up to 4 weeks from Screening.
[b]. ET = Early Termination

5.2 Handling of Dropouts, Missing Data, and Outliers

For subjects who discontinue treatment prior to study completion, every attempt will be made to have them continue with clinic visits and study assessments. Particular attention will be given to collecting Week 56 assessments of weight and height, regardless of when subjects discontinued treatment.

Missing data will not be imputed for safety analyses. The safety evaluations will be performed on observed data only.

For the MMRM (mixed effects model with repeated measures) method used for the primary analysis on the primary endpoint, the retrieved dropouts will be used to impute missing data for subjects who discontinue the study prematurely. If there are no sufficient retrieved dropouts, then the wash-out imputation method will be applied.

The following sensitivity analyses will be considered to explore the impact of missing data on the conclusion of the primary analysis.

The first sensitivity analysis is using a multiple imputation method based on the monotonic missing pattern under the assumption of missing at random (MAR). The intermittent missing data will be imputed using multiple imputation MCMC (Markov chain Monte Carlo) procedure.

The second sensitivity analysis is also using multiple imputation, however, under the assumption of missing not at random (MNAR) to explore the validity of MAR using pattern-mixture model:

1) For subjects who discontinue study participation prior to Week 56 and do not have follow-up visit, the missing data will be imputed using the observed data from the subjects in the same arm who discontinue the study treatment but have the primary endpoint measurement in the follow up visit using a regression method. The intermittent missing data will be imputed using multiple imputation MCMC procedure. An ANCOVA (analysis of covariance) model using a similar mixed procedure (without the repeated measures) as the primary analysis will be applied to these multiple-imputed % change in BMI at Week 56 with treatment, baseline BMI value as a covariate, and age and gender as stratification factors. The results of ANCOVA analysis on the multiple imputed datasets will be combined and summarized.
2) Tipping point analyses: Subjects from the treatment arm who drop out the study will have their unobserved efficacy data imputed by the observed data from completers in the same arm using the multiple imputation method based on the monotonic missing pattern under the assumption of MAR with the resulting imputed values further worsened by an amount δ. Subjects who drop out the study from the control arm will be assumed to exhibit the same evolution of the disease as the completers in control arms and their values will be imputed by the multiple imputation method based on the monotonic missing pattern under the assumption of MAR above without the addition of δ. Sensitivity analysis may be performed for a range of δ to find a "tipping point" value of δ at which study conclusions start to change. When δ=0 the missing data are assumed to be MAR. When δ > 0, the missing data are assumed to be MNAR.

The third sensitivity analysis is the last observation carried forward (LOCF). For those subjects who discontinue study participation prior to Week 56, the last observed weight and height will be used to derive the change in BMI.

Similar analyses will be performed for the primary endpoint for the mITT population.

6. Statistical Methods

6.1 General Principles

All data processing, summarization and analyses will be performed using SAS Environment / Version 9.3 (or later) of the SAS® statistical software package.

The following principles will be applied to all TFLs unless otherwise stated:

Principle	Value
Significant tests	Two-sided and use a 5% significance level.
Treatment group labels and order presented	Placebo VI-0521 Mid VI-0521 Top
Tables	Data in summary tables presented by treatment group, assessment and visit (where applicable).
Listings	All data collected presented by treatment group, site, subject, and visit (where applicable), unless otherwise specified.
Descriptive summary statistics for continuous variables	Number of observations (N), mean, standard deviation (SD), minimum, median and maximum.
Descriptive summary statistics for categorical variables	Frequency counts and percentages [n (%)].
Denominator for percentages	Number of subjects in the pertinent analysis population, unless stated otherwise in table shells.
Include “Missing” as category	Demographics and Other Baseline Characteristics only
Display for 0 percentages	Blank
Display to one more decimal place than collected value	Mean Median Minimum Maximum
Display to two more decimal places than collected value	Standard Deviation Confidence Interval
Limit of precision for displays	3 decimal places
Date Format	DDMMMYYYY

6.2 Subject Disposition and Data Sets Analyzed

Subject disposition will be listed and summarized by treatment group and overall and will include the number and percentage of subjects:

- Screened;
- Randomized;
- Not randomized;
- Randomized and not treated;
- Treated;
- Included in each study population (Safety, ITT, mITT, DXA Substudy);
- Completed all study visits;
- Completed all study visits on study drug;
- Randomized but discontinue study drug and discontinue from all study visits and procedures;

- Randomized but discontinue study drug but continue with all study visits and procedures; and
- Randomized but discontinue from the study and returned for the Week 56 weight measurement.

For subjects who are not randomized, randomized subjects who discontinue study drug but continue in the study, and randomized subjects who discontinue study drug and study participation, a summary regarding reason of discontinuation will also be provided.

A summary of patient enrollment by site will also be provided by treatment group and overall for the Safety population.

6.3 Protocol Deviations

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol. Protocol deviations for the study include, but are not limited to, the following:

- Failure to meet inclusion/ exclusion criteria;
- Non-compliance of protocol guidelines;
- Inability to adequately complete study assessments per protocol, etc.

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol deviation. The Sponsor will determine if a protocol deviation will result in withdrawal of a subject.

All protocol deviations and deviation categories will be listed and summarized for the Safety population.

6.4 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics will be listed and summarized by treatment group and overall for randomized, Safety and DXA substudy populations. Standard descriptive statistics will be presented for the continuous variables of:

- Age at screening (years)
- weight (kg)
- height (cm)
- body mass index (kg/m^2)
- Waist Circumference (cm)
- Fasting insulin
- Whole Body Insulin Sensitivity Index (Matsuda)
- Triglycerides
- HDL-C

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)

The total counts and percentages of subjects will be presented for the categorical variables of:

- Age at screening (12-14 years, 15-16 years)
- Gender
- Race
- Ethnicity
- BMI categories ≥95th to <99th, and ≥99th percentile)

No formal tests of statistical significance will be performed on the demographic and baseline data.

Other baseline measurements, such as vital signs, ECG, will be summarized by treatment group with the post-baseline measurements.

6.4.1 Medical History

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 21.3 (or a later version if updated during the study). All medical history will be listed, and the number and percentage of subjects with any medical history will be summarized for Safety population by system organ class (SOC) and preferred term (PT) for each treatment group and overall.

6.4.2 Prior and Concomitant Medications

Medications received prior to or concomitantly with study drug treatment will be coded by Covance using the WHO Drug Global Dictionary, Version September 2018 (or a later version if updated during the study), Anatomical Therapeutic Chemical (ATC) Classification codes.

Medications, other than study medication, taken within 30 days prior to screening will be considered as prior medications; while those taken during the study will be considered as concomitant medications.

If a medication cannot be classified as “prior” or “concomitant” after applying imputation rules for missing/incomplete dates, it will be classified as concomitant.

Prior medications and concomitant medications will be listed and summarized together for Safety population.

The number and percentage of subjects using each medication will be displayed together with the number and percentage of subjects using at least one medication within each therapeutic class (ATC-Level 2), chemical subgroup (ATC-Level 4), and preferred term.

6.5 Measurements of Treatment Compliance

Percentage compliance is calculated as:

100 * actual capsules taken/expected capsules taken

Where actual capsules taken is defined as (total number of capsules dispensed – total number of capsules returned) and expected taken is defined as the number of capsules prescribed per day times the number of days taken for study treatment.

Percentage compliance will be summarized descriptively by treatment group for the Safety population.

The number and percentage of compliant subjects will be presented for the Safety population, where compliant is defined as percentage compliance between 80.0% and 120.0% inclusive. The following percentage compliance categories will also be presented:

- <80.0%
- 80% to 120%
- >120.0%

6.6 Efficacy

6.6.1 Primary Efficacy Analysis

The primary endpoint for this study is the mean % change in BMI from baseline to end of study (Week 56).

For subjects who discontinue treatment prior to trial completion, every attempt will be made to have them continue with clinic visits and study assessments. Particular attention will be given to collecting Week 56 assessments of weight and height, regardless of when subjects discontinued treatment. These retrieved dropouts will be used to impute missing data using multiple imputation method for the primary analysis for subjects who discontinue the study prematurely and are missing follow-up observations. This is based on the assumption that the group that best reflects what happened to the non-retrieved dropouts at week 56, are the retrieved dropouts. For patients who terminate the treatment early but decide to stay in the study and have all the data after being off treatment, those data will be used to impute the missing data off-treatment. For any patient who terminates the treatment and study prematurely and permanently, if the patient has the final measurement at Week 56, the measurement will be used for analyses at Week 56. The missing data between the last available measurement and Week 56 will be imputed by interpolation for analyses.

If there are no sufficient retrieved dropouts, the washout imputation method will be applied. This imputation method will only impute the time point at Week 56 for the

active treatment arms using multiple imputation regression with randomization strata and baseline BMI as the predictors. This approach ignores any post-baseline changes in the BMI values when predicting missing Week 56 values and will impute all patients similar to an average placebo patient. For patients in placebo arm, missing data at any time point will be imputed assuming MAR mechanism. The variables used as explanatory variables for imputation include Randomization strata and baseline BMI.

After such imputation, comparisons in the primary endpoint of change from the baseline BMI between treatment groups be assessed for the ITT population using a mixed effects model with repeated measures (MMRM) with factors of treatment, visit, treatment by visit interaction, baseline BMI value, age stratification, and gender stratification. Appropriate contrast will be applied for treatment comparisons at Week 56. The pairwise comparisons of interest are top-dose vs. placebo, and mid-dose vs. placebo, and top-dose vs. mid-dose. The primary null hypothesis will be that there is no treatment difference between any VI-0521 treatment groups and the placebo in the percent change from baseline to Week 56 in BMI. An appropriate contrast will be used for the comparisons at Week 56. The family-wise type 1 error for the comparisons will be controlled by Fisher's protected least significant difference (LSD) method at the 0.05 significance level: placebo, mid-dose, and top-dose will be first compared for overall difference in the percent change from baseline in BMI. Once the overall difference is significant at the 0.05 significance level, the above 3 pairwise comparisons will be conducted using Fisher's LSD method at the 0.05 significance levels. The order for comparisons of interest is top-dose vs. placebo, mid-dose vs. placebo, and top-dose vs. mid-dose. Due to the fact that only three treatments are compared, the above procedure strongly controls the family-wise type 1 error.

6.6.2 Secondary Efficacy Analysis

If both the mid- and top-dose are shown to be statistically significantly better than placebo for the primary endpoint using the Fisher's LSD procedure, then the secondary endpoints will be tested in a stepwise way to preserve the familywise type 1 errors.

Starting from top-dose of VI-0521 treatment, hypothesis tests for secondary efficacy endpoints will be based on null hypotheses that assume no *a priori* differences between placebo and top-dose treatment.

A closed or sequential testing procedure will be used for testing the key secondary efficacy variables. With this hierarchical procedure, the key secondary efficacy variables will only be tested if the primary efficacy analysis is statistically significant.

Analyses will be carried out for the key secondary variables.

Within the key secondary variables, the statistical significance level will be adjusted using the Hochberg method, controlling the familywise error rate at 5%. Correlation

analysis will be implemented among the key secondary variables to ensure the conditions required for Hochberg procedure are satisfied. All endpoints have to be statistically significant in favor of top-dose VI-0521 treatment compared to placebo, after the Hochberg adjustment, in order for the next set in the hierarchy to be tested. The testing is only stopped when all of the alpha is 'exhausted'. The sequential testing will stop at the first endpoint set where top-dose VI-0521 treatment does not demonstrate statistical superiority over placebo.

The above process will be repeated on mid-dose of VI-0521 treatment.

Percent of subjects achieving a reduction ≥ 5% from baseline in BMI at Week 56 will be analyzed using a logistic regression, with treatment, age and gender stratification as the main effect and baseline BMI value as a covariate at the 0.05 significance level. The adjusted odds ratios between the top-dose and placebo, between the mid-dose and placebo, and between the top-dose and mid-dose will be calculated together with their 95% confidence intervals. The p-values for the comparisons will also be generated.

The percent of subjects achieving a reduction ≥ 10% and ≥ 15% from baseline in BMI at Week 56 will be analyzed similarly.

Secondary efficacy endpoints that are continuous variables (change from baseline in waist circumference, fasting insulin, whole body insulin sensitivity index (Matsuda), triglycerides, HDL-C, and systolic and diastolic blood pressure) will be analyzed by a similar MMRM model as for the primary endpoint where the baseline BMI value will be replaced by the baseline value of the corresponding endpoint as a covariate.

The above analyses will be conducted for both the ITT and mITT populations.

6.6.3 Sensitivity Analysis

The MMRM method used for the analysis will be applied to the mITT population with the observed data without imputation. The following sensitivity analyses will also be considered to explore the impact of missing data on the conclusion of the primary analysis.

The first sensitivity analysis is using a multiple imputation method based on the monotonic missing pattern under the assumption of MAR. The intermittent missing data will be imputed using multiple imputation MCMC procedure.

The second sensitivity analysis is also using multiple imputation, however, under the assumption of MNAR to explore the validity of MAR using pattern-mixture model:

1) For subjects who discontinue study participation prior to Week 56 and do not have follow-up visit, the missing data will be imputed using the observed data from the subjects in the same arm who discontinue the study treatment but have the primary endpoint measurement in the follow up visit using a regression method. The

intermittent missing data will be imputed using multiple imputation MCMC procedure. An ANCOVA model using a similar mixed procedure (without the repeated measures) as the primary analysis will be applied to these multiple-imputed % change in BMI at Week 56 with treatment, baseline BMI value as a covariate, and age and gender as stratification factors. The results of ANCOVA analysis on the multiple imputed datasets will be combined and summarized.

2) Tipping point analyses: An additional sensitivity analysis using a 2-way tipping-point strategy will be conducted on the primary endpoint to explore the influence of missing data from active treatment and placebo arms on the overall conclusion from statistical inference. In this approach, a wide spectrum of assumptions regarding the magnitude of missingness (from less conservative to more conservative) is proposed for replacing missing data. All subjects who drop out the study will have their unobserved efficacy data imputed by the observed data from completers in the same arm using the multiple imputation method based on the monotonic missing pattern under the assumption of MAR with the resulting imputed values further worsened by an amount δ. Scenarios where dropouts on active arms have worse outcomes than dropouts on placebo will be included. The analysis finds a 'tipping' point from among these assumptions under which the study conclusions shift from being favorable to the active treatments to being unfavorable. After such a tipping point is determined, clinical judgment can be applied as to the plausibility of the assumptions underlying this tipping point. The tipping point can be identified while the result is no longer statistically significant.

The third sensitivity analysis is the LOCF. For those subjects who discontinue study participation prior to Week 56, the last observed weight and height will be used to derive the change in BMI.

Similar analyses will be performed for the primary endpoint for the mITT population.

6.6.4 Subgroup Analysis

BMI change will be tabulated by age and gender. Additionally, further exploratory subgroup analyses of the primary efficacy endpoints may include evaluation by race and/or other subgroups deemed medically and/or scientifically important.

6.6.5 Exploratory Analysis

IWQOL-Kids will be analyzed by a similar MMRM model as for the primary endpoint where the baseline BMI value will be replaced by the baseline value of the corresponding endpoint as a covariate to evaluate effects of treatment on Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire scores.

Change from baseline will be presented for various glycemic, lipid markers and BMI Z-score parameters with numerical measures using descriptive statistics. BMI Z-score will be calculated as $[(BMI/M)^{L}-1]/(L*S)$ where L, M and S values are available in percentile data files.

6.7 Safety

All safety analyses will be done for the Safety population. Safety data will be summarized for all treatment groups.

Safety will be assessed by an evaluation of adverse events (each study visit); laboratory parameters (screening, periodically during the study and end of study); electrocardiograms; physical examinations (screening, end of study); PHQ-9: Modified for Teens, C-SSRS, and vital signs (at each study visit). Descriptive statistics will be generated for the questionnaire data.

6.7.1 CANTAB

Cognitive testing will include CANTAB Paired Associates Learning (PAL), Pattern Recognition Memory (PRM) and Spatial Span (SSP) and will be collected at Screening, Baseline, Week 16 and Week 56 for each treatment assignment. The tasks will evaluate effects on episodic memory, visual pattern recognition memory and working memory capacity, respectively. The key outcome measures to be included in the analysis are described in Table 2.

For each key CANTAB outcome measure, descriptive summary statistics (n, mean, median, standard deviation, minimum and maximum) for change from baseline will be reported for visits at Week 16 and Week 56 across all treatment groups (Placebo, Mid-dose and Top-dose of VI-0521) and stratification factors for age and gender. Line graphs of mean change from baseline to Week 16 and Week 56 by treatment groups and stratification factors will also be produced.

Mixed effects models with repeated measures will be used to generate least squares means and standard errors for change from baseline to Weeks 16 and 56 for each treatment group, controlling for stratification factors age and gender and baseline performance for each CANTAB outcome measure.

The standardized mean difference (effect size) between placebo and each treatment group will be calculated using the least squares mean change from baseline to Week 16 and Week 56 estimates and the pooled standard deviation of change across both treatment and placebo groups.

Table 2 CANTAB Key outcome measures

CANTAB Task	Key Outcome Measure (code)	Description	Cognitive Domain / Direction of Effect
PAL	Total Errors Adjusted (PALTEA)	The number of times the subject chose the incorrect box for a stimulus on assessment problems, plus an adjustment for the estimated number of errors they would have made on any problems, attempts and recalls they did not reach. This measure allows you to compare performance on errors made across all subjects regardless of those who terminated early versus those completing the final stage of the task	Episodic memory/ Lower is better
PAL	First Attempt Memory Score (PALFAMS)	The number of times a subject chose the correct box on their first attempt when recalling the pattern locations. Calculated across all assessed trials	Episodic memory/ Higher is better
PRM	Percent Correct Immediate (PRMPCI)	The number of correct patterns selected by the subject in the immediate forced-choice condition, expressed as a percentage	Visual pattern recognition memory/ Higher is better
PRM	Percent Correct Delayed (PRMPCD)	The number of correct patterns selected by the subject in the delayed forced-choice condition, expressed as a percentage	Visual pattern recognition memory/ Higher is better
SSP	Forward Span Length (SSPFSL)	The longest sequence of boxes successfully recalled by the subject. Applicable to Forward variants only	Working Memory Capacity/ Higher is better
SSP	Reverse Span Length (SSPRSL)	The longest sequence of boxes successfully recalled by the subject. Applicable to Reverse variants only	Working Memory Capacity/

6.7.2 PHQ-9

The PHQ-9 questionnaire will be completed at every study visit.

The mean change in PHQ-9 score from baseline to Week 56, along with the percentage of subjects with at least 1 PHQ-9 score indicative of depression of moderate or greater severity (PHQ-9 score of 10 or more), the percentage of subjects with at least 1 PHQ-9 score indicative of major depression (Kroenke), and the percentage of subjects with at least 1 positive answer to question 9 relating to suicidal ideation will be presented by treatment group. A listing of all subjects presenting with any of the outcomes listed above, or a PHQ-9 score of 15 or more will be provided.

6.7.3 C-SSRS

For each item of the C-SSRS, counts and percentages will be presented by treatment group and in total summarizing the number of yes responses at each study visit. In addition, a composite measure will be summarized at each study visit that includes the following C-SSRS items: Active suicidal ideation with some intent to act without specific plan, Active suicidal ideal with specific plan and intent, Actual attempt, Engaged in non-suicidal non-injurious behavior, Interrupted attempt, Aborted attempt, Preparatory acts or behavior, and Suicidal behavior. The baseline distribution of responses to the C-SSRS will also be presented.

6.7.4 Hand and Wrist X-Ray

Changes of bone age from baseline to Week 56 in hand and wrist X-ray will be evaluated. Differences between treatment groups will be evaluated using methods similar to those used to evaluate other continuous variables.

6.7.5 DXA

In the subset of subjects treated at sites where DXA scans are being done, mean changes from baseline to Week 56 in bone mineral density (BMD) and bone mineral content (BMC)-Z scores will be evaluated. The mean change in BMD and BMC will be summarized descriptively as a continuous variable.

6.7.6 Adverse Events

All adverse events (AEs) recorded on the eCRF will be coded using the MedDRA dictionary Version 21.1 (or a later version if updated during the study) and classified as either pre-treat AEs or treatment – emergent AEs (TEAEs) as follows:

- Pre-treat AEs are events that start prior to the date of first dose of study treatment.
- TEAEs are events with start date on or after the date and time of first dose of study treatment and up to 28 days after date and time of last dose of study treatment or events with start date and time prior to the date and time of first dose of study treatment whose severity worsens on or after the date and time of first dose of study treatment.

All AE data will be listed by treatment group. Treatment-emergence status will be flagged in the listing. In addition, corresponding listings of serious AEs (SAEs), AEs leading to discontinuation of study treatment and AEs resulting in death will be produced.

Summary tables of TEAEs by treatment group will be produced for the Safety population.

The severity of all AEs is recorded as mild, moderate, or severe. If severity is missing for a TEAE, it will be considered severe only in the overall category in the summary tables.

The relationship between an AE and study treatment is assessed as Related or Not Related by the investigator.

An overview table will summarize the number and percentage of subjects with at least one of the following TEAEs, where subjects with more than one TEAE in a particular category are counted only once in that category:

- Any TEAE
- Any TEAE by severity (mild, moderate, severe)
- Drug-related TEAE
- TEAE leading to dose reduction
- Drug-related TEAE leading to dose reduction
- TEAE leading to study treatment discontinuation
- Treatment-emergent SAE
- Drug-related Treatment-emergent SAE
- Treatment-emergent SAE leading to death;
- Drug-related Treatment-emergent SAE leading to death
- Treatment-emergent SAE leading to treatment discontinuation

The number and percentage of subjects reporting each TEAE will be summarized by System Organ Class (SOC) and Preferred Term (PT) for the Safety population. Tables will be sorted alphabetically by SOC. PTs will be sorted by descending overall total. The following summaries will be produced:

- TEAEs by SOC and PT
- Drug-related TEAEs by SOC and PT
- TEAEs by maximum severity by SOC and PT
- TEAEs related to treatment by maximum severity by SOC and PT
- TEAEs causing discontinuation from treatment by SOC and PT
- TEAEs related to treatment causing discontinuation from treatment by SOC and PT
- SAEs by SOC and PT

In the above summaries, subjects with more than one AE within a particular SOC are counted only once for that SOC. Similarly, subjects with more than one AE within a particular PT are counted only once for that PT. For summaries by maximum severity, subjects with multiple AEs within a particular SOC or PT will be counted under the category of their most severe AE within that SOC or PT.

No statistical comparisons of AEs between treatment groups will be performed.

6.7.7 Laboratory Evaluations

A summary of observed values and change from baseline will be presented for all laboratory parameters with numerical measures using descriptive statistics. Shift tables displaying low-normal-high at baseline versus low-normal-high at end of study in a 3-by-3 contingency table will be provided. For selected laboratory parameters, scatter plots of baseline versus Week 56 results, will be produced by treatment group.

A laboratory value that is above or below normal range will be considered an abnormal value. For selected laboratory parameters, threshold limits of clinical concern will be defined as multiplicative factors of the normal ranges. The list of multiplicative factors for each laboratory parameter will be included in the Statistical Analysis Plan. The frequency and percentage of subjects with laboratory results above or below the normal range and threshold limits at each scheduled assessment or any time during the treatment will be summarized by treatment group.

Table 3: Clinical Laboratory Tests

<table>
<tr><th>Fasting blood chemistry</th><th>Hematology</th><th>Other</th></tr>
<tr><td rowspan="8">• albumin
• alkaline phosphatase
• ALT
• AST
• GGT
• bicarbonate
• blood urea nitrogen
• serum calcium
• serum chloride
• serum sodium
• creatinine (and estimated creatinine clearance)
• glucose
• lactate dehydrogenase
• serum phosphorus
• serum potassium
• total and direct bilirubin
• total protein
• uric acid</td><td rowspan="3">• hemoglobin
• hematocrit
• red blood cell count
• red blood cell indices
• total white blood cell count
• white blood cell differential (neutrophils, lymphocytes, monocytes, eosinophils, and basophils)
• platelet count</td><td>• thyroid stimulating hormone</td></tr>
<tr><td>Urinalysis</td></tr>
<tr><td>• midstream urinalysis with reflex microscopic evaluation
• pregnancy test (all female subjects)</td></tr>
<tr><td rowspan="2">Lipid panel</td><td>Urine Drug Screen</td></tr>
<tr><td rowspan="2">• total cholesterol
• LDL-C
• HDL-C
• triglycerides</td><td rowspan="2">• cannabinoids
• amphetamines
• cocaine
• barbiturates
• benzodiazepine
• opiates</td></tr>
<tr><td>Glycemic testing</td><td>Serology</td></tr>
<tr><td>• HbA1c
• insulin
• glucose</td><td>• HBsAg
• HCV
• HIV</td></tr>
</table>

All laboratory data will be reported in International System of Units (SI) and Conventional units. Out-of-reference-range values will be flagged as high (H) or low (L) in the listings.

For analysis purposes, values preceded by a “<” or a “>” sign (i.e. those below or above the limits of quantification) will be considered equal to the lower or upper limit of quantification, respectively.

For analysis by visit, analysis windowing as described in Section 5.1 will be utilized for each scheduled visit such that unscheduled visits will also be considered. For each laboratory analyte, the baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of treatment.

6.7.8 Vital Signs

The following vital signs will be listed and summarized by treatment group and visit.

- Systolic and diastolic blood pressure (mmHg)
- Heart rate (breaths/min)
- Weight (kg)
- respiration rate (breaths/min)
- body temperature (°C or °F)

Vital signs data and changes from baseline in vital signs will be summarized by visit using standard descriptive statistics for the Safety population. The baseline value will be defined as last scheduled or unscheduled value collected prior to the first dose of study treatment. For post-baseline, only data from scheduled visits will be included in the summary tables.

6.7.9 Electrocardiograms

The following quantitative ECG measurements will be listed and summarized by treatment group and visit for the Safety population:

- heart rate (bpm)
- RR interval (msec)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)

An overall clinically significant Investigator assessment of ECG will be provided (categories “Yes”, “No”).

6.7.10 Physical Examination

Abnormalities identified from physical examination are recorded in the eCRF will be listed.

For each physical examination body system, the number and percentage of subjects with abnormalities at baseline and post-baseline will be summarized by treatment group for the Safety population.

6.8 Interim Analysis

No interim analysis is planned.

6.9 Data Monitoring Committee

An independent Data Monitoring Committee (DMC) with multidisciplinary representation will be established to evaluate accumulating study data on a periodic basis and to assess the ongoing safety of the study for the subjects enrolled and to be enrolled. As a result, following each data review, the DMC will make a recommendation to the sponsor regarding continuation, revision, or termination of the study. Details related to DMC responsibilities, authorities, and procedures will be documented in the DMC charter, which will be finalized by the DMC prior to the first DMC data review meeting.

7. Changes in Planned Analysis

None

8. Data Issues

None

9. References

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14 Modified z-scores in the CDC growth charts http://www.cdc.gov/nccdphp/dnpa/growthcharts/resources/BIV-cutoffs.pdf

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