Supplementary Appendix

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

Supplement to: 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.

Supplementary Appendix

List of Investigators and Study Sites	2
Data Monitoring Committee Members	4
Inclusion/Exclusion Criteria	5
Study Drug Dose Titration	7
Table S1. Representativeness of Study Participants	8
Table S2. Characteristics of Completers vs. Non-Completers	9
Table S3. Serious Adverse Events	10
Table S4. Events Related to Psychiatric Disorders	11

List of Investigators and Study Sites

Site No.	Investigator Name	Address
101	Adil Aryaman Fatakia	Tandem Clinical Research, LLC 1111 Medical Center Boulevard N502 Marrero, LA 70072
102	Derek Muse	Highland Clinical Research 4460 South Highland Drive, #410 Salt Lake City, UT 84124
103	Ashley Shoemaker	VUMC - Monroe Carell Jr. Children's Hospital - Endocrinology Clinic 1500 21st Avenue South 8410 Medical Center East, South Tower Nashville, TN 37232
104	Daniel Hsia	Pennington Biomedical Research Center 6400 Perkins Road Baton Rouge, LA 70808-4124
105	Tollie Elliott	Emerson Clinical Research Institute 508 Kennedy Street NW, Suite 306 Washington, DC 20011-3010
107	Eli Shalenberg	Richmond Behavioral Associates 4349 Hylan Boulevard Staten Island, NY 10312-6501
108	John Kirby	Summit Medical Group - Tennessee Valley Primary Care 120 Hospital Drive, Suite 130 Jefferson City, TN 37760-5279
109	Corey Anderson	Clinical Research Consortium- Tempe 2737 W Baseline Road, Suite 19 Tempe, AZ 85283-1051
111	Lisa Connery	Intend Research 1010 24th Avenue NW, Suite 110 Norman, OK 73069
112	Megan Oberle Bensignor, Aaron Kelly	University of Minnesota - Center for Pediatric Obesity Medicine 717 Delaware Street SE Minneapolis, MN 55414-2903
113	Richard Egelhof	Heartland Clinical Research 3730 N Ridge Road, Suite 600 Wichita, KS 67205-1235
114	Mark Adams	Central Kentucky Research Associates 3475 Richmond Road, 3rd Floor Lexington, KY 40509
115	Khozema Palanpurwala	DM Clinical Research 13406 Medical Complex Drive Suite 53 Tomball, TX 77375

Site No.	Investigator Name	Address
116	Joe Pouzar	Centex Studies, Inc. – Houston 1045 Gemini Street, Suite 200A Houston, TX 77058-2705
120	George Freeman	Health Research of Hampton Roads, Inc. 720 Thimble Shoals Boulevard Suite 110 Newport News, VA 23606
123	Michelle Galen	Deaconess Clinic - Gateway Health Center 4233 Gateway Boulevard Newburgh, IN 47630-8900
124	William Smith	New Orleans Center for Clinical Research (NOCCR), Inc. 1928 Alcoa Highway, Suite 107 Knoxville, TN 37920
125	Michael Jacobs	Clinical Research Consortium (CRC) - Nevada Location 2110 E. Flamingo Road, Suite 119 Las Vegas, NV 89119
126	Austina Cho	Advanced Research Center – Anaheim 1020 S Anaheim Blvd Ste 316 Anaheim, CA 92805-5854
129	Joel Solis	Centex Studies, Inc. – McAllen 1020 Zinnia Avenue Mcallen, TX 78504

Data Monitoring Committee Members

DMC Chairperson	Name	Gary Cutter
	Title	Professor of Biostatistics Research Methods and Clinical Trials Department of Biostatistics
	Address	403b Ryals Public Health Building 1665 University Boulevard Birmingham, AL 35294
	email	cutterg@prodigy.net cutterg@uab.edu
	Telephone Number	205-975-5048
DMC Member	Name	John Paul Foreyt
	Title	Professor, Departments of Medicine and Psychiatry and Behavioral Sciences Director, Behavioral Medicine Research Center Baylor College of Medicine
	Address	Behavioral Medicine Research Center 6655 Travis St., Suite 320 Houston, Texas 77030
	email	jforeyt@bcm.edu
	Telephone Number	(713) 798 3839
DMC Member	Name	Alberta S. Kong
	Title	Professor and Chief Division of Adolescent Medicine Department of Pediatrics
	Address	Department of Pediatrics MSC 10 5590, 1 University of New Mexico Albuquerque, NM 87131-0001
	email	AKong@salud.unm.edu
	Telephone Number	505-925-7600

Inclusion and Exclusion Criteria

Inclusion Criteria

Participants who met all of the following criteria as stated in the protocol were included in the study:

- Provided written informed consent (of a parent or legal guardian) who accompanied the subject to all study visits
- Provided written assent (of study participant)
- Was an adolescent ≥ 12 years and < 17 years of age with Tanner Staging of ≥ 2 at the time of screening
- Had a BMI ≥ the 95th percentile of BMI for age and gender with documented history of failure to lose sufficient weight or failure to maintain weight loss in a lifestyle modification program
- Was willing and able to comply with scheduled study visits, treatment plan, laboratory tests, and other study procedures
- If female, must have been using adequate contraception, defined as double barrier methods, stable hormonal contraception plus single barrier method, tubal ligation, or abstinence

Exclusion Criteria

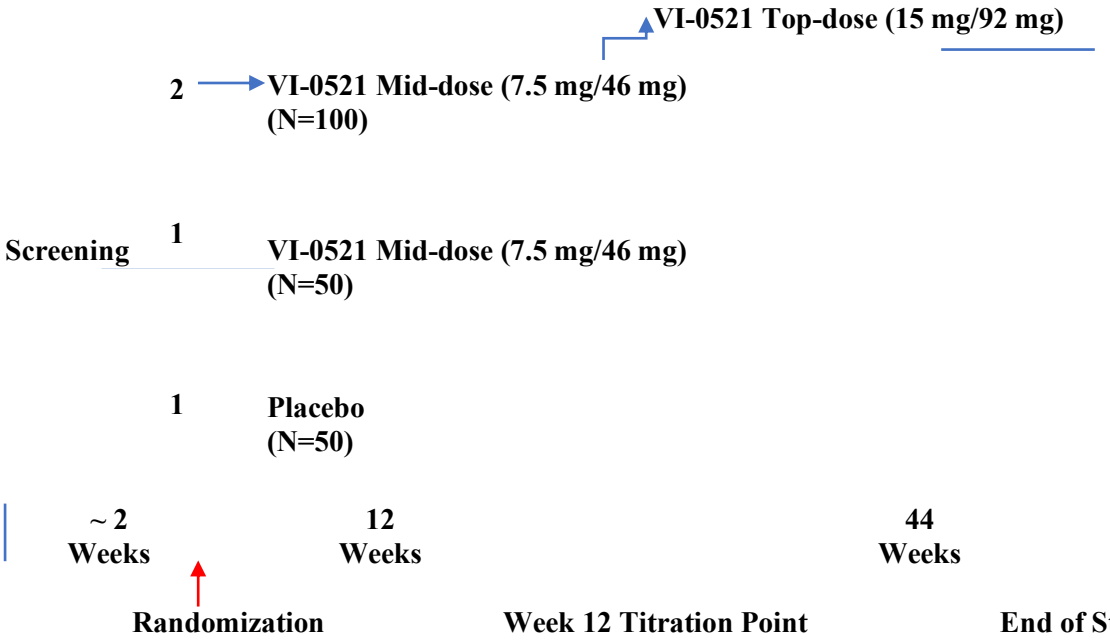
Participants who met any of the following criteria as stated in the protocol were excluded from the study:

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

    - Aspartate aminotransferase and alanine aminotransferase > 3 × upper limit of normal (ULN)
    - Hemoglobin A1c ≥ 8.0%
    - Fasting glucose ≥ 270 mg/dL
    - Triglyceride ≥ 400 mg/dL
    - Creatinine clearance < 60 mL/minute (Schwartz Formula)
    - Thyroid stimulating hormone > 1.5 ULN
- Clinically significant hepatic or renal disease
- Clinically significant thyroid dysfunction as evidenced by signs or symptoms of hypothyroidism, a thyroid stimulating hormone > 1.5 × ULN, or use of thyroid hormone treatment that had not been stable for at least 3 months
- Systolic blood pressure > 140 mmHg, diastolic blood pressure > 90 mmHg, or concurrent antihypertensive medication that had not been stable for 3 months
- 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 (MAOI), lithium, levodopa, and dopamine receptor agonists; or allowed antidepressant use that had not been stable for at least 3 months
- Use of chronic systemic glucocorticoid therapy (i.e., glucocorticoids, anabolic steroids) or any other steroid hormone therapy other than oral contraceptives that had not been stable for at least 3 months
- Pregnancy or breastfeeding
- Any history of eating disorders (e.g., bulimia; binge eating disorder; anorexia)
- Any history of laxative abuse
- 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
- Prior bariatric surgery
- Any history of nephrolithiasis
- Any history of epilepsy, or requirement for anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, gamma-aminobutyric acid analogues, hydantoins, phenyltriazines, succinimides, and other agents (valproic acid and its derivatives, carbamazepine and its derivatives, zonisamide, and felbamate)
- Positive urine drug screen
- Current smoker or smoking cessation within 3 months of screening
- Obesity of a known genetic or endocrine origin, such as Prader Willi Syndrome
- Known allergy or hypersensitivity to phentermine or topiramate or history of anaphylaxis to any drug
- Use of any investigational medication or device for any indication or participation in a clinical study within 30 days prior to screening
- Other clinically significant medical or psychiatric condition or laboratory abnormality that could 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

Study Drug Dose Titration

The titration schema is consistent with the current labeling for Qsymia® (VI-0521), which recommends that patients titrate up to the PHEN/TPM 7.5 mg/46 mg dose for a period of 12 weeks prior to initiating possible titration up to the PHEN/TPM 15 mg/92 mg dose. For this study, however, all participants randomized to the PHEN/TPM 15 mg/92 mg dose were required to attempt titration up to that dose at the Week 12 visit.



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-dose	7.5/46	3.75/23	7.5/46	7.5/46	7.5/46
VI-0521 Top-dose	15/92	3.75/23	7.5/46	11.25/69	15/92

Table S1. Representativeness of Study Participants

Disease under investigation:	Adolescent obesity
Special considerations related to:	
Sex and gender	Roughly equivalent prevalence of obesity in boys and girls
Age	Prevalence of obesity is approximately 20% among United States adolescents ages 12-18 years old
Race/ethnicity	Obesity prevalence is higher among African American and Hispanic/Latino adolescents as compared to Non-Hispanic White adolescents
Geography	In the United States, the prevalence of adolescent obesity is generally the highest in the Southeast region
Overall representativeness of this trial:	The participants in the present trial demonstrated the expected ratio of girls and boys. Sex identification was reported by the participants; they were asked to select either male or female. African American (~27%) and Hispanic/Latino (~32%) representation was relatively high in the present trial.

Table S2. Characteristics of Completers vs. Non-Completers

	Study Completers	Study Non-Completers
	(N = 139)	(N = 84)
Age at Screening (Years)		
Mean (SD)	14.1 (1.33)	13.8 (1.37)
Median	14.0	14.0
Min, Max	12, 16	12, 16
Sex, n (%)		
Female	71 (51.1)	50 (59.5)
Male	68 (48.9)	34 (40.5)
Race, n (%)		
White	100 (71.9)	49 (58.3)
Black or African American	28 (20.1)	32 (38.1)
Other	9 (6.5)	3 (3.6)
American Indian or Alaska Native	1 (0.7)	0
Asian	1 (0.7)	0
Native Hawaiian or Other Pacific Islander	0	0
Ethnicity, n (%)		
Hispanic or Latino	44 (31.7)	28 (33.3)
Not Hispanic or Latino	94 (67.6)	55 (65.5)
Not Stated	1 (0.7)	1 (1.2)
Unknown	0	0
Weight (kg)		
Mean (SD)	105.30 (21.804)	107.41 (26.584)
Median	101.70	102.90
Min, Max	58.8, 175.1	61.4, 217.8
Height (cm)		
Mean (SD)	167.12 (8.257)	167.00 (7.148)
Median	167.00	166.40
Min, Max	147.6, 190.7	149.4, 184.2
Body Mass Index (BMI) (kg/m^2)		
Mean (SD)	37.55 (6.512)	38.27 (7.970)
Median	36.10	36.60
Min, Max	26.6, 62.9	27.2, 72.4
Waist Circumference (cm)		
Mean (SD)	114.74 (15.977)	112.86 (15.882)
Median	113.00	111.65
Min, Max	84.5, 165.0	81.8, 157.0

Table S3. Serious Adverse Events

Summary of Serious Adverse Events by System Organ Class and Preferred Term, Safety Population

System Organ Class Preferred Term	Placebo (N = 56) n (%)	VI-0521 Mid-dose (N = 54) n (%)	VI-0521 Top-dose (N = 113) n (%)	Overall (N = 223) n (%)
Any Serious Adverse Event	0	0	2 (1.8)	2 (0.9)
Hepatobiliary disorders	0	0	1 (0.9)	1 (0.4)
Bile duct stone	0	0	1 (0.9)	1 (0.4)
Psychiatric disorders	0	0	1 (0.9)	1 (0.4)
Depression	0	0	1 (0.9)	1 (0.4)
Suicidal ideation	0	0	1 (0.9)	1 (0.4)

VI-0521 Mid-dose = PHEN/TPM 7.5 mg/46 mg; VI-0521 Top-dose = PHEN/TPM 15 mg/92 mg
The denominator for percentages is the number of subjects in the safety population.
MedDRA Dictionary (Version 23.1) was used for coding.
If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term. If a subject experienced more than one adverse event within a system organ class, the subject is counted once for each preferred term and once for the system organ class.

Table S4. Events Related to Psychiatric Disorders

Summary of Treatment-emergent Adverse Events from the SOC Psychiatric Disorders, Safety Population

System Organ Class	Placebo (N = 56) n (%)		VI-0521 Mid-dose (N = 54) n (%)		VI-0521 Top-dose (N = 113) n (%)		Overall (N = 223) n (%)	
Preferred Term	Any	Related	Any	Related	Any	Related	Any	Related
Psychiatric disorders	1 (1.8)	0	4 (7.4)	3 (5.6)	10 (8.8)	4 (3.5)	15 (6.7)	7 (3.1)
Adjustment disorder	0	0	0	0	1 (0.9)	0	1 (0.4)	0
Agitation	0	0	0	0	1 (0.9)	1 (0.9)	1 (0.4)	1 (0.4)
Anxiety	0	0	1 (1.9)	0	3 (2.7)	1 (0.9)	4 (1.8)	1 (0.4)
Depression	0	0	1 (1.9)	0	5 (4.4)	1 (0.9)	6 (2.7)	1 (0.4)
Generalised anxiety disorder	1 (1.8)	0	0	0	0	0	1 (0.4)	0
Insomnia	0	0	1 (1.9)	1 (1.9)	2 (1.8)	1 (0.9)	3 (1.3)	2 (0.9)
Irritability	0	0	1 (1.9)	1 (1.9)	0	0	1 (0.4)	1 (0.4)
Mood altered	0	0	0	0	1 (0.9)	1 (0.9)	1 (0.4)	1 (0.4)
Mood swings	0	0	1 (1.9)	1 (1.9)	0	0	1 (0.4)	1 (0.4)
Suicidal ideation	0	0	0	0	1 (0.9)	1 (0.9)	1 (0.4)	1 (0.4)

Abbreviations: SOC = System Organ Class; VI-0521 Mid-dose = PHEN/TPM 7.5 mg/46 mg; VI-0521 Top-dose = PHEN/TPM 15 mg/92 mg
The denominator for percentages is the number of subjects in the safety population.
MedDRA Dictionary (Version 23.1) was used for coding.
If a subject experienced more than one episode of an adverse event, the subject is counted only once within a preferred term. If a subject experienced more than one adverse event within a system organ class, the subject is counted once for each preferred term and once for the system organ class.