CLINICAL REVIEW

Application Type	NDA
Application Number(s)	022580
Priority or Standard	Standard
Submit Date(s)	August 25, 2021 (SD#1129)
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Division/Office	DDLO/OCHEN
Reviewer Name(s)	Mary Roberts
Review Completion Date	June 23, 2022
Established/Proper Name	Phentermine and Topiramate ER
(Proposed) Trade Name	Qsymia
Applicant	Vivus, LLC
Dosage Form(s)	Capsules
Applicant Proposed Dosing Regimen(s)	Titrate to daily dose of mid-dose Qsymia (7.5 mg phentermine/46 mg topiramate ER); escalate to high-dose Qsymia (15 mg phentermine/92 mg topiramate ER) daily if less than 3% BMI reduction achieved after 12 weeks of treatment with mid-dose Qsymia
Applicant Proposed Indication(s)/Population(s)	Qsymia is indicated in adolescents 12 to 17 years of age with BMI in the 95th percentile or greater standardized for age and gender.
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Qsymia is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in: ○ Pediatric patients aged 12 and older with an initial BMI in the 95th percentile or greater standardized for age and sex

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event

NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Qsymia is a fixed-combination prescription drug containing proprietary formulations of immediate-release phentermine (PHEN) and extended-release topiramate (TPM). Qsymia capsules are referred to as PHEN/TPM in this review. Phentermine is a sympathomimetic amine anorectic, and topiramate, a sulfamate-substituted monosaccharide antiepileptic drug.

PHEN/TPM was approved in 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of ≥30 kg/m^2 or ≥27 kg/m^2 with at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia.

At the time of the PHEN/TPM approval for chronic weight management in adults, pediatric post-marketing requirements (PMRs) of clinical trials to assess the pharmacokinetics, pharmacodynamics, efficacy, and safety of PHEN/TPM in obese adolescents 12 to 17 years of age were issued. This efficacy supplement, providing data from Study OB-403, is intended to fulfill PMR 1901-2 and support the applicant's request for a treatment indication for chronic weight management in adolescents 12 to 17 years of age with BMI in the 95th percentile or greater standardized for age and sex.

Four fixed-dose strengths are available: PHEN/TPM 3.75/23 mg (low-dose), 7.5/46 mg (mid-dose), 11.25/69 mg (three-quarter-dose), and 15/92 mg (high-dose). The proposed treatment regimen for obese adolescents is similar to adults and includes a once daily dose of PHEN/TPM, beginning with low-dose PHEN/TPM for two weeks, then up-titrating to mid-dose PHEN/TPM, the recommended maintenance dose. Individuals not achieving adequate reduction in BMI on mid-dose PHEN/TPM for 12 weeks are recommended to titrate up via the three-quarter PHEN/TPM dose to high-dose PHEN/TPM.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The single pivotal trial, OB-403, provides substantial evidence that mid-dose PHEN/TPM and high-dose PHEN/TPM compared to placebo reduce BMI in obese pediatric individuals 12 to 17 years of age. The change in mean percent BMI from baseline to week 56 was -4.8% for the mid-dose PHEN/TPM group, -7.1% for the high-dose PHEN/TPM group, and 3.3% for the placebo group, yielding a -8.1% and -10.4% treatment difference for mid-dose and high-dose PHEN/TPM versus placebo, respectively (both doses p-value <0.0001).

This trial is supported by confirmatory evidence from adequate and well-controlled clinical

investigations that established effectiveness of PHEN/TPM for the closely related indication of chronic weight management in obese and overweight adults approved in the original NDA in 2012.

There are limitations to be considered in the interpretation of the efficacy results. The first is the study's high attrition rate and resulting missing data which challenge the reliability of the study results. The applicant used statistical procedures such as multiple imputation to account for the uncertainty of missing data in Study OB-403 and conducted several sensitivity analyses to test the statistical robustness of the primary analysis. The statistical review team assessed the statistical methods conducted to deal with missing data and determined the statistical approach was sufficient, and the sensitivity analyses are supportive of the primary analysis of PHEN/TPM's treatment effect.

Second, improvements in cardiometabolic parameters (e.g., blood pressure, lipids, HbA1c) typically associated with weight loss were underwhelming in obese adolescents treated with PHEN/TPM. Interestingly, similar observations were noted in the orlistat and liraglutide weight loss trials in adolescents. Although this study, like others, did not demonstrate a substantial effect on cardiometabolic parameters, this likely represents the absence of significant metabolic decompensation at baseline in this pediatric population. Use of an effective treatment for chronic weight management in this population may provide an opportunity for prevention of co-morbidities, which is an important treatment goal; nevertheless, the data from Study OB-403 do not support a prevention claim.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The proportion of adolescents with obesity has dramatically increased over the last 50 years with 21% of U.S. adolescents now considered obese (BMI ≥95th percentile for age and sex). Obesity in pediatric individuals is serious and adversely impacts almost every organ system and has significant psychosocial consequences. Intensive lifestyle modification is recommended as first-line therapy; however, initial significant improvements are difficult to sustain long-term. When lifestyle intervention is unsuccessful in reaching weight loss goals, adjunct pharmacotherapy may be warranted. Saxenda (liraglutide), a GLP1 receptor agonist, is the only FDA approved product with an indication for chronic weight management in pediatric patients 12 years and older, although orlistat contains pediatric labeling; other drugs without pediatric indications for weight loss (e.g., metformin, orlistat) are used. Bariatric surgery is also an option in certain clinical scenarios.

Qsymia, a fixed-combination drug containing proprietary formulations of phentermine and extended-release (ER) topiramate, was approved July 17, 2012, for chronic weight management in adults. The daily recommended regimen of Qsymia for both adults and adolescents contains 7.5 mg of phentermine and 46 mg of topiramate ER (mid-dose PHEN/TPM); the highest dose contains 15 mg phentermine/92 mg topiramate ER (high-dose PHEN/TPM) and is reserved for inadequate weight loss with mid-dose PHEN/TPM.

The efficacy and safety of mid- and high-dose PHEN/TPM for chronic weight management was evaluated in Study OB-403, a 56-week, randomized, placebo-controlled trial in 223 obese adolescents 12 to <17 years old. This study demonstrated substantial evidence of effectiveness to support an indication for chronic weight management in the adolescent obese population. A statistically significant change in the primary endpoint, mean percent change from baseline BMI at Week 56 of -4.8% for the mid-dose PHEN/TPM group, -7.1% for the high-dose PHEN/TPM group, and 3.3% for the placebo group was demonstrated, yielding a -8.1% and -10.4% treatment difference for mid-dose and high-dose PHEN/TPM versus placebo, respectively (p-value <0.0001). A change of 5% or greater in weight is considered clinically meaningful in adults. The change observed in the Qsymia trial could be considered clinically meaningful in pediatrics, given that guidelines recommend discontinuation of pharmacotherapy for weight loss in the absence of >4% BMI reduction after 12 weeks of treatment. Supportive endpoints, such as the proportion of subjects achieving a reduction in baseline BMI of ≥5, ≥10, ≥15%, and waist circumference, support the efficacy of PHEN/TPM. The magnitude of the anticipated clinical benefit of PHEN/TPM is less certain given the amount of missing data in this trial and the lack of substantial improvements in cardiometabolic parameters such as blood pressure, lipids, and HbA1c. However, the applicant applied a pre-specified conservative imputation approach to impute missing data for the primary analysis, and sensitivity analyses further supported the robustness of the primary efficacy analysis. The absence of substantive changes in cardiometabolic parameters is consistent with other pharmacologic interventions for obesity in this age group and likely reflects the relatively low number of cardiometabolic risk factors observed

in Study OB-403 at baseline.

The safety profile of PHEN/TPM is well described in adults. There is also broad experience and characterization of topiramate's risks in children and adolescents (topiramate [Topamax] is approved for treatment of epilepsy 2 years and older and migraine 12 years and older). The results of OB-403 were generally consistent with the known safety profile of PHEN/TPM in adults and pediatric experience with topiramate, although there are findings that should be considered in labeling and future pediatric trials.

One subject randomized to high-dose PHEN/TPM group reported serious suicidal ideation requiring hospitalization and pharmacologic therapy; although this event occurred when the subject was not on study drug, the subject had discontinued study drug due to an earlier episode of serious depression and suicidal ideation. Overall, obese adolescents treated with PHEN/TPM (mid-dose 7.4%; high-dose 8.8% PHEN/TPM) compared to peers treated with placebo (1.8%) had a higher incidence of adverse psychiatric events, specifically depression, anxiety, and insomnia. Antidepressant medication was initiated in 5 PHEN/TPM-treated subjects versus no placebo-treated subjects. There was also a larger proportion of PHEN/TPM-treated adolescents with PHQ-9 and C-SSRS individual responses and/or total scores that were potentially clinically important. Risk of suicidal behavior and ideation and changes in mood are already included in Section 5 (Warnings and Precautions) of the Qsymia label, but imbalances noted in this trial population should be included.

There was one serious adverse event (SAE) of bile duct stone, requiring cholecystectomy in a high-dose PHEN/TPM-treated individual, and one non-serious event of gallstones also in a high-dose PHEN/TPM subject. Rapid weight loss may lead to increased risk of gallbladder and associated duct disorders.

Unique pediatric safety concerns such as bone health, linear growth, pubertal development, and cognitive function were evaluated. Increases in bone mineral density (BMD) and bone mineral content at the lumbar spine and total body less head (TBLH) measured in a DXA substudy were numerically smaller in the PHEN/TPM-treated group compared to the placebo-treated group after 1 year of treatment. Similar results were observed in the Topamax pediatric epilepsy trial. The cause and long-term significance of PHEN/TPM-related effects on bone in this study are unclear. No association with bicarbonate reduction or weight loss and change in BMD was observed, BMD Z-scores remained greater than 0 (above average for age and sex) in most subjects, and no subjects demonstrated a decline in Z-score to less than -2.0, a cut-off used in combination with fracture history to diagnose osteoporosis. This overall pattern is similar to findings in post-bariatric surgery trials.

Height on average increased in all treatment groups; however, the height velocity was lower in the PHEN/TPM-treated subjects compared to

placebo-treated subjects (estimated treatment difference approximately -1.3 to -1.4 cm/year). Reasons for the numerical difference in height velocity between the PHEN/TPM-treated and placebo-treated group and the clinical significance, if any, on final adult height is not known. Of note, all treatment groups had a height Z-score that was slightly above zero (or above the average in the reference population) at Week 56. There were no appreciable differences among treatment groups on skeletal maturation assessed by bone age or pubertal development evaluated by Tanner staging.

The results of cognitive testing were inconclusive, in part, due to the limited ability to detect small differences given the sample size and lack of assessments of verbal fluency, an area of interest given adverse effects observed with topiramate. There were too few cognitive-related adverse events observed to support a causality assessment.

Because of the teratogenic potential of PHEN/TPM, all females of reproductive potential were required to use contraception. No pregnancies were reported. Similar to adults treated with PHEN/TPM, increased heart rate, metabolic acidosis, and increases in creatinine were observed. In addition to psychiatric events of depression and anxiety, other common adverse events (incidence ≥4%) associated with PHEN/TPM included dizziness, arthralgia, pyrexia, influenza, and ligament sprain.

Given the serious consequences of pediatric obesity, the paucity of effective pharmacologic treatments, and the statistically significant treatment effect, it is this reviewer's assessment that the benefits of PHEN/TPM outweigh the risks in adolescents with obesity. Mitigation of safety concerns can be addressed through labeling. This efficacy supplement, providing data from Study OB-403, fulfills PMR 1901-2 and supports the applicant's request for a treatment indication for chronic weight management in obese adolescents 12 years of age and older.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Pediatric obesity is defined in the United States as a BMI ≥95th percentile for age and sex on growth charts. • One in 5 adolescents meet the definition of obesity, and approximately 7.5 to 9.5% are severely obese. • Obesity in adolescents may be associated with hypertension, non-	A substantial number of adolescents in the United States are obese. Pediatric obesity has significant health and social ramifications. Children and adolescents with obesity are at high risk of remaining obese as adults,

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	alcoholic fatty liver disease, obstructive sleep apnea, and bone and joint problems. There are also significant psychosocial impacts. • Obese children and adolescents are likely to be obese as adults.	underscoring the need for effective treatments.
Current Treatment Options	• Lifestyle and behavior modification is first line therapy for weight loss in obese pediatric adolescents, but sustainable weight loss is rare. • Saxenda (liraglutide) is currently the only drug indicated for chronic weight management in adolescents; orlistat has adolescent data in labeling but is not approved for this indication. • Other drugs (e.g., metformin, amphetamine-like congeners) are used off-label. • Bariatric surgery is used to treat adolescents with refractory severe obesity, safety and long-term efficacy data is emerging; accessibility and cost are barriers to treatment.	Successful long-term weight loss in the pediatric obese adolescent population is difficult, and there are few pharmacologic treatment options for children and adolescents. More therapeutic options to bridge the gap between lifestyle and surgical interventions to treat obesity are warranted.
Benefit	• The primary endpoint was change in mean percent BMI from baseline. At Week 56 change from baseline was -4.8% for the mid-dose PHEN/TPM group, -7.1% for the high-dose PHEN/TPM group, and 3.3% for the placebo group. • The treatment difference in percent change in BMI between mid-dose PHEN/TPM and placebo was -8.1% (95% CI -11.9, -4.3; p<0.0001) and -10.4% (95% CI -13.9, -7.0; p<0.0001) between high-dose PHEN/TPM and placebo. • A change of 5% or greater in BMI in the pediatric population may be considered clinically meaningful. • Per the pre-specified statistical plan for secondary endpoints, statistical significance was observed in the proportion of subjects	Mid-dose and high-dose PHEN/TPM are effective in reducing mean percent BMI in obese adolescents. The recommended treatment dose is mid-dose PHEN/TPM. High-dose PHEN/TPM may be used when there is inadequate reduction in BMI. The precise magnitude of the anticipated clinical benefit of PHEN/TPM is less certain given the amount of missing data in this trial, however, statistical procedures to address this uncertainty were appropriate and confirmed

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	achieving a reduction in BMI of ≥5, ≥10, ≥15%, and change in waist circumference in the high-dose PHEN/TPM group. Nominal p-values for these endpoints were observed for the mid-dose PHEN/TPM group and were <0.05 compared to placebo. These results support the efficacy of PHEN/TPM. • There was a numerical difference in weight loss between high-dose and mid-dose PHEN/TPM that was not statistically significant. • There was a large amount of missing data (38% of subjects with Week 56 missing data), but this did not affect the study conclusion as the primary analysis was based on a conservative imputation method for missing data. Sensitivity analyses were supportive of the primary treatment estimates. • No statistically significant improvements in cardiometabolic parameters such as blood pressure, lipids, and HbA1c were observed.	the treatment effect. The lack of substantial improvements in cardiometabolic parameters such as blood pressure and HbA1c, may reflect less metabolic derangement in this younger age group.
Risk and Risk Management	• There were no fatalities. • One SAE of suicidal ideation, requiring hospitalization and pharmacologic therapy, occurred in a subject randomized to high-dose PHEN/TPM. Although the SAE occurred off treatment, the subject had discontinued treatment earlier due to serious depression and suicidal ideation, therefore, a causal association cannot be definitively excluded. • Obese adolescents treated with PHEN/TPM (mid-dose 7.4%; high-dose 8.8% PHEN/TPM) compared to peers treated with placebo (1.8%) had a higher incidence of adverse psychiatric events, specifically depression, anxiety, and insomnia. Five (3%) PHEN/TPM-treated subjects initiated antidepressant therapy versus no placebo-	The overall safety profile for PHEN/TPM in this trial was consistent with the known risks, including effect of topiramate on bone in a pediatric population. Mitigation of safety concerns can be addressed with labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	treated subjects • One SAE of bile duct stone requiring cholecystectomy in a high-dose PHEN/TPM treated subject was reported; a non-serious case of gall stones was reported in an additional high-dose PHEN/TPM-treated subject. Rapid weight loss is a risk factor for gallstone formation. • Other adverse events of interest included: ○ Teratogenicity/Fetal exposure: No pregnancies were reported. ○ Bone health/linear growth: Increases in bone mineral density, bone mineral content, and height velocity were attenuated in the PHEN/TPM versus placebo groups. No association with weight or bicarbonate reductions were observed. Z-scores remained above average or above clinically important thresholds. ○ Increased heart rate: A higher proportion of PHEN/TPM subjects demonstrated categorical increases in heart rate of 5, 10, and 20 beats/min and heart rate of 100 bpm or greater at 2 consecutive visits. ○ Metabolic acidosis: Reductions in bicarbonate were observed in the PHEN/TPM groups versus the placebo group. Approximately 9% and 16% of mid-dose and high-dose PHEN/TPM-treated subjects versus 0% of placebo-treated subjects had a post-randomization bicarbonate value <17 mmol/L. ○ Increase in creatinine: 17% of mid- and high-dose PHEN/TPM obese adolescents exhibited increases in serum creatinine of 0.3	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	mg/dL or greater compared to 0% in the placebo group. A post-market study of Qsymia in adults noted the increase in serum creatinine represents a reduction in measured GFR. In adults, this effect was reversible upon discontinuation of study drug. In this study, follow-up laboratory values were not available to determine if a similar pattern would be observed in younger subjects. • The safety profile of PHEN/TPM is adolescents was consistent with that previously established in adults. • No novel safety concerns were present requiring additional risk management beyond labeling	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	Sec 6.1.2 Study Results
	X Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
□	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

Childhood obesity has been described as a global epidemic, with 158 million children and adolescents considered obese worldwide.[1] In the United States, the latest data from the National Health and Nutrition Survey (2017-2018) show the prevalence of obesity in adolescents 12 to 19 years was 21.2% (1 in 5 children).[2] Data from the NHANES 2015-2016 showed the prevalence of severe obesity, defined as a BMI ≥35 kg/m^2 or 120% the 95th percentile BMI (whichever was lower), was approximately 7.5% in 12- to 15-year-olds, and 9.5% in 16- to 19-year-olds.[3] The figure below shows the increasing prevalence of obesity over time by age groups. The obesity prevalence in 12- to 19-year-olds (light green line) has quintupled in the past 5 decades.

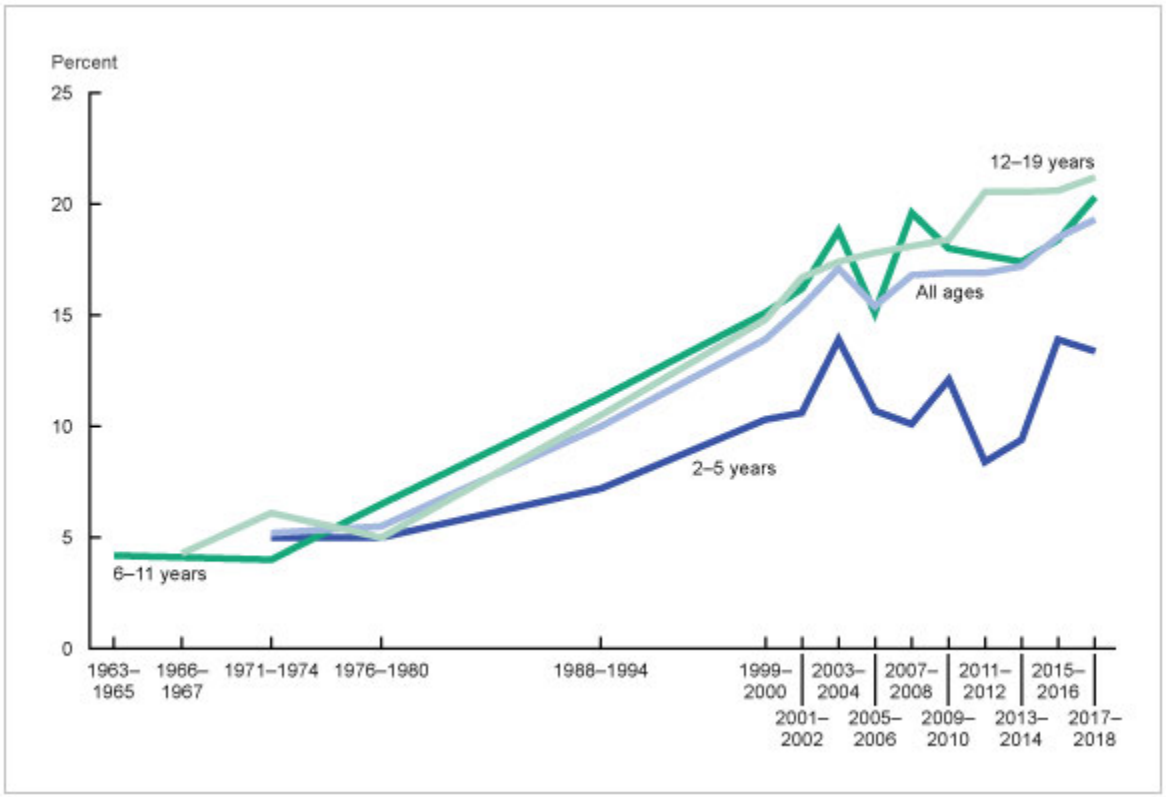


Figure 1. Trends in obesity in pediatric population (2 to 19 years), United States, 1963-1965 through 2017-2018

[1] World Obesity Federation. Global Atlas on Childhood Obesity [Internet]. London; 2019. Available from: https://www.worldobesity.org/nlsegmentation/global-atlas-on-childhood-obesity. Accessed 3 Sept 2020.
[2] Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2017–2018. NCHS Health E-Stats. 2020
[3] Skinner AC, Ravanbakht SN, Skelton JA, Perrin EM, Armstrong SC. Prevalence of Obesity and Severe Obesity in US Children, 1999-2016. Pediatrics. 2018 Mar;141(3):e20173459. doi: 10.1542/peds.2017-3459. Erratum in: Pediatrics. 2018 Sep;142(3): PMID: 29483202; PMCID: PMC6109602.

Childhood obesity impacts almost every organ system, including the cardiovascular, musculoskeletal, endocrine, gastrointestinal, and pulmonary systems (Figure 2).[4]

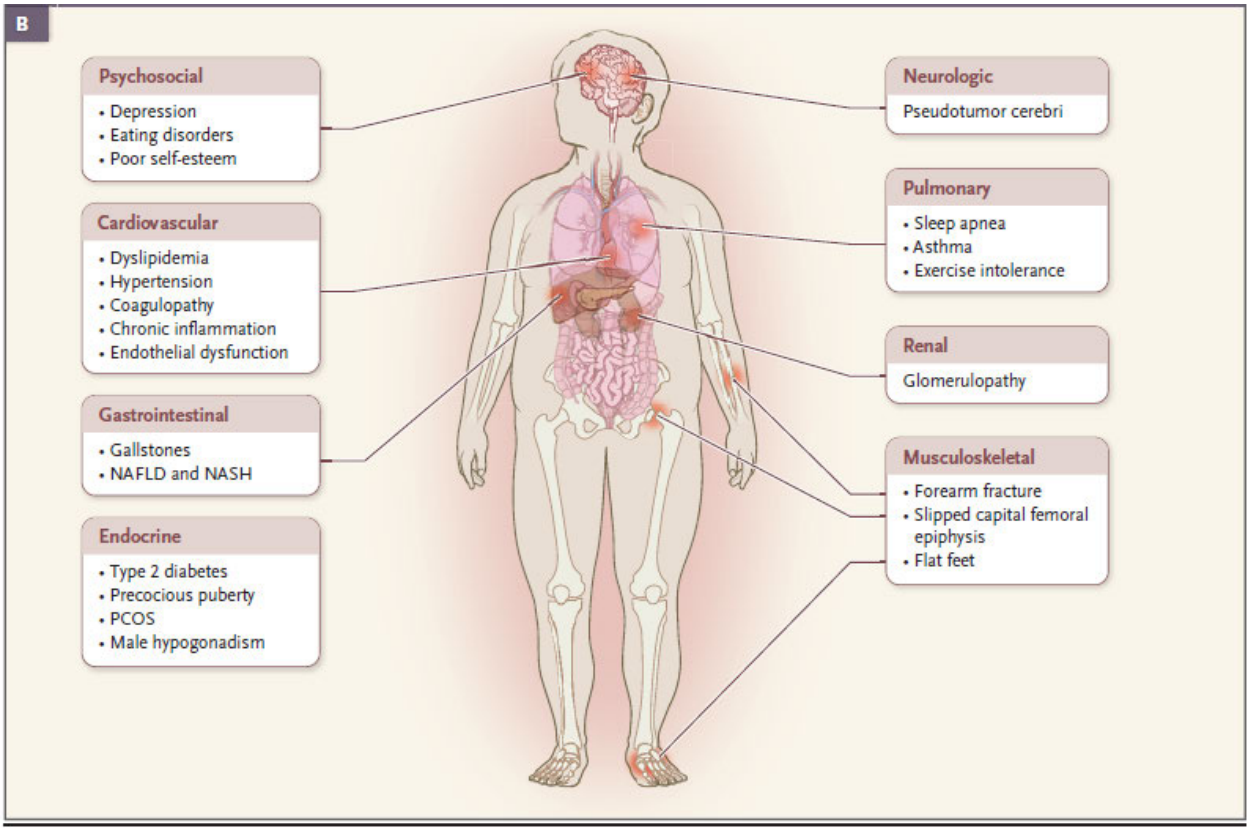


Figure 2. Complications of Obesity in Children and Adolescents[5]

Obesity in childhood or adolescence increases the risk of adult obesity, type 2 diabetes mellitus, and dyslipidemia.[6, 7, 8] Other comorbidities seen in adolescents with obesity include

[4] Kumar S, Kelly AS. Review of Childhood Obesity: From Epidemiology, Etiology, and Comorbidities to Clinical Assessment and Treatment. Mayo Clin Proc. 2017;92(2):251-65.
[5] Cypess AM. Reassessing Human Adipose Tissue. N Engl J Med. 2022 Feb 24;386(8):768-779. doi: 10.1056/NEJMra2032804. PMID: 35196429.
[6] Steinberger J., Daniels S. R. Obesity, insulin resistance, diabetes, and cardiovascular risk in children: an American heart association scientific statement from the atherosclerosis, hypertension, and obesity in the young committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). Circulation. 2003;107(10):1448-1453.
[7] Mary Ann Liebert, Inc./Genetic Engineering News. "Childhood obesity linked to increased risk of adult cardiovascular and metabolic disorders." ScienceDaily. ScienceDaily, 19 November 2010. https://www.sciencedaily.com/releases/2010/11/101119120845.htm.
[8] Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med. 2011;365(20):1876-1885.

hypertension, non-alcoholic fatty liver disease, obstructive sleep apnea, and bone and joint problems. There are also significant psychosocial impacts as a consequence of childhood obesity, including negative body image, depression, and eating disorders.[9]

Notably, based on cohort studies and modeling of growth trajectories, many obese children and adolescents will not "outgrow their baby fat"; instead the majority remain obese as adults, which underscores the need for effective treatment options.[10, 11]

2.2. Analysis of Current Treatment Options

Intensive lifestyle modification therapy is recommended as first-line therapy; however, these measures are labor intensive for both patients and health care providers and provide small incremental weight loss with limited sustainability.[12] When intensive lifestyle modification is unsuccessful in reaching weight loss goals, adjunct pharmacotherapy may be warranted. Bariatric surgery is also an option in certain clinical scenarios.[13]

Saxenda (liraglutide), a GLP1 receptor agonist, is the only FDA approved product with a labeled indication for chronic weight management in adolescents 12 to 17 years old. In the liraglutide trial, the primary endpoint was change in BMI standard deviation score (SDS) from baseline to week 56. The estimated mean change in BMI SDS from baseline to week 56 was -0.23 in the liraglutide group and -0.00 in the placebo group with an estimated mean treatment difference between groups of -0.22 (95% CI -0.37, -0.08), p=0.0022. A BMI SDS score of at least 0.20 has been suggested to be clinically meaningful.[14]

Currently approved drugs for weight management, chronic and short-term, are used off-label in

[9] Rankin J, Matthews L, Cobley S, Han A, Sanders R, Wiltshire HD, et al. Psychological consequences of childhood obesity: psychiatric comorbidity and prevention. Adolesc Health Med Ther. 2016;7:125-46.
[10] Wang LY, Chyen D, Lee S, Lowry R. The association between body mass index in adolescence and obesity in adulthood. J Adolesc Health. 2008 May;42(5):512-8. doi: 10.1016/j.jadohealth.2007.10.010. Epub 2008 Jan 31. PMID: 18407047.
[11] Ward ZJ, Long MW, Resch SC, Giles CM, Cradock AL, Gortmaker SL. Simulation of Growth Trajectories of Childhood Obesity into Adulthood. N Engl J Med. 2017 Nov 30;377(22):2145-2153. doi: 10.1056/NEJMoa1703860. PMID: 29171811.
[12] Al-Khudairy L, Loveman E, Colquitt JL, Mead E, Johnson RE, Fraser H, Olajide J, Murphy M, Velho RM, O'Malley C, Azevedo LB, Ells LJ, Metzendorf MI, Rees K. Diet, physical activity and behavioural interventions for the treatment of overweight or obese adolescents aged 12 to 17 years. Cochrane Database Syst Rev. 2017 Jun 22;6(6):CD012691. doi: 10.1002/14651858.CD012691. PMID: 28639320; PMCID: PMC6481371.
[13] Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, Yanovski JA. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Mar 1;102(3):709-757. doi: 10.1210/jc.2016-2573. PMID: 28359099; PMCID: PMC6283429.
[14] Kelly AS, et al. A randomized, controlled trial of liraglutide for adolescents with obesity. N Engl J Med 2020; 382: 2117-28.

pediatric patients. Prescription orlistat (Xenical) does not have a formal pediatric indication but results of an adolescent trial were added to product labeling in 2003. In the orlistat trial, the primary endpoint was absolute change in BMI, with orlistat-treated patients achieving -0.55 kg/m^2 decrease and placebo-treated patients +0.31 kg/m^2 after 54 weeks of treatment, p=0.001.[15] Phentermine is approved above the age of 16 years. To our knowledge, no randomized, placebo-controlled trials with phentermine in adolescents have been completed. Other medications reported in the literature for treatment of adolescent obesity include metformin and exenatide (both off-label).[16]

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Qsymia, a fixed-combination drug containing proprietary formulations of phentermine and extended-release (ER) topiramate, was approved July 17, 2012, for chronic weight management in adults. The highest dose of Qsymia contains 15 mg of phentermine and 92 mg of topiramate ER.

Both phentermine and topiramate are approved in the United States and are currently available as generics. Phentermine was approved in 1959 for obesity. Phentermine is currently available in 8 mg to 37.5 mg capsules. As a result of a perceived risk for addiction to amphetamine congeners used as anorectic drugs, the indication for phentermine (among others) was restricted to "short-term use (a few weeks)" in the 1970s.

Topiramate was approved in 1996 for the treatment of seizures at doses up to 400 mg/day in adults and pediatric patients (≥2 years old). It is also approved for the prevention of migraine headaches at doses up to 100 mg/day in adults and adolescents (≥12 years old). Topiramate is available in immediate and extended-release formulations.

3.2. Summary of Presubmission/Submission Regulatory Activity

At the time of Qsymia's approval, four PMRs were issued under the Pediatric Research Equity Act (PREA) (Table 1). In addition, PMR 1901-5, requiring a juvenile toxicity study to be completed prior to initiation of the PREA PMRs, was issued as a condition of approval (Table 2).

[15] https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=6240792b-9224-2d10-e053-2a91aa0a2c3e, Xenical Label 1/2018

[16] Axon E, et al. Drug interventions for the treatment of obesity in children and adolescents. Cochrane Database of Systematic Reviews 2016, Issue 11.

The pre-requisite PMRs for completion of the adolescent clinical trial, PMR 1901-2 (the juvenile toxicity study [PMR 1901-5] and clinical pharmacology study [PMR 1901-1] in adolescents) were fulfilled respectively in November 2015 and June 2017. The initial protocol for Study OB-403 to fulfill PMR 1901-2 was submitted in May 2016 and was finalized in August 2017 following review of study results from OB-402 (PMR 1901-1) to determine dosing. No written request was issued for the Qsymia pediatric program.

Table 1. Postmarketing requirements issued under the Pediatric Research Equity Act

PMR #	Description
1901-1	A clinical pharmacology trial to assess pharmacokinetic and pharmacodynamics parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 12 to 17 years (inclusive). Data from this trial should be considered when choosing dose(s) for the safety and efficacy trial in this pediatric population. This trial should not be initiated until after the data from the juvenile animal study have been submitted and reviewed by the Agency.
1901-2	A 52-week randomized, double-blind, placebo-controlled pediatric trial to evaluate the safety and efficacy of Qsymia for the treatment of obesity in pediatric patients ages 12 to 17 years (inclusive). This trial should not be initiated until after the data from the juvenile animal study have been submitted and reviewed by the Agency.
1901-3	A clinical pharmacology trial to assess pharmacokinetic and pharmacodynamics parameters related to Qsymia doses of 3.75 mg/23 mg, 7.5 mg/46 mg, 11.25 mg/69 mg, and 15 mg/92 mg in pediatric patients ages 7 to 11 years (inclusive). Data from this trial should be considered when choosing dose(s) for the safety and efficacy trial in this pediatric population. You may not initiate this trial until the results of the Qsymia adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.
1901-4	A 52-week randomized, double-blind, placebo-controlled pediatric trial to evaluate the safety and efficacy of Qsymia for the treatment of obesity in pediatric patients ages 7 to 11 years (inclusive). You may not initiate this trial until results from the Qsymia adolescent safety and efficacy trial have been submitted to and reviewed by the Agency.

Table 2. Postmarketing requirement to be completed before initiation of PREA PMRs

1901-5	A juvenile animal study with phentermine and topiramate extended-release coadministration to assess effects on behavior, learning and memory; ocular toxicity; and effects on general nervous system and bone/teeth development. The study should include assessments of drug exposure and reversibility of any observed toxicity.

3.3. Foreign Regulatory Actions and Marketing History

PHEN/TPM is currently licensed for use in South Korea as of 2019 and in five European Economic Area countries (Sweden, Finland, Denmark, Iceland, and Norway) as of 2021.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Clinical investigators (CI), Drs. Khozema Palanpurwala and George Freeman at sites 115 and 120 respectively, were selected for inspection based on enrolling a high number of subjects into the study. In addition, the Contract Research Organization (CRO), (b) (4) was also inspected. The OSI report states, "Inspections of the investigators and the CRO found no significant regulatory violations. Based on the results of inspections and regulatory assessments, Study OB-403 appears to have been conducted adequately, and the data generated by the CI sites and submitted by the sponsor appear acceptable in support of the respective indication."

4.2. Product Quality

No new product quality information was submitted with this supplement.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

As Dr. David Carlson noted in his memo dated November 6, 2015, PMR 1901-5 was fulfilled by a conducting a toxicity study with phentermine and topiramate in juvenile rats.[17] There was no evidence of additive or synergistic effects of combination treatment. Findings were generally attributable to the individual drugs and consistent with prior findings for monotherapy with either phentermine or topiramate. No new toxicity was identified with the combination of phentermine and topiramate, particularly on specific endpoints of concern regarding behavior, learning, memory, ocular toxicity, and effects on general nervous system and bone/teeth development. Toxicity and developmental observations of note included clinical signs and neurobehavioral signs of amphetamine-like toxicity from phentermine and delayed growth and commensurate slight delays in sexual maturation endpoints consistent with the expected pharmacodynamic effect of reduced body weight (or reduced weight gain in juveniles). There were no effects on bone growth endpoints during treatment or end of recovery period assessments. No new nonclinical information was submitted with this application.

4.5. Clinical Pharmacology

The clinical pharmacology team reviewed the relevant clinical pharmacology information for this supplement. No pharmacokinetic sampling was done in Study OB-403.

[17] Pharm/Tox Review, Dr. David Carlson, DARRTS ID 3844104

A separate pharmacokinetic/pharmacodynamic (PK/PD) study (PMR 1901-1, Study OB-402) in adolescents was required before Study OB-403. Study OB-402 was previously reviewed by the clinical pharmacology and clinical review teams.[18, 19]

Briefly, Study OB-402 was a randomized, double-blind, placebo-controlled, dose-finding trial to assess safety, tolerability, and pharmacokinetics of PHEN/TPM in obese adolescents aged 12 to <18 years. Subjects were randomly assigned in a 1:1:1 ratio to placebo, mid-dose PHEN/TPM, or high-dose PHEN/TPM. Randomization was stratified by sex and age (12 to 14 versus 15 to 17 years old). The study consisted of a 14-day (maximum) Screening Period followed by a 56-day Treatment Period. Within each active treatment arm, drugs were titrated at 2-week intervals starting with low-dose PHEN/TPM and increased by 3.75 mg/23 mg at each interval until the randomized dose was achieved. Of the 42 randomized subjects, 37 (88%) subjects completed all study visits and 5 (12%) discontinued from the study. The majority of subjects were female (26 [62%] subjects) and black (25 [60%] subjects). No individuals identifying as Hispanic were enrolled. The number of patients between 12 to 14 years (n=23, 54.8%) and 15 to 17 years (n=19, 45.2%) of age was relatively balanced. Within the age cohort of 12 to 14 years, 6 subjects were 12 years of age. At baseline, mean weight was 103 kg and BMI was 36.9 kg/m^2.

The clinical pharmacology review noted that, in Study OB-402, exposures of PHEN/TPM were comparable in adolescents and adults.[17] Therefore, no dose adjustments were warranted in adolescents (12 to 17 years of age), and the mid and high doses of PHEN/TPM approved in adults were considered appropriate to study in the subsequent efficacy and safety adolescent trial, Study OB-403.

Despite the relatively small sample size (42 subjects in the ITT Set) and short treatment duration (8 weeks) in Study OB-402 for treatment effect comparison, both the mid-dose and high dose PHEN/TPM resulted in statistically significant mean weight loss compared to placebo (baseline to Day 56 with last observation carried forward) with least-square mean differences of 4.8% and 6.0%, respectively. The results were consistent with the mean weight loss observed in adult patents at 8-week duration, suggesting a similar dose-response relationship might be expected in adolescents.

Regarding safety:

- There were no deaths.
- There were two discontinuations due to an adverse event in 2 subjects treated with high-dose PHEN/TPM – 1 syncopal event following a blood draw and 1 SAE of severe muscle spasm in subject with a history of Charcot-Marie Tooth disease.

[18] Clinical Pharmacology Review Study OB-402, Dr. Jing Niu, DARRTS ID# 4105346, 31 May 2017
[19] Clinical Review Study OB-402, Dr. Mary Roberts, DARRTS ID# 4112722, 6 June 2017

- Overall, 40% mid-dose PHEN/TPM, 77% high-dose PHEN/TPM, and 50% placebo subjects reported at least one TEAE.
- Similar to the adult PHEN/TPM clinical trials, high-dose PHEN/TPM-treated subjects had the highest incidence of paraesthesia (n=4, 30.8%); no subjects in the mid-dose PHEN/TPM group reported this TEAE, and 1 (7.1%) placebo subject reported this event.
- Treatment with PHEN/TPM did not demonstrate significant shifts in depression symptoms as measured by the PHQ-9 questionnaire. There were no reports of suicidality. Note C-SRRS was not used in this trial.
- Small average increases in serum creatinine and decreases in potassium and bicarbonate were noted with PHEN/TPM treatment. Three PHEN/TPM-treated adolescents had a shift in bicarbonate from a normal value to low value (lowest value observed 20 mmol/L)
- The mean reduction (standard deviation, SD) in systolic blood pressure (mmHg) in the PHEN/TPM group at Day 56 (or early termination) from baseline [mid-dose, -3.3 (10.2); high-dose, -2.7 (9.2)] was not as numerically large as the change observed in the placebo group [-6.0 (12.4)].
- From baseline to Day 56 (or early termination), mean (SD) heart rate increased 1.5 (7.0) and 4.1 (13.9) bpm with placebo treatment and high-dose PHEN/TPM, respectively. For the mid-dose PHEN/TPM group, mean (SD) heart rate decreased 4.5 (9.7) bpm.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The following table lists the studies pertinent to the evaluation of efficacy and safety of PHEN/TPM in obese adolescents.

Table 3. Listing of Clinical Trials Relevant to this NDA

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
OB-403	NCT03922945	Phase IV Safety and Efficacy Study of Qsymia in Obese Adolescents	• Mid-dose Qsymia (7.5 mg phentermine/46 mg topiramate ER) • High-dose Qsymia (15 mg phentermine/92 mg topiramate ER) • Placebo • One capsule once a day	% change in BMI	56 weeks	227	Obese, 12- to <17-year-olds	20 centers US only
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
OB-402	NCT02714062	Pharmacokinetic Study Comparing Qsymia with Placebo in Obese Adolescents	• Mid-dose Qsymia (7.5 mg phentermine/46 mg topiramate ER) • High-dose Qsymia (15 mg phentermine/92 mg topiramate ER) • Placebo • One capsule once a day	PK parameters	8 weeks	42	Obese, 12- to 18-year-olds	4 centers US only

5.2. Review Strategy

The clinical review for this supplement consisted of the single efficacy and safety trial in adolescents, Study OB-403. A summary of the safety for the PK/PD trial Study OB-402 is in Section 4.5, Clinical Pharmacology. This study was previously reviewed; see the clinical and clinical pharmacology reviews, DARRTS ID 4112722 and 4105346 respectively, for further information.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. OB-403: A Phase IV, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Design Study to Determine the Safety and Efficacy of Qsymia in Obese Adolescents

6.1.1. Study Design

Overview and Objective

The primary objective of the trial was to compare the efficacy and safety of PHEN/TPM versus placebo on weight loss in adolescent patients with obesity after 56 weeks of treatment. The secondary objective was to characterize changes in obesity-related risk factors.

Trial Design

This was a 56-week double-blind, randomized, parallel-group, placebo-controlled, multi-center trial. The trial was conducted in pubertal adolescents with obesity ages 12 to less than 17 years.

Key inclusion criteria included BMI corresponding to ≥95th percentile for age and sex, stable weight within the previous 3 months, and history of failing to lose or sustain weight loss by lifestyle modification. Key exclusion criteria included type 1 diabetes or treatment with medications for diabetes treatment with the exception of metformin, congenital heart disease, clinically significant arrhythmia or ECG abnormality, blood pressure >140/90 mmHg, bicarbonate less than the lower limit of normal, history of glaucoma, history of nephrolithiasis, secondary causes of obesity, treatment with medications that could significantly impact weight, bariatric surgery, history of an eating disorder, >1 episode of major depressive disorder, history of bipolar disorder, or psychosis, PHQ-9 score ≥10 at screening, or presence or history of suicidal ideation or behavior with some intent to act. Female subjects must have been using adequate contraception if sexually active.

Family-based lifestyle and diet modification (500-calorie/day deficit) was implemented for all

participants. Eligible subjects were randomized in a 1:1:2 ratio to placebo, mid-dose PHEN/TPM 7.5/46 mg, or high-dose PHEN/TPM 15/92 mg. Randomization was stratified by sex and age (12-14 versus 15-16 years old). There were two titration periods that all subjects participated in regardless of assigned treatment to maintain blinding. The first titration period occurred during the first 4 weeks to reach the mid-dose; the second titration to high-dose occurred from week 13 to 16 (Table 4). This approach was used to approximate the labeled administration of Qsymia, which recommends up-titration after 3 months of treatment of mid-dose PHEN/TPM in those with insufficient weight loss.

Table 4. Titration Schematic by 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

Source: Table 1 OB-403 Protocol

Dose reduction or drug interruptions were allowed for tolerability issues or for rapid weight loss. For subjects with a baseline BMI of 95-98th percentile, study drug dosage was reduced when the subject's BMI was <85th percentile or when weight loss exceeded an average of 2 pounds (0.9 kg) per week. For subjects with baseline BMI ≥99th percentile, study drug was reduced when weight loss exceeded an average of 2 pounds (0.9 kg)/week.

Clinic visits occurred every 4 weeks. Subjects who discontinued study drug were encouraged to remain in the study (off study drug) for continued follow-up and study assessments.

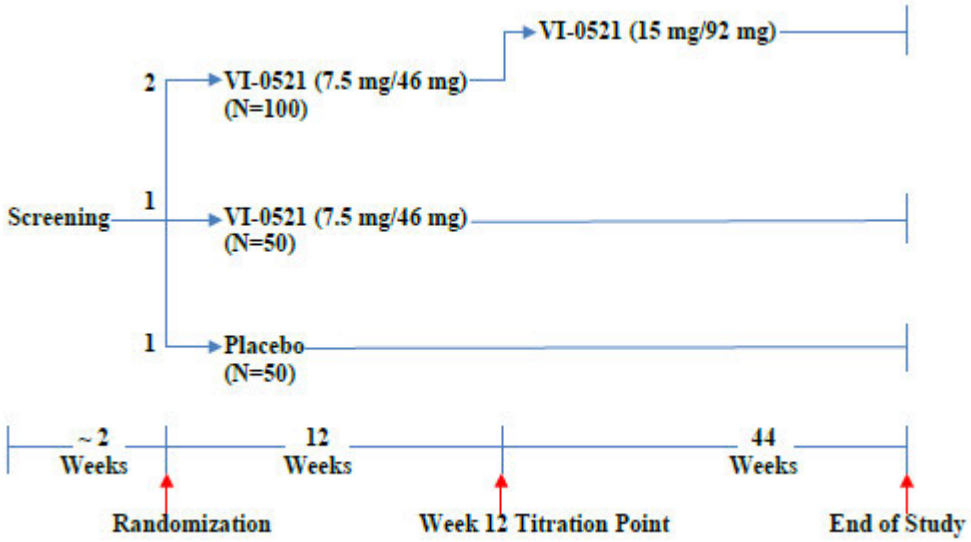


Figure 3. OB-403 Study Design
Source: Figure 1 OB-403 Protocol

Landmark Dates for Study OB-403

First subject enrolled	2 May 2019
First subject dosed with study drug	22 May 2019
Last subject randomized	28 February 2020
Last subject discontinued	16 April 2021
Database lock	27 May 2021

Study Endpoints

Primary Efficacy Endpoint - change in mean percent BMI from baseline to 56 weeks.

Secondary Efficacy Endpoints – Assessed at Week 56

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

Exploratory Endpoints

- Impact of Weight on Quality of Life-Kids (IWQOL-Kids) questionnaire scores
- Changes glycemic and lipid markers

- Change in BMI Z-score

Safety Endpoints

- Adverse events/Serious Adverse Events
- Pregnancy testing
- Vital signs
- Laboratory parameters (Table 60)
- ECG
- Physical exam
- Cognitive function using the Cambridge Neuropsychological Test Automated Battery (CANTAB)
- Depression/Suicidality as assessed by the PHQ-9 and C-SSRS questionnaires
- Bone age
- DXA (selected sites only)

The study flowchart can be found in Appendix 13.3 .

Statistical Analysis Plan

The applicant analyzed the study results based on the final statistical analysis plan (SAP) which is summarized below.

Analysis populations defined by the applicant and the FDA statistical review team are listed in the table below.

Table 5. Study Analyses Populations

	Applicant Definition	FDA Statistical Definition	Analyses
Intent-to-Treat (ITT)	All subjects randomized and who received at least one dose of drug	All subjects randomized regardless of whether treatment is received	Primary population for Efficacy Analyses
Total Subjects in ITT	223	227	
Modified Intent-to-Treat (mITT)	All randomized subjects who receive treatment and have one post-randomization assessment of height and weight	None	Sensitivity Analyses
Total Subjects in mITT	212	NA	
Safety population	All randomized subjects and receive at least one dose of drug	Same	Subject disposition, baseline characteristics, safety analyses
Total Subjects in Safety	223	223	

Reviewer Comment: The statistical reviewer conducted an analysis of the primary endpoint using the FDA definition of the ITT population. Data for the 4 subjects randomized but not treated was imputed and analyzed. No meaningful differences were observed between the analysis using the applicant ITT population (n=223) and the FDA ITT population (n=227) for the primary efficacy endpoint. Therefore, the statistical efficacy analyses presented in this document reflect the results using the applicant's ITT population which was pre-specified in SAP. For further information, please refer to the statistical review team's review document.

Primary Efficacy Analysis

The primary analysis used a mixed effects model with repeated measures (MMRM). Retrieved dropouts (i.e., subjects who discontinued treatment but returned for the Week 56 visit) were to be used to impute missing data for subjects who discontinued the study prematurely; however, there were not enough retrieved dropouts, therefore a wash-out imputation method was utilized as outlined in the SAP.

The family-wise type 1 error for the comparisons were controlled by Fisher's protected least significant difference (LSD) method at the 0.05 significance level: placebo, mid-dose, and high-dose were first compared for overall difference in the percent change from baseline in BMI. If the overall difference was significant at the 0.05 significance level, 3 pairwise comparisons were conducted using Fisher's LSD method at the 0.05 significance levels. The order for comparisons of interest was high-dose vs. placebo, mid-dose vs. placebo, and high-dose vs. mid-dose.

Sensitivity analyses

Sensitivity analyses to explore the impact of missing data were conducted. The first was a multiple imputation method under the assumption of missing at random (MAR). The second sensitivity analysis used multiple imputation under the assumption of missing not at random (MNAR).

An additional sensitivity analysis using a 2-way tipping-point strategy was 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. Missing data were imputed according to the primary multiple imputation approach. Then a penalty was added to the imputed values to both active arm and placebo. 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 treatment 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.

Sensitivity analyses using observed data and the last observation carried forward method were also conducted.

Secondary Endpoint Analyses

Secondary endpoints were tested in a stepwise way to preserve the family-wise type 1 error, once mid- and high-dose PHEN/TPM were shown to be statistically significantly better than placebo for the primary endpoint using the Fisher's LSD procedure.

Within the key secondary endpoints, the statistical significance level was adjusted using the Hochberg method to control the family-wise error rate at 5%. Starting from high-dose PHEN/TPM versus placebo comparison, analyses were carried out for all key secondary endpoints. All endpoints had to be statistically significant in favor of high-dose PHEN/TPM treatment compared to placebo, after the Hochberg adjustment, in order for the next set in the hierarchy to be tested. The sequential testing was to stop at the first endpoint set where high-dose PHEN/TPM treatment did not demonstrate statistical superiority over placebo. The above process was repeated on mid-dose PHEN/TPM treatment.

Protocol Amendments

There were two protocol amendments. Both amendments did not involve substantive changes to the subject population or study procedures.

6.1.2. Study Results

Compliance with Good Clinical Practices

The study was conducted in accordance with the Declaration of Helsinki and its most recent update, and the International Council for Harmonization (ICH) E6 (R2) Good Clinical Practices guideline.

Financial Disclosure

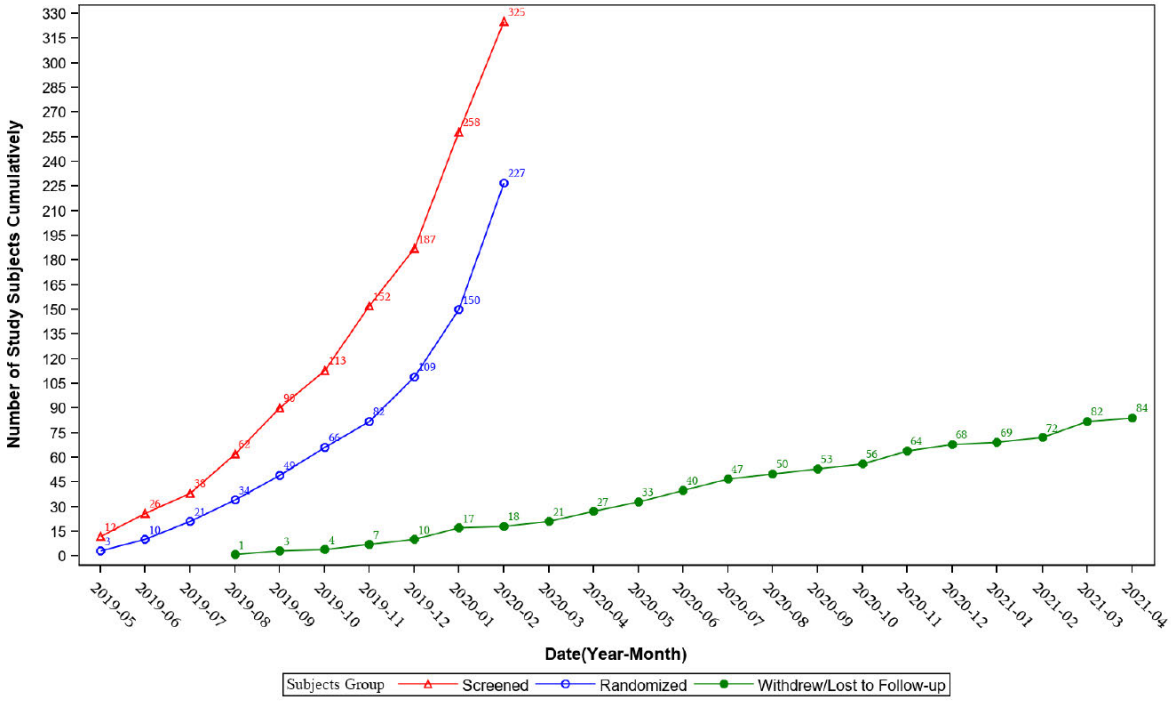
None of the 110 investigators in this trial had disclosable financial interests; see the Appendix Section 13.2.

Patient Disposition

A total of 325 individuals were screened and 227 were randomized. Four subjects randomized were not exposed to study drug, resulting in 56 treated with placebo, 54 treated with mid-dose

PHEN/TPM, and 113 treated with high-dose PHEN/TPM (safety analysis set, and ITT analysis as defined by the applicant). Of the 223 randomized and treated subjects, 135 (60.5%) completed study drug treatment, and an additional 4 subjects completed the study despite discontinuing drug – for a total 139 subjects who completed the study. Almost all of the study subjects who discontinued study drug did not continue other study visits and did not return for the Week 56 height and weight measurement. The most frequently reported reason for discontinuation was "lost-to-follow-up" and "withdrawal of consent".

Reviewer Comment: There were a large number of subjects who discontinued study drug treatment and did not contribute additional data. Missing data can result in bias and undermine the reliability of the study results. The reason for the missing data in this trial is not certain; however, the applicant notes that this study was conducted during the COVID-19 pandemic (last subject randomized was February 2020; WHO declared COVID-19 outbreak a pandemic and U.S. President declared a national emergency March 2020) and may have contributed to the substantial number of subjects that were lost-to-follow-up or withdrew consent. Interestingly, more placebo-treated subjects discontinued than PHEN/TPM-treated subjects, which could suggest lack of efficacy as one possible explanation (although not supported by data). The statistical review team has evaluated the statistical methods applied to address the missing data and found them to be sufficient. Please the statistical review team's review for additional information.



Screened Subjects used Date of Informed Consent, Randomized Subjects used Date of Randomization, Withdrew/Lost to Follow-up Subjects used Date of Completion/Discontinuation.

Figure 4. Disposition of Subjects over time

Source: Response to IR, Submitted 10 November 2021 (SD#1154), Figure 4

Table 6. Summary of Disposition of Study Subjects

	Mid-dose PHEN/TPM n (%)	**High-dose PHEN/TPM** n (%)	**Placebo** n (%)	**Overall** n (%)
Subjects Randomized	55	115	57	227
Subjects Treated (Applicant ITT population)	54	113	56	223
Completed Study Drug Treatment	38 (70.4)	69 (61.1)	28 (50.0)	135 (60.5)[1]
Discontinued Study Drug Treatment	15 (27.8)	44 (38.9)	28 (50.0)	87 (39.0)
Reason for Discontinuation of Study Drug Treatment				
Adverse event[2]	1 (1.9)	5 (4.4)	3 (5.4)	9 (4.0)
Lost to Follow-up	9 (16.7)	20 (17.7)	13 (23.2)	42 (18.8)
Withdrawal of Consent	5 (9.3)	12 (12.4)	8 (14.3)	25 (11.2)
Lack of Efficacy	0	1 (0.9)	2 (3.6)	3 (1.3)
Investigator Decision	0	0	0	0
Protocol non-compliance	0	1 (0.9)	0	1 (0.4)
Other	0	5 (4.4)	2 (3.6)	7 (3.1)
Subjects with Missing Data at Week 56	17 (31.5)	41 (36.3)	26 (46.4)	84 (37.7)
Subjects that Completed Study	37 (68.5)	73 (64.6)	29 (51.8)	139 (62.3)

Source: OB-403 CSR, Table 6, Response to IR, submitted 18 February 2022 (SD#1173)

1. Percentages are based on the Applicant's ITT population as denominator
2. Based on review of discontinuation narratives by the clinical reviewer a total of 9 subjects discontinued due to an adverse event. The original number was 4 subjects. See Section 8.4.3 for further details

Note: There was 1 subject in the mid-dose group that did not have a "complete study treatment" question completed by the site, and therefore was not included in either the count of subjects that completed study drug treatment (n=38) or in the count of subjects that discontinued study treatment (n=15).

Protocol Violations/Deviations

Protocol deviations were identified prior to database lock. A total of 134 subjects had 404 important protocol deviations:

- Study Assessment: 336 protocol deviations in 123 subjects
- Dose Formulation/Dose Administration: 52 protocol deviations in 27 subjects
- Handling/ Storage/ Retention: 6 protocol deviations in 4 subjects
- Sample Collection: 4 protocol deviations in 3 subjects
- Consent Process: 3 protocol deviations in 3 subjects

The most common deviations were study assessments, the majority of which were instances where the subject participated in phone visits due to specific requirements for COVID-19. All subjects had been randomized by February 2020; in March 2020, a public health emergency

was declared in response to COVID-19.

The table below lists provides the categories of important protocol deviations by treatment group.

Table 7. Important Protocol Deviations by Sub-Category and Treatment Group

	Mid-dose PHEN/TPM (N=54)		**High-dose PHEN/TPM** (N=113)		**Placebo** (N=56)	
	n (%)	Events		Events	n (%)	Events
Total Important Protocol Deviations	**31 (57.4)**	**95**	**71 (62.8)**	**192**	**32 (57.1)**	**117**
Study Assessment	29 (53.7)	80	63 (55.8)	153	31 (55.4)	103
Dose Formulation/Dose Administration	7 (13.0)	12	13 (11.5)	28	7 (12.5)	12
Handling/Storage/Retention	1 (1.9)	1	2 (1.8)	4	1 (1.8)	1
Sample Collection	0	0	2 (1.8)	3	1 (1.8)	1
Consent Process	1 (1.9)	1	2 (1.8)	2	0	0
Sample Processing/Storage	0	0	1 (0.9)	1	0	0
Inclusion/Exclusion Criteria	0	0	1 (0.9)	1	0	0
Study Restrictions/Withdrawal Criteria	1 (1.9)	1	0	0	0	0
COVID-19 Related	**14 (25.9)**	**44**	**41 (36.3)**	**87**	**21 (37.5)**	**66**

Source: Reviewer's analysis, database addv.xpt

Reviewer Comment: There was a similar distribution of important protocol deviations, including study assessments, across the treatment groups. The applicant supplied a listing of all the protocol deviations, which was reviewed. Study assessments including weight and height measurements were missed for many subjects due to COVID-19 restrictions. A listing of one subject assigned to placebo is shown below as an example. This subject had 12 important protocol deviations, almost all related to COVID-19 restrictions including no measurement of height and weight at 8 study visits. This subject ultimately discontinued from the study. There are only four post-baseline height and weight values available for this subject (the last one at Week 44).

Table 8. Subject Listing of Verbatim Terms for Protocol Deviations

Site	Subject	Any Deviations?	Occurred Date (day) [a]	Deviation Category	Criticality	COVID-19 Related	Details of Deviation
103	(b) (6)	Yes	25MAR2020 (29)	Study Assessment	Important	Yes	V3 labs and vitals were not collected due due to Covid-19.
			20APR2020 (55)	Study Assessment	Important	Yes	V4 labs and vitals not done due to modified visit due to Covid-19.
			19MAY2020 (84)	Study Assessment	Important	Yes	COVID-19. V5 Vital signs assessments and, HbA1c assessments missed.
			11JUN2020 (107)	Study Assessment	Important	Yes	COVID-19. V6 - Vital signs assessments not performed.
			07JUL2020 (133)	Study Assessment	Important	Yes	COVID-19 - V7 The following assessments were missed: Weight, Waist Circumference, Height, Vital Signs and BMI.
			17AUG2020 (174)	Study Assessment	Important	Yes	COVID-19 -V8 . The following assessments were missed: Weight, Waist Circumference, Height, Vital Signs and BMI.
			14SEP2020 (202)	Study Assessment	Important	Yes	V9 labs completed OOW (+61 days) due to Covid-19 and modified visit. Labs collected during V11 on 12Nov2020.
			12OCT2020 (230)	Study Assessment	Important	Yes	V10 visit conducted via telephone as a modified visit due to Covid-19 restrictions.
			12NOV2020 (261)	Study Assessment	Important	Yes	V11 visit was partially conducted via telephone as a modified visit due to Covid-19 restrictions.
			30NOV2020 (279)	Study Assessment	Important	No	V12 no physical assessments not done: Weight, Waist Circumference, Height, Vital Signs and BMI.
			05JAN2021 (315)	Study Assessment	Important	No	V13 OOW
			28JAN2021 (338)	Study Assessment	Important	No	V14 Weight, Waist Circumference, Height, Vital Signs and BMI were not done

Source: OB 403, Listing 16.2.2.1 Protocol Deviations, Submitted 25 August 2021 (SD#1129)

The statistical review team has evaluated whether the statistical methods used to address this issue of missing data are sufficient and concluded they were.

Table of Demographic Characteristics

Demographic characteristics were generally well-balanced among groups. The median age was 14 years old, 61% were between 12 and 14 years old at enrollment, 54% were female, 67% were white, 27% were black, 32% were of Hispanic ethnicity, and 100% were from the United States.

Table 9. Demographic characteristics of the primary efficacy analysis population

Demographic Parameters	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Sex			
Male	26 (48.1)	50 (44.2)	26 (46.4)
Female	28 (51.9)	63 (55.8)	30 (53.6)
Age			
Mean, years (SD)	14.1 (1.3)	13.9 (1.4)	14.0 (1.4)
Median, years	14.0	14.0	14.0
Min, max, years	12, 16	12, 16	12, 16
Age Group			
12 – 14 years	33 (61.1)	69 (61.1)	34 (60.7)
15 – 16 years	21 (38.9)	44 (38.9)	22 (39.3)
Race			
White	36 (66.7)	71 (62.8)	42 (75.0)
Black or African American	14 (25.9)	36 (31.9)	10 (17.9)
Asian	0	1 (0.9)	0
American Indian or Alaska Native	0	1 (0.9)	0
Other	4 (7.4)	4 (3.5)	4 (7.1)
Ethnicity			
Hispanic or Latino	25 (46.3)	34 (30.1)	13 (23.2)
Not Hispanic or Latino	28 (51.9)	79 (69.9)	42 (75.0)
Not stated	1 (1.9)	0	1 (1.8)
Region			
United States	54 (100)	113 (100)	56 (100)
Rest of the World	0	0	0

Source: OB-403 CSR Table 7

Reviewer Comment: Typically, adult weight loss trials are predominantly female and white. In this pediatric trial, the baseline demographics of this study population include more males (~45%) and individuals that do not identify as white (~33%) which is more likely to reflect the diversity of the obese adolescent population.[20] The number and age range of the individuals enrolled will allow for adequate assessment of PHEN/TPM in the upper as well as lower age groups.

Other Baseline Characteristics

Other baseline characteristics were generally well-balanced across treatment groups. Overall, mean body weight was 106.1 kg, mean BMI was 37.8 kg/m^2, and the majority, 81%, were ≥ 120% of the 95th percentile, which is considered severely obese/Class II obesity.[21] Most girls were either Tanner stage IV or V and most boys were Tanner II or III. The high-dose PHEN/TPM group had a numerically higher mean BMI, and a slightly higher proportion of subjects classified as severely obese. In the total study population, mean blood pressure was 119/73 mmHg, and mean HbA1c was 5.5%. As defined by laboratory values at baseline, no subjects had type 2 diabetes and a small percentage overall (6%) had pre-diabetes at baseline. However, there were two subjects with a medical history of type 2 diabetes (1 randomized to mid-dose PHEN/TPM, 1 randomized to high-dose PHEN/TPM). The table below enumerates other selected baseline characteristics.

Table 10. Baseline Characteristics

Demographic Parameters	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Tanner Stage			
Male	(n=26)	(n=50)	(n=26)
Tanner stage I[1]	0	1 (2.0)	0
Tanner stage II	4 (15.4)	17 (34.0)	5 (19.2)
Tanner stage III	6 (23.1)	10 (20.0)	11 (42.3)
Tanner stage IV	9 (34.6)	15 (30.0)	5 (19.2)
Tanner stage V	7 (26.9)	7 (14.0)	5 (19.2)
Female	(n=28)	(n=63)	(n=30)
Tanner stage I	0	0	0
Tanner stage II	2 (7.1)	4 (6.3)	2 (6.7)

[20] Ogden CL, Fryar CD, Hales CM, Carroll MD, Aoki Y, Freedman DS. Differences in Obesity Prevalence by Demographics and Urbanization in US Children and Adolescents, 2013-2016. JAMA. 2018 Jun 19;319(23):2410-2418. doi: 10.1001/jama.2018.5158. PMID: 29922826; PMCID: PMC6393914.

[21] Racette SB, et al. BMI-for-age graphs with severe obesity percentile curves: tools for plotting cross-sectional and longitudinal youth BMI data. BMC Pediatrics, 2017; 17:130-136.

Demographic Parameters	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Tanner stage III	4 (14.3)	6 (9.5)	5 (16.7)
Tanner stage IV	11 (39.3)	22 (34.9)	9 (30.0)
Tanner stage V	11 (39.3)	31(49.2)	14 (46.7)
Height (cm)			
Mean (SD)	168.6 (8.0)	166.3 (7.8)	167.2 (7.6)
Median	167.6	166.4	166.6
Min, max	150.0, 185.0	147.6, 184.1	148.2, 190.7
Body weight (kg)			
Mean (SD)	105.2 (22.4)	108.5 (25.0)	102.2 (21.8)
Median	101.5	104.3	98.1
Min, max	64.4, 166.2	69.8, 217.8	58.8, 158.6
BMI (kg/m2)			
Mean (SD)	36.9 (6.7)	39.0 (7.4)	36.4 (6.4)
Median	35.0	37.2	34.4
Min, max	26.6, 55.5	27.2, 72.4	26.8, 50.9
BMI categories			
≥95th to <99th percentile	23 (43.4)	33 (29.5)	26 (46.4)
≥99th percentile	30 (56.6)	79 (70.5)	30 (53.6)
≥120% of the 95th percentile	40 (74.1)	100 (88.5)	41 (73.2)
HbA1c (%)			
Mean (SD)	5.55 (0.41)	5.49 (0.41)	5.50 (0.35)
Median	5.6	5.5	5.5
Min, max	4.8, 6.6	4.6, 6.5	4.7, 6.4
Glycemic status[2]			
Diabetes	0	0	0
Pre-diabetes	3 (5.6)	7 (6.2)	4 (7.1)
Systolic Blood Pressure (mmHg)			
Mean (SD)	121.4 (9.2)	117.4 (10.2)	117.7 (10.4)
Median	121.5	117.0	118.0
Min, max	98, 140	91, 139	89, 137
Diastolic Blood Pressure (mmHg)			
Mean (SD)	75.8 (6.7)	72.9 (7.3)	71.7 (8.3)
Median	76.5	74.0	72.5
Min, max	59, 88	52, 86	54, 88
Blood Pressure ≥130/80 mmHg			
Yes	5 (9.3)	7 (6.2)	6 (10.7)
Triglycerides (mg/dL)			
Mean (SD)	120.1 (61.6)	112.2 (63.2)	118.3 (46.1)
Median	103.0	92.0	102.5

Demographic Parameters	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Min, max	49, 313	33, 315	46, 241
Triglycerides ≥150 mg/dL	12 (22.2)	22 (19.5)	13 (23.2)
LDL-C (mg/dL)			
Mean (SD)	89.4 (23.7)	90.2 (27.3)	94.1 (26.8)
Median	85.5	85.1	95.9
Min, max	42, 163	42, 186	23, 160

1. One subject (b) (6) Tanner stage 1 was randomized. This was listed as a protocol violation
2. Diabetes: Fasting plasma glucose ≥126 mg/dL, 2h OGTT ≥200 mg/dL, or HbA1c ≥6.5% at baseline
   Pre-diabetes: Fasting plasma glucose 100 to 125 mg/dL, 2h OGTT ≥140 to 199 mg/dL, or HbA1c 5.7% to 6.4% at baseline

Source: OB 403 CSR, Table 7, Table 14.3.2.6; Response to FDA IR, Submitted 10 November 2021 (SD#1154), Table 6; Response to FDA IR, Submitted 19 January 2022 (SD#1165), Q2, Table 3

At baseline, 50 (22.4%) subjects had a history of a psychiatric disorder, with the following conditions of note reported:

- The most frequently condition reported was attention deficit disorder in 18 (8.1%) of subjects.
- Depression was reported in 15 (6.7%) subjects (7.4% mid-dose PHEN/TPM, 7.1% high-dose PHEN/TPM, 5.4% placebo).
- Anxiety was reported in 14 (6.3%) subjects (5.6% mid-dose PHEN/TPM, 5.3% high-dose PHEN/TPM, 8.9% placebo).
- A history of suicidal ideation was reported in 2 subjects (1 in the mid-dose PHEN/TPM and 1 in the high-dose PHEN/TPM group). The subject in the mid-dose PHEN/TPM group (Subject (b) (6)) also had a remote history of intentional self-injury, major depression, affective disorder, anxiety disorder, post-traumatic stress disorder, and behavioral disorder (2016 was listed as end date for all the psychiatric conditions for this subject).
- Insomnia that was ongoing was reported in 5 (2.2%) subjects: 2 in placebo, 1 in mid-dose PHEN/TPM, and 2 in high-dose PHEN/TPM group.
- The preferred term 'Sleep disorder' were reported in 4 (1.8%) subjects: 1 in placebo, 1 in mid-dose PHEN/TPM group, and 2 in the high-dose PHEN/TPM group.

Sleep apnea syndrome was reported in 5 (2.2%) subjects: 1 in placebo, 1 in mid-dose PHEN/TPM group and 3 in the high-dose PHEN/TPM group.

Five (2.2%) subjects reported a history of cardiac or vascular disorders

- Sinus tachycardia in two subjects (1 in mid-dose PHEN/TPM and 1 in high-dose PHEN/TPM). Sinus tachycardia was reported as ongoing in subject (b) (6). The other subject (b) (6) also reported hypertension and was taking propranolol.

- AV first degree block in 1 subject in the placebo group was reported as ongoing.

- Palpitations in 1 subject in the high-dose PHEN/TPM group was reported as ongoing (Subject (b) (6)). This subject also had hypertension and was on concomitant medications of atenolol and hydrochlorothiazide.

- Sinus bradycardia in 1 subject in the high-dose PHEN/TPM group (reported as ongoing).

- Two subjects (b) (6) in the high-dose PHEN/TPM group had hypertension and were on anti-hypertensive medications.

The most frequently used medications by Anatomical Therapeutic Chemical (ATC) category were antiinflammatory agents (18.8%) - primarily ibuprofen (16.6%), antihistamines (16.1%), analgesics (15.2%), antibacterials (13.9%), and drugs for obstructive airway disease (10.8%).

Approximately 8.1% of subjects were taking sex hormones – primarily fixed combinations of progestins/estrogens (5.4%).

Approximately 6% of subjects were taking psychoanaleptics – 10 (4.5%) subjects were taking concomitant antidepressants (Subjects (b) (6)); other medications in this ATC category included those for the treatment of ADHD.

Four (1.8%) subjects were taking metformin ((b) (6)) for diabetes or pre-diabetes.

Reviewer Comment: The baseline characteristics of this study population reflects the population of obese adolescents which in general have higher rates of clinical depression and cardiometabolic risk factors than normal weight peers.[22, 23] However, it is notable that the majority of subjects were normoglycemic, did not have hypertriglyceridemia, or elevated blood pressure (≥130/80 mmHg) at baseline.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

[22] Rao WW, Zong QQ, Zhang JW, An FR, Jackson T, Ungvari GS, Xiang Y, Su YY, D'Arcy C, Xiang YT. Obesity increases the risk of depression in children and adolescents: Results from a systematic review and meta-analysis. J Affect Disord. 2020 Apr 15;267:78-85. doi: 10.1016/j.jad.2020.01.154. Epub 2020 Jan 27. PMID: 32063576.
[23] Chung ST, Onuzuruike AU, Magge SN. Cardiometabolic risk in obese children. Ann N Y Acad Sci. 2018 Jan;1411(1):166-183. doi: 10.1111/nyas.13602. PMID: 29377201; PMCID: PMC5931397.

Per the protocol, subjects who were unable to tolerate the assigned dose could be treated at a reduced dose level or take a drug holiday. In addition, study drug dosing was to be reduced based on rates of weight loss. For subjects with baseline BMI 95th to 98th percentile, study drug dosage was to be reduced when BMI was <85th percentile or when weight loss exceeded an average of 2 pounds (0.9 kg) per week. For subjects with baseline BMI ≥99th percentile, study drug dosage was reduced when weight loss exceeded an average of 2 pounds per week.

When dose reduction was not appropriate, subjects could temporarily discontinue from treatment (up to 7 days) on one or more occasions. Dose interruptions longer than 7 days were possible with agreement from the medical monitor. All subjects undergoing dose interruptions for any duration could be titrated back up to the original dose level based on discretion of the investigator.

The table below describes the number of subjects with a drug interruption or drug reduction, number of events, duration of drug holidays, and the reason for the drug interruption or drug reduction. Subjects treated with high-dose PHEN/TPM had a slightly higher incidence of drug interruptions/drug reductions, compared to mid-dose or the placebo group, however the overall incidence was low. Across the treatment groups, the duration of drug interruptions was similar with average duration of approximately 40 days. The most common reported reason for a drug interruption or drug reduction was for weight loss. The subjects that had adverse events that led to a drug interruption or drug reduction are described in the Section 8.4.3.

Table 11. Drug Interruption or Drug Reduction by Treatment Group

Demographic Parameters	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Subjects with Drug Interruption or Drug Reduction	6 (11.1)	20 (17.7)	7 (12.5)
Drug Interruption	3 (5.6)	10 (8.8)	6 (10.7)
Drug Reduction	3 (5.6)	10 (8.8)	1 (1.8)
Events of Drug Holidays or Drug Reductions			
Drug Interruption	3	10	7
Drug Reduction	4	13	1
Duration of Drug Interruption (Days)			
n[1]	3	8	5
Mean (SD)	40.7 (26.8)	37.9 (41.5)	41.8 (14.0)
Reason for Drug Interruption or Drug Reduction			
Adverse Event	2	7	3
Weight loss	3	13	1
Unknown	3	6	5

1. Subjects who did not return drug kits, were excluded from this analysis

Source: Response to FDA IR, submitted 10 November 2021 (SD#1154), Table 16, FDA IR, submitted 19 January 2022, Q.10

Efficacy Results – Primary Endpoint

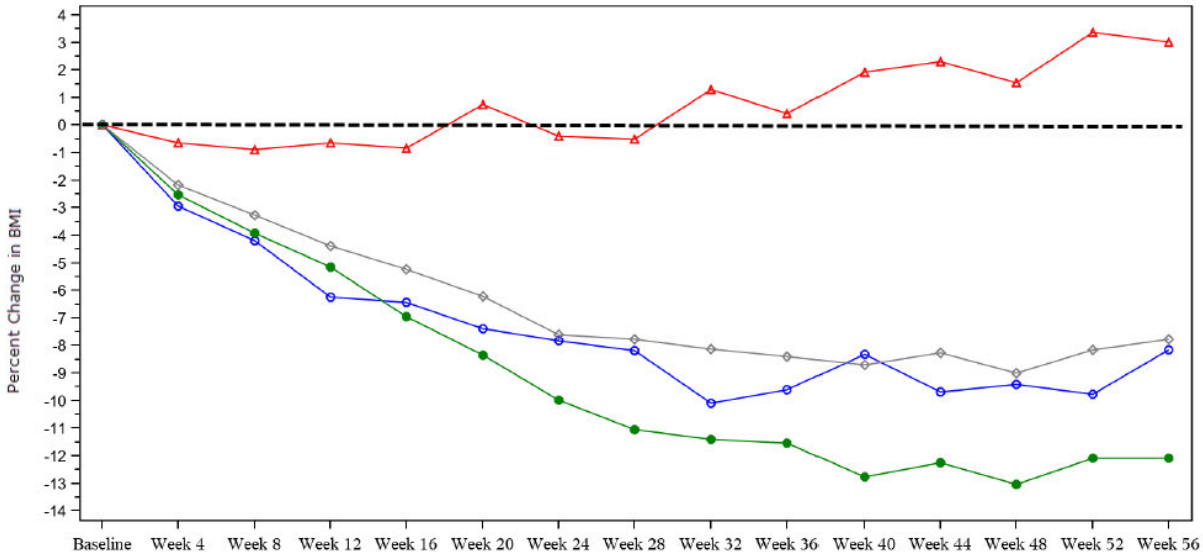
The primary endpoint was change in mean percent BMI from baseline to week 56. Statistical significance in this trial was met, with the change in LS mean percent BMI from baseline to week 56 of -4.8% for the mid-dose PHEN/TPM group, -7.1% for the high-dose PHEN/TPM group, and 3.3% for the placebo group. The least square difference between mid-dose PHEN/TPM and placebo was -8.1% and between high-dose PHEN/TPM and placebo was -10.4%.

Table 12. Change in Mean Percent BMI from Baseline to Week 56 – Washout Multiple Imputation

Treatment Group	N	LS Mean (SE) Change from Baseline	
Mid-dose PHEN/TPM	54	-4.78 (1.30)	
High-dose PHEN/TPM	113	-7.11 (1.76)	
Placebo	56	3.34 (1.44)	
Treatment Comparison		**Difference in LS Mean (95% CI)**	**p-value**
Mid-dose vs. Placebo		-8.11 (-11.92, -4.31)	<0.0001
High-dose vs. Placebo		-10.44 (-13.89, -6.99)	<0.0001
Mid-dose vs. High-dose		-2.33 (-5.27, 0.62)	0.1216

Source: Study OB-403 CSR, Table 9

The figure below illustrates the change in mean percent BMI from baseline over time using observed data in the ITT population.



Number of Subjects															
Placebo	56	48	42	40	44	32	29	35	30	31	25	31	26	26	30
VI-0521 Mid	54	46	40	43	40	40	38	38	33	38	35	33	37	33	37
VI-0521 Top	113	107	96	90	85	82	84	73	66	73	69	71	64	62	72
Overall	223	201	178	173	169	154	151	146	129	142	129	135	127	121	139

Figure 5. Mean Percent Change in BMI from Baseline Over Time (Observed Data) – ITT population

Source: Response to IR, submitted 10 November 2021, Figure 8.1

Reviewer Comment: In Figure 5, the numbers of subjects contributing to the timepoints decreases over time. At Week 56, the majority of these subjects are completers (i.e., completed the study on study drug). Of the 87 subjects that discontinued prematurely, only 3 returned to contribute height and weight data at Week 56. The results shown in the figure represent a best-case scenario and may overestimate the true treatment effect.

Subgroup Analyses

The treatment difference of the primary efficacy endpoint was generally consistent across multiple subgroups:

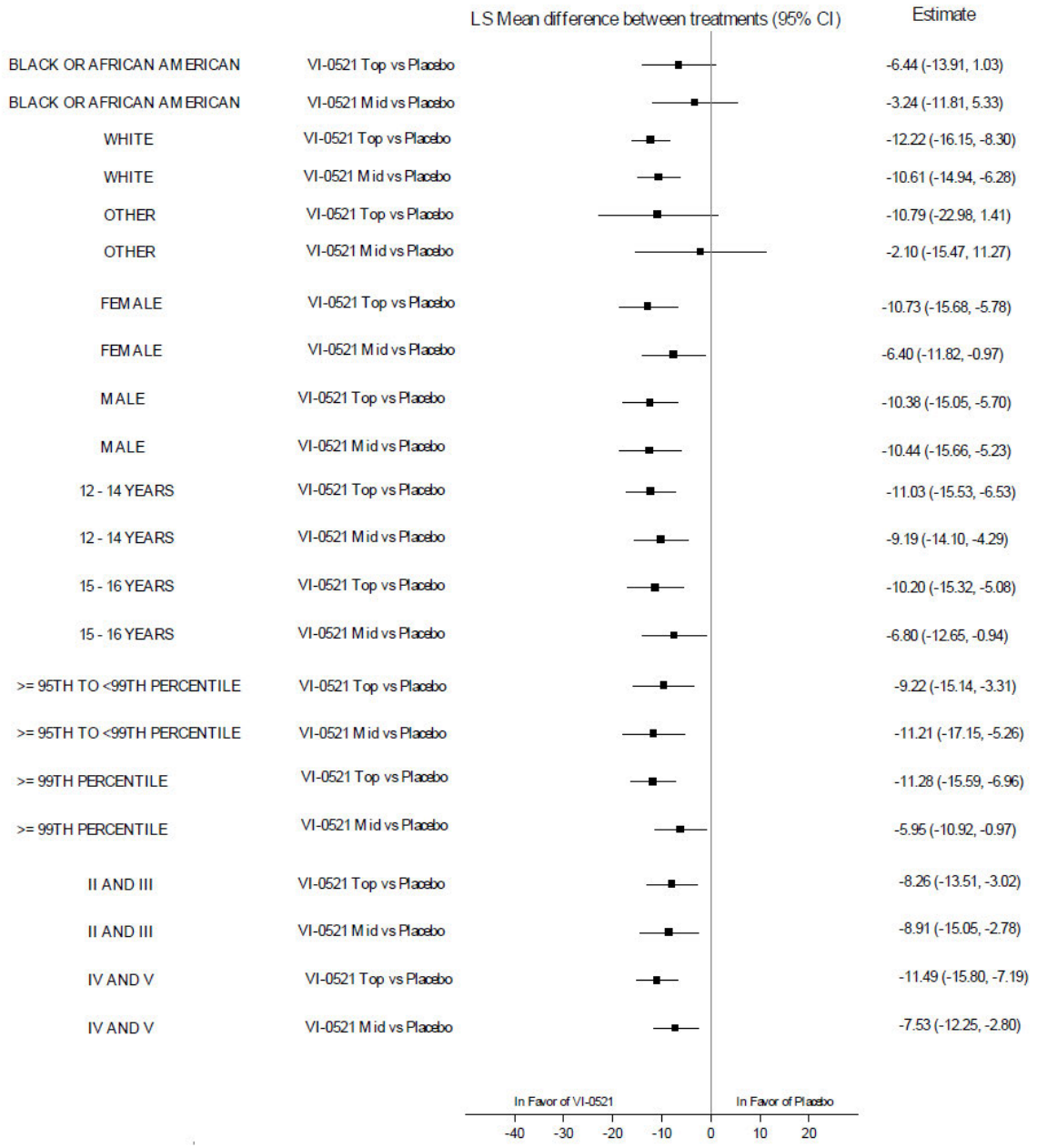


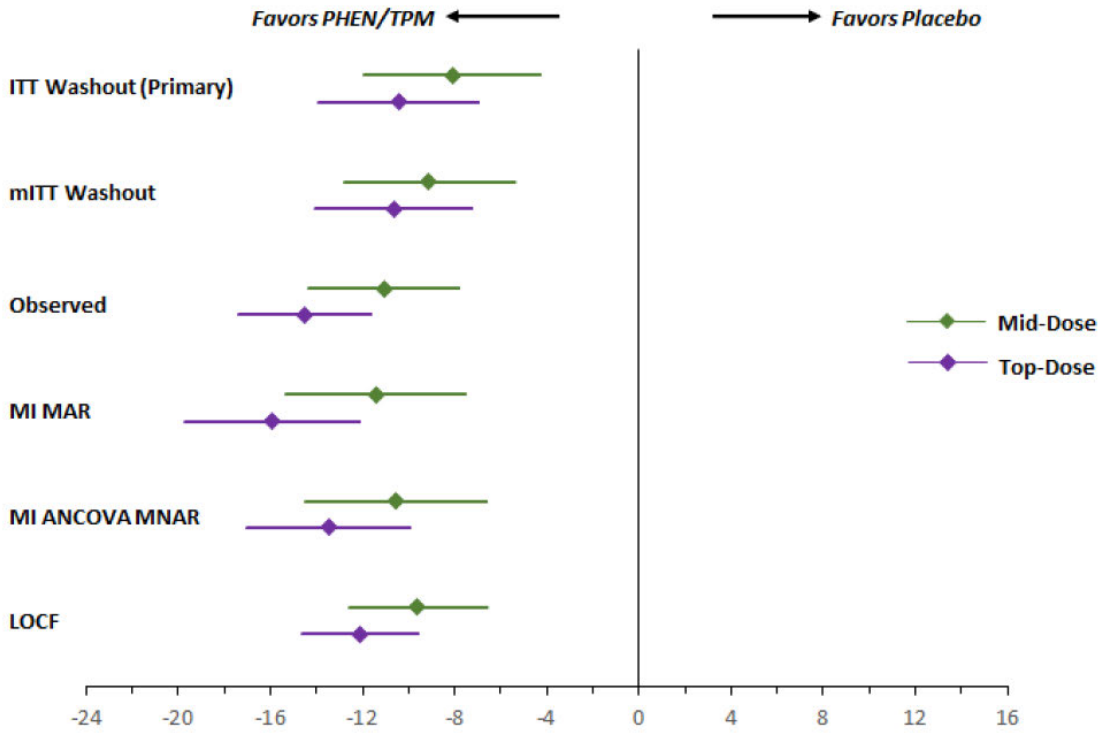
Figure 6. Forest Plot of Mean Percent BMI Treatment Difference by Subgroup – ITT population
Source: Response to FDA IR, submitted 18 February 2022 (SD#1173), Adapted from Figure 5a

Sensitivity Analyses

Different sensitivity analyses to support the primary analysis were conducted. Because a total of 84 (37.7%) subjects did not contribute Week 56/End of Treatment BMI data, analyses to evaluate the consistency of the data given the large amount of missing data at week 56 were conducted using MAR and MNAR assumptions. As shown in Figure 7, the treatment difference

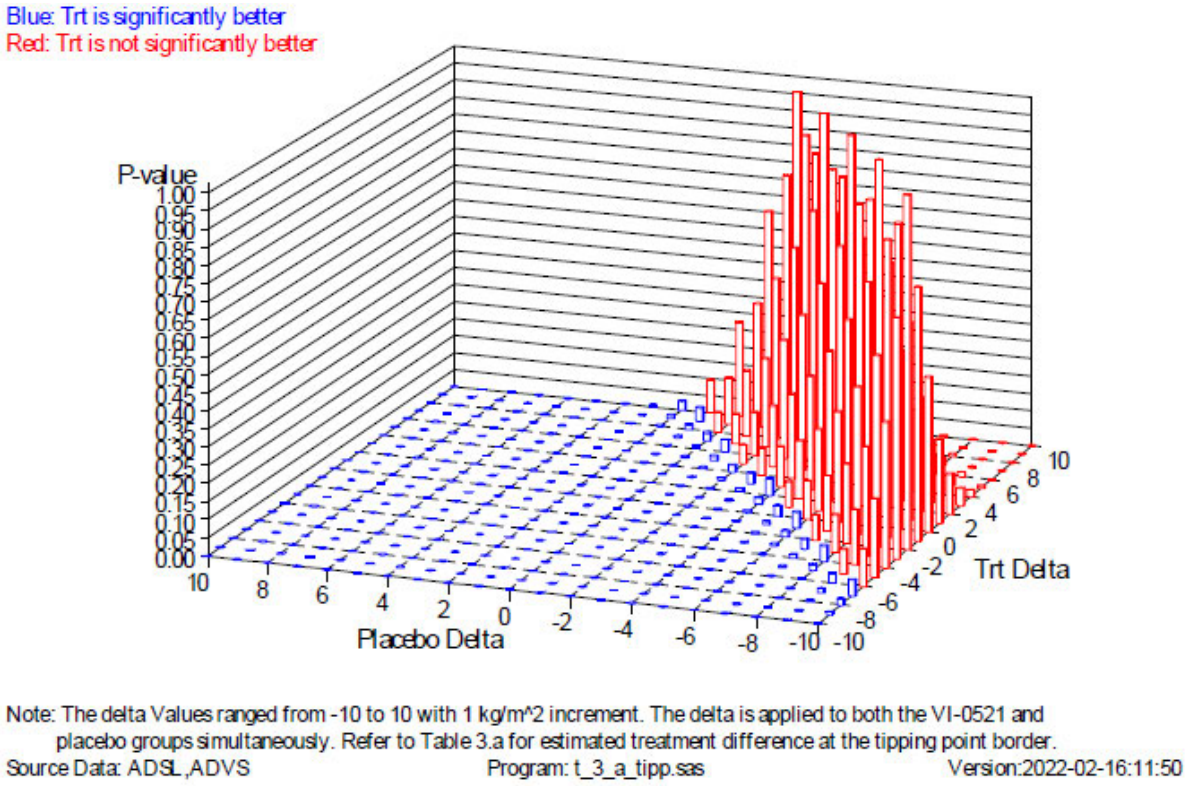
was robust across the different sensitivity analyses.

The applicant also conducted a tipping analysis, in which missing data are imputed according to the multiple imputation approach and then a penalty is applied to the imputed values over a range of possible treatment outcomes in order to identify the "tipping point", or the point at which the imputed data overturn the results of the primary analysis. The BMI penalty ranged from -10 kg/m^2 to +10 kg/m^2 using 1 kg/m^2 increments. If the imputed data needed to reverse the statistical significance of the results are unlikely (low probability), this supports the strength of the primary statistical analysis. The tipping point for both the mid- and high-dose PHEN/TPM groups are considered unlikely. For example, in the mid-dose PHEN/TPM tipping point analysis, the point at which statistical significance was lost occurred when the placebo group had no change and the mid-dose PHEN/TPM group experienced an 8 kg/m^2 increase in BMI (Figure 8).



Abbreviations: BMI = body mass index; LOCF = last observation carried forward; MI = multiple imputation; MAR = missing at random; MNAR = missing not at random; VI-0521 Mid-dose = PHEN/TPM 7.5 mg/46 mg; VI-0521 Top-dose = PHEN/TPM 15 mg/92 mg.
Source: Tables 14.2.1.2, 14.2.3.1, 14.2.3.2, 14.2.3.3, 14.2.3.5, 14.2.3.7.

Figure 7. LS Mean (95% CI) Placebo-subtracted Percent Change in BMI at Week 56 by Sensitivity Analysis
Source: OB-403 CSR, Figure 3



Note: The delta Values ranged from -10 to 10 with 1 kg/m^2 increment. The delta is applied to both the VI-0521 and placebo groups simultaneously. Refer to Table 3.a for estimated treatment difference at the tipping point border.
Source Data: ADSL,ADVS Program: t_3_a_tipp.sas Version:2022-02-16:11:50

Figure 8. Mid-dose PHEN/TPM Two-Dimensional Tipping Point Analysis: Percent Change in BMI from Baseline to Week 56 – ITT population

Source: Response to FDA IR, submitted 18 February 2022 (SD#1173), Figure 3a

Data Quality and Integrity

The accuracy of subject height measurements, which is a component of the primary endpoint, was of concern on review of the data.

Per the protocol, height measurements were to be made using a calibrated stadiometer without shoes, socks, or hats. At each study visit, 3 independent measurements of height should have been made, and the median value from these measurements recorded on the eCRF. Height should have been recorded to the nearest centimeter (measurements were actually recorded to the tenth decimal place). The same stadiometer was to be used for all visits and the stadiometer was to be calibrated, at least daily, if used according to the site standard operating procedures or manufacturer instructions.

Review of figures plotting height and weight for each study subject revealed that 4 sites (126, 129, 115, and 120) had at least 1 subject with 10 identical consecutive heights. Some variation in height, even for a subject that is near final adult height, would be expected. Identical consecutive heights over the course of the trial could suggest that height was not measured at

each visit and were instead replicated from a previous visit.

The applicant was queried regarding this concern. They observed that 19 subjects had at least 10 identical consecutive heights across these 4 sites. The applicant confirmed that study heights were "actually made and documented at study sites."[24] For these 19 subjects, the applicant noted that most were Tanner IV or V, suggesting that they likely had either obtained or were near their final adult height. The applicant concluded given that the height measurements were performed, combined with the attainment of near or final adult height, "the observed absence of variability does not suggest a significant negative impact on the validity of the overall study data or conclusions."

Although height might not be crucial for the evaluation of the study results because the affected subjects are at or near final adult height, the lack of height variability raises questions about the validity of overall data collected from these sites. Two sites, 115 and 120, enrolled the greatest number of subjects and had subjects with at least 10 identical consecutive heights, and therefore they were selected to be inspected. The Office of Scientific Investigations found no significant regulatory violations at these two sites. In addition, an exploratory sensitivity analysis of the primary endpoint excluding these two sites (which contributed 30% of the ITT population) was conducted. The results were similar to the overall results, providing confidence in results of the primary analysis.

Table 13. Change from Baseline in Percent BMI at Week 56, Excluding Sites 115 and 120

N=155	N	LS mean (SE)	Treatment Difference to placebo [95%CI]; p-value
Placebo	41	3.61 (1.59)	
Mid-dose	33	-4.26 (1.72)	-7.87 [-12.43, -3.32]; 0.0007
High-dose	81	-7.16 (1.18)	-10.77 [-14.57, -6.96]; <0.0001

Source: FDA Statistical Reviewer's Analysis

Efficacy Results – Secondary and other relevant endpoints

To control for Type 1 error, the Hochberg multiplicity adjustment was applied to the key secondary endpoints with high-dose PHEN/TPM compared to placebo first, and then the mid-dose PHEN/TPM compared to placebo. The family-wise type 1 error rate was controlled at 0.05.

Secondary Endpoints

Categorical analyses of percent change in BMI

At week 56, the proportion of subjects who achieved a reduction in BMI of ≥5%, ≥10% or ≥15%

[24] Response to IR, submitted 3 March 2022 (SD#1176)

from baseline was numerically greater in the mid-dose PHEN/TPM and high-dose PHEN/TPM groups than in the placebo group (Figure 9). Statistical significance according to the pre-specified testing procedure was observed with high-dose PHEN/TPM at all BMI thresholds (shaded in table); the difference between mid-dose PHEN/TPM and placebo achieved nominal p-values <0.05 (Table 14).

Table 14. Categorical Analyses of BMI Reduction at Week 56 with Washout Imputation – ITT population

Treatment Group	N	≥5% BMI Reduction		≥10% BMI Reduction		≥15% BMI Reduction	
Mid-dose PHEN/TPM	54	44.0%		33.5%		13.6%	
High-dose PHEN/TPM	113	52.2%		44.4%		28.9%	
Placebo	56	13.6%		4.5%		2.9%	
Treatment Comparison		**Adjusted Risk Diff[1] (95% CI)**	**p-value**	**Adjusted Risk Diff (95% CI)**	**p-value**	**Adjusted Risk Diff (95% CI)**	**p-value**
Mid-dose vs. Placebo		0.30 (0.11, 0.48)	0.0017	0.29 (0.14, 0.44)	0.0002	0.12 (0.01, 0.22)	0.0277
High-dose vs. Placebo		0.39 (0.23, 0.54)	<0.0001	0.40 (0.28, 0.53)	<0.0001	0.27 (0.18, 0.37)	<0.0001
High-dose vs. Mid-dose		0.08 (-0.09, 0.25)	0.3394	0.11 (-0.05, 0.27)	0.1789	0.15 (0.02, 0.28)	0.0195

1. Cochran-Mantel-Haenszel (CMH) test for risk difference between treatments, controlling for age and sex stratification factors

Source: Response to FDA IR, submitted 24 March 2022 (SD#1183), Table 1.a.2

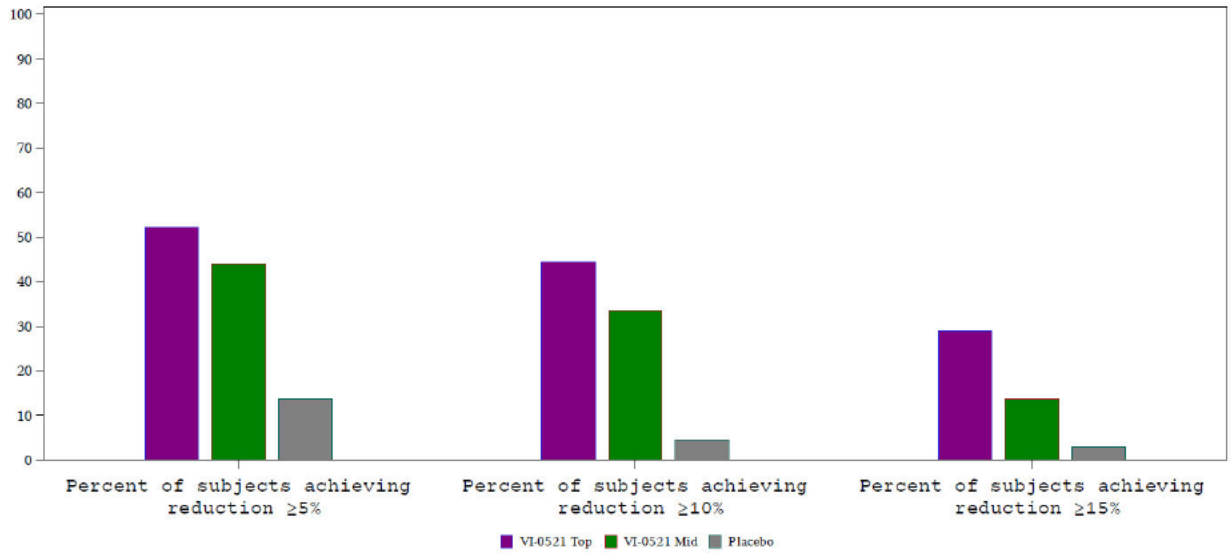


Figure 9. Percentage of Subjects Achieving Different Thresholds of BMI Reduction with Washout Imputation – ITT population

VI-0521 is Applicant's term for PHEN/TPM

Source: Response to FDA IR, submitted 24 March 2022 (SD#1183), Figure 1.b.

Note: Imputed percent of subjects is calculated by taking the mean of the percentages from multiple sets of imputed data

The following shows the percent change in BMI for observed values (i.e., no imputed data) in a waterfall plot, with the horizontal dashed lines approximating the 5% and 10% threshold.

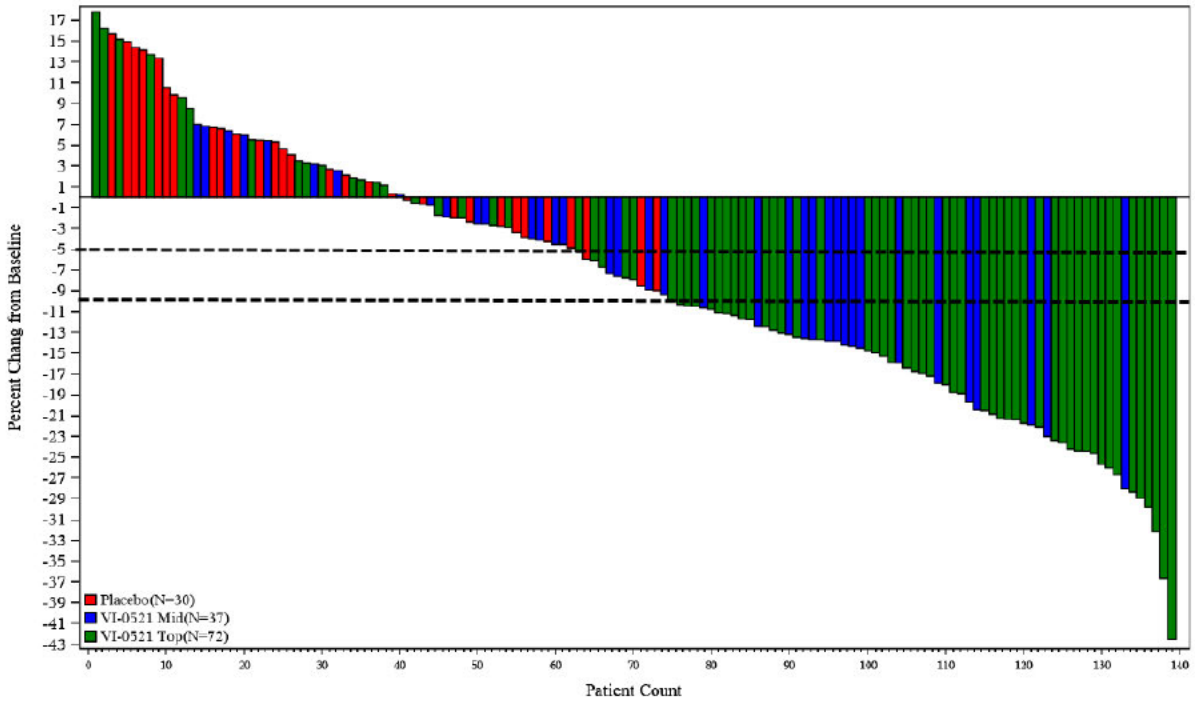


Figure 10. Percent Change in BMI at Week 56 – ITT population (observed data n=139)
VI-0521 is Applicant's term for PHEN/TPM
Source: Response to IR submitted 10 November 2021 (SD #1154), Figure 9.2

Waist Circumference

Larger numerical reductions in waist circumference from baseline were observed with both doses of PHEN/TPM compared to placebo. High-dose PHEN/TPM achieved a statistically significant difference (shaded in the table below); mid-dose PHEN/TPM comparisons with placebo achieved nominal p-values <0.05 according to the pre-specified statistical plan.

Table 15. Change in Waist Circumference (cm) at Week 56 – MMRM with Washout Imputation – ITT population

Treatment Group	N	Baseline	LS Mean (SE) Change from Baseline
Mid-dose PHEN/TPM	54	111.88	-5.03 (1.38)
High-dose PHEN/TPM	113	116.49	-6.98 (1.07)
Placebo	56	111.13	0.61 (1.40)

Treatment Comparison	Difference in LS Mean (95% CI)	p-value
Mid-dose vs. Placebo	-5.63 (-9.44, -1.82)	0.0038
High-dose vs. Placebo	-7.58 (-11.01, -4.16)	<0.0001
High-dose vs. Mid-dose	-1.95 (-5.08, 1.17)	0.2208

Source: Response to FDA IR, submitted 18 February 2022 (SD#1173); Table 2.1.1; OB 403 CSR, Table 14.2.2.5

Whole Body Sensitivity Index (Matsuda) and Fasting Insulin

Small changes in measures of insulin sensitivity and fasting insulin were noted. A numerically larger reduction in fasting insulin was noted with PHEN/TPM treatment, however, it was not statistically significant. The clinical meaningfulness of these small numerical changes is not known.

Table 16. Mean Change in Whole Body Sensitivity Index (Matsuda) and Fasting Insulin (uIU/mL) at Week 56 – MMRM with Washout Imputation – ITT population

Treatment Group	N	Whole Body Insulin Sensitivity Index			Fasting Insulin		
		Baseline	LS Mean (SE) Change from Baseline		Baseline	LS Mean (SE) Change from Baseline	
Mid-dose PHEN/TPM	54	2.97	-3.93 (7.65)		26.94	-11.47 (7.43)	
High-dose PHEN/TPM	113	2.71	-2.99 (6.45)		26.63	-7.99 (6.30)	
Placebo	56	2.51	-3.70 (8.89)		33.16	-3.32 (8.96)	
Treatment Comparison		**Difference in LS Mean (95% CI)**		**p-value**	**Difference in LS Mean (95% CI)**		**p-value**
Mid-dose vs. Placebo		-0.23 (-22.42, 21.95)		0.9835	-8.15 (-30.10, 13.79)		0.4664
High-dose vs. Placebo		0.71 (-20.11, 21.52)		0.9470	-4.67 (-25.33, 15.99)		0.6574
High-dose vs. Mid-dose		0.94 (-14.47, 16.35)		0.9049	3.48 (-11.99, 18.95)		0.6592

Source: Response to FDA IR, submitted 18 February 2022 (SD#1173), Table 2.2.1; OB 403 CSR, Table 14.2.2.9

HDL-C and Triglycerides

Small increases in HDL-C and reductions in TG were observed from baseline with PHEN/TPM treatment, however, there were no statistically significant differences when compared to placebo treatment.

Table 17. Mean Percent Change in HDL-C (mg/dL) and Triglycerides (mg/dL) at Week 56 – MMRM with Washout Imputation – ITT population

Treatment Group	N	HDL-C (mg/dL)			Triglycerides (mg/dL)		
		Baseline	LS Mean (SE) Percent Change from Baseline		Baseline	LS Mean (SE) Percent Change from Baseline	
Mid-dose PHEN/TPM	54	47.2	2.11 (11.50)		120.1	-6.18 (7.96)	
High-dose PHEN/TPM	113	46.7	0.65 (9.56)		112.2	-5.59 (7.17)	
Placebo	56	47.2	-4.30 (15.10)		118.3	5.56 (8.41)	
Treatment Comparison		**Difference in LS Mean Percent (95% CI)**		**p-value**	**Difference in LS Mean Percent (95% CI)**		**p-value**
Mid-dose vs. Placebo		6.41 (-31.15, 43.96)		0.7380	-11.74 (-34.34, 10.85)		0.3084
High-dose vs. Placebo		4.95 (-30.31, 40.21)		0.7831	-11.15 (-32.81, 10.52)		0.3130
High-dose vs. Mid-dose		-1.46 (-25.18, 22.27)		0.9042	0.59 (-17.00, 18.18)		0.9474

Source: Response to FDA IR, submitted 14 December 2021 (SD#1157), Table 2.3.1; OB 403 CSR, Table 14.2.2.13

Blood Pressure

The LS mean average change from baseline in blood pressure increased in all treatment groups, although the placebo group had a numerically larger LS mean increase compared to the mid-dose and high-dose PHEN/TPM groups. There were no statistically significant differences observed.

Table 18. Mean Change in Blood Pressure (mmHg) at Week 56 – MMRM with Washout Imputation – ITT population

Treatment Group	N	Systolic BP (mmHg)		Diastolic BP (mmHg)	
		Baseline	LS Mean (SE) Change from Baseline	Baseline	LS Mean (SE) Change from Baseline
Mid-dose PHEN/TPM	54	121.4	0.09 (1.50)	75.8	0.24 (1.32)
High-dose PHEN/TPM	113	117.4	1.84 (1.11)	72.9	1.22 (0.99)
Placebo	56	117.7	2.86 (1.63)	71.7	3.41 (1.51)

Treatment Comparison	Difference in LS Mean (95% CI)	p-value	Difference in LS Mean (95% CI)	p-value
Mid-dose vs. Placebo	-2.77 (-7.14, 1.61)	0.2148	-3.18 (-7.10, 0.74)	0.1123
High-dose vs. Placebo	-1.01 (-4.90, 2.87)	0.6086	-2.19 (-5.73, 1.35)	0.2254
High-dose vs. Mid-dose	1.75 (-1.65, 5.15)	0.3122	0.99 (-1.91, 3.88)	0.5046

Source: Response to FDA IR, submitted 18 February 2022 (SD#1173), Table 2.4.1; OB 403 CSR, Table 14.2.2.17

Exploratory Endpoints

Other Weight-Related Measurements

The absolute changes in BMI, BMI Z-score (or standard deviation score), and weight are shown descriptively in the table below. Only BMI Z-score was a pre-specified exploratory endpoint, although it was not controlled for multiplicity. The average baseline values for BMI and BMI Z-score for adolescents in this trial meet at least one of the definitions of severe obesity (severe obesity BMI of ≥35 kg/m^2 or BMI Z-score ≥2.33). Numerically larger reductions in absolute BMI, BMI Z-score, and weight with PHEN/TPM treatment was observed. Although an absolute change in BMI Z-score of at least 0.20 has been suggested to be clinically meaningful, no hypothesis testing was planned or conducted for these endpoints.

Table 19. Mean Change in Absolute BMI, BMI Z-score, and weight – ITT population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
BMI (kg/m^2)			
Baseline			
n	54	113	56
Mean	36.9	39.0	36.4
Week 56			
n	37	72	30

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Mean	34.3	33.7	37.3
Change from Baseline	-2.7	-4.6	1.1
Treatment difference	-3.8	-5.7	
BMI Z-score			
Baseline			
n	54	113	56
Mean	2.37	2.47	2.34
Week 56			
n	37	72	30
Mean	2.10	2.09	2.38
Change from Baseline	-0.28	-0.36	0.04
Treatment difference	-0.32	-0.40	
Weight (kg)			
Baseline			
n	54	113	56
Mean	105.2	108.5	102.2
Week 56			
n	37	72	30
Mean	99.8	94.9	108.0
Change from Baseline	-5.9	-11.0	6.6
Treatment difference	-12.5	-17.6	

Source: OB 403 CSR, Table 14.2.1.1, Response to IR, submitted 11 November 2021 (SD#1154), Table 8.2; Treatment difference manually derived from mean values

Other Glycemic Parameters

Changes in HbA1c and 2-hour post OGTT glucose level are summarized descriptively below. Similar small decreases in HbA1c were observed across all treatment groups.

Table 20. Mean Change from Baseline in HbA1c (%) and 2-hour OGTT glucose (mg/dL) – Safety population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Hemoglobin A1c (%)			
Baseline			
n	54	113	56
Mean	5.55	5.49	5.50
Week 56			
N	38	80	29
Mean	5.17	5.24	5.28

Change from Baseline	-0.35	-0.20	-0.16
Treatment difference	-0.19	-0.04	
2-hour glucose OGTT (mg/dL)			
Baseline			
n	50	105	53
Mean	109.3 (24.3)	116.6 (31.9)	115.2 (23.8)
Week 56			
n	34	66	27
Mean (SD)	110.7 (22.3)	107.3 (32.6)	103.5 (25.4)
Change from Baseline	0.2	-11.5	-11.9
Treatment difference	12.1	0.4	

Source: OB 403 CSR, Table 14.3.2.6

Other Lipoprotein Markers

There were no meaningful differences in percent change from baseline in total cholesterol or calculated LDL-C. At baseline, the LDL-C values were similar across treatment groups. The overall baseline mean LDL-C was 91 mg/dL. The mean percent change at Week 56 was -3.7% in the mid-dose PHEN/TPM group, -2.3% in the high-dose PHEN/TPM group, and +0.21% in the placebo group.[25]

Quality of Life Questionnaire – Impact of Weight on Quality of Life-Kids (IWQOL-Kids)

The IWQOL-Kids questionnaire, a 27-item evaluating the impact of excess weight on the following domains was answered by subjects:

- Physical Comfort
- Body Esteem
- Social Life
- Family Relations

The scale scores range from 0–100, with higher scores representing better health-related quality of life. Only the total score was reported.

Baseline mean total scores were similar across treatment groups: 85.11 for mid-dose PHEN/TPM, 82.70 for high-dose PHEN/TPM, and 87.12 for placebo. All treatment groups had a numerical increase in total score during the trial; however, the changes were small and differences between groups were not statistically significant. Scores for mid-dose PHEN/TPM increased 4.36, high-dose PHEN/TPM increased 3.21, and Placebo increased 2.26.

Dose/Dose Response

Per the titration regimen for PHEN/TPM, during the first 12 weeks all subjects randomized to

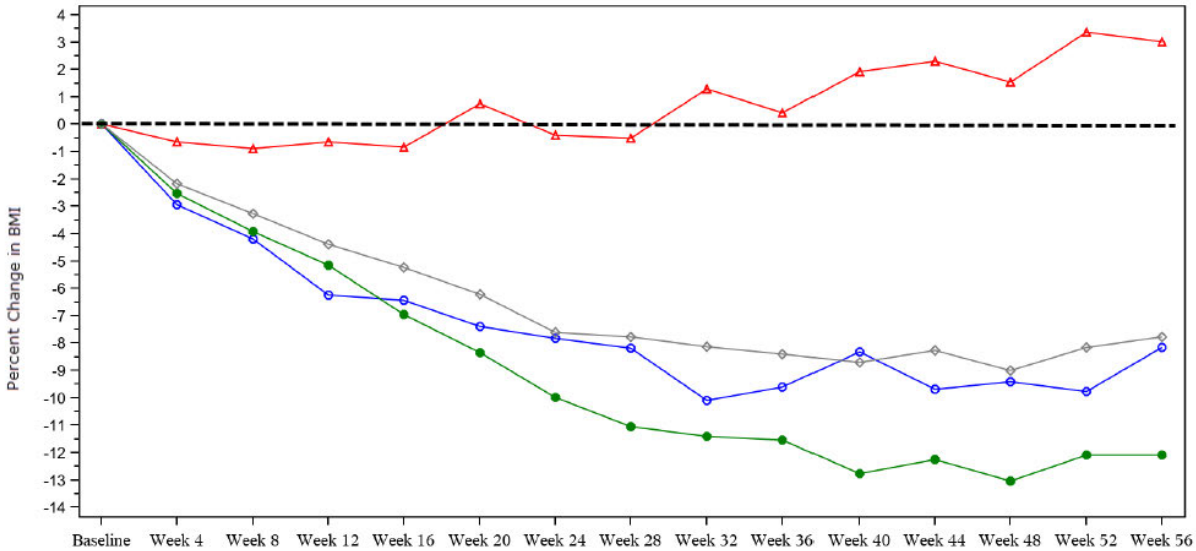
[25] Response to FDA IR, submitted 19 January 2022 (SD#1165), Table 3

PHEN/TPM were on the same dosing schedule (low-dose 3.75 mg/23 mg PHEN/TPM for two weeks, then up-titrated to mid-dose PHEN/TPM through Week 12). Beginning at Week 13, subjects randomized to high-dose PHEN/TPM were up-titrated to their assigned dose. Titration to high-dose PHEN/TPM was complete by the end of Week 16.

The figure below shows separation of the weight curves for mid-dose and high-dose PHEN/TPM beginning at Week 20 which is maintained through the duration of the study and provides evidence of a dose-response with higher doses of PHEN/TPM.

At week 56, there was a numerical treatment difference of -2.3% in BMI between mid-dose and high-dose PHEN/TPM, but not a statistically significant one (LS mean difference of -2.33% (95% CI: -5.27, 0.62); p=0.12). Numerical differences in reductions (but not statistically significant differences) in BMI of at least 5% were also observed between these two groups (mid-dose PHEN/TPM 44%; high-dose PHEN/TPM 52%) and at BMI reductions of ≥10% and ≥15% (Table 14).

Reviewer Comment: Additional BMI reduction of approximately 2% was observed in subjects treated with high-dose PHEN/TPM compared to mid-dose PHEN/TPM. The small number of subjects and less exposure time to high-dose PHEN/TPM may have contributed to an inability to detect a statistically significant effect.



Number of Subjects															
Placebo	56	48	42	40	44	32	29	35	30	31	25	31	26	26	30
VI-0521 Mid	54	46	40	43	40	40	38	38	33	38	35	33	37	33	37
VI-0521 Top	113	107	96	90	85	82	84	73	66	73	69	71	64	62	72
Overall	223	201	178	173	169	154	151	146	129	142	129	135	127	121	139

Figure 11. Mean Percent Change in BMI from Baseline Over Time (Observed Data) – ITT population

Source: Response to IR, submitted 10 November 2021 (SD#1154), Figure 8.1

Durability of Response

See Figure 11 which illustrates the mean percent change in BMI in observed data over the 56-week duration of the trial. The effect was durable over the treatment period in subjects taking PHEN/TPM.

Persistence of Effect

Because the design of the trial did not have a follow-up period after Week 56 and because few subjects continued in the study after early discontinuation of study drug, there is insufficient information to conduct this analysis.

Additional Analyses Conducted on the Individual Trial

None

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

Not applicable; there was only one safety and efficacy trial conducted in pediatric patients ≥12 years.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The weight loss benefit of PHEN/TPM in this population in the postmarket setting is anticipated to reflect the experience of the adult population. It will also depend, in part, on physicians' and healthcare providers' willingness to prescribe PHEN/TPM after considering the weight loss observed in the clinical trial, PHEN/TPM's safety profile, the patient's current health issues, and drug cost/insurance coverage. For potential consumers, the benefits are dependent on daily adherence to a chronic medication, tolerance of PHEN/TPM's anticipated side effects, consistent practice of foundational behavioral and lifestyle modifications to lose weight, and willingness to cover out-of-pocket drug costs.

Although the clinical trial did not demonstrate a substantial effect on cardiometabolic parameters, this may represent the absence of significant metabolic decompensation at baseline in this young population. Potential benefits to consider with an effective treatment of

obesity may be the opportunity for prevention of co-morbidities.[26] This possibility may convince some healthcare providers to prescribe PHEN/TPM to obese adolescents in the absence of co-morbidities.

7.2.2. Other Relevant Benefits

Not applicable.

7.3. Integrated Assessment of Effectiveness

The pediatric clinical development of PHEN/TPM for obese adolescents was designed and executed according to the guidelines outlined in the Division's 2007 draft Guidance for Developing Products for Weight Management.[27] The pivotal efficacy data was generated in Study OB-403, a single, randomized, double-blind, placebo-controlled clinical trial of 56 weeks duration. Eligible individuals were obese (age- and sex-matched BMIs greater than or equal to the 95th percentile according to the 2000 CDC BMI charts) and had a documented history of failing to lose sufficient weight with lifestyle modification. Approximately 80% of subjects were classified as having severe obesity, 21% had high triglycerides, 8% had elevated blood pressure, and 6% had pre-diabetes at baseline.

This trial is supported by confirmatory evidence from adequate and well-controlled clinical investigations that established effectiveness of PHEN/TPM for the closely related indication of chronic weight management in obese and overweight adults approved in the original NDA in 2012 [Studies OB-301[28], OB-302, and OB-303]. Please refer to the Qsymia label and/or the review of the original NDA for additional information.

In alignment with the Guidance, the BMI-based primary efficacy parameter evaluated was mean percent change in BMI. A mean percent change in BMI of 5% or greater may be considered clinically meaningful, given guidelines that recommend discontinuation of pharmacotherapy for weight loss if a pediatric individual does not have a >4% BMI or BMI Z-score reduction after 12 weeks of therapy.[29]

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[26] Juonala M, Magnussen CG, Berenson GS, Venn A, Burns TL, Sabin MA, Srinivasan SR, Daniels SR, Davis PH, Chen W, Sun C, Cheung M, Viikari JS, Dwyer T, Raitakari OT. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med. 2011 Nov 17;365(20):1876-85. doi: 10.1056/NEJMoa1010112. PMID: 22087679.
[27] Draft Guidance for Industry Developing Products for Weight Management – 2007 https://www.fda.gov/media/71252/download
[28] Factorial study to satisfy the fixed-dose combination rule 21 CFR 300.50
[29] Styne DM, Arslanian SA, Connor EL, Farooqi IS, Murad MH, Silverstein JH, Yanovski JA. Pediatric Obesity-Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Mar 1;102(3):709-757. doi: 10.1210/jc.2016-2573. PMID: 28359099; PMCID: PMC6283429.

Statistical significance in this trial was met, with mid-dose and high-dose PHEN/TPM recipients achieving placebo-subtracted least square mean percent reductions in BMI of ≥5%. The least square difference between mid-dose PHEN/TPM and placebo was -8.11% and between high-dose PHEN/TPM and placebo was -10.44% (all p<0.0001).

At week 56, the proportion of subjects who achieved a reduction in BMI of ≥5%, ≥10% or ≥15% from baseline was numerically greater in the mid-dose PHEN/TPM and high-dose PHEN/TPM groups than in the placebo group. The proportion of subjects with a reduction in BMI of at least 5% was 44% of subjects in the mid-dose PHEN/TPM group and 52% of subjects in the high-dose PHEN/TPM group (vs. 14% in the placebo group) based on the imputed datasets. Statistical significance according to the pre-specified testing procedure was observed with high-dose PHEN/TPM at all BMI thresholds; nominal p-values were <0.05 for mid-dose PHEN/TPM at these same thresholds.

Compared to placebo-treated subjects, statistically significant changes were observed in high-dose PHEN/TPM-treated subjects for reductions in waist circumference (treatment difference -7.6 cm); a treatment difference favoring mid-dose PHEN/TPM versus placebo in waist circumference was observed with nominal p-values <0.05. Greater numerical reductions in blood pressure, triglycerides, and insulin/insulin sensitivity measures and increases in HDL-C were noted in PHEN/TPM groups compared to placebo; however, none achieved statistical significance based on the pre-specified testing procedures or had a nominal p-value <0.05. Based on adult clinical trials of PHEN/TPM, one might expect larger changes in these cardiometabolic parameters given the weight loss observed; however, the lack of improvement in cardiometabolic parameters has been observed in the liraglutide [30] and orlistat [31] pediatric trials and likely reflects less cardiometabolic derangement at baseline in a younger obese population.

The retention of clinical trial subjects was poor, a challenge noted for other weight loss interventions [32], but particularly difficult in the setting of the COVID-19 pandemic and national emergency declaration. The trial drop-out rate was high; 38% of subjects did not provide Week 56/ET data. The statistical review team evaluated the primary efficacy analysis based on a conservative imputation method to address missing data in this trial, and the sensitivity analyses were supportive of the treatment effect observed in the primary efficacy analysis.

In conclusion, the data submitted from Study OB-403 meets the evidentiary standard for substantial evidence of effectiveness for PHEN/TPM for reduction of BMI in obese adolescents.

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[30] Golden J, clinical review of NDA 206321 S-, 3 Dec 2020
[31] Kehoe T, clinical review of NDA 20766 S-018, 12 Dec 2003
[32] Skelton JA, Beech BM. Attrition in paediatric weight management: a review of the literature and new directions. Obes Rev. 2011 May;12(5):e273-81. doi: 10.1111/j.1467-789X.2010.00803.x. Epub 2010 Sep 29. PMID: 20880126; PMCID: PMC3079805.

The weight loss associated with PHEN/TPM treatment is clinically meaningful and confers potential clinical benefits on weight-related comorbidities which are consistent with the effects noted in other pediatric adolescent weight loss drug trials.

8. Review of Safety

8.1. Safety Review Approach

There was only one trial submitted with this supplement. However, the applicant previously conducted Study OB-402, a small (n=42), short-term study of 8 weeks to evaluate the PK/PD parameters of PHEN/TPM in obese adolescents. OB-402 was previously reviewed and no new safety issues were observed. In this review, summary data from OB-402 regarding serious adverse events, adverse events leading to discontinuations, or other relevant events are included in Section 4.5 Clinical Pharmacology.

The following safety topics were reviewed based on the safety profile of phentermine and topiramate when used alone and in combination in adults and from the topiramate experience in the pediatric population, as well as standard safety review practices.

- Psychiatric-related adverse events
  - Depression and/or suicidality
- Cardiovascular effects
  - Increase in heart rate
- Renal-related adverse events
  - Increases in creatinine
  - Nephrolithiasis
- Metabolic acidosis
- Hypokalemia
- Myopia and angle closure glaucoma
- Abuse potential
- Oligohydrosis and hyperthermia
- Hepatic-related adverse events
- Bone metabolism and linear growth
- Pubertal development
- Cognitive effects
- Fetal toxicity

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety population was comprised of all subjects who were randomized and received at least one dose of study drug which includes 223 subjects.

Treatment duration was calculated using 212 subjects from this population. The subjects not included are those who did not return study medication at the final visit, and therefore an assessment of the actual treatment duration could not be calculated.

Using this subset of the safety population, the mean duration of exposure was 345 and 311 days in the mid-dose and high-dose PHEN/TPM groups and 288 days in the placebo group.

Table 21. Duration of Exposure

	Number of patients exposed to the study drug:			Number of Days[1]	
Dosage	≥ 1 dose	≥6 months[1]	≥12 months	Mean (SD)	Median
Mid-dose PHEN/TPM N=49[2]	n=49	n=45	n=44	344.5 (109.3)	392.0
High-dose PHEN/TPM N=109	n=109	n=98	n=91	311.4 (127.2)	389.0
Placebo N=54	n=53[3]	n=48	n=43	288.2 (141.4)	388.5

Source: OB-403 CSR Table 14.1.6, Response to FDA IR submitted 11 November 2021 (SD#1154) Table 18, 19 January 2022 (SD#1165) Q.1

1. Treatment duration is calculated as last treatment date – first treatment date + 1
2. N represents a subset of the safety population used to calculate the treatment duration. These subjects had non-missing data such as treatment dates and drug accountability data. There is a difference in the number of subjects comprising the safety population (N=223) and the number of subjects used in the treatment duration calculations (N=212)
3. The one subject difference in the placebo group is caused by Subject (b) (6), who was randomized on 24-Oct-2019, but was lost to follow up soon after. The site indicated the study drug was not returned but provided the treatment date as 24-Oct-2019. As a result, this subject was excluded from subjects who received at least one dose (≥1 dose) since drug accountability data is missing but included in the calculation of treatment exposure since last treatment date was provided.

8.2.2. Relevant characteristics of the safety population:

Refer to Section 6.1.2 for discussion of demographic and baseline characteristics of ITT population which is the same as the safety population.

8.2.3. Adequacy of the safety database:

The number of adolescents and extent of exposure to PHEN/TPM in this trial meets the expectation of the Division.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no important issues regarding data quality or the quality of the overall submission that had an effect on the safety review.

8.3.2. Categorization of Adverse Events

Treatment emergent adverse events (TEAEs) were defined as events that started or worsened on or after the date and time of the first dose of study treatment and up to 28 days after the last dose of study drug. The Applicant's definition of a TEAE is reasonable, based on the anticipated toxicities and half-life of PHEN/TPM.

MedDRA version 23.1 was used to code adverse events. There were 395 adverse events reported. A visual review of the ae.xpt dataset of all verbatim terms used by investigators compared to the preferred term was conducted. Categorization of the adverse events was determined to be appropriate by this reviewer.

8.3.3. Routine Clinical Tests

Safety assessments and their timing can be found in the study flowchart (Appendix 13.3).

8.4. Safety Results

8.4.1. Deaths

There were no deaths reported in this submission.

8.4.2. Serious Adverse Events

Two subjects (1.8%) in Study OB-403 randomized to the high-dose PHEN/TPM group reported a total of 6 serious adverse events. One subject reported a bile duct stone requiring hospitalization, and the other subject reported depression (2 events) and suicidal ideation (3 events). The narrative for the subject with depression and suicidal ideation is included in Section 8.4.4, in a dedicated safety subsection on psychiatric events including suicidality. The narrative of the subject with a bile duct stone is summarized here.

- Bile duct stone SAE (verbatim term: choledocholithiasis): Subject (b) (6) was a 12-year-old white female with a baseline weight of 108.3 kg and BMI of 36.4 kg/m^2, with no significant medical history. The subject completed the study on Study Day 392. The

following day (Study Day 393), the subject presented with nausea, vomiting, and epigastric pain. She was admitted to the hospital, was diagnosed with a bile duct stone, and underwent a cholecystectomy. The event was considered resolved and the subject was discharged on Study Day 395. At the end of the study visit (Week 56), the subject's weight was 88.8 kg and BMI was 28.8 kg/m^2, which represents an absolute body weight loss of 19.5 kg, absolute reduction in BMI of 7.6 kg/m^2, percent body weight reduction of 18%, and 21% reduction in BMI.

Reviewer Comment: The development of stones in the gallbladder or bile ducts is a known complication of weight loss. Given the temporal relationship with PHEN/TPM and the associated weight loss for this subject it is likely that this adverse event is related to PHEN/TPM use. There was one non-serious event of gallstones in another high-dose PHEN/TPM treated individual (Subject (b) (6)) who lost 29.8 kg over the course of the study.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Study OB-403, a total of 9 subjects discontinued study drug due to an AE (DAE). One (1.9%) in the mid-dose group, 5 (4.4%) in the high-dose group, and 3 (5.4%) in the placebo group.

Reviewer Comment: The applicant categorized only 3 subjects as having a DAE – 2 subjects in the placebo group, and 1 in the high-dose PHEN/TPM group. They also noted the following: "A discrepancy in AEs leading to study drug discontinuation was noted for 8 subjects due to an AE CRF with Drug Withdrawn being checked. However, only 4 of the 8 also had an AE as a reason for termination of study drugs on the End of Treatment CRF (Table 14.1.1). Thus, there are more subject narratives provided than what would be anticipated from Table 14.1.1 and Table 14.3.1.1." Please note this reviewer read all of the narratives provided and determined 9 subjects were more accurately categorized as study drug discontinuations due to an adverse event.

Of the nine, 3 subjects, all treated with PHEN/TPM, discontinued due to a psychiatric TEAE. The psychiatric adverse events leading to discontinuation were depression (n=3), anxiety (n=2), and suicidal ideation (n=1). The narratives for the psychiatric disorders which led to treatment discontinuation are discussed in Section 8.4.4. Summaries of the 9 subjects with DAEs are described in Table 22 below.

Table 22. Adverse Events Leading to Study Drug Discontinuation

Subject Number	Treatment Group	Preferred Term	Duration of Study Drug Administration	Summary
(b) (6)	Mid-dose	Depression Anxiety	273 days	14 yo white male, on Study Day 259, presented with adverse events of anxiety and depression. Study drug

Subject Number	Treatment Group	Preferred Term	Duration of Study Drug Administration	Summary
				was discontinued on Study Day 273. See Section 8.4.4 for further details.
(b) (6)	High-dose	Depression Suicidal ideation Depression Suicidal Ideation Suicidal Ideation	22 days	16 yo white female, on Study Day 30 experiencing worsening events of depression and suicidal ideation. See Section 8.4.4 for further details. *Reviewer Comment: Study Drug was discontinued on Study Day 30 after worsening depression and suicidal ideation according to narrative. The adsl.xpt dataset lists "adverse event" as the reason for study discontinuation which occurred later after further episodes of depression and suicidal ideation, but "investigator decision" for discontinuation of study drug. This reviewer considers the initial event as a DAE.*
(b) (6)	High-dose	Fatigue	250 days	13 yo white female presented on Study Day 220 with adverse event of fatigue that led to study drug discontinuation on Study Day 250. The subject was on high-dose PHEN/TPM. No other treatment for this event was received. The event resolved on Study Day 258. No other AEs were experienced by this subject. (Recorded as a DAE by applicant). *Reviewer comment: Fatigue is a labeled adverse reaction (Table 3 of label).*
(b) (6)	High-dose	Depression Anxiety	100 days	15 yo white female presented on Study Day 101 with anxiety and depression, which led to study drug discontinuation. The subject was started on an SSRI for depression. Anxiety and depression were not resolved at last recorded subject outcome. The subject was withdrawn from the study on Study Day 175 (the primary reason for study drug and study discontinuation was withdrawal by subject/parent/legal guardian). See Section 8.4.4 for further details. *Reviewer Comment: This reviewer considers this a discontinuation of study drug due to an AE. Adverse event of depression and anxiety on Day 101, that led to study drug discontinuation on Day 101.*

Subject Number	Treatment Group	Preferred Term	Duration of Study Drug Administration	Summary
(b) (6)	High-dose	Fatigue Nausea	13 days	13 yo black female on Study Day 5 presented with adverse event of fatigue and with nausea on Study Day 8 that led to study drug discontinuation on Study Day 13. At this point in the study, the individual was in the titration period and had not reached the high-dose PHEN/TPM level. The event of fatigue was resolved on Study Day 14. Nausea was resolved on Study Day 75. The subject had the last study visit on Study Day 57 and was withdrawn from the study on the same day (primary reason for study and treatment discontinuation was withdrawal by subject/parent/legal guardian). *Reviewer comment: Although the reason for study drug discontinuation and study withdrawal was listed as "by subject/parent/legal guardian", the narrative states study drug was discontinued due to the adverse events of nausea and fatigue. This reviewer therefore considers this a DAE. Fatigue and nausea are labeled adverse reactions for Qsymia in adults (Table 3)*
(b) (6)	High-dose	Increased Transaminases Metabolic Acidosis	195 days	14 yo black female on Study Day 53 had an increase in ALT (14x ULN) and AST (3x ULN). Bilirubin was normal 0.6 mg/dL. Study drug was interrupted for 87 days. The event resolved on Study Day 137 and study drug was restarted. On Study Day 193, the subject's ALT again increased (~6x ULN). Bicarbonate was also low at 14.6 umol/L (lower level of normal 17 umol/L). Study drug was discontinued on Study 195, and elevated transaminases and metabolic acidosis were resolved on Study Day 224 and 204, respectively. The subject continued in the study and completed the Study on Day 396. See Section 8.4.4 hepatic-related adverse events for additional information. *Reviewer Comment: A decrease in bicarbonate is a well-known adverse reaction of topiramate and is included in the W&P section of Qsymia labeling. Increased transaminase levels are not currently labeled for Qsymia. Given the temporal association and positive rechallenge noted with increase in ALT, a*

Subject Number	Treatment Group	Preferred Term	Duration of Study Drug Administration	Summary
				causal association with PHEN/TPM cannot be ruled out. The reason for study drug discontinuation is listed as "Investigator decision", however based on the adverse events which occurred on the same day as study drug discontinuation, this reviewer considers this a DAE.
(b) (6)	Placebo	Migraine	13 days	16 yo black female on Study Day 9 presented with the adverse event of migraine. Ibuprofen was taken as treatment for this event. Study drug was discontinued on Study Day 13. The event resolved on Study Day 14. The subject had the last study visit on Study Day 0 and did not complete the treatment period or end of treatment visit due to lost to follow-up. She was technically withdrawn from the study on Study Day 140 (the primary reason for study discontinuation was withdrawal by subject/parent/legal guardian). *Reviewer Comment: The subject discontinued the drug of their own accord according to site staff due to the adverse event of migraine and then was lost to follow-up. This reviewer considers this a discontinuation of study treatment due to an adverse event.*
(b) (6)	Placebo	Educational Problem	107 days	13 yo white and American Indian male with a history of ADHD. On Study Day 77, the subject presented with the adverse event of "educational problem" (not further defined). The subject discontinued study drug on Study Day 107 and started methylphenidate on Study Day 110. The event was ongoing at the subject's last recorded outcome. The subject was withdrawn from the study on Study Day 124 (Listed as a DAE by applicant)
(b) (6)	Placebo	Decreased Appetite Headache Asthenia	15 days	16 yo white female with medical history of tension headache. On Study Day 7, the subject presented with adverse events of decreased appetite, headache, and asthenia. The events were resolved on Study Day 15. Study drug with discontinued on Study Day 15. Study withdrawal occurred on the same day. (Listed as a DAE by applicant)

Drug interruptions or dose reductions were permitted for intolerable adverse events or excessive weight loss. There were 12 subjects that interrupted or reduced their dose of study drug due to adverse events. Two in the mid-dose PHEN/TPM group, 7 in the high-dose group, and 3 in the placebo group. Upon review of the narratives for these 12 subjects the following is notable:

- COVID-19 and tonsillectomy were the most common adverse events for drug interruption
- Possible *study drug related* adverse events that led to dose reduction or interruption in 6 of the 12 subjects included paraesthesia, hypertension, tachycardia, constipation, elevated liver enzymes, dermatitis, and headache.
- For most subjects with a study drug related adverse event leading to drug reduction or interruption, the events resolved, and study was completed.

For further details on these 12 subjects, see Appendix 13.2, Table 61.

8.4.4. Significant Adverse Events

This section describes safety issues that are known to be associated with use of either phentermine, topiramate, or PHEN/TPM. In addition, events reviewed as part of the standard safety review are included.

Depression and Suicidality

Suicidality and depression are safety issues of concern for all centrally acting obesity drugs.[33, 34, 35, 36] In addition, the Agency reported an almost 2-fold increased risk of suicidal ideation or behavior for 11 anti-epileptic drugs (AEDs), including topiramate in 2008.[37] Suicidal behavior and ideation are labeled in the Warnings and Precautions section of the PHEN/TPM label based on this data and AED class labeling.

In 1-year adult trials of PHEN/TPM, there were no suicide attempts or completed suicides. However, there was a higher proportion of adult subjects reporting adverse events of anxiety and depression treated with PHEN/TPM compared to adult subjects treated with placebo.

(b) (4)

[34] Golden J. FDA Clinical Review of NDA 22529 (lorcaserin), EMDAC 16 September 2010, 10 May 2012
[35] Craig E. FDA Clinical Review of NDA 200063 (naltrexone/bupropion), EMDAC 7 December 2010
[36] Golden J. FDA Clinical Review of NDA 206321 (liraglutide)
[37] https://www.fda.gov/files/drugs/published/Statistical-Review-and-Evaluation--Antiepileptic-Drugs-and-Suicidality.pdf. Accessed December 7, 2021

The adolescent population (of any BMI) might be especially vulnerable to risk of depression and thoughts of suicide.[38, 39] Notably, children and adolescents have been shown to be at increased risk of suicidality when treated with antidepressant medications.[40]

Mental health was prospectively monitored in this adolescent trial using adverse events and questionnaires recommended by FDA for suicidality (Columbia-Suicide Severity Rating Scale, C-SSRS[41, 42]) and mood (Patient Health Questionnaire-9, PHQ-9[43]). Individuals were not eligible to participate in this trial if they had 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 ≥10), or presence or history of suicidal behavior or ideation with some intent to act. Stable anti-depressant medication was allowed with some exceptions.[44] Any subject with a PHQ-9 score of ≥15 was to be referred for further work-up and treatment.

Psychiatric Adverse Events

Table 23 presents all the TEAEs in the 'Psychiatric disorders' MedDRA system organ class (SOC) and by preferred term (PT). A higher proportion of PHEN/TPM treated subjects reported an event within this SOC compared to their placebo-treated peers. The preferred terms of 'depression', 'anxiety', and 'insomnia' were reported in the greatest proportion of PHEN/TPM subjects. Of note, no placebo-treated subject reported depression as an adverse event. There was one PHEN/TPM-treated subject with a serious adverse event of suicidal ideation requiring hospitalization. Narratives of psychiatric SAEs, discontinuations of study drug due to psychiatric events, and other psychiatric responses of interest related to the PHQ-9 and C-SSRS questionnaires are presented below.

Table 23. Psychiatric Treatment-Emergent Adverse Events

[38] Protecting Youth Mental Health. The U.S. Surgeon General's Advisory 2021 https://www.hhs.gov/sites/default/files/surgeon-general-youth-mental-health-advisory.pdf
[39] Centers for Disease Control and Prevention. (2020). Youth Risk Behavior Surveillance Data Summary & Trends Report: 2009-2019. Retrieved from https://www.cdc.gov/nchhstp/dear_colleague/2020/dcl-102320-YRBS-2009-2019-report.html
[40] https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/suicidality-children-and-adolescents-being-treated-antidepressant-medications. Accessed December 7, 2021
[41] https://cssrs.columbia.edu/
[42] FDA *Guidance for Industry: Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials*, August 2012
[43] Kroenke K, et al. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001; 16(9): 606-13.
[44] Tricyclic antidepressants, monoamine oxidase inhibitors, lithium, levodopa, and dopamine receptor agonists were not allowed.

SOC Preferred Term	Mid-dose PHEN/TPM (N=54) n (%)	High-dose PHEN/TPM (N=113) n (%)	Placebo (N=56) n (%)
Psychiatric disorders SOC	**4 (7.4)**	**10 (8.8)**	**1 (1.8)**
Depression	1 (1.9)	5 (4.4)	0
Anxiety	1 (1.9)	3 (2.7)	0
Insomnia	1 (1.9)	2 (1.8)	0
Adjustment disorder	0	1 (0.9)	0
Agitation	0	1 (0.9)	0
Mood altered	0	1 (0.9)	0
Suicidal ideation	0	1 (0.9)	0
Irritability	1 (1.9)	0	0
Mood swings	1 (1.9)	0	0
Generalized anxiety disorder	0	0	1 (1.8)

Source: OB-403 CSR Table 20

Psychiatric Event Narratives of Interest – SAE and DAEs

- SAE Depression and Suicidal ideation: Subject (b) (6) was a 16-year-old white female (baseline BMI 38 kg/m^2), with a medical history significant for irritability. She was randomized to high-dose PHEN/TPM. On Study Day 11, she experienced the events of depression (moderate), suicidal ideation (moderate), and worsening agitation (mild).

  On Study Day 30, the events of depression and suicidal ideation worsened to severe and became serious. She became more depressed, felt like she was stuck in a pit, lost hope, felt like life was not worth living, and expressed suicidal ideation. Study drug was discontinued at that time. She did not receive any treatment for these events. The events of depression and suicidal ideation resolved on Study Day 32.

  On Study Day 49, she again reported depression (moderate) and suicidal ideation (moderate) that resolved on the same day.

  On Study Day 69, she presented with a serious adverse event of depression and on Study Day 71, she presented with an adverse event of suicidal ideation that was considered serious. She described a feeling of wanting to die or feeling that she would better off dead. She wrote a suicidal note without a specific plan. The subject received no treatment for the event. These events resolved on Study Day 83.

  On Study Day 135, the subject presented with suicidal ideation that resulted in hospitalization. She started treatment with fluoxetine. The event of suicidal ideation resolved on the same day.

The subject's last visit was on Study Day 158, and she was withdrawn from the study on the same day.

The subject's relevant depression and suicidality results from the PHQ-9 and C-SSRS questionnaires are shown in the table below.

Table 24. C-SSRS and PHQ-9 scores: Subject (b) (6)

	C-SSRS Ideation Level[a]	C-SSRS Behavior	PHQ-9 Total Score	PHQ-9 Q9[b]
Study Day -17 (Screening)	0	No	2	1
Study Day 8 (Baseline)	0	No	6	0
Study Day 36 (Week 4)	4	No	16	3
Study Day 64 (Week 8)	0	No	0	0
Study Day 96 (Week 12)	4	Preparatory Act	11	1
Study Day 124 (Week 16)	0	No	2	0
Study Day 158 (Week 56/ET)	4	No	8	1

a. Ideation level: 1= least severe - wish to be dead; 2= non-specific active suicidal thoughts; 3= active suicidal ideation with any methods (not plan) without intent to act; 4= active suicidal ideation with some intent to act, without specific plan; 5= most severe - active suicidal ideation with specific plan and intent)

b. The score for thoughts that you would be better off dead, or of hurting yourself in some way? (0= not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day)

c. PHQ-9 total score ranges from 0 to 27. Total scores of 0–4 represent no to minimal depression, total scores of 5–9 represent mild depression, total scores of 10–14 represent moderate depression, total scores of 15–19 represent moderately severe depression, and total scores of 20–27 represent severe depression.
Source: OB-403 CSR Narratives

Reviewer Comment: Subject was randomized to high-dose PHEN/TPM, but while on mid-dose PHEN/TPM during the titration period, this individual experienced serious depression and suicidal ideation. After discontinuation of PHEN/TPM, and resolution of the initial psychiatric events, additional serious episodes of depression and suicidal ideation occurred. A causal relationship with PHEN/TPM cannot be definitively excluded. It is of concern after review of this narrative, that this individual had written a suicidal note on Study Day 71 but did not receive any treatment for this event and on Study Day 96 had a C-SSRS score of 4 and preparatory act, and again did not receive any treatment until Study Day 135, when she was hospitalized for suicidal ideation.

- Anxiety, Depression DAEs: Subject (b) (6) was a 15-year-old white female (baseline BMI 55.8 kg/m^2), with no psychiatric medical history. She was randomized to high-dose PHEN/TPM. On Study Day 101, the subject presented with the adverse events of anxiety and depression that led to discontinuation of study drug, and initiation of treatment with escitalopram for depression. C-SSRS scores did not show any suicidal ideation or behavior. The PHQ-9 score at baseline was 7, on Study Day 98 the PHQ-9 score was 5, and on Study Day 175, the PHQ-9 score was 6. At last recorded outcome, these events were ongoing. The subject was withdrawn from the study on Study Day 175 (withdrawal by subject/parent/legal guardian listed as reason).

Reviewer Comment: Temporal association with PHEN/TPM cannot exclude a causal relationship with PHEN/TPM, although symptoms persisted following discontinuation of study drug and initiation of treatment.

- Anxiety, Depression DAEs: Subject (b) (6) was a 14-year-old white male (baseline BMI of 41 kg/m2), with no significant medical history. He was randomized to mid-dose PHEN/TPM. On Study Day 259, the subject presented with the adverse events of anxiety and depression, that led to discontinuation of study drug on Study Day 273. On Study Day 271 the PHQ-9 score was 8 (PHQ-9 scores at previous visits were zero). There were no positive C-SSRS scores for suicidal ideation or behavior. The subject was treated with escitalopram for both of these events. The events were ongoing at the time of the last recorded outcome. The subject discontinued from the study on Study Day 309.

Reviewer Comment: There was a temporal relationship with PHEN/TPM, so a causal relationship cannot be completely dismissed.

Change in antidepressant medication

Of subjects not on treatment for either depression and/or anxiety at baseline, five (3.0%) PHEN/TPM-treated subjects initiated treatment for these conditions versus zero placebo-treated subjects. No subjects on antidepressants at baseline had a change in these medications (i.e., increase in dose, addition of new medication).

Table 25. Initiation of Antidepressant Medication

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Initiated treatment for depression, anxiety, or both	**1 (1.9)**	**4 (3.5)**	**0**
Fluoxetine hydrochloride	0	1 (0.9)	0
Escitalopram oxalate	1 (1.9)	1 (0.9)	0

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Sertraline hydrochloride	0	2 (1.8)	0

Source: Response to IR submitted 1 March 2022 (SD#1175), Question 3

PHQ-9: Modified for Teens

The PHQ-9 is a 9-item depression subscale of the self-administered patient health questionnaire (mental disorder instrument for use in primary care).[45] The patient rates the frequency of the following 9 items on the scale from 0 (not at all) to 3 (nearly every day) in the last 2 weeks:

1. Feeling down, depressed, irritable, or hopeless
2. Little interest or pleasure in doing things
3. Trouble falling or 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 that you are a failure or have let yourself or your family down
7. Trouble concentrating on things like schoolwork, reading, or watching television
8. Moving or speaking so slowly that other people could have noticed, or the opposite – being so fidgety or restless that you have been moving around a lot more than usual
9. Thoughts that you would be better off dead or hurting yourself in some way

There are an additional three Yes/No questions that are not included in the total score and one question answered on a scale of 'not difficult at all' to 'extremely difficult' which are included in the PHQ-9 teen assessment as follows:

- In the past year have you felt depressed or sad most days, even if you felt okay sometimes?
- 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

[45] Kroenke K, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. J Gen Intern Med. 2001 Sep;16(9):606-13. doi: 10.1046/j.1525-1497.2001.016009606.x. PMID: 11556941; PMCID: PMC1495268.

- Has there been a time in the past month when you have had serious thoughts about ending your life?
- Have you ever in your whole life, tried to kill yourself or made a suicide attempt?

The total score ranges from 0 to 27. Total scores of 0–4 represent no to minimal depression, total scores of 5–9 represent mild depression, total scores of 10–14 represent moderate depression, total scores of 15–19 represent moderately severe depression, and total scores of 20–27 represent severe depression.

To use the PHQ-9 as a diagnostic aid for Major Depressive Disorder in teens:

- Questions 1 and/or 2 need to be endorsed as a "2" or "3"
- Need five or more positive symptoms (positive is defined by a "2" or "3" in questions 1-8 and by a "1", "2", or "3" in question 9
- The functional impairment question (How difficult….) needs to be rated at least as "somewhat difficult."

Major depression for adults is diagnosed if 5 or more of the 9 criteria have been present at least "more than half the days" in the past 2 weeks and one of the symptoms is depressed mood or anhedonia.

The symptom criterion in Question 9, "thoughts that you would be better off dead or hurting yourself in some way," counts if present at all, regardless of duration. Before making a final diagnosis, the clinician is expected to rule out physical causes of depression, normal bereavement, and history of a manic episode.

Reviewer Comment: Please note, the applicant used the adult criteria for major depressive disorder in the evaluation of subjects' PHQ-9 scores. The definition for adults is more inclusive than the criteria for teens.

Mean PHQ-9 scores at baseline were low and similar among treatment groups at baseline and remained that way throughout the study (Table 26); however, there was a higher proportion of PHEN/TPM treated subjects with responses from the PHQ-9 that were suggestive of depression/suicidality compared to placebo treated subjects (Table 27).

Table 26. Total PHQ-9 scores

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Baseline			
N	54	113	56

	Mid-dose PHEN/TPM (N=54) n (%)	High-dose PHEN/TPM (N=113) n (%)	Placebo (N=56) n (%)
Mean (SD)	2.1 (2.6)	2.9 (3.4)	2.2 (2.4)
Median	1.0	2.0	1.0
Min, Max	0, 11	0, 19	0, 12
Week 28			
N	43	81	37
Mean (SD)	0.5 (1.1)	0.9 (2.0)	0.6 (0.9)
Median	0	0	0
Min, Max	0, 5	0, 12	0, 3
Week 56			
N	38	81	32
Mean (SD)	1.8 (3.2)	1.8 (2.5)	1.3 (2.3)
Median	0	1.0	0
Min, Max	0, 15	0, 11	0, 9

Source: OB-403 CSR Table 14.3.5.6

Table 27. PHQ-9 responses of potential clinical importance

	Mid-dose PHEN/TPM (N=54) n (%)	High-dose PHEN/TPM (N=113) n (%)	Placebo (N=56) n (%)
Major depression at any post-dose visit [(a)]	1 (1.9)	5 (4.4)	0
PHQ-9 total score >10	1 (1.9)	10 (8.8)	0
PHQ-9 total score >15	0	1 (0.9)	0
Feel like it would be better to be dead or think of hurting themselves [Q9] [(b)]	0	6 (5.3)	1 (1.8)
Had serious thoughts of ending their life or have attempted suicide [Q12/13] [(c)]	1 (1.9)	10 (8.8)	1 (1.8)

a. Major depression criteria defined as having answers of 'more than half the days' or 'nearly every day' to at least five of the nine questions, with one such answer being to Question 1 or Question 2 (depressed mood or anhedonia)
b. Subjects who answered question number 9 ("Thoughts that you would be better off dead or hurting yourself in some way") as ≥1
c. Subjects who answered "Yes" to either or both question 12 (Has there been a time in the past month when you have had serious thoughts about ending your life?) or question 13 (Have you ever in your whole life, tried to kill yourself or made a suicide attempt?)

Source: OB-403 CSR Table 14.3.5.7

Reviewer Comment: Narratives were requested for subjects in the above table and reviewed. In several cases, a positive response to Questions 9, 12, or 13 of the PHQ-9 did not correspond with actual suicidal ideation or attempts, and the C-SSRS responses did not reflect suicidality.

There were 6 subjects with a PHQ-9 response consistent with a diagnosis of major depression as defined using the criteria for adults; three of these subjects also reported suicidal ideation by C-SSRS. All 6 of these subjects were randomized to PHEN/TPM. Please note that using the definition for major depression in teens, 4 subjects (b) (6) *instead of 6 subjects would be screened for major depression. Subject narratives for all 6 are summarized here.*

Psychiatric Narratives of Interest – PHQ-9 or C-SSRS

- (b) (6) (high-dose PHEN/TPM) – 15-year-old white male with a medical history significant for anxiety and depression not on antidepressant medication was randomized to high-dose PHEN/TPM. At baseline, the subject's total PHQ-9 score was 9 with negative C-SSRS responses regarding suicidal behavior or ideation. On Study Day 201 (Week 28), his total PHQ-9 score was consistent with major depression. There was no adverse event reported for this incident and there were no subsequent visits with PHQ-9 responses that were consistent with major depression, however on Study Day 314 (Week 44), the subject had a total PHQ-9 score of 10, a PHQ-9 question 9 (think that you would be better off dead, or of hurting yourself in some way?) of "more than half the days", and a C-SSRS questionnaire indicating suicidal ideation level 1 (wish to be dead) with a response of "Lasted for a few days, off and on thoughts of not wanting to be alive, but no actual thoughts of killing himself, feels down about his school being closed for COVID outbreak". There was no indication of suicidal behavior at this visit. No changes were made to this subject's medication and he completed the study. The remaining study visits on Week 48, 52, and 56 did not have indications of suicidal behavior or ideation and the total PHQ-9 score was at or below baseline.

Reviewer Comment: This case is confounded by medical history of depression and anxiety and absence of baseline antidepressant medication. There are also situational circumstances related to COVID-associated school closures that may have influenced this subject's mood. It is also notable that the subject continued PHEN/TPM without any treatment for depression and suicidal ideation and scores on the PHQ-9 were at or below baseline after potentially clinically significant scores on Study Day 201 and 314. However, given the temporal association with PHEN/TPM, a definitive association cannot be ruled out.

- (b) (6) (high-dose PHEN/TPM) – 13-year-old multi-racial female with no psychiatric history, yet at screening had a C-SSRS response which indicated a lifetime suicidal ideation level of 2 and previous suicidal behavior. She was randomized to high-dose PHEN/TPM. At baseline, her PHQ-9 score was 12 and her response to PHQ-9 question 9 (think that you would be better off dead, or of hurting yourself in some way?) was "several days". C-SSRS at baseline was negative for suicidal ideation or behavior. On Study Day 28, the subject presented with a response to C-SSRS questionnaire indicating suicidal ideation level 1 (wish to be dead) with a frequency of 2-5 times a week and a

response of "Stuff went on with me and my best friend. She has been ignoring me for a while and we talked for a few minutes on New Year but that's it. We've known each other ever since 3rd grade. It just made me want to disappear because even the one person I thought I could trust the most didn't want anything to do with me". The PHQ-9 total score at that visit was 8 and the PHQ-9 question 9 was 0.

On Study Day 142, the subject presented with a non-serious adverse event of anxiety. Investigator considered the event to be mild in severity and not related to investigational product. The event of anxiety was not resolved at the subject's last recorded outcome.

On Study Day 167, the subject completed a PHQ-9 questionnaire with responses consistent with a diagnosis of major depression. Although there was no adverse event reported for this incident, the event of anxiety was still listed as continuing at the time of this PHQ-9 assessment, and there were no subsequent visits with PHQ-9 response consistent with a diagnosis of major depression. The subject completed the study on study drug.

Reviewer Comment: This case is confounded by baseline scores that were high. No treatment for these events occurred and the subject continued in the trial and scores were lower and below baseline for remainder of the study.

- (b) (6) (high-dose PHEN/TPM) – 12-year-old black female on Study Day -25 (screening) completed the PHQ-9 questionnaire with a total score of 14. At Baseline, the subject completed a PHQ-9 questionnaire with a total score of 19 and with responses consistent with a diagnosis of major depression. The scores at both visits should have disqualified the subject for study participation. However, the subject was enrolled in the study.

  On Study Day 28, the subject completed a PHQ-9 questionnaire with a total score of 11 and with responses consistent with a diagnosis of major depression. A non-serious adverse event of depression was reported. The Investigator considered the event to be mild in severity and not related to investigational product. The event was resolved on Study Day 56. There were no subsequent visits with PHQ-9 responses consistent with a diagnosis of major depression. The subject last study visit was on Study Day 280 and she was lost to follow-up.

Reviewer Comment: Based on screening and baseline scores, this subject should not have been enrolled in the study. All PHQ-9 scores were less than those at screening and baseline. There were no C-SSRS responses indicating suicidal ideation or behavior.

- (b) (6) (high-dose PHEN/TPM) – The narrative of this subject is described above in the section of serious psychiatric adverse events.

- (b) (6) (mid-dose PHEN/TPM) – 12-year-old white female with no psychiatric medical history randomized to mid-dose PHEN/TPM. PHQ-9 scores at screening and baseline were 8 and 5, respectively. PHQ-9 scores were generally less than 10 up until Week 40 when she had increasing PHQ-9 scores 10 to 13 and then on Study Day 392 (Week 56) had a PHQ-9 score of 15 with responses consistent with major depression (Table 28**Error! Reference source not found.**) There was no C-SSRS suicidal ideation or behavior noted throughout the study. The subject completed the study and the last visit was on Study Day 392.

Table 28. Subject (b) (6) – PHQ-9 Responses that had a total score of 10 or higher

PHQ-9 Responses		Responses[a]					
		Study Day 56	Study Day 291	Study Day 310	Study Day 343	Study Day 367	Study Day 392
1	Feeling Down, depressed	2	1	2	0	1	2
2	Little interest or pleasure	2	2	2	2	3	3
3	Trouble Falling Asleep	0	0	0	1	1	1
4	Poor appetite	0	0	0	0	1	1
5	Tired, little energy	1	3	2	2	2	2
6	Feeling bad about yourself	1	1	1	1	1	1
7	Trouble Concentrating	1	1	1	1	2	2
8	Moving or speaking so slowly	3	3	3	3	2	3
9	Think that you would be better off dead	0	0	0	0	0	0
PHQ-9 Total Score		10	11	11	10	13	15
Depressed or sad in the past year		Yes	Yes	Yes	Yes	Yes	Yes
Experiencing any of the problems[b]		1	1	1	1	2	1
Ending one's life		No	No	No	No	No	No
Tried to kill yourself		No	No	No	No	No	No

*0 = Not At All; 1 = Several Days; 2 = More Than Half the Days; 3 = Nearly Every Day
0 = Not difficult at all, 1 = Somewhat difficult, 2 = Very difficult, 3 = Extremely difficult)

Source: Response to FDA IR, submitted November 10, 2021 (SD#1154), narratives

Reviewer Comment: It appears that there was an increasing trend in PHQ-9 scores starting at Week 40 (Study Day 291). No other adverse events were reported for this subject. Given the temporal association a definitive causal relationship with PHEN/TPM cannot be ruled out.

- (b) (6) (high-dose PHEN/TPM) – 13-year-old black male with no known psychiatric medical history was randomized to high-dose PHEN/TPM. On Study Day 170, the subject completed a PHQ-9 questionnaire with responses consistent with a diagnosis of major depression. There were no subsequent visits with PHQ-9 responses consistent with a diagnosis of major depression. This subject discontinued study drug sometime after the Week 20 visit on Study Day 170, and subsequently skipped study visits for Week 24, Week 28, Week 32, Week 36, and Week 40 for unknown reasons. The subject returned for the Week 44 visit on Study Day 303 and restarted study drug. There were no adverse events reported for the skipped visits nor for the restart of the study drug. The subject completed the remaining study visits and had the last visit on Study Day 394.

Reviewer Comment: It is interesting that the subject discontinued study drug and missed several study visits after this report on the PHQ-9; however, given the lack of further information, an association with this event and study drug discontinuation cannot be definitively made. Of note, the subject returned to the study and restarted drug without further incident.

C-SSRS

The C-SSRS is a standardized assessment to quantify the severity of suicidal ideation and behavior and was utilized at all visits. The C-SSRS has 5 questions addressing suicidal ideation, 5 sub-questions assessing the intensity of the ideation, and 6 questions addressing suicidal behavior. The following categories are used in order to classify the events:

- Suicidal ideation:
  1. Wish to be dead (type 1)
  2. Non-specific active suicidal thoughts (type 2)
  3. Active suicidal ideation with any methods (not plan) without intent to act (type 3)
  4. Active suicidal ideation with some intent to act, without specific plan (type 4)
  5. Active suicidal ideation with specific plan and intent (type 5)

- Suicidal behavior:
  1. Completed suicide
  2. Actual suicide attempt
  3. Interrupted suicidal attempt
  4. Aborted suicide attempt
  5. Preparatory acts or behavior towards making a suicidal attempt

There were 4 subjects that reported suicidal ideation by C-SSRS. All were treated with high-dose PHEN/TPM. One of these individuals, Subject (b) (6), reported the highest levels of suicidal ideation and behavior with a type 4 response for suicidal ideation and type 5 response for suicidal behavior. This subject's narrative has been reviewed in the section on psychiatric

adverse events above. Two of the other subjects (Subject (b) (6)) also had PHQ-9 scores consistent with major depression and are discussed in the section describing the PHQ-9 results. The fourth subject had a type 1 suicidal ideation on C-SSRS, however their PHQ-9 scores did not meet the definition of major depression. A brief narrative of this individual is below.

- (b) (6) (high-dose PHEN/TPM): 15-year-old white male with no psychiatric history was randomized to high-dose PHEN/TPM. At the Week 56 (end of treatment) visit (Study Day 399), the subject presented with a response to C-SSRS questionnaire indicating suicidal ideation level 1 (wish to be dead) with a frequency of less than once a week and a response of "I had pushed my little sister earlier that day which led to thoughts that being alive was putting the people around me in danger. I did not take the medication that day" and "My most severe suicidal ideation is my first and only, which I've described in the previous text box". The subject completed the study and had the last visit on Study Day 399.

Reviewer Comment: There is no available follow-up after the End of Treatment study visit to determine if C-SSRS score changed following end of the study. However, there is a temporal association with PHEN/TPM so a causal association cannot be ruled out.

Reviewer Comment: Changes in mood including risk for depression and suicidality is a labeled adverse reaction of topiramate, a component of Qsymia. Obese adolescents treated with PHEN/TPM compared to peers treated with placebo had a higher incidence of adverse events related to depression and suicidality. Five (3%) PHEN/TPM-treated subjects and no placebo-treated subjects initiated treatment for depression and/or anxiety in this study. There was also a larger proportion of PHEN/TPM-treated adolescents with PHQ-9 and C-SSRS responses and/or total scores that were potentially clinically important.

Review of the individual narratives identified temporal associations with PHEN/TPM use; however, it is notable that in several cases questionnaire scores went down or symptoms resolved without treatment or referral to a mental health provider. Of the 9 subject narratives reviewed, there was a history of psychiatric disorders in 1 case and another subject had high baseline PHQ-9 scores which confounds the causality assessment. One individual treated with PHEN/TPM experienced a serious event of suicidal ideation requiring hospitalization and pharmacologic intervention. While this event occurred off treatment, this subject had discontinued PHEN/TPM due to an earlier serious adverse event of depression and suicidal ideation.

In aggregate there is an imbalance in psychiatric adverse events associated with PHEN/TPM use compared to the control population and therefore it is this reviewer's opinion that an increased risk of suicidality and depression is an adverse reaction with the use of PHEN/TPM in the obese adolescent population.

Cardiovascular effects

Phentermine is a sympathomimetic amine which is associated with tachycardia, palpitations, and increased heart rate. Rare severe adverse events associated with phentermine include pulmonary hypertension[46] and ischemic events.[47, 48,49]

A total of 6 subjects reported an adverse event in either the cardiac or vascular SOC. There were no serious cardiac events or major adverse cardiac events. Expected events of palpitations and/or tachycardia were observed in PHEN/TPM treated subjects but not in placebo-treated subjects. The preferred term 'hypertension' was observed in both the placebo and high-dose PHEN/TPM groups (Table 29). No antihypertensive medications were started. However, one subject randomized to PHEN/TPM had worsening hypertension and had a dose increase of their antihypertensive medication.

Reviewer Comment: Given the age range of the study population and duration of the study, serious major adverse cardiac events would not be expected to occur.

Table 29. Cardiovascular adverse events

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Vascular and Cardiac SOC Combined	**1 (1.9)**	**3 (2.7)**	**2 (3.6)**
Hypertension	0	2 (1.8)	2 (3.6)
Palpitations	1 (1.9)	1 (0.9)	0
Tachycardia	0	1 (0.9)	0

Source: OB-403 CSR Table 14.3.1.2.1 and review of adae.xpt

Increased heart rate is a labeled event for Qsymia. At Week 56, the observed mean change in heart rate was -3.1 beats per minute (bpm) in the mid-dose PHEN/TPM group, +5.7 bpm in the high-dose group, and +2.5 bpm in the placebo group. While mean changes at Week 56 do not demonstrate a consistent dose response for change in heart rate with PHEN/TPM treatment versus placebo treatment, a dose response in the proportion of PHEN/TPM-treated subjects

[46] Seferian A, Chaumais MC, Savale L, Günther S, Tubert-Bitter P, Humbert M, Montani D. Drugs induced pulmonary arterial hypertension. Presse Med. 2013 Sep;42(9 Pt 2):e303-10. doi: 10.1016/j.lpm.2013.07.005. Epub 2013 Aug 22. PMID: 23972547.

[47] Azarisman SM et al. Myocardial infarction induced by appetite suppressants in Malaysia (letter to the editor). NEJM 2007; 357; 1873-74.

[48] Makaryus et al. Case report: Cardiac arrest in the setting of diet pill consumption. Am J of Emergency Medicine 2008; 26, 732.e1—732.e3

[49] Kokkinos J et al. Possible association of ischemic stroke with phentermine. Stroke 1993;24:310-313.

compared to placebo-treated subjects with categorical increases in heart rate was noted (Table 32).

The figure below shows the average heart rate over time during the study. Mean heart rate did not exceed 100 bpm.

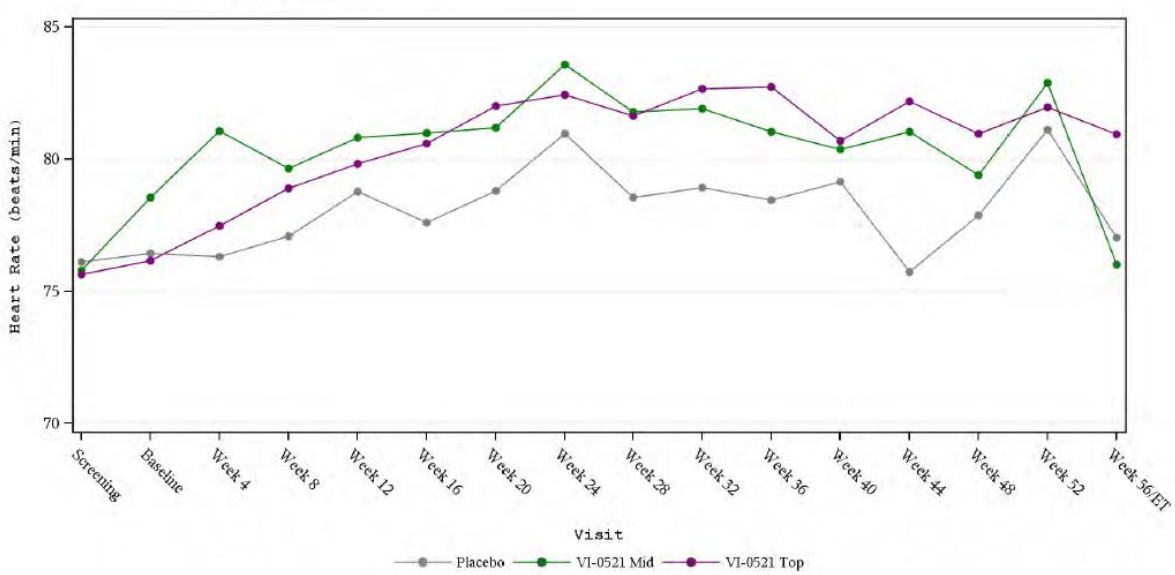

Table 30. Plot of observed average heart rate

VI-0521 is Applicant's term for PHEN/TPM; Top is high-dose PHEN/TPM (15 mg phentermine/92 mg topiramate)
Source: OB-403 CSR, Figure 14.3.5.1.3

Average systolic and diastolic blood pressures in the PHEN/TPM groups fluctuated but in general showed small reductions over the duration of the study period. At Week 56, the observed mean change from baseline in SBP was -1.8 mmHg in the mid-dose PHEN/TPM group, 0.2 mmHg in the high-dose group, and 2.5 mmHg in the placebo group. For diastolic blood pressure, at Week 56, the observed mean change from baseline was -2.4 mmHg in the mid-dose PHEN/TPM group, 1.4 mmHg in the high-dose PHEN/TPM group, and 3.1 mmHg in the placebo group.

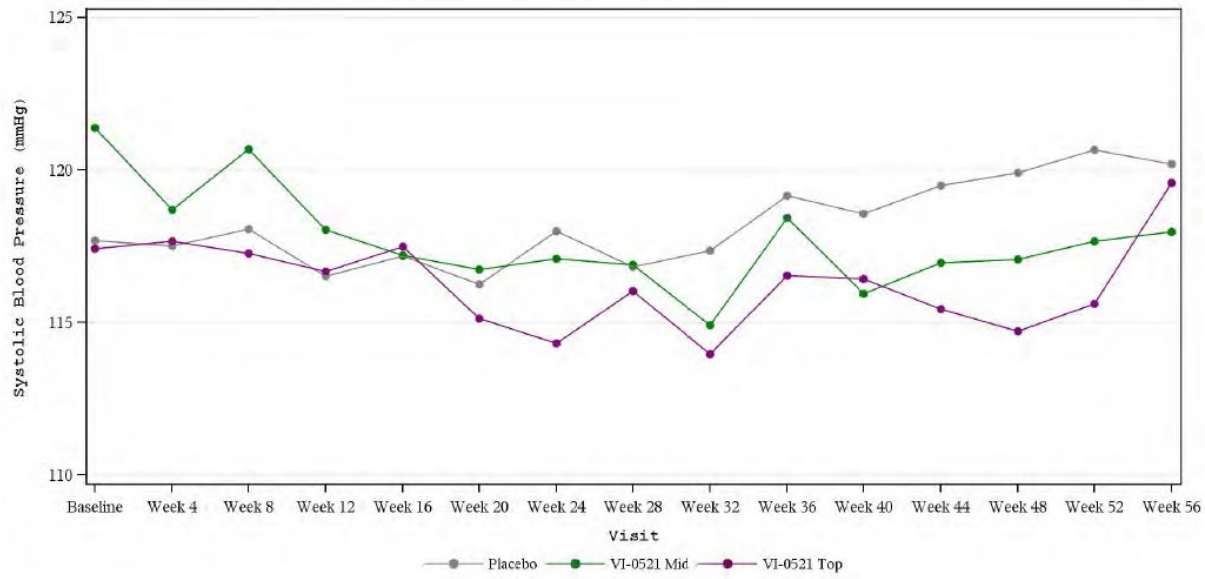

Table 31. Plot of observed systolic blood pressure

VI-0521 is Applicant's term for PHEN/TPM; Top is high-dose PHEN/TPM (15 mg phentermine/92 mg topiramate)
Source: OB-403 CSR, Figure 14.3.5.1.1

Categorical changes in heart rate and blood pressure further characterize the changes observed with PHEN/TPM treatment. A dose-response in the proportion of subjects with heart rate changes of greater than 5, 10, 15, or 20 bpm over baseline was observed. The number of subjects with a heart rate at any time post-randomization greater than 100 bpm also showed a dose-response.

The proportion of subjects with categorical increases in SBP and DBP was generally larger in the placebo group compared to the PHEN/TPM groups; however, a higher proportion of subjects in the high-dose PHEN/TPM group had a categorical increase of SBP of >20 mmHg.

Table 32. Categorical changes in blood pressure and heart rate at any time post-randomization

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Systolic Blood Pressure Change from BL			
>5 mmHg	26 (48.1)	70 (61.9)	36 (64.3)
>10 mmHg	15 (27.8)	45 (39.8)	21 (37.5)
>15 mmHg	6 (11.1)	26 (23.0)	15 (26.8)
>20 mmHg	2 (3.7)	15 (13.3)	5 (8.9)
Diastolic Blood Pressure Change from BL			

>5 mmHg	21 (38.9)	63 (55.8)	38 (67.9)
>10 mmHg	12 (22.2)	39 (34.5)	19 (33.9)
>15 mmHg	6 (11.1)	24 (21.2)	12 (21.4)
>20 mmHg	5 (9.3)	9 (8.0)	6 (10.7)
Heart Rate Change from BL			
>5 bpm	38 (70.4)	92 (81.4)	37 (66.1)
>10 bpm	30 (55.6)	73 (64.6)	26 (46.4)
>15 bpm	18 (33.3)	48 (42.5)	17 (30.4)
>20 bpm	10 (18.5)	27 (23.9)	10 (17.9)
Heart Rate >100 bpm	4 (7.4)	15 (13.3)	1 (1.8)
Heart Rate >100 bpm 2 consecutive visits	2 (3.7)	7 (6.2)	0

Source: Response to FDA IR, Table 17, submitted 10 November 2021 (SD#1154); Table 8, submitted 19 January 2022 (SD#1165)

Reviewer Comment: Consistent with the experience with PHEN/TPM in adults, a higher proportion of obese adolescents treated with PHEN/TPM had categorical increases in heart rate compared to their placebo-treated counterparts. In general, average blood pressure values trended downward in the PHEN/TPM groups particularly in the first 6 months but did not change substantially from baseline at Week 56. The proportion of subjects with categorical increases in blood pressure was generally similar between treatment groups. The high-dose PHEN/TPM group had a higher proportion of subjects with a SBP >20 mmHg (13.3%) versus the placebo (8.9%) and mid-dose group (3.7%), although this observation was not supported by changes in diastolic blood pressure or other systolic blood pressure thresholds. The clinical significance of these changes in this population or in the adult population treated with PHEN/TPM is unknown.

Eye disorders

Acute myopia, secondary angle closure glaucoma, and increased intraocular pressure has been reported with the use of topiramate in adults and pediatric patients and in postmarketing reports with PHEN/TPM in adults. Visual field defects are listed as a Warning and Precaution in topiramate labeling. The number of subjects reporting an adverse event within the 'eye disorders' SOC was small with 2 subjects in each of the PHEN/TPM groups and none in the placebo group. None of these events were serious or resulted in study drug discontinuation.

Table 33. Eye Disorders SOC and preferred terms

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Eye Disorders	**2 (3.7)**	**2 (1.8)**	**0**

	Mid-dose PHEN/TPM (N=54) n (%)	High-dose PHEN/TPM (N=113) n (%)	Placebo (N=56) n (%)
Visual impairment	1 (1.9)	1 (0.9)	0
Eye pain	1 (1.9)	0	0
Eye ulcer	0	1 (0.9)	0

Source: OB-403 CSR, Table 14.3.1.2.1

Reviewer Comment: A small imbalance in TEAE in the eye disorder SOC against PHEN/TPM was observed; however, no serious eye conditions occurred during this study. In the PHEN/TPM adult clinical trials, there was a higher incidence of TEAEs within the eye disorder SOC, including the preferred term of eye pain which occurred in approximately 2% of PHEN/TPM treated subjects. Visual impairment and eye pain are symptoms that can be associated with a wide range of ocular ailments including common, less serious complaints to serious eye conditions such as secondary angle closure glaucoma and intraocular pressure.

Metabolic acidosis

Among its various pharmacologic actions, topiramate is a carbonic anhydrase inhibitor and may induce metabolic acidosis through its effects on acid handling in the proximal renal tubule.[50] Metabolic acidosis is a labeled Warning & Precaution in the topiramate and Qsymia label. The preferred term 'metabolic acidosis' (severity rated as mild) was reported in 2 high-dose PHEN/TPM treated subjects. In one of these subjects ((b) (6)), metabolic acidosis [bicarbonate value of 14.6 umol/L (reference range 17 to 30.6)] in addition to elevation in liver enzymes led to discontinuation of PHEN/TPM. With discontinuation of the study drug, bicarbonate levels returned to a normal range. See the Section below on hepatic events and related laboratories for a narrative of this individual.

In the adult clinical trials of PHEN/TPM, metabolic acidosis was manifested as asymptomatic serum reductions in bicarbonate and increases in chloride. This was also observed in this trial. Evidence suggests a dose-response relationship for reduced serum bicarbonate values in PHEN/TPM exposed obese adolescents. Larger reductions in bicarbonate (mean change and proportion with categorical reductions) were observed in the PHEN/TPM groups versus the placebo group (Table 34, Table 35). Mean chloride values increased by 2.0 mmol/L and 2.5 mmol/L at Week 56 in the mid-dose and high-dose PHEN/TPM groups, respectively versus a 1.1 mmol/L average increase in the placebo group.

[50] Sinha A, Oo P, Asghar MU, Cheema HA, Mehta SS, Leinwand JC, Janga K. Type II Renal Tubular Acidosis Secondary to Topiramate: A Review. Cureus. 2018 Nov 26;10(11):e3635. doi: 10.7759/cureus.3635. PMID: 30755834; PMCID: PMC6351003.

Table 34. Bicarbonate (mmol/L) values at Baseline, Week 56, and Change from Baseline – Safety population

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Baseline			
N	54	113	56
Mean	22.4	22.1	21.6
Median	22.1	22.1	21.4
Min, Max	18.3, 27.1	17.5, 27.7	18.3, 25.0
Week 56			
N	38	81	28
Mean	20.9	20.3	21.2
Median	21.2	20.5	21.5
Min, Max	15.1, 27.8	15.9, 24.6	18.2, 23.8
Change from Baseline at Week 56			
N	38	81	28
Mean	-1.4	-1.7	-0.1
Median	-1.8	-1.7	-0.1
Min, Max	-6.5, 4.7	-7.9, 2.5	-4.5, 3.2

Source: OB-403 CSR, Table 14.3.2.5

Table 35. Number (%) of subjects with low bicarbonate values – Safety population

	Mid-dose PHEN/TPM (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Serum bicarbonate <21 mmol/L			
Any time post-randomization	42 (77.8)	93 (82.3)	31 (55.4)
Last Visit on Drug	4 (7.4)	6 (5.3)	1 (1.8)
Persistence	33 (61.1)	79 (69.9)	24 (42.9)
Serum bicarbonate <17 mmol/L			
Any time post-randomization	5 (9.3)	18 (15.9)	0
Last Visit on Drug	0	1 (0.9)	0
Persistence	1 (1.9)	5 (4.4)	0

Persistence defined as two consecutive values and/or present at final visit
Source: Response to FDA IR, submitted 10 November 2021 (SD#1154), Table 12

Concerns with chronic metabolic acidosis include nephrolithiasis and bone mineralization defects. There were no subjects reporting nephrolithiasis in this study. The impact of PHEN/TPM on bone density was evaluated in a subset of subjects and is further described in Section 8.5.

Elevation in creatinine/Renal-related events

Increases in serum creatinine that reflect a decrease in renal function (measured glomerular filtration rate) occur with PHEN/TPM use in adults.

In this study, mean serum creatinine values increased in all treatment groups (Figure 12); however, categorical increases in creatinine (≥0.3 mg/dL from baseline), which in some cases were persistent, were observed only in PHEN/TPM-treated subjects (Table 36).

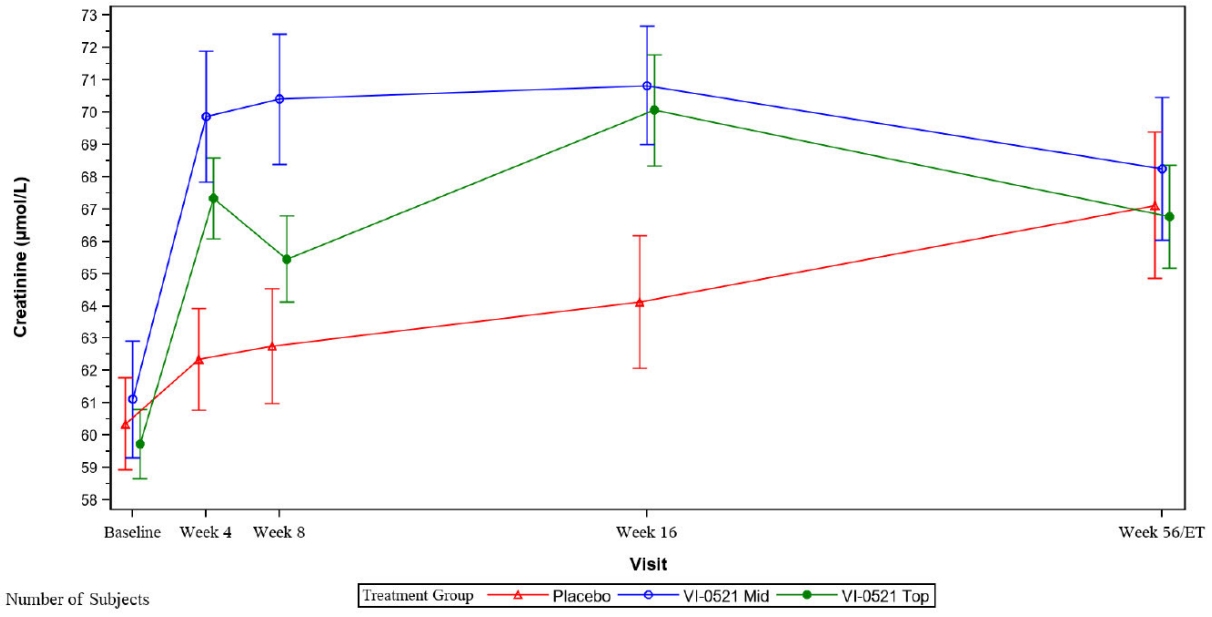

Figure 12. Mean (SE) creatinine values over time by treatment group – Safety population
Source: Response to FDA IR, submitted 19 January 2022 (SD#1165), Figure 11

Table 36. Number (%) of subjects with increase in creatinine ≥0.3 mg/dL – Safety population

	Mid-dose PHEN/TPM (N=54) n (%)	High-dose PHEN/TPM (N=113) n (%)	Placebo (N=56) n (%)
Serum Creatinine Increase ≥0.3 mg/dL from BL			
Any time post-randomization	9 (16.7)	19 (16.8)	0
Last Visit on Drug	0	0	0
Persistence	2 (3.7)	10 (8.8)	0

Persistence defined as two consecutive values and/or present at final visit
Source: Response to FDA IR, submitted 10 November 2021 (SD#1154), Table 11

Reviewer Comment: The applicant was queried regarding follow-up creatinine values after discontinuation of PHEN/TPM treatment. No follow-up laboratory values were available for review, therefore, no conclusions regarding the trajectory of creatinine values off-treatment can be made. However, in adults, the changes in creatinine were noted to be reversible, which provides some reassurance that these effects are not persistent off-treatment.

The only renal-related event reported was dysuria in an individual in the high-dose PHEN/TPM group.

Hypokalemia

Reductions in potassium are associated with topiramate. In clinical trials of PHEN/TPM in adults, a higher proportion of PHEN/TPM-treated adults had low potassium values (<3.5 mmol/L) compared to placebo-treated adults. In the adolescent population, a higher incidence of low potassium levels <3 mmol/L in the PHEN/TPM group compared to placebo group was not observed.

Table 37. Number (%) of subjects with low potassium – Safety population

	Mid-dose PHEN/TPM (N=54) n (%)	High-dose PHEN/TPM (N=113) n (%)	Placebo (N=56) n (%)
Potassium <3.5 mmol/L			
Any time post-randomization	0	3 (2.7)	3 (5.4)
Last Visit on Drug	0	0	0
Persistence	0	0	0

Persistence defined as two consecutive values and/or present at final visit
Source: Response to FDA IR, submitted 10 November 2021 (SD#1154), Table 13

Hepatic events and related laboratory values

A total of 5 subjects (1 treated with mid-dose PHEN/TPM and 4 treated with high-dose PHEN/TPM) experienced a hepatobiliary TEAE. Two of the subjects experienced gallbladder

disorders, one of which was a serious event and is described earlier in this review. There were 3 subjects (1 treated with mid-dose PHEN/TPM and 2 treated with high-dose PHEN/TPM) with a TEAE related to liver enzyme increases. There were no other hepatic adverse events noted. Subject (b) (6) was the only subject with an ALT or AST >3x ULN. However, no subjects, including Subject (b) (6) demonstrated biochemical parameters consistent with drug-induced liver injury or Hy's Law. This subject was previously discussed (in Metabolic Acidosis subsection) since study drug was discontinued due to elevations in liver enzymes and a low bicarbonate. A summary of this subject's case is included in this section with further details regarding liver enzymes.

Table 38. Hepatic-related Adverse Events

Preferred term	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Hepatobiliary adverse events	**1 (1.8)**	**4 (3.5)**	**0**
ALT increased	1 (1.8)	1 (1.9)	0
Transaminases increased	0	1 (1.9)	0
Bile Duct Stone	0	1 (1.9)	0
Cholelithiasis	0	1 (1.9)	0

Source: adae.xpt

Subject (b) (6) "Transaminases increased": Black 14-year-old female with normal liver enzymes at baseline (ALT 21 U/L, AST 16 U/L) was randomized to high-dose PHEN/TPM, on Study Day 53, experienced an adverse event of increased transaminases (ALT 498 U/L or 14x ULN; AST 133 U/L or 3x ULN), bilirubin was normal 0.6 mg/dL and study drug was interrupted for approximately 87 days. Drug was restarted on Study Day 137, and on Study Day 193 (June 19, 2020), the subject's ALT again increased (203 U/L, ~6x ULN), AST also increased to 61 U/L, bilirubin remained in normal range. Bicarbonate was also low at 14.6 mmol/L (lower level of normal 17 mmol/L). Study drug was discontinued on Study 195, and elevated transaminases and metabolic acidosis were resolved on Study Day 224 and 204, respectively.

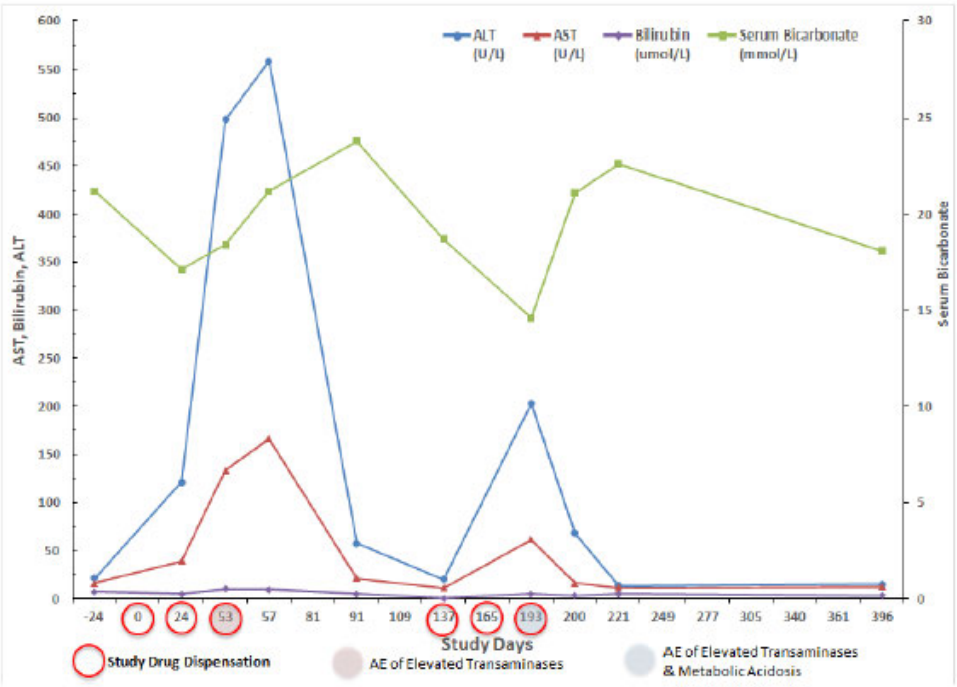

Figure 13. Subject (b) (6) Profile
Source: Response to IR, submitted 19 January 2022 (SD#1165), Question 6

Reviewer Comment: The subject's elevated transaminases were coincident with PHEN/TPM treatment. A causal association with PHEN/TPM cannot be ruled out given the negative dechallenge and positive rechallenge observed. No elevation in bilirubin was noted and liver enzymes returned to normal with PHEN/TPM discontinuation. The applicant noted that the rate of weight loss prior to the first episode of elevated transaminases was "approximately double the maximum desirable rate of 0.9 kg/week specified by the protocol and may have contributed to the elevation in transaminases." The applicant's rationale does not necessarily explain the second episode of elevated transaminases. An association of Qsymia, or its individual components, with elevated transaminases or drug-induced liver injury has not been previously observed or reported.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Overall, 48% of subjects reported at least one TEAE. High-dose PHEN/TPM and placebo had a similar proportion of subjects (52%) reporting an event; mid-dose PHEN/TPM reported 37% of subjects with a TEAE. The SOC of 'Infections and Infestations' had the highest proportion of subjects reporting an event; the highest percentage of subjects reporting an event in this SOC was observed in the placebo group.

The SOCs that had both the mid- and high-dose PHEN/TPM groups with a higher proportion of subjects reporting an event was in the SOC of 'Psychiatric disorders', 'Skin and subcutaneous tissue disorders', 'Eye disorders', and 'Cardiac disorders'. Please see the previous section for a discussion of these SOCs with the exception of 'skin and subcutaneous tissue disorders' and 'investigations' which is discussed here.

In the 'Skin and subcutaneous tissue disorder' SOC, there were 3 (5.6%) subjects in the mid-dose PHEN/TPM group, 7 (6.2%) subjects in the high-dose PHEN/TPM group, and 2 (3.6%) subjects in the placebo group reporting an event in this SOC. The most common adverse events occurring in the PHEN/TPM group that did not occur in the placebo group were rash (n=1 in the mid-dose group, n=2 in the high-dose group) and alopecia (n=2 in the high-dose group).

A total of 5 PHEN/TPM-treated subjects [1 (1.9%) mid-dose; 4 (3.5%) high-dose)] and no placebo-treated subjects reported a TEAE in the 'investigations' SOC. The terms included alanine aminotransferase increased (n=2 subjects), transaminases (n=1), hematocrit decreased (n=1), and hemoglobin decreased (n=1), and low-density lipoprotein increased (n=1). The hepatic-related TEAEs are discussed in the previous section. The one subject that reported hematocrit and hemoglobin reduction is discussed in Section 8.4.6.

The following preferred terms occurred in approximately 3% of subjects in a treatment group and in a greater proportion of PHEN/TPM treated subjects compared to placebo. The preferred terms are listed in descending order based on frequency in the high-dose PHEN/TPM group.

Table 39. TEAEs reported in ~3% and higher in PHEN/TPM group compared to placebo

Preferred term	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Any TEAE	20 (37.0)	59 (52.2)	29 (51.8)
Depression	1 (1.9)	5 (4.4)	0
Nausea	2 (3.7)	5 (4.4)	2 (3.6)
Pyrexia	1 (1.9)	5 (4.4)	1 (1.8)
Arthralgia	1 (1.9)	4 (3.5)	0
Dizziness	1 (1.9)	4 (3.5)	0
Paraesthesia	1 (1.9)	3 (2.7)	0
Upper abdominal pain	0	3 (2.7)	0
Fatigue	0	3 (2.7)	1 (1.8)
Anxiety	1 (1.9)	3 (2.7)	0
Musculoskeletal chest pain	0	3 (2.7)	0
Ear infection	1 (1.9)	3 (2.7)	0

Preferred term	**Mid-dose PHEN/TPM** (N=54) n (%)	**High-dose PHEN/TPM** (N=113) n (%)	**Placebo** (N=56) n (%)
Influenza	2 (3.7)	2 (1.8)	0
Ligament sprain	2 (3.7)	2 (1.8)	0

Source: OB-403 CSR, Table 14.3.1.2.1

8.4.6. Laboratory Findings

Hepatic and renal-related laboratory values are discussed in Section 8.4.4.

Most of the laboratory parameters measured were within normal limits during the trial, with a similar proportion of subjects experiencing out-of-range values for biochemistry and hematological parameters.

There was one high-dose PHEN/TPM-treated subject with 'hematocrit decreased' and 'hemoglobin decreased' reported on Study Day 47. This subject also reported 'dizziness' on the same study day. The notes in the cm.xpt dataset state that Ferrous sulfate was started due to 'dizziness with position changes Hgb and HCT lower end of normal'. Ferrous sulfate was discontinued two days later. This subject also reported 'syncope' on Study Day 107. Review of this subject's hemoglobin and hematocrit recorded at baseline, Week 28, and Week 56 were within normal limits. Baseline hemoglobin was 12.3 g/dL (reference 11.6-16.4 g/dL) and hematocrit was 35% (reference 34-48%) which was the closest lab available to this date. On Study Day 203 (Week 28) and 395 (Week 56), the hemoglobin was 11.7 g/dL and 11.8 g/dL respectively and hematocrit was 35% (both study days). The applicant was queried for unscheduled related laboratory values. No additional laboratory values were available.

8.4.7. Vital Signs

Please see section 8.4.4 Significant Adverse Events: Cardiovascular effects for discussion on PHEN/TPM's effect on heart rate and blood pressure.

No clinically relevant trends were noted in respiratory rate or temperature.

8.4.8. Electrocardiograms (ECGs)

ECGs were assessed at Baseline and at Week 56. At baseline there were 3 subjects (1 placebo and 2 in the high-dose PHEN/TPM group) with a 'clinically significant' ECG. At Week 56, 1 of the subjects with a baseline 'clinically significant' ECG still qualified as 'clinically significant' at Week 56. The Week 56 ECG was consistent with the anomaly at Baseline and no adverse events related to this anomaly were reported.

Table 40. Subjects with Clinically Significant ECG at Baseline

Subject	Treatment Group	Visit with CS ECG	Relevant Med Hx	Comment on ECG CRF
(b) (6)	Top-dose	Baseline	No	Left ventricular hypertrophy
	Placebo	Baseline	First degree AV block on EKG	First degree AV block NCS per sub-investigator
	Top-dose	Baseline	Sinus bradycardia on EKG	Sinus bradycardia, ST elevation probably early repolarization NCS per sub-investigator
	Top-dose	Week 56/EOS		Early repolarization

Note: CS = Clinically Significant; EOS = End of Study.

Source: Response to IR, submitted 19 January 2022 (SD#1165), Request 12

There were no AEs related to abnormal ECG ('Investigations' SOC) in the trial.

8.4.9. QT

A thorough QT study was reviewed by the Agency's interdisciplinary review team for QT studies with the original NDA for adults. According to their review, the effect of PHEN/TPM on the QTc interval was evaluated in a randomized, double-blind, placebo- and active-controlled (400 mg moxifloxacin), parallel group/crossover thorough QT/QTc study. A total of 54 healthy individuals were administered PHEN/TPM 7.5/46 mg at steady state and then titrated to PHEN/TPM 22.5/138 mg at steady state. In a study with demonstrated ability to detect small effects, the upper bound of the 90% confidence interval for the largest placebo-adjusted, baseline-corrected QTc based on study-specific correction was below 10 msec, the threshold for regulatory concern.

There were no AEs related to QT ('Investigations' SOC) nor were there any AEs of torsades de pointes in the trial.

8.4.10. Immunogenicity

There are no immunogenicity safety issues related to PHEN/TPM.

8.5. Analysis of Submission-Specific Safety Issues

The impact of weight loss in pediatric patients on linear growth, bone density, and sexual development is an area of interest, given the complexities of body adiposity, nutritional status, and weight loss affecting growth and development, particularly over the pubertal period.

Obese children are often taller, have a more advanced bone age, and increased bone mineral

density, relative to normal weight peers.[51, 52] Obesity is also associated with earlier onset of pubertal development. Weight loss is associated with loss of bone mineral density in adolescents that have undergone bariatric surgery.[53, 54]

Of note, topiramate is a carbonic anhydrase inhibitor and may induce metabolic acidosis. Chronic metabolic acidosis, as seen with end-stage renal disease, may be associated with decreased bone mineral density and growth rates. During review of this application, the Division of Neurology updated the Topamax (topiramate) label with new Warnings & Precautions regarding a reduction in bone mineral density observed in a 1-year active-controlled, open-label study in pediatric patients (6 to 15 years, mean age 10 years old) with epilepsy treated with Topamax (average dose ~200 mg/day). Reductions in lumbar spine BMD was correlated with the lowest and average post-randomization serum bicarbonate, a marker of metabolic acidosis. In addition, reductions in weight and attenuation of height change from baseline were observed in this study.[55]

In addition, impaired cognitive function in adolescents with obesity has also been reported.[56, 57] Biologic factors posited as mediating this association include impaired glucose metabolism, inflammation, and iron deficiency.[58] PHEN/TPM has also been associated with an increase in cognitive-related adverse reactions, such as difficulty with concentration/attention, memory and language (word finding) in adults; therefore, the effect of weight loss associated with phentermine and topiramate, two neuroactive drugs, on cognitive function in obese adolescents was also of interest.

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[56] Reinert KR, Po'e EK, Barkin SL. The relationship between executive function and obesity in children and adolescents: a systematic literature review. J Obes. 2013;2013:820956. doi: 10.1155/2013/820956. Epub 2013 Feb 21. PMID: 23533726; PMCID: PMC3595670.
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[58] Smith L, Toussaint L, Micoli A, Lynch B. Obesity, putative biological mediators, and cognitive function in a national sample of children and adolescents. Prev Med. 2021 Sep;150:106659. doi: 10.1016/j.ypmed.2021.106659. Epub 2021 Jun 5. PMID: 34097950.

8.5.1. Bone Mineral Density, Bone Age, and Linear Growth

Bone Mineral Density

To assess the effect of PHEN/TPM on bone mineral density, dual-energy X-ray absorptiometry (DXA) scans of the lumbar spine and total body less head (TBLH) were performed on a subset of subjects at baseline and Week 56/ET.[59] Subjects with juvenile osteoporosis or a history of non-traumatic fracture were excluded from participation in the DXA substudy. Mean changes from baseline in bone mineral density (BMD) and bone mineral content (BMC) and BMD Z-scores (age- and sex-normalized) were evaluated as the safety endpoint and summarized descriptively. No bone-related biomarkers such as PTH, markers of bone resorption or bone formation, or vitamin D levels were obtained. To aid in our interpretation of the results, the Division of General Endocrinology (DGE), which regulates products related to bone and growth, was consulted. The following text, tables, and figures are adapted from Dr. Stephen Voss's consult report. The full consult is located in the Appendix.

A total of 119 subjects (53% of the ITT population) enrolled in the DXA substudy and were randomized to either mid-dose PHEN/TPM (n=29), high-dose PHEN/TPM (n=58), or placebo (n=32). Demographics were similar between the DXA and ITT populations. There were 107 subjects with lumbar spine and/or TBLH scan at baseline, and 66 subjects with a Week 56/ET scan. All subjects were actively taking study drug at the time of their Week 56/ET evaluation. Four subjects had a DXA scan before Week 56 as part of end of treatment assessments.

Lumbar spine DXA

In the subjects with DXA scans at both baseline and week 56, lumbar spine BMD increased by approximately 3.4% in each of the PHEN/TPM treatment groups and 5.5% in the placebo group; bone mineral content also increased in all treatment groups by approximately 8.0% in the PHEN/TPM treatment groups and 11.0% in the placebo group. Absolute and percent change in lumbar BMD and BMC are presented in the table below.

Reviewer Comment: Discrepancies in the number of subjects contributing data across the study report, dataset, and listings were noted. The applicant was queried and responded there were three subjects with baseline DXA scans that were collected after the randomization date. The applicant included information from these subjects in the baseline data and listings, but these subjects were not used for the applicant's analyses of mean change from baseline. Dr. Voss reviewed the data and noted that the excluded subjects had baseline DXA scans within 5 to 8

[59] Posterior-anterior (pa) spine and total body less head are the preferred skeletal sites for performing bone density assessments in pediatric subjects – ICSD 2019 Official Positions https://iscd.org/wp-content/uploads/2021/09/2019-Official-Positions-Pediatric-1.pdf

days of randomization. He calculated that there was little difference in the overall means with or without these subjects (n=3). Dr. Voss noted, however, two of these subjects had categorical reductions in either lumbar spine or TBLH of ≥0.5.

Table 41. Lumbar Spine BMD – Mean and Percent Change at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Baseline, n	20	51	27
Mean (SD), g/cm^2	1.16 (0.14)	1.10 (0.19)	1.06 (0.20)
Week 56, n	16	32	18
Mean (SD), g/cm^2	1.22 (0.16)	1.13 (0.19)	1.09 (0.21)
Change from Baseline, n	14	32	17
Mean (SD), g/cm^2	0.038 (0.080)	0.035 (0.043)	0.048 (0.065)
Treatment difference PHEN/TPM-Pbo, g/cm^2	-0.010	-0.013	
Percent change, n*	16	32	18
Mean (SD)*	3.35% (6.76)	3.37% (4.31)	5.54% (6.93)
Treatment difference PHEN/TPM-Pbo	-2.19%	-2.17%	

*Percent change data are derived from mo.xpt dataset (which matches Listing 16.2.10) by Dr. Voss and includes the 3 subjects with baseline DXA 5 to 8 days post-randomization; other data in this table are from CSR Table 14.3.2.4
Source: Table adapted from Dr. Stephen Voss's consult report

Table 42. Lumbar Spine BMC – Mean and Percent Change at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Baseline, n	20	51	27
Mean (SD), g	59.6 (15.2)	58.1 (13.3)	58.0 (13.9)
Week 56, n	16	32	18
Mean (SD), g	69.6 (13.1)	60.9 (10.2)	63.0 (15.0)
Change from Baseline, n	14	32	17
Mean (SD), g	4.7 (5.2)	4.2 (4.7)	5.3 (5.8)
Treatment difference PHEN/TPM-Pbo, g	-0.6	-1.1	
Percent change, n*	14	32	17
Mean (SD)*	7.7% (9.0)	8.4% (10.6)	10.9% (12.9)
Treatment difference PHEN/TPM-Pbo	-3.2%	-2.5%	

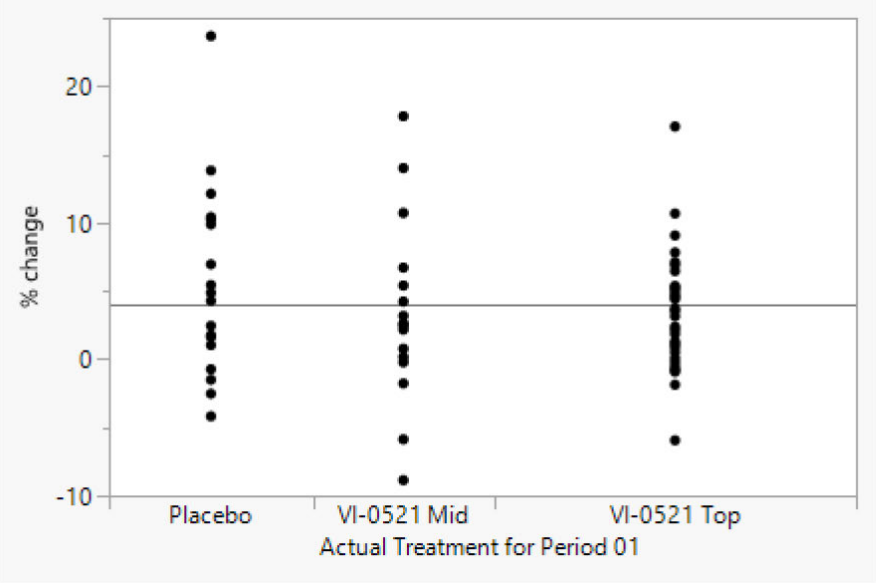
*Percent change data are derived from admo.xpt dataset by Dr. Roberts; other data in this table are from response to FDA IR, submitted 24 March 2022 (SD#1183), Table 2a

Individual percent changes in lumbar spine BMD are shown in the figure below. There were 3 subjects with BMD declines >5% from baseline, including one mid-dose PHEN/TPM and one high-dose PHEN/TPM treated subject who each had changes of -5.9%; another mid-dose PHEN/TPM treated subject had a -8.9% change. This latter subject's baseline and Week 56/ET scans were performed on different machines, therefore, this change may be artefactual. It is

generally recommended that serial DXA measurements should use the same instrument, model, and software version.

Reviewer Comment: The applicant confirmed that all other subjects were scanned on the same scanner at both Baseline and Week 56/ET assessments.

Lumbar spine BMD, % change from baseline at week 56/EOT by individual subject /treatment group



Source: mo.xpt dataset

Figure 14. Lumbar Spine Percent Change in BMD at Week 56/ET – DXA population
VI-0521 is Applicant's term for PHEN/TPM; Top is high-dose PHEN/TPM (15 mg phentermine/92 mg topiramate)
Source: Voss, S. Consult Report, DGE

Evaluation by subgroups showed that treatment group differences in BMD tended to be greater in the 12–14-year-old and male subgroups. This is partly due to the outlier subjects mentioned above, given the small numbers of subjects in each group.

Table 43. Lumbar spine BMD – Mean Percent Change at Week 56/ET by treatment group and demographic subgroup – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Age 12-14 years, n	8	19	9
Mean (SD)	4.09% (8.59)	3.57% (4.33)	7.48% (8.35)
Treatment difference PHEN/TPM-Pbo	-3.39%	-3.91%	
Age 15-16 years, n	8	13	9
Mean (SD)	2.61% (4.78)	3.08% (4.42)	3.59% (4.89)

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Treatment difference PHEN/TPM-Pbo	-0.98%	-0.51%	
Female, n	10	18	10
Mean (SD)	3.92% (7.28)	2.07% (3.26)	1.94% (3.09)
Treatment difference PHEN/TPM-Pbo	1.98%	0.13%	
Male, n	6	14	8
Mean (SD)	2.40% (6.32)	5.04% (4.99)	10.03% (7.93)
Treatment difference PHEN/TPM-Pbo	-7.63%	-4.99%	

Data Source: mo.xpt dataset
Source: Table adapted from Dr. Stephen Voss's consult report

Mean lumbar spine BMD Z-scores at baseline were greater than zero in each treatment group, (i.e., above age- and sex-referenced means). This is consistent with bone mineral density findings in healthy overweight or obese adolescents. At Week 56 there were modest dose-related declines in mean Z-score (-0.11, -0.18) from baseline in the two active treatment groups; however, the results remained greater than zero.

Table 44. Lumbar Spine BMD[60] Z-score – Mean Change at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Baseline, n	20	50	27
Mean (SD)	1.13 (1.09)	0.79 (1.08)	0.54 (0.93)
Week 56, n	16	32	18
Mean (SD)	1.04 (1.03)	0.54 (1.10)	0.41 (0.92)
Change from Baseline, n	14	31	17
Mean (SD)	-0.09 (0.54)	-0.18 (0.43)	-0.01 (0.44)
Treatment difference PHEN/TPM-Pbo	-0.08	-0.17	
Change from Baseline, n*	16	31	18
Mean (SD)*	-0.11 (0.51)	-0.18 (0.43)	0.01 (0.44)
Treatment difference PHEN/TPM-Pbo	-0.12	-0.19	

*Data derived from mo.xpt dataset (which matches Listing 16.2.10) by Dr. Voss and includes the 3 subjects with baseline DXA 5 to 8 days post-randomization; other data in this table are from CSR Table 14.3.2.4
Source: Table adapted from Dr. Stephen Voss's consult report (See Appendix).

[60] Please note the information originally presented in the CSR post-text Table 14.3.2.4 and used in this table was incorrectly labeled as the BMC Z-score. In response to an information request, the applicant noted the error and stated Table 14.3.2.4 reflects the BMD Z-score. This explains the reason the table in Dr. Voss's consult report entitled "Lumbar Spine BMC Z-score, by treatment group" is mislabeled; the table in the consult lists the BMD Z-score results.

Lumbar spine BMD Z-score reductions of 0.5 SD or greater, a level that was considered potentially clinically significant in the TOPAMAX pediatric epilepsy trial evaluating bone health, were reported in a total of 16 subjects. A higher proportion of PHEN/TPM-treated subjects had a Z-score reduction of 0.5 SD or greater. The largest decline of 1.0 SD was observed in a placebo-treated subject. No subjects with reductions in Z-score achieved a Z-score that was lower than -2.0 SD, a cut-off used in combination with a clinically significant fracture history for the diagnosis of osteoporosis in the pediatric population.[61]

Table 45. Categorical reductions in Lumbar Spine BMD Z-score at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
n[1]	16	31	18
Decrease of ≥0.5 SD	5 (31.2%)	9 (29.0%)	2 (11.1%)
Decrease of ≥1.0 SD	0	0	1 (5.5%)
Decrease of ≥2.0 SD	0	0	0

1 n is the number of subjects with a Baseline and Week 56 Z-score, includes 3 subjects that had a baseline DXA 5 to 8 days post-randomization.
Source: Dr. Voss, DGE consult

Total Body Less Head DXA[62]

In subjects with DXA scans at baseline and Week 56/ET, TBLH BMD increased by a mean of 2.0% in the mid-dose PHEN/TPM group, 0.2% in the high-dose PHEN/TPM group, and 4.5% in the placebo group. Mean percent increases in BMC were 3.2% in the mid-dose PHEN/TPM group, 0.2% in the high-dose PHEN/TPM group, and 6.7% in the placebo group.

Table 46. TBLH BMD – Mean and Percent Change at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Baseline, n	18	49	27
Mean (SD), g/cm2	1.11 (0.12)	1.05 (0.12)	1.02 (0.13)
Week 56, n	16	32	18
Mean (SD, g/cm2)	1.11 (0.14)	1.04 (0.12)	1.06 (0.13)
Change from Baseline, n	13	32	16
Mean (SD, g/cm2)	0.025 (0.035)	0.003 (0.045)	0.042 (0.032)
Treatment difference PHEN/TPM-Pbo	-0.017	-0.039	
Percent change, n*	15	32	17

[61] A clinically significant fracture history is one or more of the following: 1) two or more long bone fractures by age 10 years; 2) three or more long bone fractures at any age up to age 19 years. ICSD 2019 Official Positions https://iscd.org/wp-content/uploads/2021/09/2019-Official-Positions-Pediatric-1.pdf
[62] The OB-403 CSR and Final Imaging Report report "Whole Body" results. The applicant confirmed that whole body is the same as total body less head.

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Mean (SD)*	1.98% (3.26)	0.23% (4.53)	4.52% (3.30)
Treatment difference PHEN/TPM-Pbo	-2.54%	-4.29%	

*Data for percent change are derived from mo.xpt dataset (which matches Listing 16.2.10); other data in this table are from CSR Table 14.3.2.4
Source: Table adapted from Dr. Stephen Voss's consult report (See Appendix)

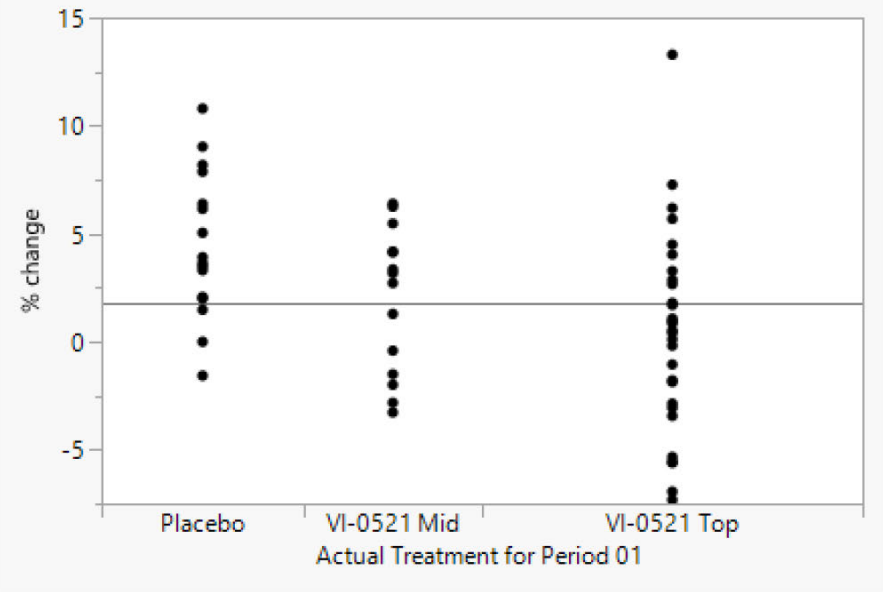
Table 47. TBLH BMC – Mean and Percent Change at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Baseline, n	18	49	27
Mean (SD), g	2237.2 (457.8)	2086.4 (420.5)	1988.4 (364.3)
Week 56, n	16	32	18
Mean (SD), g	2274.4 (499.7)	2053.4 (359.9)	2098.5 (404.9)
Change from Baseline, n	13	32	16
Mean (SD), g	61.4 (150.8)	0.73 (116.4)	112.1 (116.0)
Treatment difference PHEN/TPM-Pbo, g	-50.7	-111.4	
Percent change, n*	13	32	16
Mean (SD)*	3.2% (7.7)	0.2% (5.8)	6.7% (8.8)
Treatment difference PHEN/TPM-Pbo	-3.5%	-6.5%	

*Percent change data are derived from admo.xpt dataset by Dr. Roberts; other data in this table are from response to FDA IR, submitted 24 March 2022 (SD#1183), Table 2a

Individual-subject percent changes in TBLH BMD are shown in the figure below. All 6 of the subjects with TLBH BMD declines >5% were in the high-dose group (ranging from -5.3% to -7.3%). The high-dose group also included one positive outlier, a 13-year-old male with TBLH BMD increase of 13.3%.

Whole body BMD, percent change from baseline at week 56/EOT by individual subject and treatment group



Source: mo.xpt

Figure 15. TBLH Percent Change in BMD at Week 56/ET – DXA population
VI-0521 is Applicant's term for PHEN/TPM; Top is high-dose PHEN/TPM (15 mg phentermine/92 mg topiramate)
Source: Voss, S. Consult Report, DGE

All 6 of the subjects with TBLH BMD reductions >5% were in the younger (age 12 to 14-year-old) subgroup (and as mentioned above, in the high-dose PHEN/TPM group). The table below shows that the younger subgroup had larger treatment differences. Both the female and male subgroups had smaller TBLH BMD increases in the PHEN/TPM treatment groups relative to placebo; among the 6 subjects with >5% reduction in BMD, 2 were female and 4 were male.

Table 48. TBLH BMD – Mean Percent Change at Week 56/ET by treatment group and demographic subgroup – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Age 12-14 years, n	7	19	8
Mean (SD)	3.02% (3.74)	-0.54% (5.23)	6.36% (3.31)
Treatment difference PHEN/TPM-Pbo	-3.34%	-6.90%	
Age 15-16 years, n	8	13	9
Mean (SD)	1.06% (2.69)	1.36% (3.09)	2.90% (2.41)
Treatment difference PHEN/TPM-Pbo	-1.84%	-1.54%	
Female, n	10	18	9
Mean (SD)	1.79% (3.38)	-0.93% (2.76)	2.59% (2.23)

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Treatment difference PHEN/TPM-Pbo	-0.80%	-3.52%	
Male, n	5	14	8
Mean (SD)	2.36% (3.35)	1.73% (5.88)	6.70% (2.99)
Treatment difference PHEN/TPM-Pbo	-4.34%	-4.97%	

Data Source: mo.xpt dataset
Source: Table adapted from Dr. Stephen Voss's consult report

The available TBLH Z-score data, summarized in the table below, show dose-related declines in the PHEN/TPM groups; compared to the lumbar spine Z-score data, the mean differences from placebo are somewhat greater.

Table 49. TBLH BMD Z-score – Mean Change at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
Baseline, n	11	35	24
Mean (SD)	1.57 (0.92)	0.78 (0.91)	0.68 (1.17)
Week 56, n	12	23	16
Mean (SD)	0.95 (1.18)	0.31 (1.09)	0.73 (1.22)
Change from Baseline, n	9	23	14
Mean (SD)	-0.02 (0.26)	-0.24 (0.52)	0.20 (0.30)
Treatment difference PHEN/TPM-Pbo	-0.22	-0.44	
Change from Baseline, n*	11	23	15
Mean (SD)*	-0.08 (0.29)	-0.24 (0.52)	0.19 (0.29)
Treatment difference PHEN/TPM-Pbo	-0.27	-0.43	

*Data derived from mo.xpt dataset (which matches the data in Listing 16.2.10) by this reviewer; other data in this table are from CSR Table 14.3.2.4
Source: Table adapted from Dr. Stephen Voss's consult report

Reviewer Comment: Dr. Voss noted that there were numerous subjects with TBLH bone mineral density data reported but no corresponding Z-scores. The applicant clarified that the GE scanner had no normative data for TBLH for black pediatric subjects, therefore, a Z-score was not generated for these subjects. Of subjects with TBLH data at Baseline and Week 56, there were a total of 15 subjects with no Z-score.

In subjects with available Z-scores, declines in TBLH BMD Z-scores of 0.5 SD or greater only occurred in PHEN/TPM-treated subjects. Subjects treated with high-dose PHEN/TPM had a higher proportion of subjects with categorical changes compared to mid-dose PHEN/TPM-treated subjects. There was one subject with a Z-score decline greater than 1.0: a 14-year-old in the high-dose group with a change of -1.5 SD from baseline. However, subjects with reductions

in Z-score did not achieve a Z-score of ≤-2.0 SD, a clinically significant threshold in combination with fracture history for the diagnosis of osteoporosis.

Table 50. Categorical reductions in TBLH BMD Z-score at Week 56/ET – DXA population

	Mid-dose PHEN/TPM	High-dose PHEN/TPM	Placebo
n[1]	11	23	15
Decrease of ≥0.5 SD	1 (9.1%)	7 (30.4%)	0
Decrease of ≥1.0 SD	0	1 (4.3%)	0
Decrease of ≥2.0 SD	0	0	0

1 n is the number of subjects with Z-scores generated with Baseline and Week 56, includes subjects with a Baseline DXA occurring 5 to 8 days post-randomization
Source: Voss, S., DGE consult

Reviewer Comment: Dr. Voss noted in his consult that the "cause of PHEN/TPM related bone loss in this study is unclear and may be multifactorial, for example a combination of topiramate-related metabolic acidosis and weight loss. … Further evaluation to explore potential correlations between DXA data and other parameters may help clarify the mechanism of PHEN/TPM-related bone loss."

Therefore, evaluations were conducted to evaluate the changes in bone density with changes in bicarbonate and weight loss.

Exploratory analyses were conducted to assess whether there was a correlation between lowest post-baseline serum bicarbonate and change in BMD (absolute and Z-score) for both lumbar spine (Figure 16) and TBLH (Figure 17) at Week 56.

Lowest post-treatment serum bicarbonate was chosen for the PHEN/TPM correlation analyses because this parameter was moderately correlated with change in lumbar spine BMD in the Topamax trial of pediatric subjects with epilepsy and because the degree of bicarbonate reduction achieved may be more sensitive to detecting an association.

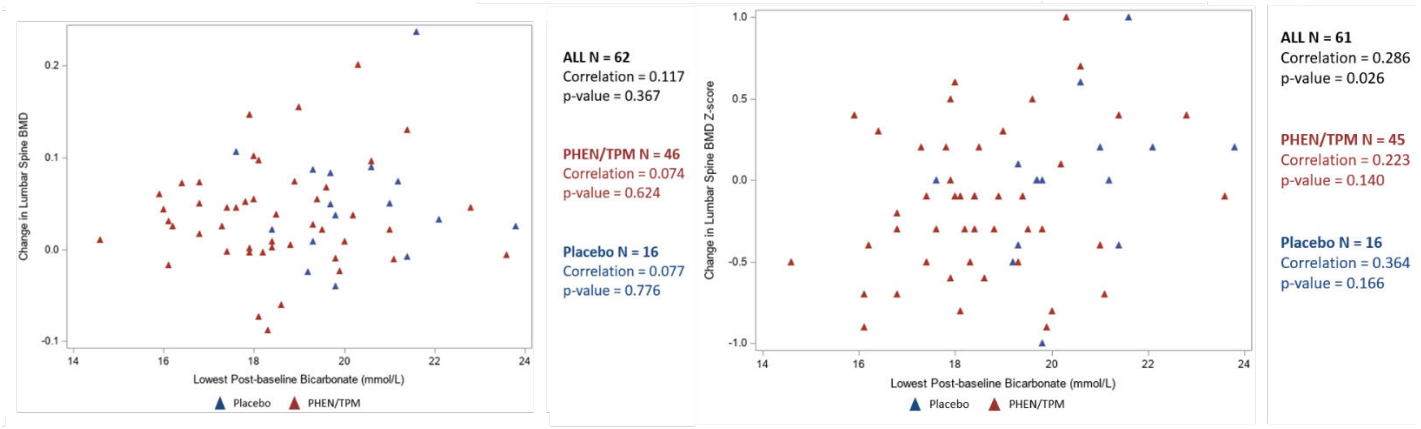


Figure 16. Correlation of Change in Lumbar Spine BMD (g/cm²) and Z-score at Week 56 and Lowest Post-Baseline Bicarbonate
Source: Dr. Bo Li, DB VII, safety statistician analysis

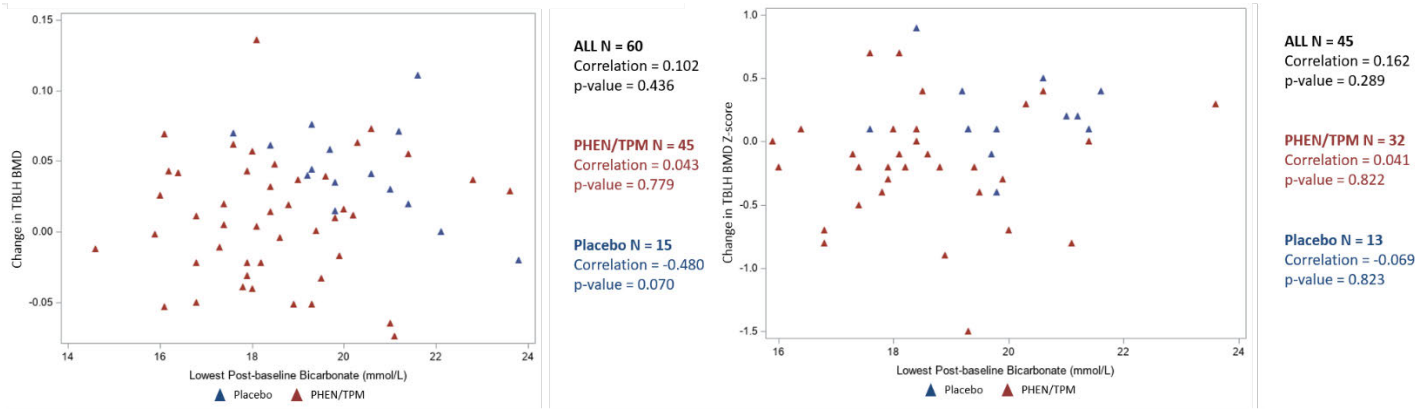


Figure 17. Correlation of Change in TBLH BMD (g/cm²) and Z-score at Week 56 and Lowest Post-Baseline Bicarbonate
Source: Dr. Bo Li, DB VII, safety statistician analysis

Reviewer Comment: The results of these analyses do not suggest a significant association between lowest post-baseline bicarbonate achieved and change in BMD in either body region. The statistical safety consultants who conducted the BMD/bicarbonate correlation analyses for the TOPAMAX and PHEN/TPM pediatric trials, noted that the moderate association between lumbar spine BMD and bicarbonate in the TOPAMAX pediatric epilepsy trial was mostly driven by subjects whose bicarbonate values dropped below 16 mmol/L during the trial. In contrast, only 2 subjects in the PHEN/TPM DXA substudy had a bicarbonate value less than 16 mmol/L. It is unknown, based on the data available from the PHEN/TPM DXA substudy, if a stronger association between BMD and bicarbonate would have been observed if more subjects had experienced extremely low bicarbonate values.

Weight loss following bariatric surgery has been associated with reductions in bone mineral density in adolescents; however, the effect on bone after non-surgical weight loss is mixed.[63, 64, 65, 66] Therefore, it was of interest to investigate the contribution of weight loss on BMD in this study. Upon request by the Division, the applicant conducted a correlation analysis evaluating the change in TBLH bone mineral density with change in weight at Week 56 (Figure 18).

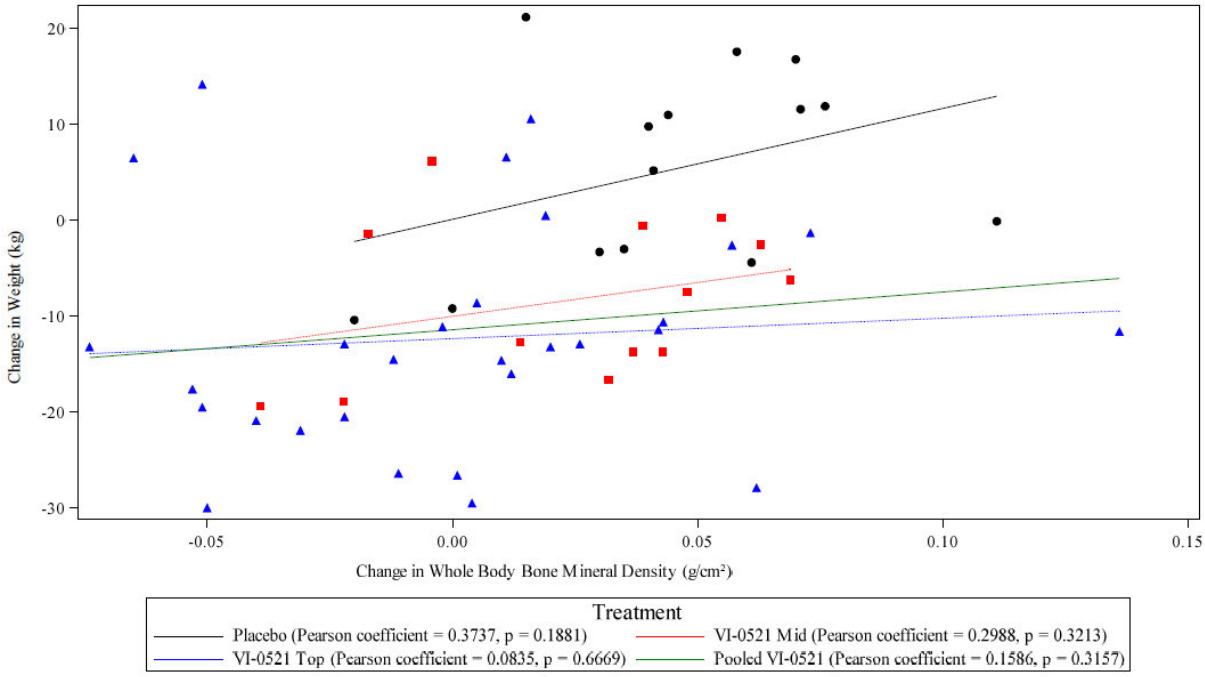


Figure 18. Correlation of Change in TBLH BMD (g/cm²) and change in weight (kg) at Week 56
VI-0521 represents PHEN/TPM; Top represents high-dose PHEN 15 mg/TPM 96 mg
Source: Response to IR, submitted 11 May 2022 (SD#1191), Figure 2

Correlations between changes in weight and changes in bone mineral density did not demonstrate a strong or statistically significant association between the two variables in any treatment group.

[63] Misra M, Singhal V, Carmine B, et al. Bone outcomes following sleeve gastrectomy in adolescents and young adults with obesity versus non-surgical controls. Bone. 2020;134:115290.
[64] Stettler N, Berkowtiz RI, Cronquist JL, Shults J, Wadden TA, Zemel BS, Leonard MB. Observational study of bone accretion during successful weight loss in obese adolescents. Obesity (Silver Spring). 2008 Jan;16(1):96-101. doi: 10.1038/oby.2007.17. PMID: 18223619.
[65] Rourke KM, Brehm BJ, Cassell C, Sethuraman G. Effect of weight change on bone mass in female adolescents. J Am Diet Assoc. 2003 Mar;103(3):369-72. doi: 10.1053/jada.2003.50051. PMID: 12616262.
[66] Kelley JC, Stettler-Davis N, Leonard MB, Hill D, Wrotniak BH, Shults J, Stallings VA, Berkowitz R, Xanthopoulos MS, Prout-Parks E, Klieger SB, Zemel BS. Effects of a Randomized Weight Loss Intervention Trial in Obese Adolescents on Tibia and Radius Bone Geometry and Volumetric Density. J Bone Miner Res. 2018 Jan;33(1):42-53. doi: 10.1002/jbmr.3288. PMID: 28884881; PMCID: PMC8527854.

Reviewer Comment: Overall, Study OB-403 indicates that increases in bone mineral density and bone mineral content at the lumbar spine and total body less head were numerically smaller in the PHEN/TPM-treated group compared to the placebo-treated group after 56 weeks of treatment. This is similar to results observed in the Topamax pediatric epilepsy trial. Larger treatment differences were observed in the total body less head region compared to the lumbar spine region. The cause of PHEN/TPM-related effects on bone in this study are unclear. No association with bicarbonate reduction (unlike the Topamax trial) or weight loss and changes in BMD were observed; however, the amount of weight loss and the degree of bicarbonate reduction may not have been substantial enough to detect an effect.

Conclusions from this study regarding the long-term clinical impact of these observed changes in adolescents with obesity treated with PHEN/TPM are limited for the following reasons. DXA measurements are affected by body composition, particularly fat mass; extreme changes in fat may overestimate bone loss and affect the interpretation of the results. [67] Other factors that may have contributed to further understanding of the effect of PHEN/TPM on bone metabolism such as bone biomarkers and calciotropic hormones were not collected in this study. Two subjects experienced a fracture (mid-dose PHEN/TPM 'left great toe fracture' and placebo 'right wrist buckle fracture')[68]; however, the duration of this study and the number and type of fractures observed are not informative in determining fracture risk with PHEN/TPM treatment. Finally, despite smaller increases in bone mineral density measurements in PHEN/TPM-treated subjects, BMD Z-scores remained greater than 0 (above average for age and sex) in most subjects, and no subjects demonstrated a decline in Z-score to less than -2.0, which is similar to the published findings in bariatric surgery studies. This suggests the changes in BMD may not be clinically significant.

Height

Average heights at baseline were similar (less than 1 inch difference between groups). Height values on average increased in all treatment groups; however, the increase was numerically smaller in the PHEN/TPM-treated subjects compared to placebo-treated subjects (Table 51). Mean height Z-scores went down in all treatment groups, although average Z-scores at Week 56 were between 0 and 1 (i.e., slightly above age- and sex-referenced means). This is not unexpected as obese children tend to be taller than their non-obese peers, in part, due to earlier onset of puberty and age of peak height velocity. However, this height differential

[67] Javed F, Yu W, Thornton J, Colt E. Effect of fat on measurement of bone mineral density. Int J Body Compos Res. 2009 Jul 1;7(1):37-40. PMID: 21318078; PMCID: PMC3035852.

[68] Subject (b) (6) randomized to placebo had baseline TBLH Z-score of -1.3 and lumbar spine of -1.0. Subject discontinued early (listed as parent withdrawal) and did not have a follow-up DXA scan; Subject (b) (6) randomized to mid-dose PHEN/TPM had baseline TBLH and lumbar spine Z-score of 0.4 and 0.1, respectively. At Week 56 visit, both the TBLH and lumbar spine Z-scores had declined to 0.3 and -0.5, respectively.

becomes smaller over time.[69] Larger reductions in height Z-scores were noted in PHEN/TPM-treated subjects versus placebo-treated subjects (Table 52). A higher proportion of PHEN/TPM subjects had a categorical reduction in Z-score compared to placebo subjects. There were 2 PHEN/TPM treated subjects with a Z-score decrease greater than 1.0 and none in the placebo group; no subjects had a reduction >2.0 at Week 56.

Reviewer Comment: The two subjects with height Z-scores that decreased greater than 1.0 were reviewed. Subject (b) (6), a 12-year-old boy at baseline stood 180.4 cm (~5ft, 11in) and had a bone age read as 15.5 years, height Z-score of 3.98. Over the course of the study, he had 16 identical heights and a bone age of 18.0 and height Z-score of 2.96 at Week 56. The other subject was a white Hispanic 13-year-old boy, who at baseline stood 156.9 cm (~5ft, 2in), Tanner II, and had a bone age read as 17.0 y. At Week 56, Tanner stage was IV, bone age was 19.0 y, height was essentially unchanged (-0.2 cm). Height Z-score at baseline was 0.14 and -1.0 at Week 56.

The first subject had 16 identical heights, which seems unlikely, and baseline and final height Z-scores are well above average. The second subject had an advanced bone age of 17 y given his chronologic age and Tanner stage at baseline, which suggests he was near or at final adult height. This subject was randomized to high-dose PHEN/TPM and lost approximately 15 kg, BMI went from 35 to 28.9 kg/m^2, representing a 17% change in BMI. The limited number of subjects with this categorical decrease in height Z-score, no previous growth trajectory information, and data inconsistencies make it difficult to determine causality.

Table 51. Summary of Height (cm) by Treatment Week and Change from Baseline – Safety population

Height (cm)	**Mid-dose PHEN/TPM** (N=54)	**High-dose PHEN/TPM** (N=113)	**Placebo** (N=56)
Baseline			
N	54	113	56
Mean (SD)	168.55 (8.04)	166.33 (7.82)	167.15 (7.6)
Median	167.55	166.40	166.55
Min, max	150.0, 185.0	147.6, 184.1	148.2, 190.7
Week 56/ET			
N	38	82	32
Mean (SD)	170.77 (8.67)	167.70 (7.95)	169.70 (7.76)
Median	171.75	167.65	167.80

[69] De Leonibus C, Marcovecchio ML, Chiavaroli V, de Giorgis T, Chiarelli F, Mohn A. Timing of puberty and physical growth in obese children: a longitudinal study in boys and girls. Pediatr Obes. 2014 Aug;9(4):292-9. doi: 10.1111/j.2047-6310.2013.00176.x. Epub 2013 May 27. PMID: 23713062.

Height (cm)	**Mid-dose PHEN/TPM** (N=54)	**High-dose PHEN/TPM** (N=113)	**Placebo** (N=56)
Min, max	151.5, 187.6	149.0, 185.0	157.0, 191.3
Change from Baseline			
N	38	82	32
Mean (SD)	1.71 (2.35)	1.60 (2.20)	3.01 (3.32)
Median	1.00	1.10	1.95
Min, max	-2.6, 6.9	-2.8, 7.8	-0.5, 12.6
Treatment Difference PHEN/TPM - PBO	-1.30	-1.41	

Source: Response to IR, submitted 1 March 2022 (SD#1175), Table 5; Treatment differences manually derived using mean values

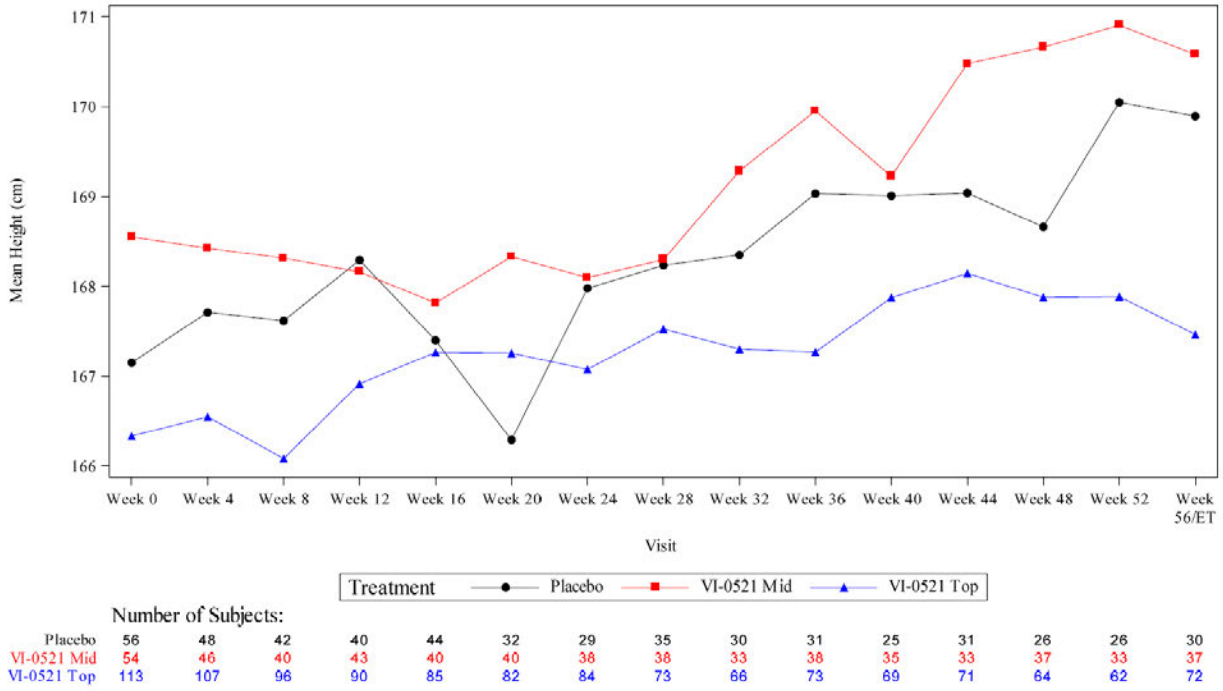


Figure 19. Height (cm) over time – Safety population (observed data)

VI-0521 represents PHEN/TPM; Top represents high-dose PHEN 15 mg/TPM 96 mg
Source: Response to FDA IR, submitted 24 March 2022 (SD#1183), Figure 6a

Table 52. Summary of Height Z-score by Treatment Week and Change from Baseline – Safety population

Height Z-score	**Mid-dose PHEN/TPM** (N=54)	**High-dose PHEN/TPM** (N=113)	**Placebo** (N=56)
Baseline			

Height Z-score	**Mid-dose PHEN/TPM** (N=54)	**High-dose PHEN/TPM** (N=113)	**Placebo** (N=56)
N	54	113	56
Mean (SD)	1.04 (0.99)	0.89 (1.03)	1.01 (0.96)
Median	1.18	0.79	1.01
Min, max	-1.46, 3.98	-1.37, 3.77	-1.09, 4.11
Week 56/ET			
N	38	82	32
Mean (SD)	0.75 (0.98)	0.53 (1.05)	0.74 (0.95)
Median	0.99	0.40	0.82
Min, max	-1.61, 2.97	-1.76, 3.11	-1.10, 3.70
Change from Baseline			
N	38	82	32
Mean (SD)	-0.28 (0.26)	-0.24 (0.35)	-0.13 (0.30)
Median	-0.27	-0.21	-0.07
Min, max	-1.01, 0.29	-1.12, 0.94	-0.66, 0.63

Source: Response to IR, submitted 1 March 2022 (SD#1175), Table 6

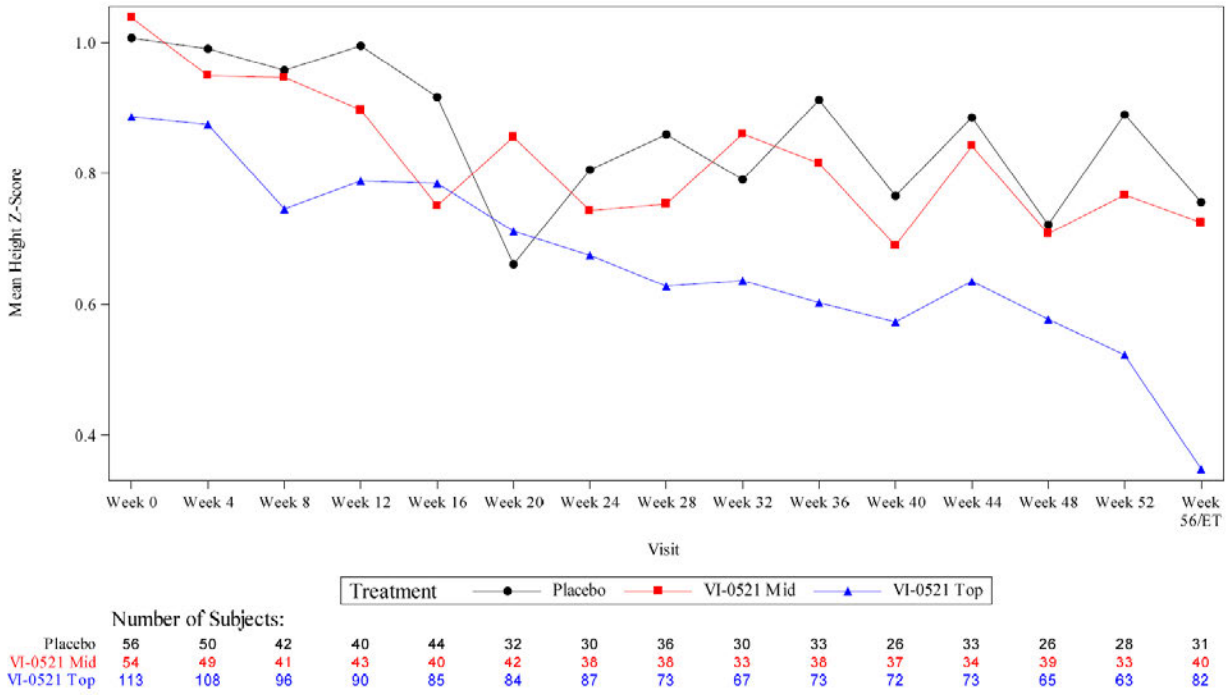


Figure 20. Mean Height Z-score over time – Safety population (observed data)

VI-0521 represents PHEN/TPM; Top represents high-dose PHEN 15 mg/TPM 96 mg
Source: Response to FDA IR, submitted 24 March 2022 (SD#1183), Figure 7a

Height velocity

After the first 2 years of life, height velocity in pre-pubertal children is typically slow at 5 to 6 cm per year until adolescence, which is characterized by substantial growth. The onset is affected by a variety of factors including pubertal onset, nutritional status, and genetics. Peak height velocity averages 9 cm/year in girls at age 12 or Tanner stage III, and 10 cm/year in boys two years later during Tanner stage IV.[70] In this study, the majority of girls (80%) and 50% of the boys were Tanner stage IV and V.

Differences in average height velocity or centimeters of linear growth achieved between baseline and Week 56 in PHEN/TPM-treated and placebo-treated subjects were evaluated. In this exploratory descriptive summary, a lower height velocity was observed in the PHEN/TPM versus placebo groups (estimated treatment difference of approximately -1.3 to -1.4 cm/year). This pattern was also noted in the subgroups defined by Tanner stage at baseline, sex, age group, and race. Numerically larger differences were noted in younger individuals, earlier pubertal stages, and in males. Height-velocity Z-scores for all treatment groups were below 0 at baseline and decreased over time.

Reviewer Comment: The lower height velocity Z-scores at baseline for this study population may not be unexpected given that the reference group used to derive height velocity Z-scores excluded obese children. Pubertal onset is earlier on average in obese children which in turn may impact the timing of peak height velocity compared to non-obese peers.[71] In a longitudinal study of obese and non-obese children, lower overall peak height velocity was exhibited in obese compared to their non-obese peers.[72] However, it remains uncertain why there is a numerical difference in height velocity between the PHEN/TPM-treated and placebo-treated groups all of whom are obese, if the observed difference is related to weight loss, and what the clinical significance, if any, there may be.[73] Note average height (not velocity) Z-scores at Week 56 were slightly above zero (or above the average in the reference population). A limitation of this study is that height velocity before entry into this study was unknown, so it is difficult to determine if these differences represent a treatment-related reduction in height velocity versus expected trajectories of growth.

[70] Rogol AD, Clark PA, Roemmich JN. Growth and pubertal development in children and adolescents: effects of diet and physical activity. Am J Clin Nutr. 2000 Aug;72(2 Suppl):521S-8S. doi: 10.1093/ajcn/72.2.521S. PMID: 10919954.
[71] Height velocity Z-score was calculated based on Equation 2 and Supplemental Table 2a from Kelly A, Winer KK, Kalkwarf H, Oberfield SE, Lappe J, Gilsanz V, Zemel BS. Age-based reference ranges for annual height velocity in US children. J Clin Endocrinol Metab. 2014 Jun;99(6):2104-12. doi: 10.1210/jc.2013-4455. Epub 2014 Mar 6. PMID: 24601728; PMCID: PMC4037731.
[72] De Leonibus C, Marcovecchio ML, Chiavaroli V, de Giorgis T, Chiarelli F, Mohn A. Timing of puberty and physical growth in obese children: a longitudinal study in boys and girls. Pediatr Obes. 2014 Aug;9(4):292-9. doi: 10.1111/j.2047-6310.2013.00176.x. Epub 2013 May 27. PMID: 23713062.
[73] Dietz WH, Hartung R. Changes in Height Velocity of Obese Preadolescents During Weight Reduction. Am J Dis Child. 1985;139(7):705–707. doi:10.1001/archpedi.1985.02140090067031

Table 53. Height velocity (cm/year) and Z-score at Week 56 overall and by subgroups – Safety population

Group	Parameter	Statistic	Mid-dose PHEN/TPM (N=54)	High-dose PHEN/TPM (N=113)	Placebo (N=56)
Overall	Height velocity	N	40	82	31
		Mean (SD)	1.57 (2.12)	1.47 (2.09)	2.84 (3.00)
		Median	0.95	1.11	1.96
		Difference	-1.27	-1.37	
	Z-score	Mean (SD)	-2.41 (3.25)	-2.23 (2.78)	-1.04 (2.36)
		Median	-1.16	-1.58	-0.49
Tanner II or III	Height velocity	N	13	30	13
		Mean (SD)	3.15 (2.23)	2.39 (2.38)	4.28 (3.68)
		Median	3.36	2.00	3.24
		Difference	-1.13	-1.89	
	Z-score	Mean (SD)	-1.63 (2.44)	-2.09 (2.04)	-0.63 (1.54)
		Median	-0.64	-1.60	-0.27
Tanner IV or V	Height velocity	N	27	52	18
		Mean (SD)	0.81 (1.62)	0.94 (1.72)	1.80 (1.90)
		Median	0.64	0.57	1.17
		Difference	-0.99	-0.86	
	Z-score	Mean (SD)	-2.78 (3.55)	-2.31 (3.15)	-1.33 (2.82)
		Median	-1.28	-1.44	-0.59
Male	Height velocity	N	19	39	16
		Mean (SD)	2.93 (1.99)	2.22 (2.42)	4.56 (3.18)
		Median	2.67	1.87	3.53
		Difference	-1.63	-2.34	
	Z-score	Mean (SD)	-0.90 (1.40)	-2.18 (2.18)	-0.41 (1.23)
		Median	-0.76	-1.65	-0.14
Female	Height velocity	N	21	43	15
		Mean (SD)	0.34 (1.38)	0.79 (1.47)	1.01 (1.23)
		Median	0.28	0.47	0.74
		Difference	-0.67	-0.22	
	Z-score	Mean (SD)	-3.77 (3.84)	-2.28 (3.26)	-1.71 (3.06)
		Median	-1.79	-1.10	-0.69
Age 12-14 yr	Height velocity	N	23	45	18
		Mean (SD)	2.17 (2.11)	1.95 (1.74)	4.08 (3.27)
		Median	1.73	1.71	3.07
		Difference	-1.91	-2.13	
	Z-score	Mean (SD)	-1.59 (1.65)	-1.89 (1.47)	-0.74 (1.41)
		Median	-1.11	-1.62	-0.59
Age 15-16 yr	Height velocity	N	17	37	13

Group	Parameter	Statistic	Mid-dose PHEN/TPM (N=54)	High-dose PHEN/TPM (N=113)	Placebo (N=56)
		Mean (SD)	0.76 (1.92)	0.88 (2.35)	1.12 (1.37)
		Median	0.63	0.28	0.74
		Difference	-0.36	-0.24	
	Z-score	Mean (SD)	-3.51 (4.44)	-2.65 (3.80)	-1.44 (3.29)
		Median	-1.24	-1.24	-0.23
Black	Height velocity	N	8	22	4
		Mean (SD)	1.19 (2.52)	1.62 (2.39)	3.06 (5.75)
		Median	0.68	0.69	0.28
		Difference	-1.87	-1.44	
	Z-score	Mean (SD)	-2.69 (3.04)	-2.08 (2.29)	-1.94 (3.08)
		Median	-1.24	-1.89	-2.00
Non-Black	Height velocity	N	32	60	27
		Mean (SD)	1.66 (2.05)	1.41 (1.99)	2.81 (2.56)
		Median	1.38	1.27	2.10
		Difference	-1.15	-1.40	
	Z-score	Mean (SD)	-2.33 (3.34)	-2.29 (2.96)	-0.90 (2.28)
		Median	-1.10	-1.49	-0.27

Source: Response to IR submitted 24 March 2022 (SD#1183), Tables 5a-e; Height velocity calculated as the difference in height, divided by the difference in age between baseline and Week 56 visit; Treatment difference from placebo manually derived by clinical reviewer using mean values.

Bone Age

X-rays of the left hand were evaluated to determine a subject's bone age at Baseline and at Week 56/ET. Bone age was determined by a radiologist using the Greulich Pyle method. The radiologist was not able to review previous bone age assessments for a given subject. The overall mean bone age at baseline was approximately 16 years which was 2 years older than the overall mean chronological age at baseline.

Table 54. Bone Age Assessments by Treatment Week – Safety population

Bone Age	Mid-dose PHEN/TPM (N=54)	High-dose PHEN/TPM (N=113)	Placebo (N=56)
Baseline			
N	35	83	42
Mean (SD)	16.21 (1.59)	15.96 (1.73)	15.73 (1.70)
Median	17.0	16.0	15.5
Min, max	13.5, 19.0	11.0, 19.0	13.0, 18.0
Week 56/ET			
N	30	70	27

Bone Age	**Mid-dose PHEN/TPM** (N=54)	**High-dose PHEN/TPM** (N=113)	**Placebo** (N=56)
Mean (SD)	16.95 (1.22)	17.09 (1.46)	16.63 (1.29)
Median	17.0	17.5	17.0
Min, max	14.0, 19.0	13.5, 19.0	14.0, 18.0

Source: OB-403 CSR, Table 14.3.2.3

The following table describes the change from baseline. The mean and median change in all treatment groups was approximately 1 year which is consistent with the length of the study.

Table 55. Change from Baseline to Week 56/ET in Bone Age – Safety population

Bone Age	**Mid-dose PHEN/TPM** (N=54)	**High-dose PHEN/TPM** (N=113)	**Placebo** (N=56)
Change from Baseline			
n	21	56	23
Mean (SD)	0.93 (0.93)	0.93 (0.94)	0.98 (1.11)
Median	1.0	1.0	1.0
Min, max	-1.0, 3.0	-1.0, 2.5	-1.0, 3.0

Source: OB-403 CSR, Table 14.3.2.3

Reviewer Comment: Obesity in adolescents is associated with accelerated bone age, and therefore, the 2 years difference between bone age and chronologic age at baseline is not unexpected in this study population.[74, 75] The exact etiology for advanced skeletal maturity is unclear, but changes in sex hormones and insulin secretion have been implicated.

There were several subjects that had Baseline and Week 56 X-rays that were not included in the change from baseline analysis because the X-ray was outside the baseline window. For example, 14 subjects in the high-dose group were not included; 3 did not have Baseline X-rays and 11 subjects had Baseline X-rays post-randomization (range Day 1 to Day 128). The change from Baseline in bone age of all excluded subjects with Baseline (post-randomization) and Week 56/ET X-rays was not different from the analyzed population. There does not appear to be a treatment effect of PHEN/TPM on skeletal maturation as measured by bone age.

[74] Klein KO, Newfield RS, Hassink SG. Bone maturation along the spectrum from normal weight to obesity: a complex interplay of sex, growth factors and weight gain. J Pediatr Endocrinol Metab. 2016 Mar;29(3):311-8. doi: 10.1515/jpem-2015-0234. PMID: 26565541.

[75] de Groot CJ, van den Berg A, Ballieux BEPB, Kroon HM, Rings EHHM, Wit JM, van den Akker ELT. Determinants of Advanced Bone Age in Childhood Obesity . Horm Res Paediatr. 2017;87(4):254-263. doi: 10.1159/000467393. Epub 2017 Mar 31. PMID: 28365712; PMCID: PMC5637288.

8.5.2. Sexual Development

Puberty maturation was assessed using Tanner staging, a sex specific 5-point scale of secondary sexual characteristics. Boys were rated for genital development and pubic hair growth, and girls were rated for breast development and pubic hair growth. Tanner staging was conducted at Baseline and Week 56/ET by site personnel trained on the proper technique for these assessments. Sex hormones were not measured in this trial. The following tables present Tanner staging at baseline and Week 56/ET.

Reviewer Comment: Interpretation of these results is complicated by missing data, but in general, there appears to be similar patterns across treatment groups (i.e., higher proportions of subjects in later stages of puberty (e.g., IV, V) at Week 56/ET than at baseline).

Table 56. Tanner staging - Females

Females	Tanner Stage	Mid-dose PHEN/TPM n=28	High-dose PHEN/TPM n=63	Placebo n=30
Baseline	I	0	0	0
	II	2 (7.1)	4 (6.3)	2 (6.7)
	III	4 (14.3)	6 (9.5)	5 (16.7)
	IV	11 (39.3)	22 (34.9)	9 (30.0)
	V	11 (39.3)	31 (49.2)	14 (46.7)
Week 56/ET	**Tanner Stage**	**Mid-dose PHEN/TPM n=19**	**High-dose PHEN/TPM n=44**	**Placebo n=14**
	I	0	0	0
	II	0	0	0
	III	0	3 (6.8)	1 (7.1)
	IV	7 (36.8)	10 (22.7)	3 (21.4)
	V	12 (63.2)	31 (70.5)	10 (71.4)

Source: Response to IR, submitted 19 February 2022 (SD#1154), Request 2
Note: Percentages are calculated using total gender-specific n's in each treatment group at each timepoint.

Table 57. Tanner staging - Males

Males	Tanner Stage	Mid-dose PHEN/TPM n=26	High-dose PHEN/TPM n=50	Placebo n=26
Baseline	I	0	1 (2.0)*	0
	II	4 (15.4)	17 (34.0)	5 (19.2)
	III	6 (23.1)	10 (20.0)	11 (42.3)
	IV	9 (34.6)	15 (30.0)	5 (19.2)
	V	7 (26.9)	7 (14.0)	5 (19.2)
Week 56/ET	**Tanner Stage**	**Mid-dose PHEN/TPM**	**High-dose PHEN/TPM**	**Placebo**

		n=19	n=34	n=16
	I	0	1 (2.9)*	0
	II	0	2 (5.9)	0
	III	4 (21.1)	5 (14.7)	3 (18.8)
	IV	5 (26.3)	14 (41.2)	8 (50.0)
	V	10 (52.6)	12 (35.3)	5 (31.3)

Source: Response to IR, submitted 19 February 2022 (SD#1154), Request 2
Note: Percentages are calculated using total gender-specific n's in each treatment group at each timepoint.
*The subject with Tanner Stage I at Baseline and Week 56/ET is the same subject (b) (6) who was early terminated from the study one month after Baseline visit.

8.5.3. Cognitive Function

To evaluate cognitive function, specifically assessments of memory, several tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB) were conducted at Baseline, Week 16, and Week 56. The tests included assessments of episodic memory and learning assessed by the Paired Associates Learning (PAL) tasks, immediate and delayed recognition memory assessed by Pattern Recognition Memory (PRM) tasks, and visuospatial working memory assessed by Spatial Span (SSP) tasks. A higher score was favorable for each test except the PALTEA task (i.e., lower score better). Approximately 131 subjects had Baseline and Week 56 CANTAB testing available for analysis. To aid in our interpretation of these results, the Division of Neurology 1 was consulted.

Specification	Sense	Description	Range
PAL Total Errors Adjusted (PALTEA)	Lower is better	'Better' means that the indicated group showed greater change from baseline in the direction of fewer errors. In this context, a lower (or more negative change) in PALTEA score = better performance.	0-137
PAL First Attempt Memory Score (PALFAMS)	Higher is better	'Better' means that the indicated group showed greater change from baseline in the direction of a higher first attempt memory score. In this context, a higher (or more positive change) in PALFAMS score = better performance.	0-27
PRM Percent Correct Immediate (PRMPCI)	Higher is better	'Better' means that the indicated group showed greater change from baseline in the direction of a higher percentage correct on immediate recall score. In this context, a higher (or more positive change) in PRMPCI score = better performance.	0-100
PRM Percent Correct Delayed (PRMPCD)	Higher is better	'Better' means that the indicated group showed greater change from baseline in the direction of a higher percentage correct on delayed recall score. In this context, a higher (or more positive change) in PRMPCI score = better performance.	0-100
SSP Forward Span Length (SSPFSL)	Higher is better	'Better' means that the indicated group showed greater change from baseline in the direction of a higher forward span length. In this context, a higher (or more positive change) in SSPFSL score = better performance.	2-9

The results from the CANTAB testing at Week 56 in subjects with both the baseline and Week 56 assessments are shown below.

Table 58. CANTAB testing results

	Mid-dose PHEN/TPM (N=34)[1] n (%)	High-dose PHEN/TPM (N=70) n (%)	Placebo (N=27) n (%)
PAL, Total Errors Adjusted (PALTEA)			
Baseline	7.8 (10.0)	8.4 (11.1)	9.1 (10.4)
Week 56	8.1 (10.9)	7.8 (10.0)	7.3 (9.0)
Change from BL	0.3 (8.4)	-0.6 (8.6)	-1.7 (7.7)
LS Mean Change from BL	0.1 (1.2)	-0.6 (0.8)	-1.4 (1.4)
LS Mean difference from Placebo (95% CI)	1.5 (-2.1, 5.0)	0.8 (-2.3, 4.0)	
p-value	0.43	0.60	

PAL, First Attempt Memory Score			
Baseline	15.0 (3.8)	15.3 (3.6)	15.0 (4.0)
Week 56	15.2 (4.2)	15.7 (3.7)	15.7 (3.3)
Change from BL	0.2 (4.2)	0.4 (3.5)	0.7 (3.6)
LS Mean Change from BL	0.1 (0.6)	0.5 (0.4)	0.6 (0.6)
LS Mean difference from Placebo (95% CI)	-0.5 (0.21, 1.1)	-0.1 (-1.5, 1.4)	
p-value	0.54	0.93	
PRM, Percent Correct Immediate			
Baseline	84.5 (17.9)	83.5 (18.3)	89.1 (12.9)
Week 56	89.6 (12.7)	83.6 (17.3)	85.8 (14.2)
Change from BL	5.1 (18.6)	0.1 (20.4)	-3.3 (17.3)
LS Mean Change from BL	4.5 (2.4)	-1.1 (1.7)	-0.7 (2.7)
LS Mean difference from Placebo (95% CI)	5.3 (-1.8, 12.3)	-0.3 (-6.5, 5.9)	
p-value	0.14	0.92	
PRM, Percent Correct Delayed			
Baseline	70.9 (17.7)	75.6 (18.8)	74.9 (20.1)
Week 56	78.0 (19.6)	77.7 (19.2)	79.2 (15.1)
Change from BL	6.7 (16.9)	1.9 (23.6)	4.3 (17.8)
LS Mean Change from BL	4.6 (2.9)	2.9 (2.0)	4.9 (3.2)
LS Mean difference from Placebo (95% CI)	-0.3 (4.4)	-2.1 (3.8)	
p-value	0.95	0.59	
SSP, Forward Span Length			
Baseline	6.9 (1.4)	7.0 (1.4)	6.7 (1.6)
Week 56	7.5 (1.5)	7.1 (1.4)	7.0 (1.4)
Change from BL	0.7 (1.4)	0.1 (1.6)	0.3 (1.5)
LS Mean Change from BL	0.7 (0.2)	0.2 (0.2)	0.3 (0.2)
LS Mean difference from Placebo (95% CI)	0.4 (-0.2, 1.1)	-0.1 (-0.7, 0.5)	
p-value	0.17	0.74	

1. Subset of subjects with both Baseline and Week 56 assessments available
Note: With the exception of the PALTEA test, a higher score represents an improvement
Source: Response to FDA IR, submitted 30 March 2022 (SD#1185), Table 5

Based on the review of the CANTAB study and the applicant's response to their information requests, the consultative team determined the results from the CANTAB cannot sufficiently determine whether PHEN/TPM affects cognitive performance for the following reasons. Please see the Appendix for the full consultative report from the Division of Neurology 1.

- The sample size at Week 56 precludes detection of smaller sized effects on cognitive function
- Cognitive domains which have been affected by topiramate treatment in topiramate trials of adolescents were not assessed this trial, specifically language
- There was no motor or visual screening to exclude subjects with limitations which might affect the results
- There was an imbalance for ADHD diagnosis at baseline. A higher percentage of placebo-treated subjects with ADHD (12.5%) versus mid-dose PHEN/TPM (7.4%) and high-dose PHEN/TPM (6.2%) may skew the results in favor of the PHEN/TPM treatment arms

The consultant and this reviewer reviewed the database for cognitive-related adverse events and noted the following TEAEs:

Table 59. Cognitive-related adverse events

Cognitive-related Preferred Term / "Verbatim Term"	**Mid-dose PHEN/TPM** (N=54)	**High-dose PHEN/TPM** (N=113)	**Placebo** (N=56)
Feeling abnormal / "mental fogginess"	0	1 (0.9)	0
Somnolence / "sleepiness"	0	2 (1.8)	0
Fatigue / "fatigue"	0	3 (2.7)	1 (1.8)
Educational Problem / "declining school performance"	0	0	1 (1.8)

Source: adae.xpt dataset; Dr. Erten-Lyons – DN1 consult report

Reviewer Comment: The number of adverse events possibly related to cognitive ability were low in number and therefore definitive conclusions regarding relatedness to PHEN/TPM cannot be made.

8.6. Safety Analyses by Demographic Subgroups

See section 8.5.1 for descriptive summaries of change in bone mineral density and height by baseline characteristics.

8.7. Specific Safety Studies/Clinical Trials

None.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No neoplasms were reported in this study.

8.8.2. Human Reproduction and Pregnancy

There were no pregnancies during this trial.

8.8.3. Pediatrics and Assessment of Effects on Growth

See Section 8.5, Analysis of Submission-Specific Safety Issues.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Phentermine is currently controlled as a Schedule IV (non-narcotic) drug. The Agency's Controlled Substance Staff (CSS) reviewed the abuse liability of PHEN/TPM as part of the original approval. CSS concluded the abuse potential of PHEN/TPM appeared consistent with a Schedule IV status.

In this trial, no adolescent subjects reported an event related to a euphoric mood. There were no reported overdoses. Abrupt withdrawal of topiramate has been associated with increases in seizure activity. The label for Qsymia recommends a gradual tapering from the highest dose of PHEN/TPM. There were no seizures reported during this trial.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

The most recent Periodic Benefit-Risk Evaluation Report (PBRER) submitted 14 September 2021 and covering the reporting period of 18 July 2020 to 17 July 2021 was reviewed as part of this submission. The estimated cumulative exposure to PHEN/TPM was 757,596 individuals exposed and interval exposure covering the PBRER reporting period was 59,184 individuals exposed. Review of the PBRER did not identify any new significant safety issues with the clinical use of PHEN/TPM in the postmarket setting.

8.9.2. Expectations on Safety in the Postmarket Setting

There is substantial postmarket experience with phentermine and topiramate alone and with PHEN/TPM. Study OB-403 was generally consistent with the known safety profile of PHEN/TPM in adults. Despite a reduction in bone mineral density observed with PHEN/TPM treatment in this population, measures of bone mineral density remained within normal range. Therefore, it is expected that postmarket safety will be consistent with the known safety profile. Safety concerns will be addressed in labeling to inform healthcare providers and consumers/caregivers.

8.9.3. Additional Safety Issues From Other Disciplines

None

8.10. Integrated Assessment of Safety

There were no fatal adverse events in this trial.

Two subjects (1.8%) in the high-dose PHEN/TPM group reported a total of 6 serious adverse events. One subject reported a bile duct stone requiring hospitalization, and the other subject reported depression (2 events) and suicidal ideation (3 events).

Nine subjects discontinued due to an adverse event. One (1.8%) in the mid-dose group, 5 (4.4%) in the high-dose group, and 3 (5.4%) in the placebo group. Most AEs leading to discontinuation were due to psychiatric disorders (depression, anxiety, suicidal ideation).

Adverse events associated with PHEN/TPM treatment in this trial of obese adolescents was generally consistent with its known safety profile, although there are findings that should be considered in labeling and in the design of future pediatric trials for weight management. Of note, there were no pregnancies and therefore no fetal exposure to PHEN/TPM. Other events of interest that were not observed in this trial include nephrolithiasis, acute angle glaucoma, oligohidrosis and hyperthermia, seizure, hypoglycemia, hypotension, overdose or abuse, or Hy's Law were observed.

- Suicidality and depression

Risk of suicidality, mood, and sleep disorders are listed as warnings and precautions in the Qsymia label. One subject while on mid-dose PHEN/TPM experienced serious depression and suicidal ideation. After discontinuation of PHEN/TPM, and resolution of the initial psychiatric events, additional episodes of depression and suicidal ideation requiring hospitalization occurred. A causal relationship with PHEN/TPM cannot be definitively excluded. Overall, obese adolescents treated with PHEN/TPM (mid-dose 7.4%; high-dose 8.8% PHEN/TPM) compared to peers treated with placebo (1.8%) had a higher incidence of adverse psychiatric events. More PHEN/TPM-treated subjects reported adverse events related to depression, anxiety, and insomnia. There was also a larger proportion of PHEN/TPM-treated adolescents with PHQ-9 and C-SSRS individual responses and/or total scores that were potentially clinically important. Five (3%) PHEN/TPM-treated subjects initiated antidepressant medication versus no placebo-treated subjects.

- Bone metabolism and growth

Increases in bone mineral density and bone mineral content at the lumbar spine and total body less head were numerically smaller in the PHEN/TPM-treated group compared to the placebo-treated group after 56 weeks of treatment. This is similar to results observed in the Topamax pediatric epilepsy trial. Larger treatment differences were observed in the total body less head region compared to the lumbar spine region. The cause of PHEN/TPM-related effects on bone in this study are unclear. No association with bicarbonate reduction or weight loss and changes in BMD were observed, however, the amount of weight loss and the degree of bicarbonate reduction may not have been substantial enough to detect an effect. Despite smaller increases in bone mineral density measurements in PHEN/TPM-treated subjects, BMD Z-scores remained greater than 0 (above average for age and sex) in most subjects, and no subjects demonstrated a decline in Z-score to less than -2.0, a BMD Z-score used in combination with fracture history to diagnose osteoporosis. The results from this trial are similar to the published findings in

bariatric surgery studies.

Average heights at baseline were similar (less than 1 inch difference between groups). Height on average increased in all treatment groups, however, the height velocity was lower in the PHEN/TPM-treated subjects compared to placebo-treated subjects (estimated treatment difference approximately -1.3 to -1.4 cm/year). It remains unclear why there is a numerical difference in height velocity between the PHEN/TPM-treated and placebo-treated group, if this difference is related to weight loss or PHEN/TPM's effect on bone, and what the clinical significance, if any, on final adult height may be. Of note, all treatment groups had a height Z-score that was slightly above zero (or above the average in the reference population) at Week 56.

There were no appreciable differences among treatment groups on skeletal maturation assessed by bone age or pubertal progression as evaluated by Tanner staging.

- Increased heart rate

Increased heart rate is a labeled event for Qsymia. At Week 56, the observed mean change in heart rate for obese adolescents was -3.1 bpm in the mid-dose PHEN/TPM group, 5.7 bpm in the high-dose group, and 2.5 bpm in the placebo group. While mean changes at Week 56 did not demonstrate a dose response elevation in heart rate with PHEN/TPM treatment versus placebo treatment, a dose response in the proportion of PHEN/TPM-treated subjects compared to placebo-treated subjects with categorical increases in heart rate of 5, 10, and 20 beats/min and heart rate of 100 beats/min or greater at 2 consecutive visits was noted.

- Metabolic acidosis

In the adult clinical trials of PHEN/TPM, metabolic acidosis manifested as asymptomatic serum reductions in bicarbonate and increase in chloride. This was also observed in this trial. Evidence suggests a dose-response relationship for reduced serum bicarbonate values in PHEN/TPM exposed obese adolescents. Larger reductions in bicarbonate were observed in the PHEN/TPM groups versus the placebo group. Approximately 9% and 16% of mid-dose and high-dose PHEN/TPM-treated subjects, respectively, versus 0% of placebo-treated subjects had a post-randomization bicarbonate value <17 mmol/L. Mean chloride values increased by 2.0 mmol/L and 2.5 mmol/L at Week 56 in the mid-dose, and high-dose PHEN/TPM groups versus a 1.1 mmol/L average increase in the placebo group.

- Increase in creatinine

Similar to observations in obese adults treated with PHEN/TPM, 17% of mid-dose PHEN/TPM and high-dose PHEN/TM obese adolescents exhibited increases in serum creatinine of 0.3

mg/dL or greater compared to 0% in the adult population. A postmarket study of PHEN/TPM in adults noted the increase in serum creatinine represents a reduction in measured GFR. In adults, this effect was reversible upon discontinuation of study drug. In this study, follow-up laboratory values were not available to determine if a similar pattern would be observed in younger subjects.

- Common Adverse Events

In addition to psychiatric events of depression and anxiety, other common adverse events (incidence ≥4%) with an imbalance not favoring PHEN/TPM included dizziness, arthralgia, pyrexia, influenza, and ligament sprain and should be considered in labeling.

9. Advisory Committee Meeting and Other External Consultations

This efficacy supplement was not taken to an advisory committee meeting.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

- Section 1
  - Add indication for chronic weight management in pediatric patients aged 12 years and older with BMI in the 95th percentile standardized for age and sex
- Section 2
  - Add BMI chart for diagnosing obesity in pediatric patients
  - Provide pediatric titration, dose escalation, and stopping rules
- Section 5
  - Include pediatric study-specific information for suicidal behavior and ideation and slowing of linear growth
  - Align section with topiramate label regarding general and pediatric specific information on visual field defects, serious skin reactions, metabolic acidosis, kidney stones, oligohidrosis and hyperthermia
- Section 6
  - Include pediatric adverse reaction table
  - Include pediatric data for increase in heart rate, mood and sleep adverse reactions,

decrease in bone mineral density, slowing of linear growth, and changes in laboratory parameters of serum bicarbonate, creatinine, potassium, and ammonia.

- Section 8
  - Add pediatric use section
- Section 12
  - Add pediatric pharmacokinetic data
- Section 14
  - Add pediatric safety and efficacy trial data:
    - Describe study design, patient population, and discontinuations
    - Describe results of primary endpoint in text
    - Provide figure with percent change in BMI in completers over time through end of randomized period (56 weeks) and ITT analysis
    - Include table of percent BMI change, and proportions losing 5%, 10%, and 15% BMI from baseline
    - Include table of waist circumference, blood pressure, HbA1c, heart rate, and lipids
- Section 17
  - Update section to align with additions to Section 5

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Qsymia currently has a REMS to inform prescribers and patients of reproductive potential about:

- Increased risk of congenital malformations, specifically orofacial clefts, in infants exposed to Qsymia during the first trimester of pregnancy
- Importance of pregnancy prevention for patients of reproductive potential receiving Qsymia
- Need to discontinue Qsymia immediately if pregnancy occurs

The REMS consists of a Medication Guide, Elements to Assure Safety Use (pharmacies that dispense Qsymia must be certified), an implementation system, and a timetable for submission of assessments of the REMS.

Based on review of the submitted application, modification to the REMS is not necessary at this time. No safety concerns requiring risk management beyond labeling were identified. The known and potential safety concerns for Qsymia are monitorable and may be mitigated with

labeling to include information regarding adverse reactions, need for laboratory evaluation and growth monitoring, and consideration of stopping rules for lack of adequate reduction in BMI.

12. Postmarketing Requirements and Commitments

None.

13. Appendices

13.1. References

Literature references are presented as footnotes within the document.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): OB-403

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 110		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)

Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Additional Study Information

Table 60. Schedule of Study Procedures

	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

Source: Appendix 1, OB-403 Protocol

Table 61. Study OB-403 Clinical Laboratory Parameters

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 • total cholesterol • LDL-C • HDL-C • triglycerides	**Urinalysis** • midstream urinalysis with reflex microscopic evaluation • pregnancy test (all female subjects)
	Glycemic testing • HbA1c • insulin • glucose	**Urine Drug Screen** • cannabinoids • amphetamines • cocaine • barbiturates • benzodiazepine • opiates
		Serology • HBsAg • HCV • HIV

Table 62. Brief narratives for subjects with adverse events that led to drug interruption or dose reduction

Subject Age, Gender Dose Group	Preferred Term	Start Study Day	End Study Day	Severity	Relationship	Action Taken	Outcome
	Brief Narratives						
(b) (6) 16, Female	Tonsillar hypertrophy	Day 266	Day 294	Moderate	Not Related	Drug Interrupted / Tonsillectomy & Adenoidectomy	Recovered / Resolved
Dose Group	**Brief Narratives**						
Top-dose	Subject had tonsillectomy and adenoidectomy for the treatment of obstructive sleep apnea. Study drug was interrupted briefly from Day 293 to Day 301. Subject resumed study treatment and completed the study on Day 385.						

Subject Age, Gender Dose Group	Preferred Term	Start Study Day	End Study Day	Severity	Relationship	Action Taken	Outcome
	Brief Narratives						
(b) (6) 16, Male Top-dose	Paraesthesia	Day 179	Day 179	Moderate	Related	Dose Reduced	Recovered / Resolved
	Non-cardiac chest pain	Day 179	Day 179	Mild	Related	Dose Reduced	Recovered / Resolved
	Abdominal pain upper	Day 179	Day 179	Mild	Related	Dose Reduced/ Unscheduled Visit to Re Evaluate Subject and Re Dispense IP	Recovered / Resolved
	Subject experienced the above 3 AEs one day after Study Visit 8 (Week 24) / Day 178 and had an unscheduled visit on the same day (Day 179). All 3 AEs resolved on the same day without sequelae. The site requested down titration on Day 179. Date of last dose was on Day 422 and subject completed the study on Day 423 without any further dose reduction.						
(b) (6) 14, Male Top-dose	Hypertension	Day 24	Ongoing	Mild	Related	Dose Reduced	Not Recovered / Not Resolved
	Tachycardia	Day 219	Day 234	Mild	Related	Dose Reduced	Recovered / Resolved
	Tachycardia	Day 386	Ongoing	Mild	Related	Dose Reduced	Not Recovered / Not Resolved
	Site requested down titration on Day 234 and Day 386. The subject completed the study on Day 402.						
(b) (6) 16, Female Top-dose	Headache	Day 73	Day 83	Mild	Related	Drug Interrupted	Recovered / Resolved
	Subject had a medical history of ongoing tension headaches. Study drug was interrupted briefly from Day 79 to Day 83. Subject resumed study treatment and completed the study on Day 356.						
(b) (6) 13, Male Placebo	Tonsillectomy	Day 35	Day 35	Moderate	Not Related	Drug Interrupted / Conmed	Recovered / Resolved
	Adenoidectomy	Day 35	Day 35	Moderate	Not Related	Drug Interrupted / Conmed	Recovered / Resolved
	Study drug was interrupted from Day 18 to Day 51. Subject was later lost to follow up and early terminated on Day 298.						

Subject Age, Gender Dose Group	Preferred Term	Start Study Day	End Study Day	Severity	Relationship	Action Taken	Outcome
	Brief Narratives						
(b) (6) 14, Male Mid-dose	COVID-19	Day 183	Day 210	Moderate	Not Related	Drug Interrupted	Recovered / Resolved
	Site did not provide specific dates of drug interruption. However, based on drug accountability record (dispensed on Day 165, returned on Day 208, 12 capsules returned), only 23 doses were taken during this 43 day interval, leaving a gap of up to 20 days. Subject resumed study treatment and returned to study visit on Day 208, but later withdrew consent and was early terminated on Day 315.						
(b) (6) 13, Female Placebo	Dermatitis	Day 302	Ongoing	Moderate	Related	Drug Interrupted / Conmed	Not Recovered / Not Resolved
	Site indicated the last dose prior to interruption was on Day 334 when subject had the last study visit. Subject was then lost to follow up and early terminated on Day 431.						
(b) (6) 14, Female Top-dose	COVID-19	Day 353	Day 377	Moderate	Not Related	Drug Interrupted	Recovered / Resolved
	Site indicated the last dose prior to interruption was on Day 358, but did not provide a date when study drug was restarted. The subject was last dispensed with study drug on Day 320 and skipped 2 visits before completing the study on Day 427. Subject did not return study drug bottle but indicated date of last dose was on Day 358. Drug dispensing and return information suggests this subject was off treatment for approximately 25 days prior to their final assessment, and missed approximately 50 days of dosing between their last dispensation and their last dose of study drug.						

Subject Age, Gender Dose Group	Preferred Term	Start Study Day	End Study Day	Severity	Relationship	Action Taken	Outcome
	Brief Narratives						
(b) (6) 14, Male Placebo	Cough	Day148	Day 174	Mild	Not Related	Drug Interrupted	Recovered / Resolved
	COVID-19	Day 158	Day 175	Moderate	Not Related	Drug Interrupted	Recovered / Resolved with Sequelae
	Site did not provide specific dates of drug interruption. The last study drug dispensation was on Day 181 and date of last dose was on Day 219. Subject had skipped several visits due to COVID restrictions but returned for final study visit on Day 398.						
(b) (6) 14, Male Top-dose	Pyrexia	Day 156	Ongoing	Moderate	Not Related	Drug Interrupted	Not Recovered / Not Resolved
	Pain	Day 156	Ongoing	Moderate	Not Related	Drug Interrupted	Not Recovered / Not Resolved
	Site did not provide specific dates of drug interruption. The last study drug dispensation was on Day 141 and date of last dose was on Day 176. Subject was later lost to follow up and early terminated on Day 378.						
(b) (6) 13, Female Mid-dose	Constipation	Day 174	Day 271	Moderate	Related	Dose Reduced	Recovered / Resolved
	Subject took concomitant medication of magnesium citrate for constipation from Day 243 till Day 271. Site requested down titration on Day 252. Date of last dose was on 392 and subject completed the study on 393						
(b) (6) 14, Female Top-dose	Transaminases increased	Day 53	Day 137	Moderate	Related	Drug Interrupted/Repeat LFTS	Recovered / Resolved
	Narrative for Subject (b) (6) was previously provided in the CSR. Also see Request #6 above for more info.						

Source: Response to IR, submitted 19 January 2022 (SD#1165), Request 10

Clinical Consultation

From: Stephen Voss MD, Clinical Reviewer DGE
Theresa Kehoe MD, Division Director DGE
To: Martin White, SRPM, DDLO
Mary Roberts MD, Clinical Reviewer DDLO
Re: NDA 022580, Qsymia (phentermine/topiramate), anti obesity drug
S-21 efficacy supplement for obese adolescents age 12 to 17 years, submitted 8/25/21
Bone health sub-study
Date: January 23, 2022

Background
Qsymia, also known as VI-0521, is a fixed dose combination of phentermine ('Phen'), a sympathomimetic, and topiramate ('Tpm'), an anticonvulsant. Qsymia was approved in 2012 as an adjunct to diet and exercise for chronic weight management in adults with BMI ≥27 kg/m^2 with weight-related comorbidities, or BMI ≥30 kg/m^2.

Topiramate, which is also approved as Topamax for treatment of seizures and migraine prevention, may induce metabolic acidosis due to carbonic anhydrase inhibition with loss of bicarbonate in the urine. Chronic metabolic acidosis may be associated with nephrolithiasis or nephrocalcinosis, decreased bone mineral density (BMD) and bone mineral content (BMC), osteomalacia or osteoporosis, and may reduce bone growth and weight gain in pediatric patients.

On 1/13/22, a labeling supplement for Topamax was approved, adding results of a 1-year pediatric study in patients age 6-15 years (mean age 10 yr) with partial onset epilepsy. Compared to an active control, the Tpm group exhibited significant reductions in each of the following: serum bicarbonate (mean change from baseline -4.1 mmol/L at month 12); height and height velocity Z-scores; weight; and lumbar spine and total body BMD and BMD Z-scores (DXA). At month 12, mean BMD Z-score declined from baseline by -0.35 SD for lumbar spine and -0.37 for total body less head (TBLH). Decrements in serum bicarbonate correlated with reduced lumbar spine BMD.

Current pediatric efficacy supplement
The Applicant is submitting the final report of a postmarketing-required study of Qsymia in obese adolescents age 12 to <17 years. Based on the association of Tpm with metabolic acidosis and potential for bone toxicity, this 1-year study included assessments of BMD and BMC by DXA. DGE is requested to review the findings and address the following:

- Are the baseline results observed consistent with the expected BMD and BMC for an obese adolescent population?
- According to final imaging report (Appendix 16.1.14), one subject ([redacted] (b) (6)) appears to have had a large decrease in BMD which the report author believes may be the result of using a different DXA scanner at the Week 56 visit. Is this a plausible explanation for this subject's result?
- In an adolescent population, what is considered a clinically significant adverse change in bone mineral density or content?
- Based on your review of the study results, do you agree with the Applicant's conclusion that the substudy results confirm that Qsymia does not have a negative impact on bone health? Why or why not?

Study OB-403
This was a multicenter, randomized, double blind, placebo controlled study to determine the safety and efficacy of Qsymia in obese adolescents. The study was planned to enroll approx. 200 subjects, randomized in a 1:1:2 ratio to receive either placebo (N ≈50), Mid-dose Qsymia (Phen 7.5 mg/Tpm 46 mg; N ≈ 50), or Top-dose (Phen 15 mg/Tpm 92 mg; N ≈ 100), for 56 weeks. The enrollment criteria included age 12 to <17 years at screening; BMI ≥95th percentile for age/gender; Tanner stage ≥2; and absence of potentially confounding factors e.g. Type 1 diabetes, thyroid dysfunction, Cushing syndrome or glucocorticoid use.

In a substudy, DXA of the PA lumbar spine (L1-L4) and whole body was conducted at baseline and week 56 (or early termination). The protocol calls for total body less head (TBLH) which, along with lumbar spine are the preferred skeletal sites for assessment of BMC and areal BMD in most pediatric subjects.[1] The imaging and study reports refer to whole body DXA, so the Applicant will be requested to clarify whether the head was included in analyses. Subjects with juvenile osteoporosis or a history of non-traumatic fracture were excluded from the substudy. DXA was conducted at the study site using Hologic or GE Lunar scanners; acquisition procedures and quality control were coordinated by an imaging contractor, (b) (4). Each site monitored DXA calibration throughout the study using their own phantom, and sent their quality control data to (b) (4) twice a year.

Participation in the substudy was dependent on the subject meeting DXA manufacturer specifications with regard to height and weight limitations, and obtaining of whole body scan was dependent on the ability to position the subject's arms within the limit lines on the table. Treatment-blinded data collection and analysis were conducted by (b) (4) Per the protocol and statistical plan, mean changes from baseline in BMD and in BMC Z-scores (age- and gender-normalized) were evaluated as safety endpoints and summarized descriptively. It does not appear that BMD Z-scores were reported; the Applicant will be requested to submit these if available, and to provide details of the normative databases used to generate Z-scores, and to clarify whether pediatric low-density software for improved bone edge detection was used.

In the overall study, the median age was 14.0 years. The study population was 54% female; 67% white/27% Black or African American/6% others; and 32% Hispanic. At baseline, mean (SD) weight and BMI were 106 (23.7) kg and 37.8 (7.09) kg/m^2, respectively. During the study, the dropout rate was 50%, 28% and 39% of subjects in the placebo, Phen/Tpm Mid-dose and Phen/Tpm Top-dose groups respectively; most of these were classified as losses to follow-up, perhaps in part Covid-related.

At week 56, mean changes from baseline BMI (the primary endpoint) were +3.0%, -8.2% and -12.1% in the placebo, Mid-dose and Top-dose groups respectively. The mean changes from baseline in height were 3.0, 1.7 and 1.6 cm in these groups at week 56. Bone age, which was evaluated by hand/wrist x-rays using the Greulich-Pyle method, showed good correlation with chronologic age and no apparent effect of treatment. Mean changes in serum bicarbonate levels at week 56 were -0.1, -1.4 and -1.7 mmol/L in the placebo, Mid dose and Top dose groups. Serum levels of 1,25-OH-vitamin D, 25-OH-vitamin D, PTH and other bone related biomarkers were not assessed.

A total of 119 subjects (52% of the total study population) enrolled in the DXA substudy, who were randomized to placebo (n=32), Mid-dose (n=29) or Top-dose (n=58). Demographics in the substudy were

[1] https://iscd.org/wp-content/uploads/2021/09/2019-Official-Positions-Pediatric-1.pdf

similar to the overall study population. There were 107 subjects with a lumbar spine and/or whole body scan at baseline, and 66 subjects with a Week 56/EOT scan.

Results - Lumbar spine DXA

Most subjects had increases in BMD, consistent with the expected rapid increase in bone size and density during adolescence. In the subjects with DXA scans at both baseline and week 56, lumbar spine BMD increased by a mean of 5.5% in the placebo group and about 3.4% in each of the active treatment groups. In the study report, the dataset and listings (lumbar spine, and also whole body) include some data on 3 subjects that were not represented in CSR Table 14.3.2.4, which the Applicant will be asked to clarify. The percent changes in the table below are derived from the dataset.

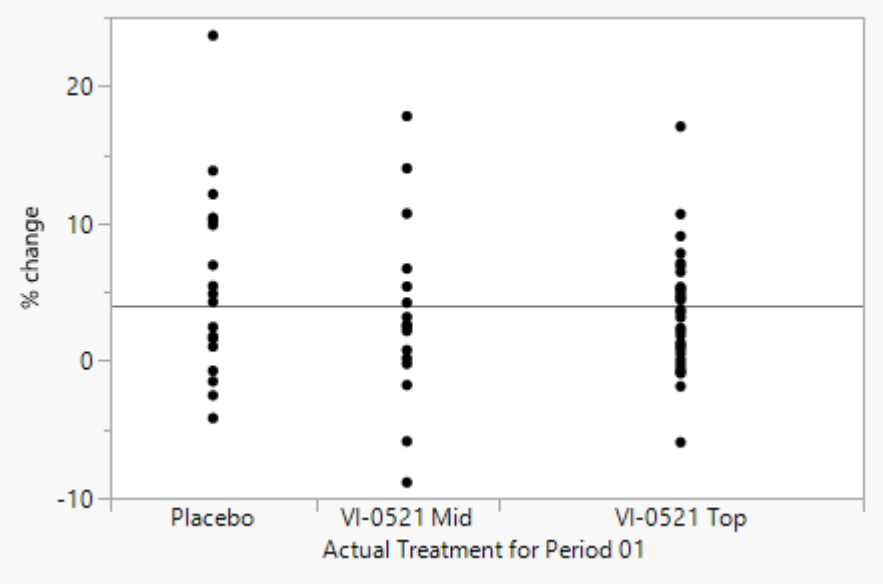
Lumbar spine BMD, by treatment group

	Placebo	Mid-dose	Top dose
Baseline, n	27	20	51
Mean (SD), g/cm^2	1.06 (0.20)	1.16 (0.14)	1.10 (0.19)
Week 56, n	18	16	32
Mean (SD), g/cm^2	1.09 (0.21)	1.22 (0.16)	1.13 (0.19)
Change from baseline, n	17	14	32
Mean (SD), g/cm^2	0.048 (0.065)	0.038 (0.080)	0.035 (0.043)
Percent change, n*	18	16	32
Mean (SD)*	5.54 (6.93)	3.35 (6.76)	3.37 (4.31)

*Percent change data are derived from mo.xpt dataset (which matches Listing 16.2.10) by this reviewer; other data in this table are from CSR Table 14.3.2.4

Individual percent changes in lumbar spine BMD are shown in the figure below. The largest increase in lumbar spine BMD occurred in subject # (b) (6), a 14 y/o male in the placebo arm, with a 23.7% change from baseline. There were 3 subjects with BMD declines >5% from baseline, including one Mid-dose and one Top-dose subject who each had changes of -5.9%; and subject # (b) (6), a 14 y/o male in the Mid-dose group with a -8.9% change. The Final Imaging Report (16.1.14) indicates that the latter subject's baseline and week 56 scans were performed on different machines, concluding that the apparent change may be artefactual. This may be consistent with evidence that BMD on an individual measured on different DXA scanners will vary, especially if the machines are from different manufacturers. Thus, it is generally recommended that, whenever possible, serial measurements should use the same instrument, model and software version. The Applicant will be asked to clarify whether any other subjects' DXA scans were conducted on different machines, and to provide details of their quality control procedures for monitoring DXA instrument stability.

Lumbar spine BMD, % change from baseline at week 56/EOT by individual subject /treatment group



Source: mo.xpt dataset

The table below shows that treatment group differences tended to be greater in the 12-14 y/o and male subgroups. This is partly due to the outlier subjects mentioned above, given the small numbers of subjects in each group. Data for racial subgroups (not shown) were generally consistent with the overall substudy.

Lumbar spine BMD, percent change from baseline by treatment group and demographic subgroup

	Placebo	Mid-dose	Top-dose
Age 12-14 years, n	9	8	19
Mean (SD)	7.48 (8.35)	4.09 (8.59)	3.57 (4.33)
Age 15-16 years, n	9	8	13
Mean (SD)	3.59 (4.89)	2.61 (4.78)	3.08 (4.42)
Female, n	10	10	18
Mean (SD)	1.94 (3.09)	3.92 (7.28)	2.07 (3.26)
Male, n	8	6	14
Mean (SD)	10.03 (7.93)	2.40 (6.32)	5.04 (4.99)

Source: mo.xpt dataset

Mean lumbar spine BMC Z-scores at baseline were > 0 in each treatment group, i.e. above age- and gender-referenced means. This is consistent with typical BMC and BMD findings in healthy overweight or obese adolescents (see discussion below). At week 56 there were modest dose-related declines in mean Z-score (-0.11, -0.18) in the two active treatment groups.

Lumbar spine BMC Z-score, by treatment group

	Placebo	Mid-dose	Top dose
Baseline, n	27	20	50
Mean (SD)	0.54 (0.93)	1.13 (1.09)	0.79 (1.08)
Week 56, n	18	16	32
Mean (SD)	0.41 (0.92)	1.04 (1.03)	0.54 (1.10)
Change from baseline, n	17	14	31
Mean (SD)	-0.01 (0.44)	-0.09 (0.54)	-0.18 (0.43)
Change from baseline, n*	18	16	31
Mean (SD)*	0.01 (0.44)	-0.11 (0.51)	-0.18 (0.43)

*Data derived from mo.xpt dataset (which matches the data in Listing 16.2.10) by this reviewer; other data in this table are from CSR Table 14.3.2.4

Lumbar spine BMC Z-score declines of -0.5 SD or greater, a level that may be considered potentially clinically significant, were reported in 16 subjects including 2/18 subjects in the placebo group (11%); 5/16 subjects in the Mid-dose group (31%), and 9/31 subjects in the Top dose group (29%). The largest decline of -1.0 was reported in a placebo subject.

Results – Whole Body DXA

In the subjects with DXA scans at baseline and week 56, whole body BMD increased by a mean of 4.5% in the placebo group, 2.0% in the Mid-dose group and 0.2% in the Top-dose group.

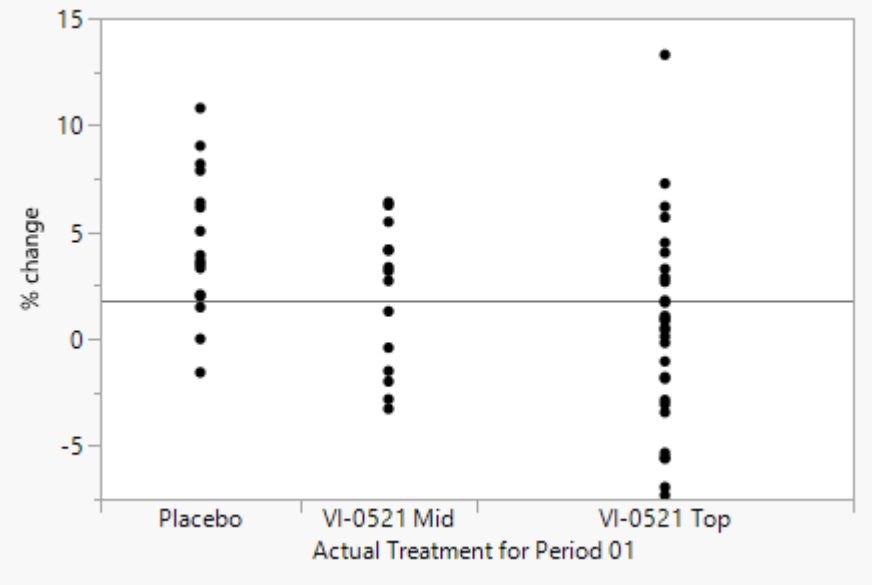
Whole Body BMD, by treatment group

	Placebo	Mid-dose	Top dose
Baseline, n	27	18	49
Mean (SD), g/cm^2	1.02 (0.13)	1.11 (0.12)	1.05 (0.12)
Week 56, n	18	16	32
Mean (SD), g/cm^2	1.06 (0.13)	1.11 (0.14)	1.04 (0.12)
Change from baseline, n	16	13	32
Mean (SD), g/cm^2	0.042 (0.032)	0.025 (0.035)	0.003 (0.045)
Percent change, n*	17	15	32
Mean (SD)*	4.52 (3.30)	1.98 (3.26)	0.23 (4.53)

*Data for percent change are derived from mo.xpt dataset (which matches Listing 16.2.10); other data in this table are from CSR Table 14.3.2.4

Individual-subject percent changes in whole body BMD are shown in the figure below. All 6 of the subjects with whole-body BMD declines >5% were in the Top-dose group (ranging from -5.3% to -7.3%). The Top-dose group also included one positive outlier, a 13 y/o male with whole body BMD increase of 13.3%.

Whole body BMD, percent change from baseline at week 56/EOT by individual subject and treatment group



Source: mo.xpt

All 6 of the subjects with whole body BMD decline >5% were in the younger (age 12-14 yr) subgroup (and as mentioned above, in the Top-dose group). The table below also appears to show that younger subjects accounted for most of the treatment-related reduction in whole body BMD accrual. Both female and male subgroups had smaller whole body BMD increase in the active treatment groups relative to placebo; among the 6 subjects with >5% decline in BMD, 2 were female and 4 were male. Data for racial subgroups (not shown) were generally consistent with the overall substudy.

Whole body BMD, percent change from baseline by treatment group and demographic subgroup

	Placebo	Mid-dose	Top-dose
Age 12-14 years, n	8	7	19
Mean (SD)	6.36 (3.31)	3.02 (3.74)	-0.54 (5.23)
Age 15-16 years, n	9	8	13
Mean (SD)	2.90 (2.41)	1.06 (2.69)	1.36 (3.09)
Female, n	9	10	18
Mean (SD)	2.59 (2.23)	1.79 (3.38)	-0.93 (2.76)
Male, n	8	5	14
Mean (SD)	6.70 (2.99)	2.36 (3.35)	1.73 (5.88)

Source: mo.xpt

There were numerous subjects with whole body BMC reported but no corresponding Z-score. The reason for this is unclear and the Applicant will be asked to clarify. The available Z-score data, summarized in the table below, show dose related declines in the Phen/Tpm groups; compared to the lumbar spine Z-score data, the mean differences from placebo are somewhat greater.

Whole body BMC Z-score, by treatment group

	Placebo	Mid-dose	Top dose
Baseline, n	24	11	35
Mean (SD)	0.68 (1.17)	1.57 (0.92)	0.78 (0.91)
Week 56, n	16	12	23
Mean (SD)	0.73 (1.22)	0.95 (1.18)	0.31 (1.09)
Change from baseline, n	14	9	23
Mean (SD)	0.20 (0.30)	-0.02 (0.26)	-0.24 (0.52)
Change from baseline, n*	15	11	23
Mean (SD)*	0.19 (0.29)	-0.08 (0.29)	-0.24 (0.52)

*Data derived from mo.xpt dataset (which matches the data in Listing 16.2.10) by this reviewer; other data in this table are from CSR Table 14.3.2.4

Relatively large declines in whole body BMC Z-score (≤ -0.5 SD) were reported in 0/15 subjects in the placebo group (0%), 1/11 subjects in the Mid-dose group (9%) and 7/23 subjects in the Top-dose group (30%). There was one subject with a Z-score decline greater than 1.0: a 14 y/o male in the Top-dose group with a change of -1.5 SD from baseline.

Discussion

In adults, studies have generally shown a positive association of BMI with BMD, believed to reflect an adaptive response to increased mechanical loading in overweight or obese individuals. In children and adolescents, most DXA studies have reported increases in whole body and lumbar spine BMD, BMC and bone area in obese compared to normal-weight individuals of the same age.[2] However, DXA data is subject to measurement artifacts related to body composition. In particular, greater thickness of soft-tissues increases the distance between the X-ray fan-beam source and the bones to be evaluated thereby diminishing BMC and bone area measures in some scanners, while having the opposite effect in other scanners with different configurations. There are no evidence-based guidelines to adjust for such factors, therefore interpretation of DXA data in obese individuals may be difficult.

Longitudinal studies in obese patients undergoing bariatric surgery have demonstrated that rapid weight loss is associated with substantial bone loss as measured by DXA. A US study of 61 adolescents and young adults (mean age 17 yr, range 13-23) undergoing Roux-en-Y gastric bypass (RYGB) found that mean whole body BMD Z-score declined from +1.5 to +0.1 in the two years following surgery, mean BMD declined by 7.4%, and change in weight was significantly correlated with change in BMC.[3] In another study in 72 overweight adolescents age 13-18 years undergoing RYGB, mean whole-body BMD Z-score was +2.0 at baseline, with a significant correlation between BMD and baseline weight; at 2 years following surgery, mean BMD Z-score had declined to +0.5, and change in BMD correlated strongly with change in weight.[4]

[2] Leonard MB et al, *Am J Clin Nutr* 80, pp. 514-523, 2004
[3] Kaulfers AD et al, *Pediatrics* 127, p. e961, April 2011
[4] Beamish AJ et al, *Pediatric Obesity* 12, pp. 239-246, June 2017

In study OB-403, subjects generally had above-average (>0) lumbar spine and whole body BMC Z-scores by DXA at baseline, which is consistent with most published data on obese adolescents. Following treatment, with substantial weight loss associated with Phen/Tpm, mean increases in BMD were smaller in the Phen/Tpm groups in comparison to the control group, especially for whole body BMD. Mean BMC Z-scores declined by 0.11 SD and 0.18 SD for lumbar spine in the Mid-dose and Top-dose groups, and by 0.08 SD and 0.24 SD for whole body. The differences from placebo were most apparent in the proportion of subjects with Z-score decline ≥0.5 SD: for lumbar spine these proportions were 11%, 31% and 29% for placebo, Mid-dose and Top-dose groups respectively; and for whole body, 0%, 9% and 30% respectively. It should be noted that despite the declines, BMC Z-scores remained >0 (above average for age/gender) in most subjects, similar to the published findings in bariatric surgery studies. Nevertheless, the data do not appear to support the Applicant's conclusion that there is no evidence of an adverse effect on bone health.

The cause of Phen/Tpm related bone loss in this study is unclear and may be multifactorial, for example a combination of Tpm-related metabolic acidosis and weight loss. If bone growth was restricted by drug treatment in the study, this would also tend to limit BMD increases as measured by DXA, because measurements were not corrected for height. Further evaluation to explore potential correlations between DXA data and other parameters may help clarify the mechanism of Phen/Tpm-related bone loss.

The clinical significance of the BMD and BMC changes in the study, if any, is unknown. DXA data are considered relevant in pediatric patients who may be at increased risk for low bone mass and/or fracture, but there are insufficient data to support a specific "fracture threshold" based on any absolute level of BMD or any extent of change. Although overweight children and adolescents generally have high bone mass, they are reported to have a greater risk of fall-related wrist and forearm fracture compared to their healthy weight peers. Some studies also have shown that fracture risk appears to increase following bariatric surgery.

DGE recommendations

There are numerous questions about DXA methodology and data that should be sent to the Applicant, as discussed in this review. Submission of BMD Z-score (in addition to BMC Z-score) data may be particularly helpful.

We recommend consultation with statistical experts to examine correlations between the observed changes in BMD and BMC Z-scores in study OB-403, with possible contributory factors including serum bicarbonate, body weight and height. Such analyses may help to clarify the mechanism of bone loss, and inform decisions about labeling.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STEPHEN R VOSS
01/24/2022 02:09:55 PM

THERESA E KEHOE
01/24/2022 02:36:39 PM

Division of Neurology Drug Products 1
Consultative Review and Evaluation of Clinical Data

NDA (Serial Number): 22580 (s-21)
Petitioner: Vivus
Drug: Qsymia
Proposed Indication: Weight management in adolescents
Material Submitted: 08/25/2021
Consult Date: 02/01/2022
Date Received / Division: 02/01/2022
Date Review Completed: 04/19/22
Reviewer: Deniz Erten-Lyons, MD

1. Introduction

The sponsor Vivus submitted an efficacy supplement NDA22-580 for V1-0521 (Qsymia) to support the efficacy and safety of Qsymia in the treatment of obesity in adolescents ages 12-17 years of age. Qsymia, a combination of phentermine and topiramate extended-release, has been approved for the treatment of obesity in adults. In adults, it has been associated with an increase in cognitive-related adverse reactions, such as difficulty with concentration/attention, memory and language (word finding). Of the components of Qsymia, phentermine is considered to be a mild stimulant, whereas topiramate has been associated with cognitive adverse events.

The Division of Diabetes, Lipid Disorders and Obesity (DDLO) has asked the Division of Neurology 1 to review the cognitive-related adverse events observed in study ob-403, which is a 1-year randomized placebo-controlled study where adolescents aged 12-17 years old were randomized to receive placebo or Qsymia at two doses: 7.5 mg phentermine/46 mg topiramate or 15 mg phentermine/92 mg topiramate. Cognition was measured using selected tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB).

Specifically, DN1 is asked to comment on the following questions:

1. Do you agree with the sponsor's conclusion that the results do not indicate that Qsymia has significant detrimental effects on any of the CANTAB outcome measures assessed, and thus memory performance, at either timepoint or at any dose level? Why or why not?
2. Based on your review of the information available, comment on the Qsymia label, which includes a warning and precaution regarding cognitive impairment, and whether you recommend any revisions or additions regarding the results of the adverse events observed and/or CANTAB testing.

2. Background

The cognitive adverse events of Qsymia and its individual components, phentermine and topiramate-extended release, are outlined in the FDA Labels for these drugs and will be briefly reviewed. If data is available on cognitive adverse effects in the pediatric population, only the pediatric data will be presented as this is most relevant for this review. For drugs without data in the pediatric population I will summarize data from adult studies.

Qsymia

According to the Qsymia FDA label (version 10/21, sections 5.6 and 6.1), Qsymia can cause cognitive dysfunction such as impairment of concentration/attention, difficulty with memory, and speech or language problems, particularly word-finding difficulties in adults. It is stated that rapid titration or high initial doses of Qsymia may be associated with higher rates of cognitive events such as attention, memory, and language/word-finding difficulties.

Since Qsymia has the potential to impair cognitive function, patients are cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain Qsymia therapy does not affect them adversely. If cognitive dysfunction persists, it is recommended to consider dose reduction or withdrawal of Qsymia for symptoms that are moderate to severe, bothersome, or those which fail to resolve with dose reduction.

In the 1-year controlled trials of Qsymia conducted in adults, the proportion of patients who experienced one or more cognitive-related adverse reactions was 2.1% for Qsymia 3.75 mg/23 mg, 5.0% for Qsymia 7.5 mg/46 mg, and 7.6% for Qsymia 15 mg/92 mg, compared to 1.5% for placebo. These adverse reactions consistent mainly of reports of problems with attention/concentration, memory, and language (word finding). According to the information in the label, these events typically began within the first 4 weeks of treatment, had a median duration of approximately 28 days or less, and were reversible upon discontinuation of treatment. However, it is also stated that individual patients did experience events later in treatment, and events of longer duration.

The safety and effectiveness of Qsymia in pediatric patients below the age of 18 have not been established and is the focus of this efficacy supplement NDA 22-580.

Phentermine

Based on a review on UpToDate (accessed 03/16/2022) phentermine (alone or in combination) has been associated with central nervous system (CNS) effects

such as delirium, mania, and psychosis. Insomnia, irritability, and anxiety have been reported in 24% to 27% of users.

A systematic review of the literature of long-term use of FDA approved medications for weight loss identified symptoms of CNS overstimulation such as insomnia, irritability, anxiety, restlessness, tremors, headache to be associated with phentermine use. [Yanovski SZ, Yanovski JA. Long-term drug treatment for obesity: a systematic and clinical review. JAMA. 2014;311(1):74-86.]

According to the phentermine FDA label Section 5.5 (version 01/2012), phentermine may impair the ability of patients to engage in potentially hazardous activities such as operating machinery or driving a motor vehicle. There are no other cognitive adverse events listed in the label.

Topiramate

Since topiramate has been studied in a population similar to the proposed population under review, adolescents aged 12-17 years old, in this section I will mainly focus on these relevant results.

According to the topiramate FDA label sections 5.6 and 8.4 (version 01/2022) in pediatric epilepsy trials (adjunctive and monotherapy), the incidence of cognitive/neuropsychiatric adverse reactions was generally lower than that observed in adults. These reactions included psychomotor slowing, difficulty with concentration/attention, speech disorders/related speech problems, and language problems.

In the label it is stated that the most frequently reported cognitive/neuropsychiatric reactions in pediatric epilepsy patients during adjunctive therapy double-blind studies were somnolence and fatigue. The most frequently reported cognitive/neuropsychiatric reactions in pediatric epilepsy patients in the 50 mg/day and 400 mg/day groups during the monotherapy double-blind study were headache, dizziness, anorexia, and somnolence.

In the pediatric trials (12 to 17 years of age) in which patients were randomized to placebo or a fixed daily dose of TOPAMAX®, the most common cognitive adverse reaction in pooled double-blind studies in pediatric patients 12 to 17 years of age was difficulty with concentration/attention.

Based on results of topiramate in pediatric migraine (Study MIGR-3006), the incidence of cognitive/neuropsychiatric adverse reactions was increased in TOPAMAX-treated patients compared to placebo. The risk for cognitive/neuropsychiatric adverse reactions was dose-dependent, and was greatest at the highest dose (200 mg). This risk for cognitive/neuropsychiatric adverse reactions was also greater in younger patients (6 to 11 years of age)

than in older patients (12 to 17 years of age). This study will be described in further detail due to its similarity and relevance to the current study under review.

Study MIGR-3006 was a study to assess topiramate treatment for migraine prophylaxis in adolescents [Pandina et al. Cognitive effects of topiramate in migraine patients aged 12-17 years. Pediatr Neurol. 2010 Mar;42(3):187-95]. This study, similar to the study under review, used the CANTAB to assess the cognitive effects of topiramate in migraine patients aged 12-17 years. In this randomized, double-blind, placebo-controlled, multicenter study participants were assigned to placebo, topiramate 50 mg/day, or topiramate 100 mg/day . The study included a pretreatment phase lasting up to 9 weeks, followed by a double-blind phase lasting 16 weeks and a taper-exit phase lasting up to 6 weeks.

In this study, cognitive function was assessed using the following CANTAB tests:

1. Pattern and spatial recognition memory (measure of object recognition)
2. Spatial span (measure of spatial memory span)
3. Paired associates learning (measure of episodic learning and hippocampal function)
4. Reaction time (measure of visual scanning and processing speed)
5. Rapid visual information processing (measure of sustained attention and reaction time),
6. Controlled oral word association test (measure of word fluency).

At the end of the double-blind phase there were 33 participants in the placebo group, 35 in the topiramate 50 mg/day group, and 35 in the topiramate 100 mg/day groups. In this study, topiramate 100 mg/day vs placebo was associated with slight increases in psychomotor reaction times.

The following statistically significant (at the two-sided 0.05 level) differences in mean changes from baseline (in milliseconds) to end of study were observed for topiramate 100 mg/day vs placebo for three tests:

Significant changes from baseline in CANTAB tests in Study MIGR-3006

Test	***Topiramate 100 mg/day***	***Placebo***	***p-value***
Five-choice reaction time	33.7 msec ± 96.0	- 3.5 msec ± 37.4	0.028
Pattern recognition memory mean correct latency	51.3 msec ± 360.6	-132.7 msec ± 256.5	0.027
Rapid visual information processing mean latency	23.0 msec ± 95.6	- 87.9 msec ± 230.1	0.040

In addition, a statistically significant reduction in the change from baseline in the total number of unique words (animals) was observed for topiramate 50 mg/day vs placebo.

No other patterns related to topiramate treatment were observed in the CANTAB measurements related to learning, memory, and visual information processing, except for a potential improvement with topiramate 100 mg/day vs placebo in an accuracy test: spatial span total errors (- 3.7 ± 8.7 vs 1.4 ± 7.6; P = 0.040).

Reviewer Comment: In the pediatric trials (12 to 17 years of age) in which patients were randomized to placebo or a fixed daily dose of TOPAMAX®, the most common adverse reactions was difficulty with concentration/attention. Based on the CANTAB administered to adolescents (12 to 17 years) to assess the effects of topiramate on cognitive function at baseline and at the end of a migraine prophylaxis study (MIGR-300), mean change from baseline in certain CANTAB tests suggests that topiramate treatment may result in psychomotor slowing and decreased verbal fluency.

3. Study Under Review

In this Phase 4, multi-center, randomized, double-blind, placebo-controlled, parallel-design study, 227 subjects were randomized as follows: 57 to placebo, 55 to PHEN/TPM 7.5 mg/ 46 mg group (mid-dose group), and 115 to PHEN/TPM 15 mg/92 mg group (top-dose group). Randomization was stratified by age group (12 to 14 versus 15 to 16 years old) and gender.

As was done in previous studies in adults, all subjects assigned to treatment with VI-0521 initiated treatment with the low-dose (PHEN/TPM 3.75 mg/23 mg) and gradually titrated up to the assigned dose level. The mid-dose group reached the maintenance dose of 7.5 /46 mg at week 3, and the top dose group reached the maintenance dose of 15/92 mg by week 15. The study had a 56-week treatment period (see Table 1 which was obtained from the OB-403 Clinical Study Report (09 August 2021).

Table 1: Study Drug Dose Titration 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-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

Reviewer Comment: The implication of this titration schedule for review of cognitive effects is that at the time of the 16-week cognitive assessments with CANTAB, the group receiving the highest dose of the study drug, 15/92 mg daily, had only been exposed to this dose for one week, while the mid dose had 13 week exposure.

Of the randomized subjects, 4 subjects did not receive study drug, resulting in 56 (24.7%) treated with placebo, 54 (23.8%) treated with mid-dose, and 113 (49.8%) treated with top-dose at the time of the baseline assessments. As a result of discontinuations, at the week 56 cognitive assessment visit, there were 27 participants in the placebo arm, 34 participants in the mid-dose arm, and 70 participants in the top-dose arm.

Since this review's main focus is one of the safety outcomes, the cognitive function tests using CANTAB; only information relevant to this review will be included in the following sections:

Key eligibility criteria were:

Inclusion:

- Being an adolescent ≥ 12 years and < 17 years of age with Tanner Staging of ≥ 2 at the time of Screening with 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.

Exclusion

- Any stimulants used for treatment of attention-deficit/hyperactivity disorder within 3 months of Screening;

- 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, lev and dopamine receptor agonists; or allowed antidepressant use that had not been stable for at least 3 months;

- 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;

Reviewer Comment: It is noted that adolescent with conditions that may impact their cognitive test scores such as ADHD, learning disabilities, or lower IQ have not been excluded from the study, and the sponsor does not provide any information on the number and distribution across study arm groups.

Prior and Concomitant Therapy and Restricted Medications:

While the list for disallowed medications is longer, only disallowed medications that may affect cognitive testing scores are listed below:

- Anticonvulsants used for treatment of seizure disorder, including barbiturates, benzodiazepines, gabapentin 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;
- Treatment for hyperactivity disorder.

Allowed medications:
Benzodiazepine and non-benzodiazepine sleep medications were permitted, provided that the dosage had been stable for at least 1 month prior to Screening, and the frequency of use did not exceed twice a week.

Reviewer Comment: The sponsor should clarify how many of the children in each treatment group are taking benzodiazepines, as even if it is only taken for sleep at night, this may impact cognitive function the following day.

Cognitive assessment of interest: The Cambridge Neuropsychological Test Automated Battery (CANTAB)

The Cambridge Neuropsychological Test Automated Battery (CANTAB) is a self-administered computer test. It contains multiple individual tests that cover 4 cognitive domains including Attention and Psychometric Speed, Executive function, Memory and Emotion and Social Cognition.

In the OB-403 study cognitive function was assessed at Screening (familiarization session only), Baseline, Week 16 (Visit 6), and end of study or early termination. The following tests from CANTAB were included in this study: the Paired Associates Learning Test, Pattern Recognition Memory, and Spatial Span.

A brief description of these tests is provided below:

Paired Associates Learning (PAL) | Cambridge Cognition (accessed March 3, 2022): This is an 8-minute test to assesses visual memory and new learning. Boxes are displayed on the screen and are "opened" in a randomized order. One or more of them will contain a pattern. The patterns are then displayed in the middle of the screen, one at a time and the participant must select the box in which the pattern was originally located. If the participant makes an error, the boxes are opened in sequence again to remind the participant of the locations of

the patterns. Increased difficulty levels can be used to test high-functioning, healthy individuals. Outcome measures include the errors made by the participant, the number of trials required to locate the pattern(s) correctly, memory scores and stages completed.

In the study under review the sponsor has selected the errors made by the participant, and the memory score as two of the outcomes of this study.

Pattern Recognition Memory (PRM) | Cambridge Cognition (*accessed March 7, 2022)*: Pattern Recognition Memory is a 4 minute test of visual pattern recognition memory in a 2-choice forced discrimination paradigm. The participant is presented with a series of visual patterns, one at a time, in the center of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the participant is required to choose between a pattern they have already seen and a novel pattern. In this phase, the test patterns are presented in the reverse order to the original order of presentation. This is then repeated, with new patterns. The second recognition phase is administered after a delay period, typically 10-20 minutes. Outcome measures include the number and percentage of correct trials and latency (speed of participant's response). In the study under review the sponsor has selected the percentage of immediate and delayed correct trials as the outcome.

Spatial Span (SSP) | Cambridge Cognition *(accessed on March 7, 2022)*: This 5-minute test, assesses visuospatial working memory capacity. White squares are shown on the screen, some of which briefly change color in a variable sequence. The participant must then select the boxes which changed color in the same order that they were displayed by the computer (for the forward variant) or in the reverse order (for backward variant). The number of boxes in the sequence increases from two at the start of the test, to nine at the end and the sequence and color are varied through the test. Outcome measures cover span length (the longest sequence successfully recalled), errors, number of attempts and latency (speed of response). In this study under review the authors used the SSP Forward Span Length as an outcome measure.

Reviewer's Comment: In a previous study of migraine prevention with topiramate in adolescents (study MIG-3006), topiramate has been shown to be associated with psychomotor slowing and language problems. In this study under review the authors did not include any specific domains that test for these areas. Data to test for psychomotor slowing may have been captured automatically under the PRM test (latency), which was one of the tests from study MIG-3006 and the SSP Forward Span (speed of response).

Additionally, it is unclear if the sponsor performed a motor screen at the beginning of the cognitive assessments to ensure there are no physical or visual barriers to completing these tests, and whether any participant had any underlying condition (ADHD, low IQ, learning disability), that may impact the

study results, and how these were distributed across treatment arms. An IR was sent regarding the issues outlined above. The IR and sponsor responses area discussed in Section 4 of this review.

Sponsor's Statistical Approach to CANTAB outcome analysis (copied and pasted from the CSR page 39 (9.7.1.11.7):

For each key CANTAB outcome measure, descriptive summary statistics (n, mean, median, SD, minimum, and maximum) for change from baseline were 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. Bar plots (originally planned to be line graphs) of mean change from Baseline to Week 16 and Week 56 by treatment groups and stratification factors were also produced.

Mixed effects models with repeated measures were used to generate least square (LS) mean and standard errors (SE) 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 was calculated using the LS mean change from Baseline to Week 16 and Week 56 estimates and the pooled SD of change across both treatment and placebo groups.

Reviewer's Comments: There are limitations to the sponsor's approach to study design and statistical methods that limit the interpretation of the results difficult.

First, it is not clear to this reviewer, why the sponsor decided to adjust the analysis for gender and age, as the distribution for these variables seems similar across the different treatment arms. An IR was sent to the sponsor to repeat the analysis without adjustment for gender or age, but only for baseline cognitive test score and the result of this repeat analysis is outlined in Section 4.

It is noted that there is a high number of discontinuations in each study arm over the course of the study which may impact the results of the mixed effects models with repeated measures, presuming that these discontinuations were not at random.

Due to the titration schedule, at the time of the 16-week cognitive assessments, the participants in the top-dose arm only had one week exposure to 15 mg/92 mg daily, compared to the mid-dose group that had been exposed to 7.5 mg/46 mg for 13 weeks at that time point, limiting the interpretation of any observed group differences in cognitive score changes from baseline.

Last the sponsor has a total of 5 cognitive outcomes, with repeated comparisons at 3 time points, compared between three arms without appropriate adjustment for multiple comparisons. Overall given the small numbers of participants that remain in each treatment arm at the end of the study, the study lacks sufficient power to detect low frequency adverse reactions related to cognitive function.

Cognitive Safety Related Study Results Reported By the Sponsor

Demographics

Table 1: Summary of Demographics and Baseline Characteristics, Safety Population

	Placebo (N = 56)	VI-0521 Mid (N = 54)	VI-0521 Top (N = 113)	Overall (N = 223)
Age at Screening (Years)				
n	56	54	113	223
Mean (SD)	14.0 (1.41)	14.1 (1.28)	13.9 (1.36)	14.0 (1.35)
Median	14.0	14.0	14.0	14.0
Min, Max	12, 16	12, 16	12, 16	12, 16
Age Categories, n (%)				
12 - 14 years	34 (60.7)	33 (61.1)	69 (61.1)	136 (61.0)
15 - 16 years	22 (39.3)	21 (38.9)	44 (38.9)	87 (39.0)
Gender, n (%)				
Female	30 (53.6)	28 (51.9)	63 (55.8)	121 (54.3)
Male	26 (46.4)	26 (48.1)	50 (44.2)	102 (45.7)

Abbreviations: VI-0521 Mid-dose = PHEN/TPM 7.5 mg/46 mg; VI-0521 Top-dose = PHEN/TPM 15 mg/92 mg
Denominators for percentages are based on the number of subjects with non-missing data in each treatment group for the relevant variable.
Source: Table 14.1.3.2

Adverse Events related to cognition

The following AEs related to cognitive disorders were noted in the AEs:

Feeling abnormal /mental fogginess in one participant (OB-403 (b) (6)) in the top-dose arm, somnolence in two participants (OB-403- (b) (6), OB-403- (b) (6) in the top dose arm, and fatigue (OB-403 (b) (6), OB-403 (b) (6), OB-403- (b) (6)) in three participants in the top-dose arm (and in one participant in the placebo arms).

CANTAB Result:

In the synopsis for the OB-403 clinical study report the sponsor concludes that the cognitive safety analysis of VI-0521 does not indicate significant detrimental

effects of VI-0521 on any of the CANTAB outcome measures assessed, and at either timepoint or at any dose level.

The sponsor reports the following study findings regarding the CANTAB cognitive subtests in the conclusion section of the document titled " The Effects of VI-0521 on Cognitive Performance in Obese Adolescents: Safety Analysis of CANTAB Outcome Measures:

1. Overall, no significant main effects of treatment were observed at either 16-or 56-week timepoints for any of the CANTAB outcome measures assessed.

Reviewer Comment: While the study results as presented do not show any significant differences in change in cognitive measures from baseline to week 56 in placebo versus study drug arms in the selected CANTAB tests, because of the discontinuations and smaller sample size at week 56, small effects on cognitive function may be missed, and meaningful interpretation of these study results is limited.

2. Pairwise comparisons did not reveal any significant negative effects of VI-0521 on memory at either dose versus placebo.

Reviewer Comment: Keeping the limitations discussed earlier in mind, as presented, these results do not show a significant difference in change from baseline to week 16 and 56 in study drug arms compared to placebo for scores of visual pattern recognition memory, visuospatial working memory and visual memory and new learning. This said, it is important to note that in a previous study of topiramate in adolescents [Pandina et al. Cognitive effects of topiramate in migraine patients aged 12-17 years. Pediatr Neurol. 2010 Mar;42(3):187-95] psychomotor slowing and reduced fluency were areas that were reported to be worsened with topiramate using a subset of CANTAB battery tests. Psychomotor speed and language domains were not included in the sponsor's submission. An IR was sent to the sponsor inquiring if there was any data to examine these cognitive domains, and the sponsor submitted results of tests of psychomotor speed which will be further discussed under section 4.

3. At Week 56, visuospatial working memory (SSP Forward Span Length was significantly greater in the mid-dose compared to top-dose (p=0.04), and a trend of improvement was seen compared to placebo (p=0.17), which may reflect early efficacy signs of mid-dose.

Reviewer Comment: Using the sponsor identified statistical significance determination based on $p < 0.05$ may lead to false positive findings, as the p-value has not been adjusted for the multiple tests conducted; 5 separate analyses for 5 cognitive outcomes. Thus the significance of the above findings is questionable.

4. Near-significant trends of improvement in immediate recognition memory (PRM Percent Correct Immediate) at Week 56 for mid-dose indicate further potential early indicators of efficacy, although further investigation would be required.

Reviewer Comment: We disagree with the sponsor, and do not believe that the study results provide any evidence that the mid-dose has any "efficacy" or any beneficial effects on cognitive functioning. Neither a p=0.06 (top-dose versus mid-dose) or a p=0.13 (mid-dose to placebo), suggest a significant finding in this study, where statistical significance determination is not appropriately assigned as there was no accounting for multiple testing.

5. For the majority of comparisons between VI-0521 doses and placebo, the standardized effect sizes were in the small range (< 0.2), with the only exceptions being increases (compared to placebo) with mid-dose in PAL Total Errors Adjusted (PALTEA) at Week 56 (0.25), in SSPFSL at Week 56 and Week 16 (0.23 and 0.26, respectively), in PRMPCI at Week 56 (0.46), and in PRM Percent Correct Delayed (PRMPCD) at Week 16 (0.53). These observations all demonstrate more favorable responses with mid-dose compared to placebo, and further support the absence of adverse cognitive effects in this study population. Cognitive safety analysis of VI-0521 does not indicate significant detrimental effects of VI-0521 on any of the CANTAB outcome measures assessed, and thus memory performance, at either timepoint or at any dose level.

Reviewer's Comments: We disagree with the sponsor that the above observations represent favorable responses with mid-dose compared to placebo. The above results reported by the sponsor are not statistically significant and not clinically meaningful. The increase in the PRM Percent Correct Delayed at 16 weeks in the mid-Dose arm, compared to placebo has a p=0.03 which may not be significant with appropriate adjustment for multiple testing. Additionally, there is no statistically significant difference in change in scores in the mid-Dose group compared to placebo at week 56, suggesting this observation at week 16 is not clinically consistent and meaningful. The increase compared to placebo in the mid-Dose in PAL Total Errors Adjusted at Week 56 does not suggest a favorable cognitive result in the mid-Dose group, since the number of errors increased in the mid-Dose group compared to baseline, whereas the number of errors declined in the placebo and top-dose groups compared to base line scores. All other changes described by the sponsor above, have p-values above p=0.05. when compared to placebo and are not significant findings.

4. DN1 IR to the sponsor and sponsor responses

To better understand aspects of the study design, study conduct and patient population that may impact interpretation of the CANTAB results, an information request (IR) was sent to the sponsor on March 21, 2022.

Outlined below are FDA comments in bold and the sponsor's responses:

DN1 COMMENT: Please provide baseline information, on the number of study participants that may have had conditions that could impact cognitive testing such as attention deficit hyperactivity disorder (ADHD), learning disability, low IQ, years of education, concomitant medications (such as benzodiazepines), and language barriers (e.g., English as a second language).

Sponsor Response: There were 18 (8.1%) subjects with a baseline history of attention deficit hyperactivity disorder (ADHD), with 7 (12.5%), 4 (7.4%), and 7 (6.2%) in the placebo, mid-dose, and top-dose groups, respectively. One subject had "educational problem" reported as medical history at screening. No subjects reported a history of learning disability, low IQ, concomitant medications, or language barriers that may impact cognitive functions.

Reviewer Comment: The percentage of patients with ADHD was higher in the placebo group (12.5 %), twice as much compared to the top-dose drug arm (6.2%). This potentially may skew the results towards worse performance on cognitive tests in the placebo group, and may affect the interpretation of the study results.

DN1 COMMENT: Please clarify whether prior to CANTAB testing, screening for any motor, visual or comprehension problems were conducted to ensure these did not impact CANTAB administration and results.

Sponsor Response:

There was no screening for any motor, visual or comprehension problems conducted. However, the CANTAB test was done by all subjects at screening as a practice test. Subjects would be excluded if they were unable to follow the instructions and complete the practice tests.

Reviewer Comment: While the sponsor's approach may have identified participants with significant barriers to following instructions or completing the testing, this approach may have missed identifying children with more subtle disabilities that may impact study results, i.e., motor problems that may result in slower test taking and slower psychomotor reaction. Given this was not assessed, it is not clear whether visual, motor and comprehension difficulties that may have affected test results existed in the study population and how they were distributed across different study arms.

DN1 COMMENT: Please explain the reason for controlling the Mixed-Effects Models Repeated Measures (MMRM) model used for analyzing CANTAB data, for age and gender. Please determine if age and gender distribution at baseline are significantly different across treatment arms. If not, please repeat the MMRM analysis without controlling for age and gender.
Sponsor Response: We controlled for age and gender in the MMRM analysis because these subject attributes were believed to have a potential impact on certain study variables (including CANTAB testing) and were used to stratify the randomization. Under these circumstances, we believed that it was appropriate to include these factors in the MMRM model. The requested table (Table 3), program (t_3_cantab_mmrm.txt), and stat output (t_3_cantab_mmrm-stats.pdf), that represent CANTAB results using a model without age category and gender as covariates, are included in this submission. Notably, removing these factors from the statistical model did not significantly change the conclusions for CANTAB analyses.

Reviewer Comment: The results provided by the sponsor in Table 3 were reviewed by this reviewer, and I agree that as presented, the results without controlling for age and gender are similar to results of analyses that controlled for age and gender.

DN1 COMMENT: We note that in a pediatric study of topiramate in adolescents aged 12-17 for migraine prevention, mean change from baseline in the selected CANTAB tests suggested that topiramate may result in psychomotor slowing (based on the mean change from baseline on Five-Choice Reaction Time, Pattern Recognition Memory Mean Correct Latency, and Rapid Visual Information Processing Mean Latency) and reduced verbal fluency (based on the mean change from baseline on the animal fluency under the Controlled Oral Word Association Test) [Pandina et al. Cognitive effects of topiramate in migraine patients aged 12 through 17 years. Pediatr Neurol 2010;42:187-195]. The selected CANTAB tests and outcomes included in Study ob-403 do not include these previously identified cognitive domains of psychomotor speed and language function. If you have neuropsychological data available for that study to assess the impact of Qsymia on psychomotor speed, or verbal fluency, please provide this data, and related analysis for review.
Sponsor Response: As agreed with the Division during the review of this protocol, cognitive testing evaluated CANTAB tasks of Paired Associates Learning (PAL) to assess episodic memory, Pattern, Recognition Memory (PRM) to assess immediate and delayed recognition memory, and Spatial Span (SSP) to assess visuospatial working memory. For the PRM task used to assess immediate and delayed recognition memory, the effect that was reported was the percent correct rather than the latency. Our datasets, however, do contain data for PRM Mean Correct Latency Immediate (PMMCLI), and PRM Mean Correct Latency Delayed (PRMMCLD). Results for these parameters are included in Table 5 (Page 6-7), and demonstrate that there were no significant differences between either dose of Qsymia and placebo for either PMMCLI or PMMCLD.

While these results may differ from previous adolescent studies of topiramate for migraine prevention, they are nonetheless consistent with adult studies of Qsymia that demonstrated no significant effect on psychomotor performance as measured using the CogScreen Psychomotor Test Battery (Study OB-205 CSR). Differences in psychomotor effects of Qsymia and topiramate may be due to the presence of phentermine, which has been shown to improve psychomotor function (Waters WF, Magill RA, Bray GA, et al. A comparison of tyrosine against placebo, phentermine, caffeine, and D-amphetamine during sleep deprivation. Nutr Neurosci. 2003;6[4]:221-23). There is no CANTAB test to assess language function, and no specific language tests were included in this protocol.

Reviewer Comment: The results provided by the sponsor were reviewed. There was worsening (increased latency) in the mean PRM Mean Correct Latency Delayed score compared to baseline in all study arms at both week 16 and 56, and these changes compared between study drug arms and placebo were not statistically significant. The mean PRM Median Correct Latency Immediate score worsened compared to baseline at week 16 and 56 in the placebo and top-dose arms. In the mid-dose arm, the mean PRM Median Correct Latency Immediate score improved from baseline at week 16, and then worsened from baseline at week 56. Overall, changes from baseline when compared between the placebo and study drug arms were not statistically significant.

DN1 COMMENT: For the CANTAB tests that you included in study ob-403 please provide the baseline, week 16 and week 56 mean scores, change from baseline scores for week 16 and week 56, as well as the results for the MMRM analysis including the Least Square Mean change, differences between LS mean for Qsymia and for placebo (SE) (95% CI), and the related p-values from the MMRM analyses ONLY for those participants that have week 56 assessments in the following table format:
Sponsor Response: The requested table (Table 5), program (t_5_cantab.txt), and stat output (t_5_cantab-stats.pdf) are included in this submission. The conclusions from this subset of subjects are similar to those submitted with the original CSR.

Reviewer's Comment: These results in Table 5 submitted by the sponsor were reviewed. These sensitivity analyses, similar to the sponsor's original analyses, did not show a significant difference between change from baseline to week 56 in cognitive measures, between the placebo group and the study drug arms.

5. Summary Comments

The consult questions by DDLO and DN1 responses are summarized below:

1. Do you agree with the sponsor's conclusion that the results do not indicate that Qsymia has significant detrimental effects on any of the CANTAB

outcome measures assessed, and thus memory performance, at either timepoint or at any dose level? Why or why not?

DN1 Response: We disagree with the sponsor's conclusion that the results do not indicate that Qsymia has significant detrimental effects on any of the CANTAB outcome measures assessed, and thus memory performance, at either timepoint or at any dose level. We believe that the results of this study do not allow a conclusion whether Qsymia does or does not affect cognitive function in adolescents.

The reason for the study results' limitations, as discussed earlier in more detail, are the small sample size at week 56 that precludes detection of smaller sized effects on cognitive function, only one week exposure to the highest dose at week 16 for the high-dose group (15 mg/92 mg), lack of inclusion of cognitive domains such as language which have been shown in another study to be affected by topiramate in adolescents ages 12-17, higher percentage of children with ADHD in the placebo group [12.5 % (n=7)], compared to mid-dose [7.4 % (n=4)], and top-dose [6.2 % (n=6)] groups which could skew the results in favor of the drug arms. Last the sponsor has not performed motor or visual screening to make sure subjects did not have any limitations to taking the tests and the test results are not impacted by unaccounted disabilities.

2. Based on your review of the information available, comment on the Qsymia label, which includes a warning and precaution regarding cognitive impairment, and whether you recommend any revisions or additions regarding the results of the adverse events observed and/or CANTAB testing.

   DN1 Response: We agree with the current information in the label which includes cognitive risks and adverse events based on previous adult and adolescent studies with Qsymia or any of its components. We do not believe that a statement that Qsymia does not cause cognitive side effects in adolescents based on the results of study ob-403 should be placed in the label.

6. Conclusion

The CANTAB results from adolescents treated with Qsymia in study OB-403 are inconclusive, and do not enable us to firmly conclude that Qsymia does or does not have an effect on cognitive function in adolescents.

Deniz Erten-Lyons, M.D.

Medical Reviewer

_____
Ranjit Mani, MD
Medical Reviewer

_____
Teresa Buracchio, MD
Director, DN1

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