U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 22580
Supplement #:	21
Drug Name:	VI-0521 (approved as Qsymia® in the United States)
Indication(s):	Addition of a pediatric indication for adolescents 12 to 17 years of age with BMI in the 95th percentile or greater for age and gender as an adjunct to a reduce calorie diet and increased physical activity for chronic weight management
Applicant:	Vivus LLC
Date(s):	Stamp Date: 8/25/2021 Filing Meeting: 10/06/2021 Review Due: 5/17/2022 PDUFA Goal Date: 6/25/2022
Review Priority:	Standard
Biometrics Division:	DB II
Statistical Reviewer:	Kyunghee K. Song, PhD
Concurring Reviewers:	Feng Li, PhD, Team Leader
Medical Division:	Division of Diabetes, Lipid Disorders, and Obesity Products
Clinical Team:	Mary Roberts, MD, Reviewer Laura Higginbotham, MD, Team Leader
Project Manager:	Martin White

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1 EXECUTIVE SUMMARY

Vivus LLC submitted an NDA supplement for Qsymia (VI-0521) to add a pediatric indication for adolescents 12 to 17 years of age with Body Mass Index (BMI) in the 95th percentile or greater for age and gender as an adjunct to a reduce calorie diet and increased physical activity for chronic weight management. The product was approved in 2012 as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adults with an initial BMI of

- 30 kg/m^2 or greater (obese) or
- 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus, or dyslipidemia

The submission mainly relies on results from one phase 4 study, OB-403. This clinical study aimed to assess the safety and efficacy of VI-0521 in obese adolescents, accompanied by a lifestyle modification program.

It was a multi-center, randomized, double-blind, parallel-design, placebo-controlled study with VI-0521 capsules administered once daily. The primary endpoint was the percent change from baseline to Week 56 in BMI.

The primary efficacy results demonstrated efficacy in BMI reduction at Week 56 for both the Top-dose and Mid-dose compared to the placebo (Table 1). Missing values were handled using a washout multiple imputation approach for the primary analysis.

Table 1: Percent Change in Body Mass Index (BMI) from Baseline to Week 56

	N	LS mean[1] (SE)	Difference from Placebo [95% CI]; p-value
Placebo	56	3.34 (1.44)	
Mid-dose	54	-4.78 (1.30)	-8.11 [-11.92, -4.31]; <0.0001
Top-dose	113	-7.11 (1.01)	-10.44 [-13.89, -6.99]; <0.0001

Abbreviations: N=number of subjects randomized and received at least one dose of study drug; LS mean=least squares mean; SE=standard error; CI=confidence interval; [1]Model based estimates from a mixed effects model with repeated measures (MMRM) with terms of treatment, visit, treatment by visit, baseline BMI value, age stratification, and gender stratification with missing data imputed with a multiple imputation approach.

The major statistical issue identified is the large percentage of missing data. Approximately 38% of subjects discontinued study early without follow-up data, likely due to the fact that the study was conducted during the pandemic. However, this does not seem to affect the study conclusion as the primary analysis was based on a relatively conservative imputation method and robustness of the study conclusion was further supported by several sensitivity analyses including tipping point analyses.

Efficacy in comparison to placebo was further supported by key secondary endpoints related to the body weight. Based on information from the clinical reviewer, it seems there were no major safety concerns identified that could impact the approval of the product.

Collectively, the study provided substantial evidence of a robust treatment effect for the study population and the benefits seem outweigh the potential risk. Based on findings from this efficacy study, I recommend approval for the proposed indication.

2 INTRODUCTION

2.1 Overview

Obesity in childhood or adolescent increases the risk of adult obesity, type 2 diabetes mellitus, and dyslipidemia. VI-0521 (marketed as Qsymia in the United States), a fixed dose combination of immediate-release phentermine (PHEN) and extended-release topiramate (TPM), was approved in July 2012 by the FDA as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in overweight and obese adults.

The clinical study was designed to assess the safety and efficacy of VI-0521, accompanied by a lifestyle modification program, in obese adolescents. It should be noted that contribution of each component to the combination product was assessed in studies supporting the adult indication.

The applicant generally complied with the statistical comments conveyed during the IND stage (IND 068651).

2.2 Data Sources

Materials for this statistical review, including the data and clinical study reports (CSR), were submitted electronically under the network path location:
\\CDSESUB1\evsprod\NDA022580\0590\m5
The information necessary for the statistical review was contained in Module 1 (cover letter and labeling) and Module 5 (clinical study report, protocols, amendments, statistical analysis plan, and datasets).

The applicant's responses to the statistics information requests for a list of analysis programs and additional analyses were submitted electronically and located under the network path:
\\CDSESUB1\evsprod\NDA022580\0596
\\CDSESUB1\evsprod\NDA022580\0603
\\CDSESUB1\evsprod\NDA022580\0605
\\CDSESUB1\evsprod\NDA022580\0613
\\CDSESUB1\evsprod\NDA022580\0619

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The submitted efficacy data and analyses are generally acceptable in quality. The statistical reviewer was able to reproduce the results from the primary and important secondary analyses and performed additional analyses as needed.

Blinding procedures were described in the study reports and acceptable.

3.2 Evaluation of Efficacy

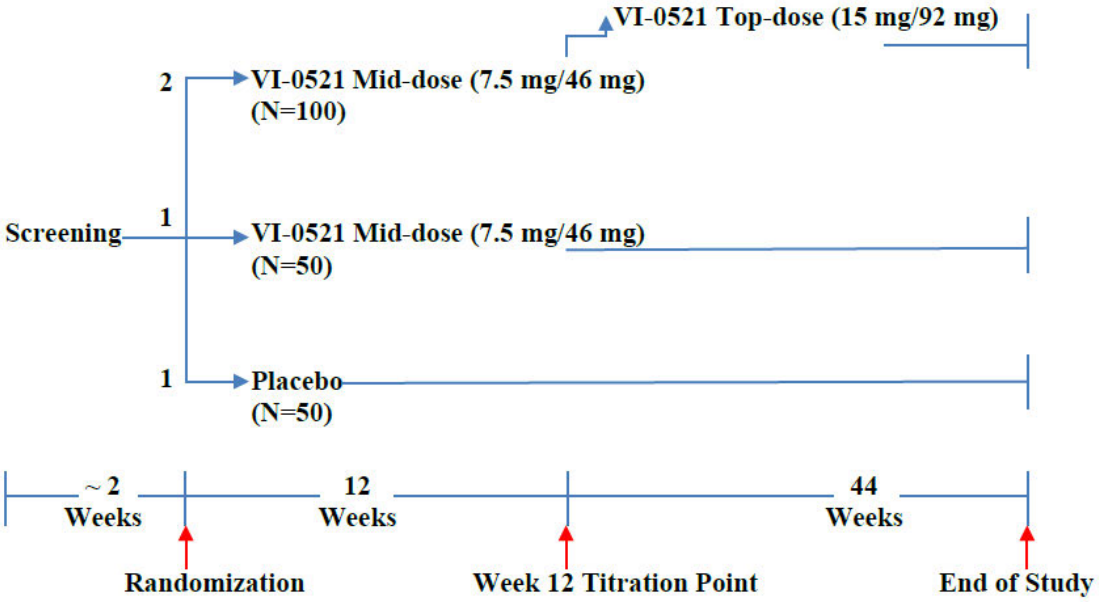
Efficacy analysis procedures were pre-specified in the protocol and these analysis procedures were followed generally according to the protocol.

3.2.1 Study Design and Endpoints

This was a phase 4, multi-center, randomized, double-blind, parallel-design, placebo-controlled study with VI-0521 capsules administered once daily.

A schematic of the study design is presented in Figure 1.

Figure 1: Trial design



[Source: excerpted from Section 9.1 of Clinical Study Report (CSR)]

All subjects assigned to treatment with VI-0521 initiated treatment with the low-dose (PHEN/TPM 3.75 mg/23 mg) for 2 weeks and gradually titrated up to the assigned dose level.Subjects who were randomized to the PHEN/TPM 15 mg/92 mg dose were required to attempt titration up to that dose at the Week 12 visit.

The study population consisted of,

- Adolescents ≥ 12 years and < 17 years of age with Tanner staging of ≥ 2 at the time of screening
- 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.

Eligible subjects were randomly assigned in a 1:1:2 ratio to placebo, Mid-dose (PHEN/TPM 7.5 mg/46 mg), or Top-dose (PHEN/TPM 15 mg/92 mg) of VI-0521. Randomization was stratified by gender and age (12 to 14 versus 15 to 16 years old). The sponsor, the subjects, and the study sites were blinded as to subject randomization.

A total of 325 subjects were screened and 227 subjects were randomized: 57 to placebo, 55 to Mid-dose group and 115 to Top-dose group. Of the randomized subjects, 4 subjects did not receive study drug, resulting 56 treated with placebo, 54 treated with Mid-dose, and 113 treated with Top-dose. The study was conducted at 20 sites in the United States.

Eligible subjects were administered the randomized treatment once daily for a period of 56 weeks. Each capsule of study drug was taken orally in the morning, with or without food, and with water.

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

Primary endpoint
Mean percent change in BMI from baseline to Week 56

Key secondary endpoints

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

3.2.2 Statistical Methodologies

Analysis population
The Intent-To-Treat (ITT) population included all randomized subjects who received at least one dose of study drug. The ITT population was based on the randomized treatment. This was the primary population for all efficacy analyses.

The safety analysis set (SAS) included all randomized subjects who received at least one dose of study drug. The safety population was based on the treatment actually received.

Modified Intent-To-Treat (mITT) population included all randomized subjects who received study drug and returned for at least 1 post-randomization assessment.

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

Primary endpoint

Primary analysis

Comparisons in the primary endpoint of percent change from baseline BMI between treatment groups were performed using a mixed effects model with repeated measures (MMRM) with terms of treatment, visit, treatment by visit, baseline BMI value, age stratification, and gender stratification. The pairwise comparisons between treatment groups were performed.

The family-wise Type 1 error for the comparisons was controlled by Fisher's protected least significant difference (LSD) method at the 0.05 significance level. Placebo, Mid-dose, and Top-dose were first compared for overall difference. Once the overall difference was significant at the 0.05 significance level, the pairwise comparisons were conducted using Fisher's LSD method. The order for comparisons of interest was Top-dose versus placebo, Mid-dose versus placebo, and Top-dose versus Mid-dose.

If both the Top-dose and Mid-dose were shown to be statistically significantly superior to placebo for the primary endpoint using the Fisher's LSD procedure, then the secondary endpoints were tested using Hochberg testing procedure at alpha=0.05.

Handling of missing data

For the primary analysis, the applicant used a washout multiple imputation to impute missing data at Week 56 as specified in the Statistical Analysis Plan, because there was not a sufficient number of retrieved dropouts. The washout imputation method imputed missing data for the active treatment arms using monotone regression with randomization strata and baseline BMI as the predictors. Intermediate values in the active treatment arms were not used for imputation. For subjects in the placebo arm, missing data were imputed using all available intermediate data assuming missing at random. This approach assumed missing data of all subjects following similar trend as an average placebo subject.

After such imputation, comparisons in the primary endpoint were assessed using a MMRM model as specified in the primary analysis, and the final results were integrated using Rubin's rule after evaluating 1000 imputed datasets.

Sensitivity and additional supplementary analyses

- mITT Washout: MMRM analysis (identical to the primary analysis) using the mITT population
- MMRM: MMRM analyses of observed data with no imputation.
- MI MAR using the mITT population: MMRM analyses with missing data imputed by multiple imputation under the assumption of missing-at-random
- MI ANCOVA MNAR using the mITT population: Analysis with missing data imputed by multiple imputation under the assumption missing-not-at-random using pattern-mixture model
- Last observation carried forward (LOCF) using the mITT population: The last observed weight and height was used to derive the change in BMI for subjects who discontinued treatment before Week 56.
- Tipping point multiple imputation: Missing data were imputed according to the primary multiple imputation approach. Then a penalty (or δ) was added to the imputed BMI values at Week 56 to both active treatment and placebo groups for a two-dimensional tipping point analysis. The δ was varied from -10 kg/m^2 to 10 kg/m^2 with 1 kg/m^2 decrement/increment shift for each combination.

Subgroup analyses for the primary efficacy endpoint

Subgroup analysis for mean percent change in BMI was performed by race, gender, age group, baseline BMI group, and baseline Tanner stage. To assess the treatment effect across various subgroups, a subgroup and a treatment-by-subgroup interaction terms were added in the primary analysis model.

Key secondary endpoints

Primary analysis

For the proportion of subjects who achieved a reduction ≥ 5% (or 10% and 15%) from baseline BMI at Week 56, the treatment difference between each active treatment group versus the placebo group was tested using a Cochran-Mantel-Haenszel (CMH) test instead of a prespecified logistic regression model due to model-fitting issues for 10% and 15% BMI reduction endpoints. The CMH test was stratified by the randomization stratification factors. The proportion difference for each BMI reduction endpoint was obtained using imputed datasets. The 95% CI and the p-values for the comparisons were also generated.

Continuous endpoints were analyzed by a similar MMRM model as for the primary endpoint. Similar to the primary endpoint, the washout multiple imputation was applied for missing data.

Multiplicity considerations

The secondary endpoints were tested in stepwise manner if both the Top-dose and Mid-dose groups were shown to be statistically significantly superior to placebo for the primary endpoint using the Fisher's LSD procedure. It was prespecified that within the key secondary endpoints, the statistical significance level was adjusted using the Hochberg method to control the familywise error rate at 5%. Starting from Top-dose versus placebo comparison, analyses were

carried out for all key secondary endpoints. All endpoints had to be statistically significant in favor of Top-dose compared to placebo after the Hochberg adjustment, in order to repeat the testing procedure for Mid-dose versus placebo comparison.

Sensitivity analyses
Sensitivity analyses were done on the mITT population.

Analysis of safety endpoints
Safety was assessed by evaluation of adverse events at each study visit, laboratory parameters, physical examinations, ECGs, vital signs, cognitive function tests using CANTAB, bone age using hand and wrist X-ray, PHQ-9: Modified for Teens, C-SSRS, and analysis of DXA. Safety data were summarized for all treatment groups, and descriptive statistics were generated for the questionnaire data.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition
The summary of the subject disposition is given in

Table 2. The proportion of subjects who completed treatment was ranged from 50% to 70.4% across treatment groups. Main reasons for discontinuing treatment were lost to follow-up and withdrawal by subjects/parent/legal guardian, followed by other and adverse event. Most subjects who discontinued treatment did not continue with study visits and did not return for Week 56 assessments. The proportion of subjects who were lost to follow-up ranged from 16.7% to 25% across treatment groups.

Table 2: Patient Disposition

	Placebo	Mid-dose	Top-dose	Total
Randomized	57	55	115	227
Randomized and treated with at least one dose of study drug	56 (100%)	54 (100%)	113 (100%)	223 (100%)
Completed treatment	28 (50.0%)	38 (70.4%)	69 (61.1%)	135 (60.5%)
Discontinued treatment	28 (50.0%)	15 (27.8%)	44 (38.9%)	87 (39.0%)
Lost to follow-up	14 (25.0%)	9 (16.7%)	20 (17.7%)	43 (19.3%)
Withdrawal by subject/parent/legal guardian	8 (14.3%)	5 (9.3%)	14 (12.4%)	27 (12.1%)
Other	2 (3.6%)	0	5 (4.4%)	7 (3.1%)
Adverse event	2 (3.6%)	1 (1.9%)	1 (0.9%)	4 (1.8%)
Lack of efficacy	2 (3.6%)	0	1 (0.9%)	3 (1.3%)
Investigator decision	0	0	2 (1.8%)	2 (0.9%)
Protocol noncompliance	0	0	1 (0.9%)	1 (0.4%)
Completed study	29 (51.8%)	37 (68.5%)	73 (64.6%)	139 (62.3%)
Discontinued study	27 (48.2%)	17 (31.5%)	40 (35.4%)	84 (37.7%)
Lost to follow-up	13 (23.2%)	9 (16.7%)	20 (17.7%)	42 (18.8%)
Withdrawal by subject/parent/legal guardian	10 (17.9%)	6 (11.1%)	14 (12.4%)	30 (13.5%)
Adverse event	1 (1.8%)	1 (1.9%)	2 (1.8%)	4 (1.8%)
Other	1 (1.8%)	1 (1.9%)	2 (1.8%)	4 (1.8%)
Lack of efficacy	2 (3.6%)	0	1 (0.9%)	3 (1.3%)
Protocol noncompliance	0	0	1 (0.9%)	1 (0.4%)

Cell contents are frequencies with relative frequencies in parentheses; [Source: excerpted from Table 6 of CSR]

Summary of COVID 19 Impact

The trial was carried out during the period in which the COVID-19 pandemic was occurring globally. First informed consent was on May 2, 2019, and the date of final post study observation was on April 16, 2021. There were 86 subjects with COVID-19 related protocol deviations. Most of them were due to study assessments such as phone visits instead of site visits and out-of-window assessments as well as missed measurements. Impact of COVID-19 included inability to bring subjects who discontinued treatment back to study visits for Week 56 assessments and reduced engagement in lifestyle modification activity. The inability to retrieve dropouts led to imputing missing values using a washout imputation as specified in the study protocol.

Demographic and other baseline characteristics

The demographics and baseline characteristics were generally similar across treatment groups (Table 3). The majority of subjects were females (54.3%), White (66.8%), $\geq 99^{th}$ percentile of BMI category (62.9%), and the mean age was 14 years, with 61% in the 12-14 year stratum and

39% in the 15-16 year stratum. There were more subjects in the ≥ 99th percentile of BMI in the Top-dose group (70.5%) compared to the other two groups (53.6% in the placebo group and 56.6% in the Mid-dose group).

Table 3: Baseline Demographics and Baseline Characteristics of Subjects

		Placebo	Mid-dose	Top-dose	Total
		N=56	N=54	N=113	N=223
Age groups	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%)
Sex	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%)
Ethnicity	Hispanic or Latino	13 (23.2%)	25 (46.3%)	34 (30.1%)	72 (32.3%)
	Not Hispanic or Latino	42 (75.0%)	28 (51.9%)	79 (69.9%)	149 (66.8%)
	Not stated	1 (1.8%)	1 (1.9%)	0	2 (0.9%)
Race	White	42 (75.0%)	36 (66.7%)	71 (62.8%)	149 (66.8%)
	Black or African American	10 (17.9%)	14 (25.9%)	36 (31.9%)	60 (26.9%)
	Other	4 (7.1%)	4 (7.4%)	4 (3.5%)	12 (5.4%)
	American Indian or Alaska Native	0	0	1 (0.9%)	1 (0.4%)
	Asian	0	0	1 (0.9%)	1 (0.4%)
BMI categories	≥95th to <99th percentile	26 (46.4%)	23 (42.6%)	33 (29.2%)	82 (36.8%)
	≥99th percentile	30 (53.6%)	30 (55.6%)	79 (69.9%)	139 (62.3%)
	missing	0	1 (1.9%)	1 (0.9%)	2 (0.9%)
Tanner stage*	II and III	23 (41.1%)	16 (29.6%)	37 (32.7%)	76 (34.1%)
	IV and V	33 (58.9%)	38 (70.4%)	75 (66.4%)	146 (65.5%)
	Inclusion error	0	0	1 (0.9%)	1 (0.4%)
Age (years): Mean (SD)		14.0 (1.4)	14.1 (1.3)	13.9 (1.4)	14.0 (1.4)
Body Weight (kg): Mean (SD)		102.2 (21.8)	105.2 (22.4)	108.5 (25.0)	106.1 (23.7)
Height (cm)		167.2 (7.6)	168.6 (8.0)	166.3 (7.8)	167.1 (7.8)
BMI (kg/m^2): Mean (SD)		36.4 (6.4)	36.9 (6.7)	39.0 (7.4)	37.8 (7.1)
Waist Circumference (cm): Mean (SD)		111.1 (14.0)	111.9 (15.5)	116.5 (16.8)	114.0 (15.9)
Fasting insulin (µIU/mL)		33.2 (40.0)	26.9 (19.3)	26.6 (22.8)	28.4(27.7)
Whole Body Insulin Sensitivity Index (Mastuda) (mmol/L)		2.5 (1.7)	3.0 (2.5)	2.7 (2.1)	2.7 (2.1)
Triglyceride (mg/dL)		118.3 (46.1)	120.1 (61.6)	112.2 (63.2)	115.7 (58.8)
HDL-C (mg/dL)		47.2 (9.7)	47.2 (8.9)	46.7 (10.1)	46.9 (9.7)
Systolic blood pressure (mmHg)		117.7 (10.4)	121.4 (9.2)	117.4 (10.2)	118.5 (10.1)
Diastolic blood pressure (mmHg)		71.1 (8.3)	75.8 (6.7)	72.9 (7.3)	73.3 (7.5)

Abbreviations: N=number of patients randomized and received at least 1 dose of study drug; BMI=body mass index; SD=standard deviation; cell contents for Age groups, Sex, Ethnicity, Race, and BMI categories are frequencies with relative frequencies in parentheses; For all other characteristics are mean and the standard deviation in parentheses; [Source: excerpted from Table 8 of CSR and Reviewer*]

3.2.4 Results and Conclusions

Missing Data

The proportion of missing data was 46% (26 out of 56) in the placebo group, 31% (17 out of 54) in the Mid-dose group, 36% (41 out of 113) in the Top-dose group at Week 56. There were only 3 retrieved dropouts, 1 from each treatment group. Because there was not a sufficient number of retrieved dropouts, the washout imputation was performed for the primary analysis as described in Section 3.2.2 of this review.

Primary endpoint results

Both Top-dose and Mid-dose resulted in statistically significant reductions in BMI compared to placebo supporting the efficacy of active treatment (Table 4). The treatment effects of the Top-dose and Mid-dose on percent change in BMI at Week 56 were -10.44% and -8.11%, respectively.

Table 4: Percent Change in BMI from Baseline to Week 56: Primary Endpoint

Primary endpoint: %change in BMI			
	N	LS mean[1] (SE)	Difference from Placebo [95% CI]; p-value
Placebo	56	3.34 (1.44)	
Mid-dose	54	-4.78 (1.30)	-8.11 [-11.92, -4.31]; <0.0001
Top-dose	113	-7.11 (1.01)	-10.44 [-13.89, -6.99]; <0.0001

Abbreviations: N=number of subjects randomized and received at least one dose of study drug; BMI=body mass index; LS mean= least squares mean; SE: standard error; CI=confidence interval; [1]Model based estimates and standard error, the analysis model was a mixed effects model with repeated measures (MMRM) with terms of treatment, visit, treatment by visit, baseline BMI value, age stratification, and gender stratification; Missing observations were multiple imputed (1000 times) using the washout imputation; [Source: Reviewer]

Pre-specified sensitivity and supplementary analyses using different imputation approaches were conducted to evaluate the robustness of the conclusions based on the primary analysis. All analyses yielded results that were consistent with the primary analysis results.

Two-dimensional tipping point analysis was conducted to assess the robustness of the primary analysis. These analyses were run by the applicant with δ varied from -10 kg/m^2 to 10 kg/m^2 with 1 kg/m^2 decrement/increment shift for each combination. The tipping point analysis showed that the loss of significance occurred at only extreme shifts added to imputed data in each group such as shift values of -2 to the placebo and +5 to the Mid-dose group (or +7 to the Top-dose group). In general, the tipping point analysis results supported the primary analysis results.

Additional analysis

The following additional analyses were conducted and the results were compared to the primary analysis results of the primary endpoint. All yielded results that were consistent with the primary analysis results:

- The primary analysis model using unequal variance for treatment groups was conducted and the results were compared to the primary analysis results. The results from these two analyses were very close with minor numerical differences.
- The primary analysis using all randomized subjects (N=227) was conducted and the results were compared to the primary analysis results. The results from these two analyses were very close with minor numerical differences.
- The primary analysis excluding subjects from site 115 and site 120 was conducted (This was a request from the clinical reviewer due to concerns on height measurements). The results were similar to the primary results.

Key secondary endpoint results

Key secondary endpoints were evaluated and the results are shown in Table 5.

There were higher percent of subjects achieved the specified thresholds for BMI reduction from baseline in the active treatment groups than in the placebo group. Assuming subjects with missing endpoint as non-responders, the observed proportion of subjects receiving placebo, Mid-dose, and Top-dose who achieved BMI reduction of at least 5% was 5.4%, 38.9%, and 46.9%, respectively. The proportion of subjects receiving placebo, Mid-dose, and Top-dose who achieved BMI reduction of at least 10% was 0%, 31.5%, and 42.5% of subjects, respectively. The proportion of subjects receiving placebo, Mid-dose, and Top-dose who achieved BMI reduction of at least 15% was 0%, 13%, and 28.3% of subjects, respectively. However, considering the high proportion of missing and the impact of the pandemic, the non-responder imputation approach might be overly conservative for each group.

The proportions presented in Table 5 are based on the imputed datasets, which was the primary analysis set. For the proportion of subjects who achieved the specified BMI reduction, the treatment difference between each active treatment group versus the placebo group was tested using a Cochran-Mantel-Haenszel (CMH) test. Nominal p-values for all BMI reduction endpoints were <0.05 indicating greater reductions in the active treatment groups than in the placebo group.

Nominal p-values for Top-dose versus placebo were <0.0001 for all BMI reduction endpoints (5%, 10% and 15% BMI reduction) and change in waist circumference endpoint. These 4 endpoints were statistically significant under the prespecified Hochberg testing procedure. Because not all endpoints were statistically significant in the comparison between the Top-dose group and the placebo group, no further statistical testing was performed for the Mid-dose group versus the placebo group.

Table 5: Key Secondary Endpoints

	N	Proportion[1] (%)	Difference from Placebo [95% CI[2]; p-value
≥ 5% BMI loss			
Placebo	56	13.58	
Mid-dose	54	44.02	29.74 [11.20, 48.28]; 0.0017
Top-dose	113	52.23	38.61 [23.15, 54.08]; <0.0001
≥ 10% BMI loss			
Placebo	56	4.54	
Mid-dose	54	33.51	28.81 [13.61, 44.00]; 0.0002
Top-dose	113	44.39	40.50 [28.36, 52.64]; <0.0001
≥ 15 % BMI loss			
Placebo	56	2.89	
Mid-dose	54	13.63	11.74 [1.29, 22.19]; 0.0277
Top-dose	113	28.91	27.40 [17.67, 37.13]; <0.0001
	N	LS mean (SE)[3]	Treatment difference [95% CI]; p-value
Change in waist circumference (cm)			
Placebo	56	0.61 (1.40)	
Mid-dose	54	-5.03 (1.38)	-5.63 [-9.44, -1.82]; 0.004
Top-dose	113	-6.98 (1.07)	-7.58 [-11.01, -4.16]; <0.0001
Change in Fasting insulin (µIU/mL)			
Placebo	56	-3.32 (8.96)	
Mid-dose	54	-11.47 (7.43)	-8.15 [-30.10, 13.79]; 0.4664
Top-dose	113	-7.99 (6.30)	-4.67 [-25.33, 15.99]; 0.6574
Change in Whole Body Insulin Sensitivity Index (Matsuda)			
Placebo	56	-3.70 (8.89)	
Mid-dose	54	-3.93 (7.65)	-0.23 [-22.42, 21.95]; 0.9835
Top-dose	113	-2.99 (6.44)	0.71 [-20.11, 21.52]; 0.9470
Percent change in Triglyceride			
Placebo	56	5.56 (8.41)	
Mid-dose	54	-6.18 (7.96)	-11.74 [-34.34, 10.85]; 0.3084
Top-dose	113	-5.59 (7.17)	-11.15 [-32.81, 10.52]; 0.3130
Percent change in HDL-C			
Placebo	56	-4.30 (15.10)	
Mid-dose	54	2.11 (11.50)	6.41 [-31.15, 43.96]; 0.7380
Top-dose	113	0.65 (9.56)	4.95 [-30.31, 40.21]; 0.7831
Change in diastolic blood pressure (mmHg)			
Placebo	56	3.41 (1.51)	
Mid-dose	54	0.24 (1.32)	-3.18 [-7.10, 0.74]; 0.1123
Top-dose	113	1.22 (0.99)	-2.19 [-5.73, 1.35]; 0.2254
Change in systolic blood pressure (mmHg)			
Placebo	56	2.86 (1.63)	
Mid-dose	54	0.09 (1.50)	-2.77 [-7.14, 1.61]; 0.2148
Top-dose	113	1.84 (1.11)	-1.01 [-4.90, 2.87]; 0.6086

Abbreviations: N=number of subjects randomized and received at least one dose of study drug; LS mean= least squares mean; SE: standard error; CI=confidence interval; BMI=body mass index; [1]Proportion from multiply imputed dataset; [2]Cochran-Mantel-Haenszel (CMH) test for risk difference between treatments, controlling for age and gender stratification factors; [3]Model based estimates and standard error, the analysis model was a mixed effects model with repeated measures (MMRM) with terms of treatment, visit, treatment by visit, baseline value, age stratification, and gender stratification; Missing observations were multiple imputed (1000 times) using a washout imputation; [Source: Reviewer]

3.3 Evaluation of Safety

All safety analyses were conducted on the safety analysis set, which was defined as all randomized subjects who were treated with at least one dose of treatment. The safety population was based on the treatment actually received.

Any treatment-emergent adverse events (TEAEs) were reported by 51.8%, 37%, and 52.2% of subjects in the placebo, Mid-dose, and Top-dose groups, respectively. There were 3 serious adverse events (bile duct stone, depression, suicidal ideation) reported in 2 subjects in the Top-dose group. No subjects died during the study. The results are summarized in Table 6.

Table 6: Overall Summary of Treatment-Emergent Adverse Events

	Placebo (N=56)	Mid-dose (N=54)	Top-dose (N=113)	Total (N=223)
TEAE	29 (51.8%)	20 (37.0%)	59 (52.2%)	108 (48.4%)
Mild	10 (17.9%)	8 (14.8%)	23 (20.4%)	41 (18.4%)
Moderate	19 (33.9%)	12 (22.2%)	34 (30.1%)	65 (29.1%)
Severe	0	0	2 (1.8%)	2 (0.9%)
Not drug-related TEAE	22 (39.3%)	16 (29.6%)	36 (31.9%)	74 (33.2%)
Drug-related TEAE	7 (12.5%)	4 (7.4%)	23 (20.4%)	34 (15.2%)
Drug-related TEAE leading to dose reduction	0	1 (1.9%)	2 (1.8%)	3 (1.3%)
TEAE leading to discontinuation of treatment	2 (3.6%)	0	1 (0.9%)	3 (1.3%)
Any TESAE	0	0	2 (1.8%)	2 (0.9%)
Drug-related TESAE	0	0	1 (0.9%)	1 (0.4%)

Abbreviations: N=number of subjects randomized and received at least one dose of study drug; TEAE=treatment-emergent adverse event; TESAE=treatment-emergent serious adverse event; cell contents are frequencies with relative frequencies in parentheses [Source: excerpted from Table 16 of CSR]

The summary of TEAEs is shown in Table 7 by system organ class and preferred term. Infections and infestations were most common adverse events followed by nervous system disorders, gastrointestinal disorders, and respiratory/thoracic/mediastinal disorders.

Table 7: Overall Summary of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term

	Placebo (N=56)	Mid-dose (N=54)	Top-dose (N=113)	Total (N=223)
TEAE	29 (51.8%)	20 (37.0%)	59 (52.2%)	108 (48.4%)
Infections and infestations	15 (26.8%)	9 (16.7%)	25 (22.1%)	49 (22.0%)
Nervous system disorders	7 (12.5%)	5 (9.3%)	16 (14.2%)	28 (12.6%)
Gastrointestinal disorders	8 (14.3%)	7 (13.0%)	12 (10.6%)	27 (12.1%)
Respiratory, thoracic and mediastinal disorders	7 (12.5%)	4 (7.4%)	13 (11.5%)	24 (10.8%)
Psychiatric disorders	1 (1.8%)	4 (7.4%)	10 (8.8)	15 (6.7%)
Injury, poisoning and procedural complications	5 (8.9%)	5 (9.3%)	7 (6.2%)	17 (7.6%)
General disorders and administration site conditions	3 (5.4%)	2 (3.7%)	13 (11.5%)	18 (8.1%)
Musculoskeletal and connective tissue disorders	3 (5.4%)	1 (1.9%)	10 (8.8%)	14 (6.3%)
Metabolism and nutrition disorders	1 (1.8%)	0	5 (4.4%)	6 (2.7%)
Skin and subcutaneous tissue disorders	2 (3.6%)	3 (5.6%)	7 (6.2%)	12 (5.4%)
Eye disorders	0	2 (3.7%)	2 (1.8%)	4 (1.8%)
Cardiac disorders	0	1 (1.9%)	2 (1.8%)	4 (1.8%)
Vascular disorders (Hypertension)	2 (3.6%)	0	2 (1.8%)	4 (1.8%)
Investigations	0	1 (1.9%)	4 (3.5%)	5 (2.2%)
Reproductive system and breast disorders	0	1 (1.9%)	2 (1.8%)	3 (1.3%)
Blood and lymphatic system disorders	0	0	2 (1.8%)	2 (0.9%)
Hepatobiliary disorders	0	0	2 (1.8%)	2 (0.9%)
Ear and labyrinth disorders	1 (1.8%)	0	0	1 (0.4%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	1 (0.9%)	1 (0.4%)
Renal and urinary disorders	0	0	1 (0.9%)	1 (0.4%)
Social circumstances (Education problem)	1 (1.8%)	0	0	1 (0.4%)
Surgical and medical procedures	1 (1.8%)	0	0	1 (0.4%)

Abbreviations: N=number of subjects randomized and received at least one dose of study drug; TEAE=treatment-emergent adverse event; cell contents are frequencies with relative frequencies in parentheses. If a subject experienced more than one adverse event within a system organ class, then the subject is counted once for each preferred term and once for the system organ class; [Source: excerpted from Table 14.3.1.2.1 of CSR]

For more details regarding the safety findings, refer to the review from the Medical Reviewer, Dr. Mary Roberts.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The subgroup analyses using a MMRM model compared percent change from baseline to Week 56 in BMI across treatment groups within corresponding subpopulations. The LS mean differences and the corresponding 95% CIs are shown in **Error! Reference source not found.** to **Error! Reference source not found.**.

There were some random highs and random lows in sample estimates of subgroup treatment effect due to small sample size and large variability for some subgroups. Therefore, we also calculated shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates. The total variability in the sample estimates is the sum of the within subgroup variability of the sample estimator and the across subgroups variability in underlying/true parameter values. A shrinkage estimate of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a "weighted" average of the sample estimate and overall estimate. We used the same flat prior to derive shrinkage estimates for all subgroups. The Bayesian hierarchical model assumptions are:

For i=1, 2,..., Y_i represents the observed sample estimate of treatment effect in a subgroup level i, assume $Yi \sim N(\mu_i, \sigma_i^2)$ where

- σ_i^2 are the observed variance for sample estimates
- $\mu_i \sim N(\mu, \tau^2)$
- $\mu \sim N(0, 30^2)$, $1/\tau^2 \sim$ Gamma(0.001, 0.001)

A standard deviation of 30 was chosen so that the standard deviation was approximately 4 times subject-level standard deviation. Results from both the sample and shrinkage estimates of the treatment effects for the subgroups are presented in Figure 2 to Figure 5.

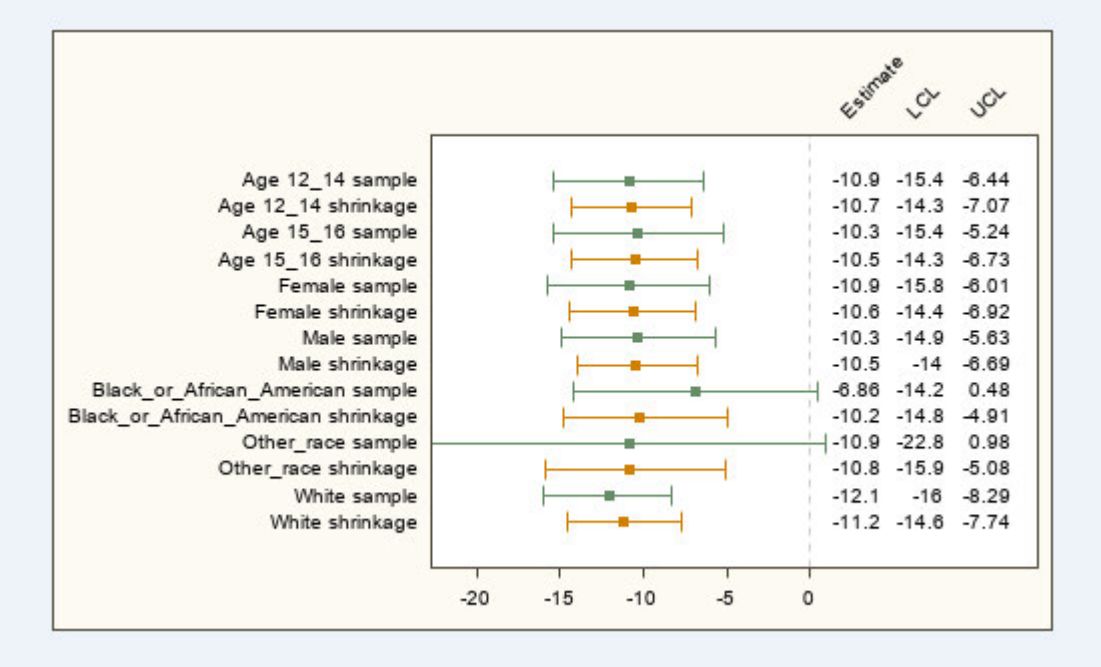
4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were performed for gender, race, and age group. Most subgroups reported the upper limit of the 95% confidence interval less than zero, in favor of active treatment groups, except for Black or African American and Other_Race. However, with shrinkage estimates, the upper limits of the 95% credible intervals were all less than zero in these groups, in favor of active treatments except for Other_Race in the Mid dose.

For all subgroups, the LS mean differences were less than zero, indicating greater numerical reduction in the active treatment groups than in the placebo group. Sample and shrinkage estimates were generally consistent with each other and in line with the overall treatment effect. Note that no subgroup analysis for geographic region was performed because the study was conducted in the United States.

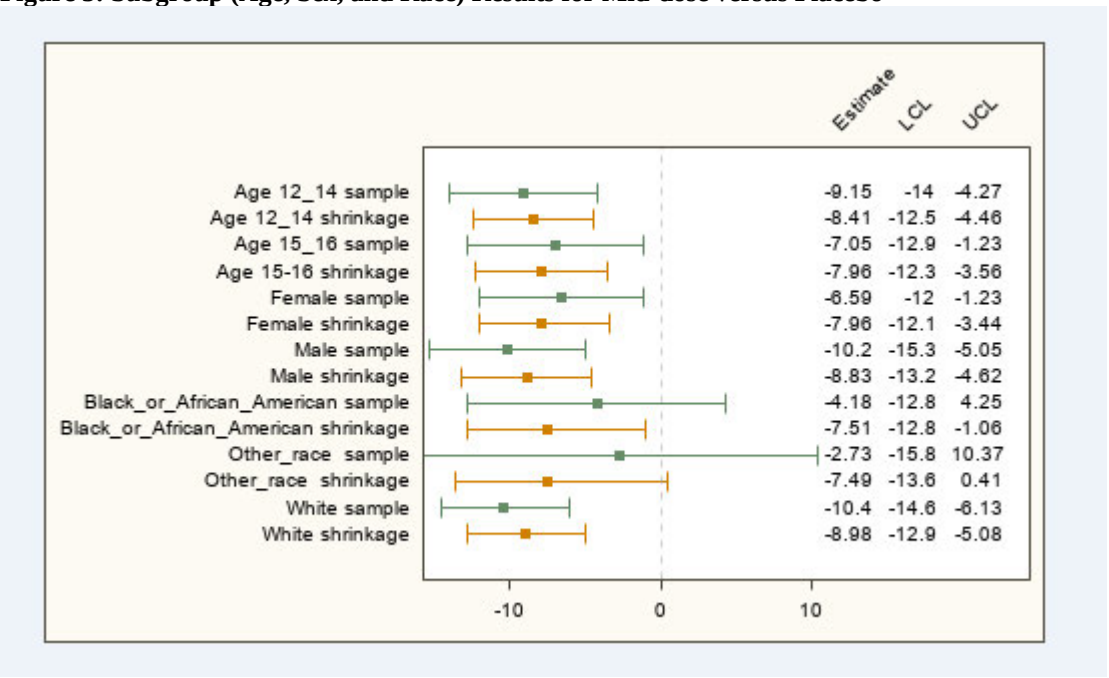
The results are presented in Figure 2 to Figure 5.

Figure 2: Subgroup (Age, Sex, and Race) Results for Top-dose versus Placebo



Sample estimates are shown with the corresponding 95% confidence interval and shrinkage estimates are shown with the corresponding 95% credible interval; LCL=lower confidence (or credible) limit; UCL=upper confidence (or credible) limit; Dotted vertical line indicates zero; [Source: Reviewer]

Figure 3: Subgroup (Age, Sex, and Race) Results for Mid-dose versus Placebo

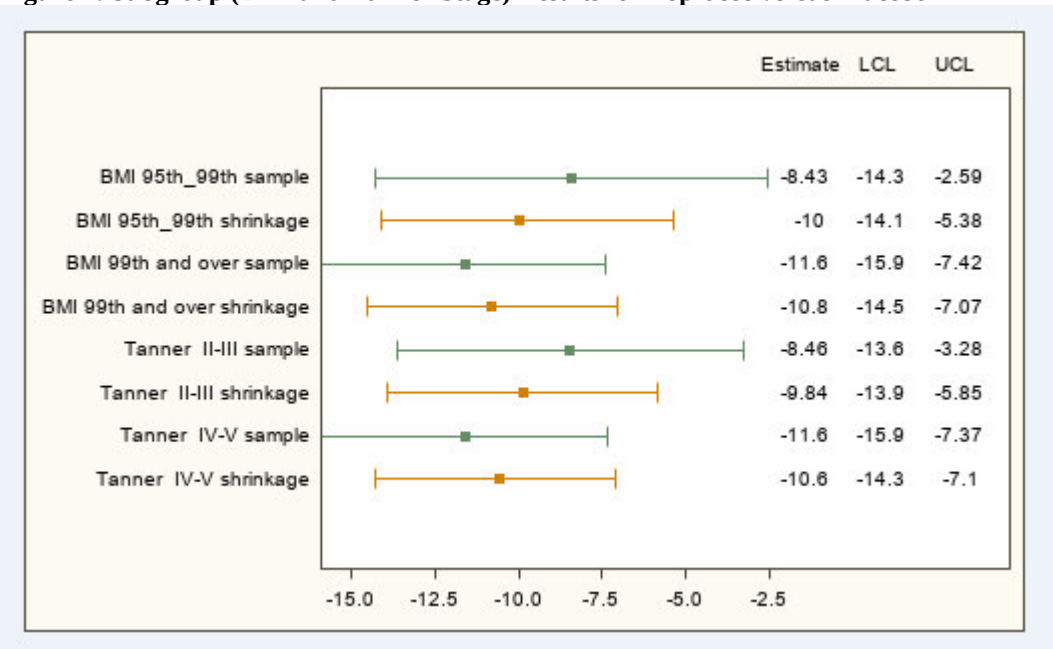


Sample estimates are shown with the corresponding 95% confidence interval and shrinkage estimates are shown with the corresponding 95% credible interval; LCL=lower confidence (or credible) limit; UCL=upper confidence (or credible) limit; Dotted vertical line indicates zero; [Source: Reviewer]

4.2 Other Special/Subgroup Populations

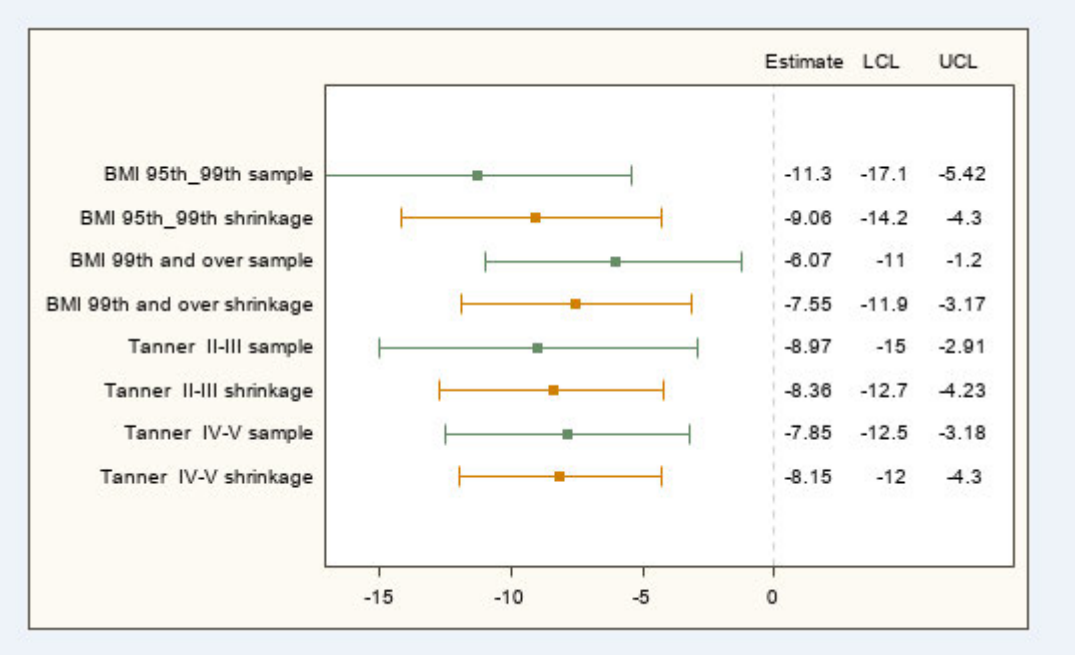
Additional subgroup analyses were performed for baseline BMI group (≥95th to <99th percentile and ≥99th percentile) and baseline Tanner stage (Tanner stage II/III and Tanner stage IV/V). All subgroups reported the upper limits of intervals less than zero, in favor of active treatments.

Figure 4: Subgroup (BMI and Tanner Stage) Results for Top-dose versus Placebo



Sample estimates are shown with the corresponding 95% confidence interval and shrinkage estimates are shown with the corresponding 95% credible interval; LCL=lower confidence (or credible) limit; UCL=upper confidence (or credible) limit; [Source: Reviewer]

Figure 5: Subgroup (BMI and Tanner Stage) Results for Mid-dose versus Placebo



Sample estimates are shown with the corresponding 95% confidence interval and shrinkage estimates are shown with the corresponding 95% credible interval; LCL=lower confidence (or credible) limit; UCL=upper confidence (or credible) limit; Dotted vertical line indicates zero; [Source: Reviewer]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There were high percentage of missing data due to the pandemic. However, it did not impact or change the overall conclusions.

Missing data were imputed using a washout imputation and the sensitivity analyses using the pre-specified approaches supported the robustness of the primary efficacy results. Although not all key secondary endpoints were statistically significant, body weight related endpoints were numerically in favor of active treatments.

5.2 Collective Evidence

The primary analysis showed statistically significant treatment effect in BMI reduction at Week 56 in both dose groups. Sensitivity analyses also supported the robustness of the conclusion from the primary efficacy analysis.

Efficacy in comparison to placebo was further supported by 4 key secondary endpoints related to the body weight (5%, 10%, and 15% BMI reductions and change in waist circumference) showing statistical significance in Top-dose versus placebo comparison.

5.3 Conclusions and Recommendations

The collective evidence from the submitted data demonstrated efficacy of VI-0521 in the study population. I recommend approval for the proposed indication based on findings from the submitted results.

5.4 Labeling Recommendations (as applicable)

Reviewing of labeling is still ongoing while this statistical review is finalized.

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/

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