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 213793
Supplement #:	Supplement-009
Drug Name:	Imcivree (Setmelanotide)
Indication(s):	To reduce excess (b) (4)
Applicant:	Rhythm
Date(s):	Stamp date - June 20, 2025 PDUFA date - March 19, 2026 (6-month priority + major amendment)
Review Priority:	Priority
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Keywords: analysis of covariance(ANCOVA), Cochran-Mantel-Haenszel, washout imputation, double-blind, rare disease, pediatric

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1 EXECUTIVE SUMMARY

The applicant, Rhythm, submitted NDA 213793/S-09 for IMCIVREE®(setmelanotide) Injection, in support of product label updates with respect to both the adult and pediatric (aged 4 years and older) indication. The label updates were based on evidence of mechanism of action and a single Phase 3 pediatric trial, RM-493-040, titled,

"A Phase 3, Double Blind, Randomized, Placebo-Controlled Trial to Evaluate the Efficacy and Safety of Setmelanotide in Patients with Acquired Hypothalamic Obesity(HO)".

- The applicant proposed to add acquired hypothalamic obesity indication in adults and pediatric patients 4 years and older along with changes in prescribing information.

1.1 Brief overview of Clinical Study

The study RM-493-040 was a randomized, double-blind, placebo-controlled, parallel-group, multicenter Phase 3 study intended to evaluate the efficacy and safety of setmelanotide injection once daily vs. placebo after around 52 weeks of treatment in adults and pediatric patients with acquired HO. The primary endpoint is percent change in body mass index (BMI) from baseline after week 52. A total of 142 subjects were randomized and dosed in a 2:1 ratio to two arms of setmelanotide and placebo. Out of 142 subjects, 12 Japanese subjects were randomized several months later than the other subjects. The applicant locked the database of 130 subjects while Japanese subjects in Japan were still on-going and submitted for the first 120 subjects as a pivotal cohort's results in this submission. Agency requested the rest of data, and the applicant will provide the data by March 6, 2026.

1.2 Statistical Issues

The applicant submitted the results in the clinical study report for the study RM-493-040 using the specified analysis set, "(b) (4) defined as the first 120 subjects who either completed 52 weeks of treatment or who discontinued after receiving at least 1 dose of study drug despite Agency's disagreement on this analysis set during the statistical analysis plan review. In this submission, the applicant submitted the data of 130 subjects out of 142 randomized subjects with data cutoff date of March 26, 2025 because 12 Japanese subjects are still on-going in Japan.

We disagree with using (b) (4) of first 120 subjects for statistical evaluation. The modified intent-to-treat population set defined as all randomized and received at least 1 dose should be used as analysis set of 142 subjects. Because of the unavailability of 12 on-going Japanese subject data at the time of this review, the primary efficacy evaluation will be focused on data from the 130 non-Japanese subjects obtained prior to the March 26, 2025, unblinding date, submitted in this submission. The measurements and amended measurements from all 142 subjects will be presented as sensitivity analyses.

1.3 Collective Evidence

The study demonstrated a statistically significant treatment effect for setmelanotide compared to

placebo with respect to the primary endpoint BMI percent change from baseline after 52 weeks (-18.65 % (95% CI: -22.39, -14.90) (Table 1). The missing data rate in the setmelanotide arm was higher (15%) than in the placebo arm (7%). Results from sensitivity analyses demonstrated robustness of the primary efficacy results to untestable assumptions on missing data. Subgroup analyses on the primary efficacy endpoint found consistent treatment effect of setmelanotide in subgroup levels on age, sex, race, ethnicity and region. The incidence of serious treatment-emergent adverse event (TEAE) is higher in the setmelanotide-treated subjects compared to placebo-treated subjects.

Table 1. Primary Efficacy Result on BMI Percent Change from Baseline after Week 52

	Setmelanotide N = 86	**Placebo N=44**
Baseline BMI, Mean (SD)	35.88 (9.27)	36.72 (9.07)
Week 52 Missing**, n (%)	13 (15.12)	3 (6.82)
Percent change from baseline to Week 52(%)* LS Mean (SE)	-15.58 (1.57)	3.06 (1.08)
Difference from Placebo (%)* LS Mean (95% CI) Two-sided P-value	-18.65 (-22.39, -14.90) <.0001	

Abbreviations: CI = confidence interval, SD = standard deviation, n = number of subjects.
* The LS Mean estimate is based on an ANCOVA model adjusted for baseline BMI and a stratification factor of age group (≥18 years old, ≥12 and <18 years old, and <12 years old) after imputing missing data with washout imputation method.
Source: Reviewer's analysis; adsl.xpt, advs.xpt

1.4 Conclusion and Recommendations

Statistical analyses based on the clinical data from the Phase 3 study RM-493-040 have demonstrated robust evidence to support the effectiveness of setmelanotide regarding weight control among adults and pediatric subjects with acquired HO. When the safety evaluation determines that risk is comparable, the statistical review team recommend approval of the proposed label updates with minor modifications in Section 14.

2 INTRODUCTION

2.1 Overview

2.1.1 Current Indication

Setmelanotide (IMCIVREE) is now a melanocortin 4 (MC4) receptor agonist indicated to reduce excess body weight and maintain weight reduction long term in adults and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to:
• Bardet-Biedl syndrome (BBS).
• Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/ kexin type1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating

variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

2.1.2 Critical Statistics-related History of RM-493-040 Drug Development

An end of Phase 2 meeting was held on October 4th, 2022, where FDA's statistics-related comments are:

- FDA strongly recommend that you extend the duration of trial to 52 weeks. The 52-week active treatment period should not include the titration period.
- Primary analysis population should include all randomized subjects. Not having sufficient data at 12 months might render the data uninterpretable to determine if the drug is effective.

In May 2023, FDA reviewed sponsor's first submitted SAP, where all randomized subjects will be used in the analyses of primary and key secondary endpoints. In October 2023, FDA reviewed a protocol amendment. In the amendment, the enrollment will include 12 subjects from sites in Japan and subpopulation (Japanese/non-Japanese) is added as a new stratification factor. In December 2024, the sponsor submitted an SAP amendment, which defined a new pivotal analysis based on the first 120 subjects who had completed or discontinued from the study. In SAP, modified intention to treat analysis set (mITT), all randomized subjects who are exposed to at least 1 dose of study treatment, was added, and mITT would be the primary population for the analysis of efficacy data. On March 7th, FDA suggested using mITT population for formal hypothesis testing, not the (b) (4). In March 2025, the sponsor proposed that the success/failure conclusion of the trial would be based on the (b) (4). However, the sponsor's new SAP Version 4.0(V4) Section 4.3.1 stated primary analysis would use the mITT analysis set. The updated SAP lacks clarification and contains contradictions in the definition of the statistical evaluation population despite FDA's continued advice on the analysis set. On March 26, 2025, the database lock and unblinding of study RM-493-040 occurred. On April 1st, FDA reiterated the suggestion of using mITT instead of using the (b) (4) for formal hypothesis testing. In this NDA submission, the sponsor submitted the statistical analyses of 120 subjects as the primary evaluation with the data of 130 subjects which were available at the time of database lock.

2.1.3 Specific Studies Reviewed

This review focuses on the results of Trial RM-493-040. Table 2 provides a summary of the trial characteristics.

Table 2. Summary Table of Trial Characteristics, RM-493-040.

Trial ID	Design	Treatment/ Sample Size	Endpoint/Analysis	Findings
RM-493-040	MC, R, DB, PC up to 8-wk scr + up to 60-wk TrtP + 2-wk sfv Subject aged > 4 years Stratification factor: age group (<12 yrs old, ≥12 to <18 yrs old, ≥18 yrs old) Background of dietary with or without the use of medications, supplements or herbal treatments associated with weight loss	130 Randomized and dosed subjects across non-Japanese sites: Setmelanotide / 86 Placebo / 44 12 subjects in Japan added after the study began: Setmelanotide / 8 Placebo / 4	Primary: 1. Percent change in BMI from baseline at Week 52 / ANCOVA with MI Key secondary (sequential testing from 1 to 3): 1. ≥5% reduction in BMI in adult subjects or BMI Z-score reduction of ≥0.2 points in pediatric subjects (<18 years of age) from baseline after 52 weeks 2. ≥5% reduction in BMI in all subjects from baseline after 52 weeks 3. Change in the weekly average of the daily most hunger score in subjects ≥12 years old from Baseline after 52 weeks	Superiority of the primary endpoint was achieved for setmelanotide. Difference [Setmelanotide-Placebo] in LS Means (CI) is -18.65% (-22.39, -14.90) with 2-sided p-value <0.0001.

* MC: multi-center, R: randomized, DB: double-blind, PC: placebo controlled, TrtP: treatment period, wk: week, scr: screening, sfv: safety follow-up visit, BMI: body mass index, MI: multiple imputation; ANCOVA: analysis of covariance.
Source: Reviewer's Analysis Using Applicant Submitted Dataset adsl.xpt and adhba1c.xpt.

2.2 Data Sources

The Electronic Document Room (EDR) location for the submission package of the original NDA submission package including the study reports, SDTM dataset, ADSL dataset, SAPs, protocols and SAS codes is \\CDSESUB1\evsprod\NDA213793\0441.

The applicant's responses to IRs are located at:

- \\CDSESUB1\evsprod\NDA213793\0445: primary analysis SAS macro codes per FDA information request(IR) dated June 30th, 2025,
- \\CDSESUB1\evsprod\NDA213793\0452: primary analysis SAS multiple imputation codes per FDA information request(IR) dated July 14th, 2025,
- \\CDSESUB1\evsprod\NDA213793\0453: corrections on efficacy evaluation of Hunger Sore on August 4, 2025,

- \\CDSESUB1\evsprod\NDA213793\0458 : primary analyses using mITT and non-Japanese mITT per FDA IR dated August 12th, 2025,
- \\CDSESUB1\evsprod\NDA213793\0471: sponsor's response[1] per FDA IR dated September12th, 2025 for correction and explanation on height data of 6 subjects aged <22 years with recorded heights less than their baseline height in trial RM-493-040 (subject IDs [redacted] (b) (6)) in the setmelanotide arm among 130 non-Japanese subjects. No height decreasing cases are observed in the placebo arm from advs dataset.
- \\CDSESUB1\evsprod\NDA213793\0476, and \\CDSESUB1\evsprod\NDA213793\0479: sponsor's response on 1)BMI zscore calculation, 2) Survival Analyses for "first occurrence of Drug-Related TEAE" and "first occurrence of Serious TEAE", and 3) ANCOVA analyses using "obsmargin" and accounting for possible unequal residual variances.
- \\CDSESUB1\evsprod\NDA213793\0488, and \\CDSESUB1\evsprod\NDA213793\0489: sponsor's responses on 1) primary analyses using correct time window of 358 to 425 for weights and hunger scores after around week 52, 2) more accurate BMI zscore calculation based on subjects' ages in month, and 3) wide format dataset (named "adallw.xpt") without imputation including all primary and key secondary relevant endpoints.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor's submitted analyses were insufficient to evaluate the efficacy results with low quality of data and programs. To calculate children's BMI Z-score, the assumption of a birth date of 01 January in the original submission is not mentioned and clarified. In the original NDA submission under folder "0441", macro codes for primary analyses and imputation are missing. Codes for primary analyses does not align with the SAP assuming unequal variance. Corrections on efficacy evaluation of Hunger Sore including key secondary analyses were submitted after over 50 Days from original NDA submission.
In addition, the updated SAP V4 submitted in the NDA submission contains a critical contradiction. In Section 2.1 Population Definitions, the mITT is defined and will be used as the primary population for the analysis of efficacy data. However, in Section 3.12 Interim Analyses, Timing of Planned Analyses, and Cohorts, the set of pivotal cohorts is defined and claimed to be used in formal hypothesis testing and success/failure.

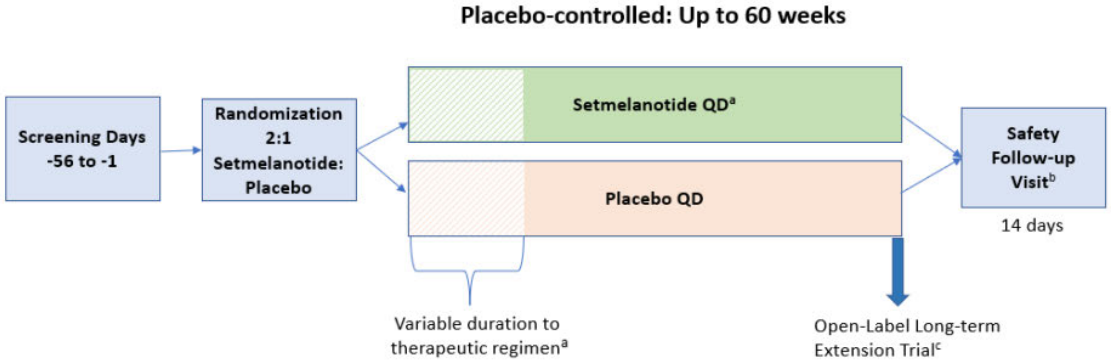
[1] Height measurements naturally display some degree of intra-individual variability over time. From the sponsor, the imbalance is likely a random occurrence. Primary analyses of BMI are more conservative due to height decreasing cases in setmelanotide.

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

The study RM-493-040 is a 52-week (up-to-60-week) randomized, double-blind, multi-center, placebo-controlled study, consisting of a screening period of up to 8 weeks, a treatment period of up to 60 weeks, and a safety follow-up visit approximately 2 weeks post-treatment period. Subjects who meet all enrollment criteria are randomly assigned in a 2:1 ratio to once-daily administration of setmelanotide or placebo with most subjects reaching their maximally tolerated therapeutic dose between 4 and a maximum of 8 weeks after the initial dose of 0.5 mg. Randomization was stratified by age group (≥18 years old, ≥12 and <18 years old, <12 years old) and subpopulation (Japanese vs non-Japanese). A diagram of the study design is showed in Figure 1.

Figure 1 Diagram of the Study Design



a. Initial doses start at 0.5 mg and escalate in increments of 0.5 to 1.0 mg until the patient reaches an individual therapeutic regimen. See Protocol Section 5.5.3 for dose and escalation scheme by age and weight.
b. The SFV is only required for patients who prematurely discontinue treatment or for patients who complete the trial and do not enroll in the LTE or Bridging Visits.
c. Patients who complete the trial and trial assessments may be eligible to participate in the LTE (or receive open-label setmelanotide and attend Bridging Visits if the LTE is not yet available).

Source: Sponsor's SAP Version 4.0 page 14 of 64.

The study originally planned to enroll 120 subjects (80 subjects in setmelanotide group vs. 40 subjects in placebo group). 12 subjects from Japan are planned to be enrolled within the 120 subjects. The planned study provides over 99% power to detect a treatment difference of 10% in percent change of BMI at 2-sided alpha of 0.05, assuming a common standard deviation of 10%.

The enrollment timeline and study population details are as follows: 86 non-Japanese subjects were randomized to the setmelanotide treatment group between April 26, 2023, and February 29, 2024. 44 non-Japanese subjects were assigned to the placebo group between May 9, 2023, and February 28, 2024.

Weight measurements following approximately 52 weeks of treatment were obtained for 127 of 130 non-Japanese subjects prior to database lock and unblinding for the pivotal cohort (i.e., first 120 randomized subjects). And all 12 Japanese subjects were still in the treatment period of the

trial when database lock and unblinding occurred on March 26, 2025. The agency requested all 12 Japanese subject data and the applicant will submit them by March 6, 2026.

Primary Endpoint:
BMI percent change (%) from baseline after 52 weeks

Key Secondary Endpoints:
1. Achievement of ≥5% reduction from baseline in BMI in adult subjects (≥18 years of age), and BMI Z-score reduction of ≥0.2 in pediatric subjects from baseline after 52 weeks
2. Achievement of ≥5% reduction in BMI from baseline after 52 weeks
3. Changes in weekly average of the daily most hunger score in subjects ≥12 years old from baseline after 52 weeks

Multiplicity Adjustment
A sequential testing procedure with 2-sided alpha at 0.05 was applied for primary and key secondary endpoints in the following order: primary endpoint, first key secondary endpoint, second key secondary endpoint, and third key secondary endpoint.

3.2.2 Statistical Methodologies

Estimand Framework

The applicant pre-specified an estimand framework in the SAP as following.
- Population: subjects (aged 4 years or older) with documented evidence of acquired HO and weight gain according to the inclusion/exclusion criteria.
- Variable: percent change from baseline in BMI after 52 weeks of treatment with either setmelanotide or placebo.
- Treatment: setmelanotide (where dose-escalation will occur based upon an age-dependent and weight-dependent regimen up to 3.0 mg QD) vs placebo.
- Intercurrent events (ICEs) (events that preclude observation of the variable or affect its interpretation): treatment discontinuation, receiving the wrong treatment, treatment interruption, non-adherence to study drug; ICEs are addressed with the treatment policy strategy, in which all collected measurements will be included in the statistical analyses. Any on-study death will be handled via the composite strategy, in which death is considered a sufficiently unfavorable outcome, and the subject will have their corresponding change and percent change from baseline artificially set to 0.
- Population-level summary: difference between treatment groups (setmelanotide and placebo) in mean percent change from baseline in BMI at Week 52.

Analyses Set

Modified Intent-To-Treat (mITT): all randomized subjects who are exposed to at least 1 dose of study treatment. The applicant specified the primary endpoint will be conducted on the mITT utilizing BMI values resultant from the multiple imputation process.

Pivotal cohort: the first 120 subjects dosed in any region who have completed the trial and any subjects who discontinued after receiving their first dose of study drug. The applicant specified that formal hypothesis testing will be considered based on pivotal subjects.

The applicant also specified that the primary analysis will also be conducted for all randomized subjects.

Reviewer's Note: *Given that the SAP V4 includes two primary analysis sets for efficacy evaluation, FDA disagreed with using the pivotal cohort. This statistical review focuses on mITT set to prevent selective analysis and maintain consistency with FDA's suggestions at drug development stage. Due to the ongoing Japanese subjects, the primary efficacy will be mainly evaluated by 130 randomized non-Japanese subjects in this review.*

Handling of Missing Data and Primary Efficacy Analyses

The difference between setmelanotide and placebo after 52 weeks on therapeutic dose is estimated using an ANCOVA model with unequal variance to account for possible unequal residual variances. The model is adjusted with the stratification factor of age group (≥18 years old, ≥12 and <18 years old, and <12 years old) and baseline endpoint.

Given that height is measured only at screening for subjects 21 years of age or older, for visits where weight is collected but height is not, last observation carried forward (LOCF) height information was used for BMI calculation.

The pre-specified primary weight imputation is based on retrieved dropout (RD) imputation and washout (WO) imputation as a back-up plan when the algorithm does not converge. Due to the limited retrieved dropout observations, the imputation method for primary analysis is confirmed as WO imputation. In addition, there was no on-study deaths. Therefore, the details of the primary analyses using WO imputation are as described below with 6 steps:

1. Multiple imputation(MI) using Monte Carlo Markov Chains is utilized according to treatment arm to impute intermediate values and to generate a monotone missingness pattern.
2. Placebo subjects are imputed assuming missing-at-random(MAR) regressing on baseline weight, visit 2 weight, visit 4 weight, visit 7 weight, visit 9 weight, visit 11 weight, and primary timepoint weight.
3. The Setmelanotide subjects are then imputed using observed placebo-based imputation regressing only on baseline value and primary timepoint value.
4. A total of 100 multiple imputations are performed.
5. After MI, each of the multiply imputed datasets are analyzed using analysis of covariance (ANCOVA) with treatment factor, stratification factor(s), and baseline of endpoint.

6. Resulting estimates are combined using Rubin's rule (SAS PROC MIANALYZE) to produce inferential results

The same 100 imputed weight datasets are used for key secondary endpoints, proportion of BMI/BMI Z-Score percent change from baseline. Then the 100 risk difference estimates obtained from Cochran–Mantel–Haenszel(CMH) method estimates with adjustment of stratification factors are combined using Rubin's rule to produce inferential results.

The statistical analysis model for the daily hunger score questionnaire is ANCOVA model with treatment factor, stratification factor(s), and baseline of endpoint. The same imputation method as the primary weight imputation method is used to impute the missing daily hunger score.

Sensitivity Analyses

A 2-way tipping point analysis is performed as a sensitivity analysis under the primary estimand to quantify robustness of results to missing data assumptions and provide a worst-case boundary.

Reviewers retrospectively applied two additional imputation methods to further examine the robustness of the efficacy results:

1. BMI was classified as missing when either weight or height data was unavailable. Missing BMI values were then imputed using the WO method based on observed BMI measurements.
2. For children with observed weight but missing height at week 52, each child's height at the time of weight measurement at week 52 was imputed based on the child's observed heights over time using the least squares (linear) method.

For the two binary key secondary endpoints, unconditional risk differences using logistic regression are also calculated to assess the population level treatment effect in this study.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

A summary of subject disposition of 130 subjects prior to the unblinding date of March 26, 2025, is presented in Table 3. Of the randomized subjects, 9 (10.5%) in the setmelanotide group and 2 (4.5%) in the placebo group encountered ICEs, and 4 (4.7%) in the setmelanotide group and 1 (2.2%) in the placebo group missed their primary endpoint assessments without reported ICEs. Of 9 subjects with ICEs in the setmelanotide arm at Week 52, 5 subjects discontinued due to adverse events and 4 subjects withdrew.

Table 3. Subject Disposition Prior to the Unblinding Date

	Setmelanotide	Placebo
Randomized	95	48
Randomized and treated (mITT) (N=142)	94	48
Pivotal cohort (N=120)	81	39
Non-Japanese (N=130)	86	44
Japanese (on-going/expected to be completed by March 6, 2026) (N=12)	8	4

Non-Japanese (N=130) for data capture at Week 52		
Non-missing values of Weight at Week 52	73	41
On treatment [n]	73	38
Off treatment (Retrieved drop-outs) [n]	0	3
Missing Values of Weight at Week 52* in the non-Japanese set, (%)	13 (15%)	3 (7%)
Subjects on treatment	1	1
Ongoing with Over 399 Treatment Days	3	0
Study discontinuation	9	2
Adverse event	5	0
Withdrawal by subject	4	2

ICEs: Intercurrent events; Unblinding date: March 26, 2025; SD: study discontinuation.
Source: Statistical Reviewer's Analysis; adsl.xpt, advs.xpt, suppdm.xpt, adallw.xpt

A summary of subject demographics and baseline characteristics is presented in Table 4. Based on the summary, demographics and baseline characteristics are generally similar between the setmelanotide and placebo groups. Among pediatric subjects, the placebo arm includes a higher proportion of females than males. Sex distribution differs across treatment groups in the pediatric population.

Reviewer's Note: *Although the mean of age and proportions in categorized age groups were similar across treatment groups, there were 20 subjects (23%) aged between 18 and 25 years old in the setmelanotide group compared to 4 subjects (8%) in the placebo group. The reviewers included an additional age group (18–25 years) as a factor in the primary analysis to address this imbalance age issue. The resulting inference for the mean difference in percent BMI change was consistent with the primary results shown in Table 5. Therefore, the observed imbalance does not affect the primary conclusion of superiority. Similar conclusions were obtained after adding sex as a model factor.*

Table 4. Demographics and Baseline Characteristics (Non-Japanese Population)

Characteristic	Setmelanotide N=86	Placebo N=44
Age, years		
Mean (SD)	19.7 (13.1)	22.0 (16.0)
[Min, Max]	[4.0, 65.0]	[4.0, 66.0]
Age Category, n (%)		
< 12 Years	20 (23%)	12 (27%)
≥ 12 Years and < 18 Years	29 (34%)	14 (32%)
≥ 18 Years	37 (43%)	18 (41%)
Sex, n (%)		
Female	47 (55%)	29 (66%)
Male	39 (45%)	15 (34%)
Race, n (%)		
Asian	3 (3%)	1 (2%)
Blace or African American	6 (7%)	1 (2%)
Not Reported***	6 (7%)	6 (14%)
White	71 (83%)	36 (82%)
Ethnicity, n (%)		
Not Reported	1 (1%)	0 (0%)
Hispanic or Latino	8 (9%)	8 (18%)
Not Hispanic or Latino	77 (90%)	36 (82%)

Geographic Region, n (%)		
Europe	24 (28%)	10 (23%)
North America	62 (72%)	34 (77%)
Country, n (%)	86	44
Non-US	29 (34%)	13 (30%)
US	57 (66%)	31 (70%)
BMI, kg/m2	86	44
Mean (SD)	35.9 (9.3)	36.7 (9.1)
[Min, Max]	[21.3, 69.2]	[21.3, 70.0]
Subjects aged < 18 years (N)	**N=49**	**N=26**
BMI Z-score *		
Mean (SD)	3.8 (1.9)	3.6 (1.4)
[Min, Max]	[2.1, 10.6]	[2.0, 8.2]
Height, cm **		
Mean (SD)	150.0 (20.9)	148.00 (18.5)
[Min, Max]	[106.0, 183.5]	[105.9, 186.7]
Age, month **		
Mean (SD)	146.2 (47.0)	145.7 (41.8)
[Min, Max]	[59.0, 214.0]	[62.0, 208.0]
Age, years		
Mean (SD)	11.6 (4.01)	11.5 (3.66)
[Min, Max]	[4,17]	[4,17]
Weight, kg **		
Mean (SD)	77.0 (33.5)	74.5 (27.4)
[Min, Max]	[24.2, 192.3]	[23.9, 139.4]
Sex, n (%) **		
Female	22 (45%)	18 (69%)
Male	27 (55%)	8 (31%)

Abbreviations: SD = standard deviation, cm = centimeter, kg/m2 = kilograms per meter squared, US = United States, BMI = body mass index, n = number of subjects.
* The BMI Z-scores are calculated by World Health Organization's WHO 2007 BMI SAS Macro Package for all subjects aged < 18 years of age using ages, weights, sexes and heights.
** Ages, weights, sexes and heights are used to calculate BMI Z-score for all subjects aged < 18 years of age.
*** There were no subjects of American Indian or Alaskan Native and Native Hawaiian or Other Pacific Islander race enrolled within this trial.
Source: Statistical Reviewer's Analysis; adsl.xpt, adallw.xpt

3.2.4 Results and Conclusions

Primary Efficacy Results

As demonstrated in Table 5, the LSMean difference (95% CI) in percent BMI change from baseline at Week 52 is -18.65 (-22.39, -14.90) for setmelanotide vs. placebo, with a two-sided p-value <0.001. Setmelanotide group achieved statistically significant superiority to the placebo group for the primary endpoint. The bottom panel of Table 5 reports the primary analysis results after imputing all missing observations for the 12 ongoing Japanese subjects as a supplemental analysis.

Table 5. Primary Results on percent change in BMI from baseline after Week 52 (Non-Japanese group N=130 and all randomized and dosed group N=142)

Non-Japanese (N=130)	**Setmelanotide N = 86**	**Placebo N=44**
Baseline BMI, Mean (SD)	35.88 (9.27)	36.72 (9.07)
Week 52 Missing BMI**, n (%)	13 (15.12)	3 (6.82)
Week 52 BMI, Mean (SD)*	29.98 (8.00)	37.92 (9.77)
Percent Change from Baseline to Week 52*, LS Mean (SE)	-15.58 (1.57)	3.06 (1.08)
Comparison to Placebo*, LS Mean difference (95% CI), Two-sided P-value	-18.65 (-22.39, -14.90) <.0001	
All Randomized and Dosed (N=142)	**N = 94**	**N= 48**
Comparison to Placebo***, LS Mean difference (95% CI), Two-sided P-value	-17.21 (-20.97, -13.45) <.0001	

Abbreviations: CI = confidence interval, SD = standard deviation, BMI = body mass index, n = number of subjects.
* The LS Mean estimate is based on an ANCOVA model adjusted for baseline BMI and a stratification factor of age group (≥18 years old, ≥12 and <18 years old, and <12 years old) after imputing missing data with washout imputation method for weights and last observation carried forward imputation for heights.
**The missing BMI is defined as the BMI missing due to the missing of weights.
*** The statistical results are based on imputing all missing observations of 12 ongoing Japanese subjects.
Source: Reviewer's analysis; adsl.xpt, advs.xpt, advs.xpt

For sensitivity analysis, 8 missing height values in subjects aged <21 years with observed weights were imputed using linear regression of longitudinal height measurements over time. The primary efficacy results based on different imputation method to compute BMIs are presented in top of Table 6, which demonstrates that the finding of significant treatment benefit is robust.

From two-way tipping point analyses on the primary efficacy analysis, the four points of the tipping points were included in Table 6. This further confirms the robustness of the significant treatment benefit, as the efficacy evaluation remains statistically significant even when assuming the most conservative scenario: missing setmelanotide-treated subjects experienced substantial increases in BMI while missing placebo-treated subjects experienced substantial decreases in BMI.

Table 6. Sensitivity Analyses for the Primary Endpoint

ANCOVA Analyses Based on Different Imputation Methods	**Mean Difference Estimate (SE)**	**95% CI**	**Nominal P-value**
Analyses with WO Imputation for BMI*	-18.54 (1.890)	(-22.24,-14.83)	<.0001
Analyses with WO Imputation for Weights and Longitudinal Linear Imputation for Heights	-18.44 (1.901)	(-22.17, -14.72)	<.0001
Tipping Point Analyses Based on the Primary Analysis			
Percent BMI Added to the Placebo Missing: 0% Percent BMI Added to the Setmelanotide Missing: 70%	-7.92 (3.99)	(-15.74, -0.00)	0.0471
Percent BMI Added to the Placebo Missing: 0% Percent BMI Added to the Setmelanotide Missing: 71%	-7.77 (3.99)	(-15.65, 0.00)	0.0536
Percent BMI Added to the Placebo Missing: -50%			

Percent BMI Added to the Setmelanotide Missing: 51%	-7.69 (3.89)	(-15.30, -0.00)	0.0480
Percent BMI Added to the Placebo Missing: -50% Percent BMI Added to the Setmelanotide Missing: 52%	-7.42 (3.94)	(-15.15, 0.00)	0.0598

Abbreviations: CI = confidence interval; SE = standard error, BMI = body mass index, n = number of subjects.
* BMI is count as a missing value if height or weight is missing instead of using LOCF imputation for heights.
Source: Statistical Reviewer's Imputation Analyses and Tipping Point Analyses; adsl.xpt, advs.xpt, adallw.xpt

Key Secondary Efficacy Results

The risk difference of proportions of setmelanotide-treated subjects who met the first key secondary endpoint, and the second key secondary endpoint compared to placebo are 62.07% and 65.8%, as demonstrated in Table 7. Also, from the analyses in both adult and pediatric subjects from Table 7, it appears setmelanotide is superior to placebo with respect to weight control in both adult and pediatric subjects.

Table 7. Key Secondary Endpoint Analysis Results (Non-Japanese group N=130 and all randomized and dosed group N=142)

Key Secondary (Non-Japanese group N=130**)**		**Setmelanotide N = 86**	**Placebo N=44**
Adult Subjects with ≥ 5% Reduction in BMI or Pediatric Subjects with ≥ 0.2 BMI Z-Score Reduction from Baseline After 52 weeks	Response Rate*(%)	81.99	20.95
	Risk Difference (%), (95% CI), P-value*	-62.07, (-76.02, -48.12) <0.001	
	Unconditional risk difference (95% CI), P-value***	-60.89, (-74.80, -46.79) <.0001	
Subjects with ≥ 5% Reduction in BMI from Baseline After 52 weeks	Response Rate*(%)	76.01	10.34
	Risk Difference (%), (95% CI), P-value*	-65.80, (-79.02, -52.58), <0.001	
	Unconditional risk difference (95% CI), P-value***	-65.78, (-79.12, -52.43), <.0001	
Adult Subgroup		**Setmelanotide N = 37**	**Placebo N=18**
Adult Subjects with ≥ 5% Reduction in BMI	Response Rate*(%)	72.32	5.56
	Risk Difference (%), (95% CI)**	-66.77, (-85.19, -48.35)	
Pediatric Subgroup		**Setmelanotide N = 49**	**Placebo N=26**
Pediatric Subjects with ≥ 0.2 Reduction in BMI Z-Score	Response Rate*(%)	86.76	31.62
	Risk Difference (%), (95% CI)	-56.32, (-76.21, -34.07)	
Pediatric	Response Rate*(%)	78.80	13.65

Subjects with ≥ 5% Reduction in BMI	Risk Difference, (95% CI)	-65.11, (-83.40, -46.82)	
Key Secondary (All Randomized and Dosed N=142)		**Setmelanotide N = 94**	**Placebo N=48**
Adult Subjects with ≥ 5% Reduction in BMI or Pediatric Subjects with ≥ 0.2 BMI Z-Score Reduction from Baseline After 52 weeks	Response Rate*^ (%)	75.03	20.33
	Risk Difference (%), (95% CI), P-value*^	-56.15, (-70.28, -42.02) <0.001	
	Unconditional risk difference (95% CI), P-value***^	-56.24, (-70.47, -42.00) <.0001	
Subjects with ≥ 5% Reduction in BMI from Baseline After 52 weeks	Response Rate*^(%)	70.76	10.79
	Risk Difference (%), (95% CI), P-value*^	-60.51, (-74.00, -47.03), <0.001	
	Unconditional risk difference (95% CI), P-value***^	-60.39, (-74.05, -46.72) <.0001	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error, BMI = body mass index, N = number of subjects in the treatment group, n = number of subjects.
* The response rate is calculated on average across multiple imputation datasets based on the same primary imputed dataset for the primary endpoints.
** The risk difference is calculated using Cochran-Mantel-Haenszel test with adjustment of stratification factors of age group on the same primary imputed dataset for the primary endpoints.
*** The risk difference is calculated using binomial test on the same primary imputed dataset for the primary endpoints.
*** The unconditional risk difference is calculated using "g-computation"[2] based on logistic regression with adjustment of stratification factors by the reviewer as an additional sensitivity analysis.
^ The statistical results are based on imputing all missing observations of 12 ongoing Japanese subjects.
Source: Reviewer's analysis; adsl.xpt, advs.xpt, adallw.xpt

The last prespecified key secondary endpoint is the change of weekly average of daily most hunger score for subjects aged ≥ 12 years old. The missing rates for this endpoint were high: 12% of subjects had missing baseline, and 28% of subjects had missing data at Week 52 among subjects with an observed baseline score. As demonstrated in the Table 8, the LSMean difference (95% CI) in Weekly Average of Daily Most Hunger Score change from baseline at Week 52 is -1 (-2, 0.01) for setmelanotide vs. placebo. The LSMean difference favors setmelanotide compared to placebo; however, since the p-value is >0.05, superiority of setmelanotide over placebo is not statistically demonstrated. Refer to clinical review for clinical meaningfulness and the validation of Hunger Score endpoint for further interpretation.

Table 8 Key Secondary Results on Weekly Average of Daily Most Hunger Scores (Non-Japanese N=130)

[2] Ye, Ting, Marlena Bannick, Yanyao Yi, and Jun Shao. 2023. "Robust Variance Estimation for Covariate-Adjusted Unconditional Treatment Effect in Randomized Clinical Trials with Binary Outcomes." Statistical Theory and Related Fields 7 (2): 159–63. https://doi.org/10.1080/24754269.2023.2205802

	Setmelanotide N = 86	Placebo N=44
Subjects Aged 12 and above, n (%) With Observed Baseline Score, n (%)	66 (76.74) 58 (67.44)	32 (72.73) 28 (63.64)
Baseline, Mean (SD)	6.78 (2.28)	7.23 (2.00)
Subjects with Observed Score at Week 52, n (%)	42 (48.84)	20 (45.45)
Change from Baseline to Week 52*, LS Mean (SE)	-2.56 (0.30)	-1.56 (0.40)
Comparison to Placebo*, LS Mean difference (95% CI), Two-sided P-value	-0.86 (-1.74, 0.01) 0.0532	

Abbreviations: CI = confidence interval, SD = standard deviation, SE = standard error, BMI = body mass index, N = number of subjects in the treatment group, n = number of subjects.
* The analyses are based on subjects with observed baseline score. The model is ANCOVA model adjusted with baseline score and age groups. The imputation method is washout imputation, similar to the primary imputation method for weights, except that the imputed score limit is constrained to a range of 0 to 10.
Source: Reviewer's analysis; adsl.xpt, advs.xpt, adallw.xpt

To further explore the treatment efficacy in weight reduction, Table 9 lists the risk difference estimates for proportion of subjects with ≥10% and 15% reduction in BMI after 52 weeks under treatment policy.

Table 9 Exploratory Secondary Results on Proportion of Subjects with ≥10% and 15% Reduction in BMI after 52 Weeks under Treatment Policy (Non-Japanese group, N=130)

	Setmelanotide N = 86	Placebo N=44
% of subjects losing greater than or equal to 10% BMI*	60.92	5.07
Risk % difference from placebo (95% CI)**	-56.06 (-68.41, -43.71)	
Unconditional % difference from placebo (95% CI)***	-55.99 (-68.44,-43.54)	
% of subjects losing greater than or equal to 15% BMI*	48.97	2.45
Risk % difference from placebo (95% CI)**	-46.34 (-58.03, -34.65)	
Unconditional % difference from placebo (95% CI)***	-46.41 (-58.11, -34.71)	

Abbreviations: CI = confidence interval, BMI = body mass index, N = number of subjects in the treatment group, % = percent.
* The % of subjects are calculated on average across multiple imputation datasets based on the same primary imputed dataset for the primary endpoints.
** The risk % difference is calculated using Cochran-Mantel-Haenszel test with adjustment of stratification factors of age group on the same primary imputed dataset for the primary endpoints.
*** The unconditional % difference is calculated using "g-computation"[3] based on logistic regression with adjustment of stratification factors.
Source: Reviewer's analysis; adsl.xpt, advs.xpt, adallw.xpt

[3] Ye, Ting, Marlena Bannick, Yanyao Yi, and Jun Shao. 2023. "Robust Variance Estimation for Covariate-Adjusted Unconditional Treatment Effect in Randomized Clinical Trials with Binary Outcomes." Statistical Theory and Related Fields 7 (2): 159–63. https://doi.org/10.1080/24754269.2023.2205802

3.3 Statistical Evaluation of Safety

Safety analysis set was based on all randomized and received at least 1 dose and the collected until the database lock including Japanese cohort. Of note, the safety database will be updated after receiving the remainder of Japanese subjects' data. A total of 34 treatment-emergent adverse events (TEAEs) of Grade ≥3 severity was reported in 26 setmelanotide-treated subjects compared with 4 in 3 placebo-treated subjects. Table 10 demonstrates the number of subjects experienced adverse events by treatment groups. It appears there are higher number of subjects experienced adverse events in the setmelanotide group.

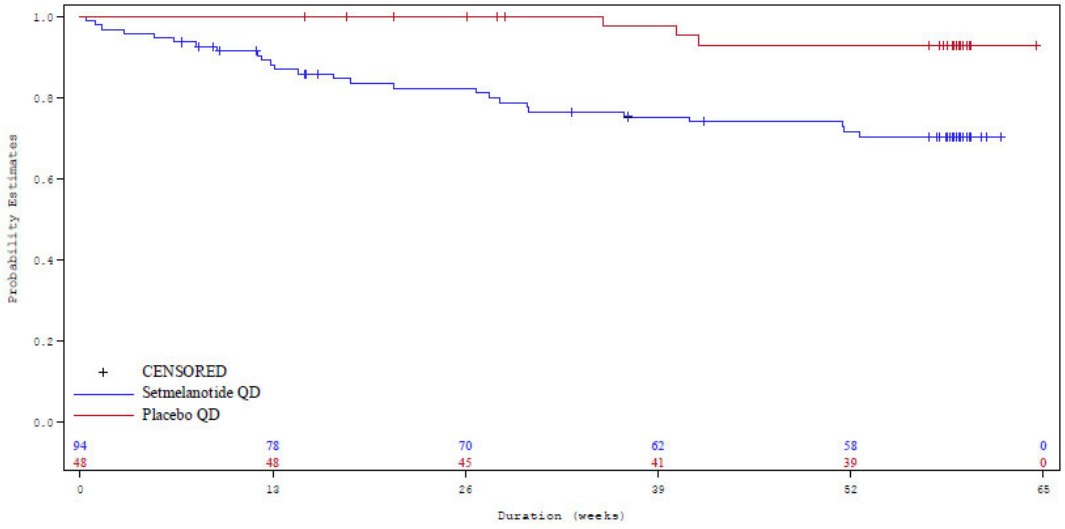
Table 10 Summary of Treatment-Emergent Adverse Events (N=142)

	Setmelanotide N=94	Placebo N=48
At Least 1 TEAE, n (%)	94 (100.0)	44 (91.7)
At Least 1 Drug-Related TEAE, n (%)	83 (88.3)	33 (68.8)
At Least 1 Serious TEAE, n (%)	26 (27.7)	3 (6.3)
Serious TEAE, n*	34	4

Abbreviations: AE = adverse event; AESI = adverse event of special interest; N = number of Patients; TEAE = treatment-emergent adverse event, n* = the total number of serious TEAEs by treatment groups.
Source: Sponsor's original clinical study report, page 111.

Since most of the serious treatment-emergent adverse events occurred once, occurred in only 1 subject each, the Kaplan-Meier plot was requested to further check time to the first occurrence of serious AE. From Figure 2, many serious adverse events (16 events) occurred in the first 13 weeks in setmelanotide group. The higher proportion of adverse events in earlier treatment period of setmelanotide group requires further qualitative review of these safety signals. Refer to the clinical review for more safety evaluation.

Figure 2 Kaplan-Meier Plot of Time to First Occurrence of Serious Treatment-Emergent Adverse Events



Source: Sponsor's response on Oct 3, 2025 , page 2 (Figure 14.3.1.2B).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 (b) (4), Race, Age, Ethnicity and Geographic Region

Subgroup analyses on percent BMI change from baseline after Week 52 were conducted with respect to the baseline characteristics: sex, age, ethnicity, race and region. Each analysis modeled the primary endpoint with an ANCOVA adjusted for baseline BMI, treatment, age stratum at randomization (except for the subgroup analysis on age), subgroup and subgroup-by-treatment interaction. Figure 4 contains the forest plot of subgroup results. The reviewers checked that all the p-values of interaction terms between subgroup and treatment are larger than 0.1.

In Figure 3 which shows all estimable subgroup LSMean difference estimates, all of subgroup estimates of LSMean difference favors setmelanotide. These findings suggest that the efficacy superiority of setmelanotide over placebo is consistent across the evaluated demographic subgroups.

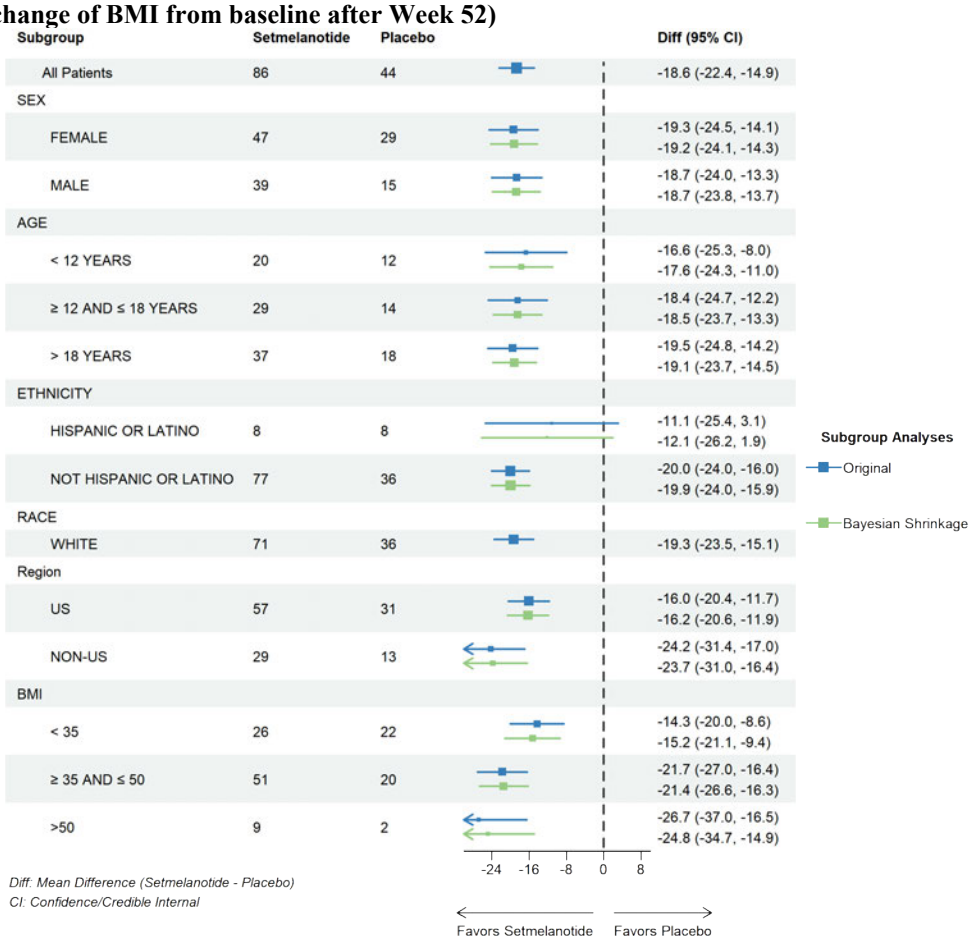
For the Race subgroups, of the 130 randomized non-Japanese subjects, 3 Asian subjects were randomized to the setmelanotide group and 1 subject to the placebo group. Among the 3 Asian setmelanotide-treated subjects, 2 demonstrated BMI reductions of -4.78% and -4.51%, while weight data at week 52 were missing for 1 subject. The single Asian placebo-treated subject experienced a BMI increase of 2.36%. Of the 130 randomized non-Japanese subjects, 6 Black or African American subjects were randomized to the setmelanotide group and 1 subject to the placebo group. Among the 6 Black or African American setmelanotide-treated subjects, 5 demonstrated BMI reductions of -4.12%, -11.52%, -22.58%, -11.21%, and -12.22%, while weight data at week 52 were missing for 1 subject. The single Black or African American placebo-treated subject experienced a BMI reduction of 0.02%.

The summary level Bayesian shrinkage analyses based on the sample estimates were performed as shown in the Figure 3. For a given baseline characteristic with k subgroups, let y_i $(i = 1,...k)$ be the observed sample estimate of the treatment effect in subgroup i. The shrinkage analysis in this review assumes the following:

- $y_i \sim N(\mu_i, \sigma_i^2)$ where μ_i is the expected treatment effect for subgroup i, and $\sigma_i^2$is the within-subgroup variance.
- $\sigma_i^2$is set to the variance for the sample estimate.
- $\mu_s \sim N(\mu, \tau^2)$, where $\mu \sim N(0, 100)$ and $\tau \sim Half\text{ - }Normal(10)$.

$N(0, 100)$ and $Half\text{ - }Normal(10)$ are selected as weakly informative prior distributions for hyper-mean, μ and hyper-standard error, σ. All of subgroup estimates of LSMean difference favors setmelanotide after Bayesian shrinkage, suggesting homogeneous treatment effects of setmelanotide across different subpopulations.

Figure 3 Forest plot of Subgroup Analysis using sample and shrinkage estimates of primary endpoint (percent change of BMI from baseline after Week 52)



*Asian and Black or African American race subjects are not shown in this Figure 3 due to insufficient sample sizes for subgroup analyses (3 Asian subjects in the treatment group vs. 1 in the placebo group; 6 Black or African American subjects in the treatment group vs. 1 in the placebo group). All subjects are not Native Hawaiians or Other Pacific Islanders.
*1 setmelanotide-treated subject with unknown ethnicity is not included in the subgroup analyses.
**Size of black square (point estimate) in the forest plot is proportional to the precision (i.e., inverse of variance) of the estimates.
Source: Reviewer's analysis; adsl.xpt, advs.xpt, adallw.xpt

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Despite FDA's advice to use all randomized and treated subjects (N=142) for evaluation of efficacy, the applicant submitted the current NDA with the results of the first 120 subjects who completed the trial (i.e., pivotal cohort). There were 130 randomized non-Japanese subjects and 12 randomized Japanese subjects who are still ongoing (expected completion March 6, 2026). To maintain the intention-to-treat policy, the submitted data of non-Japanese subjects (N=130) after

database lock was used for the evaluation of treatment efficacy in this review instead of pivotal cohort to mitigate bias and prevent potential data leakage.

5.2 Collective Evidence

For the primary efficacy analysis, superiority of setmelanotide compared to placebo was demonstrated using an ANCOVA model with WO multiple imputation method. Superiority was also demonstrated in all key secondary endpoints except the Hunger score collected in the subset of subjects aged 12 and older. Sensitivity analyses further confirmed the robustness of the primary efficacy results. Subgroup analyses of the primary efficacy endpoint demonstrated consistent treatment effects of setmelanotide across subgroups defined by age, sex, race, ethnicity, and region. However, there was higher proportion of adverse events in the setmelanotide group.

5.3 Conclusions and Recommendations

Statistical analyses based on the clinical data from the Phase 3 study including pediatric subjects, RM-493-040, have demonstrated robust evidence to support the effectiveness of setmelanotide regarding weight reduction among subjects 4 years and older with acquired hypothalamic obesity. The statistical team recommend approval of the proposed label updates for setmelanotide (IMCIVREE) injection when the benefit-risk assessment of the whole review team is favorable.

5.4 Labeling Recommendations

The sponsor proposed to add a new indication for subjects 4 years and older with acquired hypothalamic obesity.

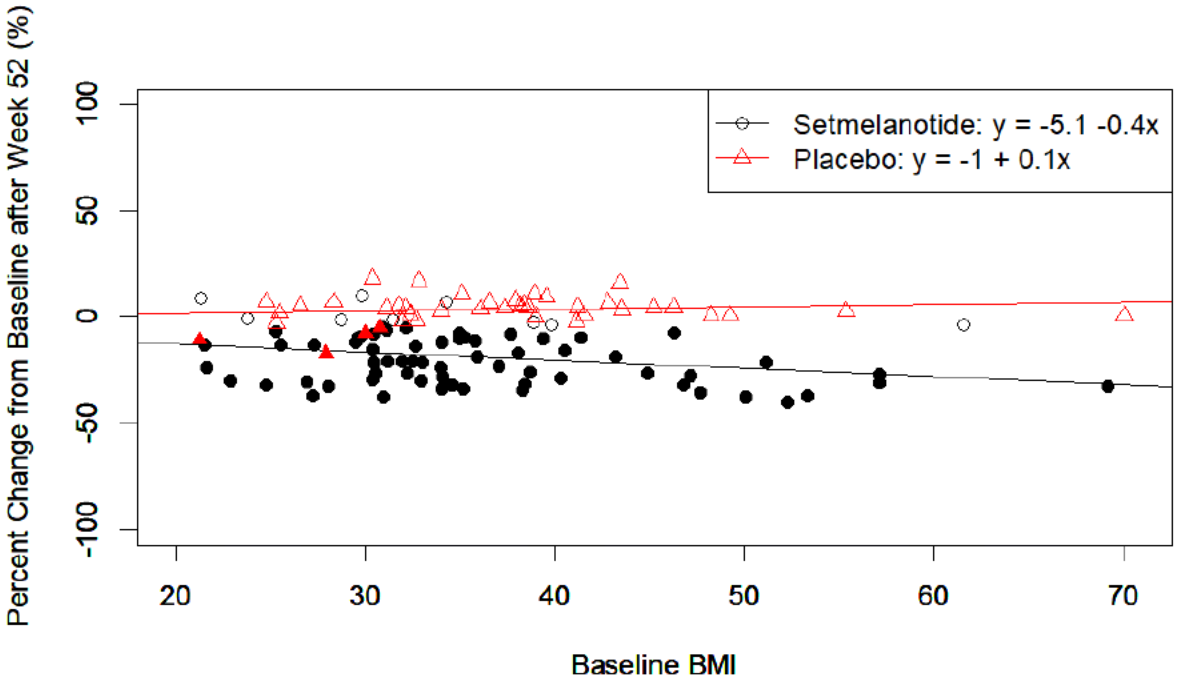
In support of this pediatric indication, a new section with statistical inference (Section 14.1 Acquired Hypothalamic Obesity) was added to Section 14 of the prescribing information. I recommend using the statistical results derived by 142 all randomized and received at least 1 dose subjects instead of the sponsor proposed first 120 subjects for the results in the Section 14. The results about daily hunger scores should be removed due to statistical insignificance. If it is clinically meaningful and informative, it should be in text form without including potentially misleading nominal p-values. The applicant also proposed the results of other secondary endpoints (e.g., blood pressure, waist circumferences, etc.); however, it is also recommended being removed due to high missing data rates of each endpoint as well as misleading information for the mixture of adult and pediatric subjects in the study.

6 Additional Analyses

6.1 Analyses of Baseline BMI as an Effect Modifier

Baseline BMI can be an effect modifier, (i.e., the treatment effect on Percent BMI change will depend on a subject's baseline BMI measurement). Figure 6 below is a scatter plot of Percent BMI change from baseline at Week 52 vs baseline BMI. The scatter points are color-coded by treatment arms. Hollow points represent observations with percent BMI change values at or above -5% at Week 52, while solid points represent observations with percent BMI change values below -5% at Week 52. Two regression lines based on completers from setmelanotide and placebo are superimposed over the scatter points. The regression line is y = 0.92-0.18x for setmelanotide, and y= 0.74-0.05x for placebo. The difference in slopes is 0.005, which implies that for every 1 increase in baseline BMI, the placebo-adjusted treatment effect measured by HbA1c change from baseline increases by 0.5%. The higher the baseline BMI, the larger the treatment effect. In the primary analysis, baseline BMI was included in the ANCOVA model to adjust for this modification effect.

Figure 4 Scatterplot of Baseline BMI vs Percent Change from Baseline after Week 52



Hollow points represent observations with percent BMI change values at or above -5% after Week 52, while solid points represent observations with percent BMI change values below -5% after Week 52.
Source: Statistical Reviewer's Analysis without Adjusting Stratification Factors; adsl.xpt, advs.xpt, adallw.xpt

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/s/

YUHAO LI
02/19/2026 05:01:11 PM

YOONHEE KIM
02/19/2026 05:57:17 PM
I concur