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

ADDENDUM MEMO

TO 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
Biometrics Division:	DB II
Statistical Reviewer:	Yuhao Li, PhD
Concurring Reviewers:	Yoonhee Kim, PhD (Team Leader)
Medical Division:	Diabetes, Lipid Disorders, and Obesity
Clinical Team:	Ginger Winston/John Sharretts
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Keywords: analysis of covariance(ANCOVA), Cochran-Mantel-Haenszel, washout imputation, double-blind, rare disease, pediatric

1 INTRODUCTION

This is addendum to the original statistical review[1] dated February 19, 2026 in DARRTS because the updated datasets for primary and secondary efficacy endpoints for the complete patient population (N=142) were received on March 3rd , 2026. The statistical review was evaluated based on the data of 130 subjects out of 142 randomized subjects with data cutoff date of March 26, 2025. This addendum review is to update the efficacy results using the complete patient population for labeling purposes.

The last patient last visit in Study RM-493-040 for the double-blind, randomized treatment period occurred on February 19, 2026. All randomized patients have either completed the study or discontinued prior to completion2. The sponsor updated additional 6 observed hunger scores that were counted as missing in the original statistical evaluation of hunger scores3.

The Electronic Document Room (EDR) location for the updated submission package of the original NDA submission package including the analysis datasets for efficacy evaluation are \\CDSESUB1\evsprod\NDA213793\0512.

The applicant's follow-up responses to IRs for efficacy updates are located at:

- \\CDSESUB1\evsprod\NDA213793\0513: primary analyses using correct time window of 358 to 425 for all endpoint evaluation after around week 52,
- \\CDSESUB1\evsprod\NDA213793\0514: SAS for the statistical evaluation of hunger score after baseline imputation,
- \\CDSESUB1\evsprod\NDA213793\0516: Sponsor's explanations on baseline imputation of Hunger Sore.

Reviewer's Note:

The sponsor imputed baseline missing Hunger score values using information from the post randomization measurements to impute the missing baseline values. As we disagree with the use of post-randomization information for imputing missing baselines, the baseline imputation based on only observed baseline values was used by the reviewer in this memo.

2 STATISTICAL EVALUATION UPDATES

2.1 Updates of Evaluation of Efficacy

[1] Link to the original statistical review: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af80805d01&sourceSys=DARRTS

[2] IR response: file://cdsesub1/evsprod/NDA213793/0512/m1/us/111-information-amendment/response-to-request-for-information-009-q1-20251106.pdf

[3] IR response: file://cdsesub1/evsprod/NDA213793/0513/m1/us/111-information-amendment/response-to-request-for-information-009-stats-20260302.pdf

Primary Efficacy Results

As demonstrated in Table 1, the LSMean difference (95% CI) in percent BMI change from baseline at Week 52 is -18.40 (-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.

Table 1. Primary Results on percent change in BMI from baseline after Week 52 (All randomized and dosed group N=142)

All Randomized and Dosed (N=142)	**Setmelanotide N = 94**	**Placebo N=48**
Baseline BMI, Mean (SD)	36.04 (9.18)	36.35 (8.77)
Week 52 Missing BMI, n (%)	12 (12.77)	3 (6.25)
Percent Change from Baseline to Week 52*, LS Mean (SE)	-15.84 (1.52)	2.55 (0.98)
Comparison to Placebo*, LS Mean difference (95% CI), Two-sided P-value	-18.40% (-21.94, -14.85) <.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 stratification factors of age group (≥18 years old, ≥12 and <18 years old, and <12 years old) and race (Japanese and non-Japanese) 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.
Source: Reviewer's analysis; adsl.xpt, adwthgw.xpt

Key Secondary Efficacy Results

In Table 2, the risk difference of proportions of setmelanotide-treated subjects compared to placebo using 142 randomized patients are shown. The results are validated by reviewer.

Table 2. Key Secondary Endpoint Analysis Results on BMI and BMI Z-Score(All randomized and dosed group N=142)

Key Secondary		**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*(%)	80.84	23.17
	Risk Difference (%), (95% CI), P-value*	-60.79, (-74.11, -47.47) <0.001	
Subjects with ≥ 5% Reduction in BMI from Baseline After 52 weeks	Response Rate*(%)	75.79	9.73.81
	Risk Difference (%), (95% CI), P-value*	-66.23, (-78.65, -53.81), <0.001	
Subjects with ≥ 10% Reduction in BMI from	Response Rate*(%)	60.99	4.69

Baseline After 52 weeks***	Risk Difference (%), (95% CI),	-56.59, (-68.32, -44.85)	
Subjects with ≥ 15% Reduction in BMI from Baseline After 52 weeks***	Response Rate*(%)	50.12	2.15
	Risk Difference (%), (95% CI)	-47.75, (-58.85, -36.66)	

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 BMI.
** The risk difference is calculated using Cochran-Mantel-Haenszel test with adjustment of stratification factors of age group and race group on the same primary imputed dataset for the primary endpoints.
*** Note: Subjects with ≥ 10% Reduction in BMI from Baseline After 52 weeks and Subjects with ≥ 15% Reduction in BMI from Baseline After 52 weeks are not controlled for multiplicity. These outcomes are included in the product label to provide additional information to the public.
Source: Sponsor's analyses; adsl.xpt, adallw.xpt, adwthgw.xpt

The last prespecified key secondary endpoint is the change of weekly average of daily most hunger score for subjects aged ≥ 12 years old. Baseline score data were missing for 11% and 11% of patients randomly assigned to IMCIVREE and placebo. The efficacy evaluation is evaluated by the reviewer as demonstrated in Table 3. Missing data at baseline were imputed using all observed scores at baseline under missing at random by normal distribution (i.e., N(6.81,4.60) with range of 0 to 10). Score data after week 52 were missing for 27% and 25% of patients randomly assigned to IMCIVREE and placebo, respectively. Missing score data after week 52 were imputed using placebo-washout multiple imputation(MI) method.

Table 3 Key Secondary Results on Weekly Average of Daily Most Hunger Scores (Non-Japanese Aged 12 and above, N=110)

	Setmelanotide N = 74	**Placebo N=36**
Subjects With Observed Baseline Score, n (%)	66 (89.18)	32 (88.88)
Baseline*, Mean (SD)	6.70 (2.20)	7.05 (2.03)
Subjects with Observed Score at Week 52, n (%)	54 (72.97)	27 (75.00)
Change from Baseline to Week 52^, LS Mean (SE)	-2.27 (0.25)	-1.44 (0.33)
Comparison to Placebo^, LS Mean difference (95% CI), Two-sided P-value	-0.82 (-1.62, -0.02) 0.045	

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 mean is computed using all observed baseline scores.
^ Missing data at baseline were imputed using all observed scores at baseline . Missing score data after week 52 were imputed using placebo-washout MI method. ANCOVA model with unequal variance to account for possible unequal residual variances was used to estimate the difference between treatment groups. The model was adjusted with the baseline weekly average hunger score, stratification factors of age group (≥18 years, and ≥12 and <18 years) and subpopulation (Japanese and non-Japanese).
Source: Reviewer's analysis; adsl.xpt, adallw.xpt, adwthgw.xpt

3 SUMMARY AND CONCLUSIONS

3.1 Conclusions and Recommendations

The conclusion in this addendum remains consistent with that of the statistical review: statistical analyses based on the complete clinical data from the Phase 3 study including pediatric subjects, RM-493-040, have demonstrated evidence to support the effectiveness of setmelanotide regarding weight reduction among subjects 4 years and older with acquired hypothalamic obesity.

3.2 Labeling Recommendations

The sponsor proposed to add a new indication for subjects 4 years and older with acquired hypothalamic obesity. The efficacy results in the Section 14 of the label should be based on correct time window of 358 to 425. In addition, the baseline imputation for the hunger score should only use the information from observed baseline scores.

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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03/16/2026 06:40:02 PM

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I concur