

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**213793Orig1s000**

**STATISTICAL REVIEW(S)**



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 #: NA  
Related IND #: IND 112595  
Product Name: Setmelanotide  
Indication(s): Treatment of obesity (b) (4) associated with *POMC*, including *PCSK1* deficiency obesity or *LEPR* deficiency obesity in adults and children 6 years of age and older  
Applicant: Rhythm Pharmaceuticals, Inc.  
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Biometrics Division: II  
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#### **Keywords:**

Rare Disease, Single Arm Study, Obesity

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## 1 EXECUTIVE SUMMARY

Rhythm Pharmaceuticals has developed setmelanotide for the treatment of obesity (b) (4) associated with pro-opiomelanocortin (*POMC*), including *PCSK1*, deficiency obesity or leptin receptor (*LEPR*) deficiency obesity in adults and children 6 years of age and older. My statistical review of the efficacy results suggests support for the weight reduction claim (b) (4). This NDA is approvable from statistical and efficacy point of view.

This submission contains two phase 3 studies with the same study design except in different populations: *POMC* deficiency patients and *LEPR* deficiency patients respectively. Both studies are single-arm, 1-year, and open-label except for a 8-week double-blind withdrawal period containing 4 weeks of placebo. The primary efficacy endpoint was the proportion of responders, defined as patients who demonstrated at least 10% weight reduction at approximately 1 year compared to baseline. It was compared to a historical reference response rate of 5% via an exact binomial test. The key secondary endpoints included mean percent change in body weight, mean percent change in weekly average “most hunger” score, and proportion of patients who demonstrated at least 25% improvement in hunger score.

The statistical reviewer used the full analysis set (FAS) for the efficacy analyses. The primary objective was met in both phase 3 studies: 8 out of 10 (80%, 95% CI: 44.4%, 97.5%) patients with *POMC* deficiency in Study 012, and 5 out 11 (45.5%, 95% CI: 16.8%, 76.6%) patients with *LEPR* deficiency in Study 015 achieved  $\geq 10\%$  weight loss from baseline at 1 year. The treatment differences in key secondary endpoints are all statistically significant at an alpha level of 0.05. The mean percent change in body weight and hunger score from baseline to 1 year was significantly different from 0 in both studies.

Despite the lack of a parallel control arm in these studies, the double-blind withdrawal period allowed each subject to serve as their own control. There was an increase in the mean percent change in body weight and hunger score after the study drug was withdrawn and a decrease in both after the study drug was reinitiated. The results suggested the decrease in body weight and hunger score were caused by treatment with setmelanotide. Comparison to historical control data of the populations and the historical data from these subjects provided additional support to the effect of setmelanotide on body weight. However, there was lack of historical control data for hunger score, making it difficult to assess the effect of setmelanotide on hunger score. Moreover, the COA team has difficulty confirming the construct validity of the instrument due to the small sample size of the studies. Refer to Section 5.1 for more details on this issue.

Overall, results from the two studies clearly supported that the drug has an effect in the proposed weight reduction indication. However, since there was no concurrent control in either study, the treatment effect that is attributable to the drug cannot be accurately quantified. This is particularly concerning for the hunger score endpoint, which has no historical control data.

## 2 INTRODUCTION

### 2.1 Overview

Rhythm Pharmaceuticals has developed setmelanotide for the treatment of obesity (b) (4) associated with *POMC*, including *PCSK1*, deficiency obesity or *LEPR* deficiency obesity in adults and children 6 years of age and older. This submission contains two phase 3 studies with the same study design except in different populations:

- RM-493-012 in patients with *POMC* or *PCSK1* mutations
- RM-493-015 in patients with *LEPR* mutations

Both studies are open-label, single-arm, 1-year, including 4-weeks of placebo in a double-blind withdrawal period. This review focuses on the pivotal cohort of patients in the two studies, prospectively defined as those who had received at least 1 year of setmelanotide treatment at the therapeutic dose at the time of data cutoff. Unless otherwise specified, the tables and figures in this review are based on the pivotal cohort. After establishment of the pivotal cohort, enrolment remained open for supplemental patients, defined as those who received <1 year of setmelanotide treatment at the therapeutic dose at the time of data cutoff.

### 2.2 Data Sources

The data and final study reports were submitted electronically. The submission was under the network path location: <\\CDSESUB1\evsprod\NDA213793\213793.enx>. My review used adsl, advs, advs\_imp, addi, addi\_imp ADAM datasets.

## 3 STATISTICAL EVALUATION

### 3.1 Data and Analysis Quality

Datasets were provided in both STDM and ADAM formats and appeared to be in good quality. Define files and reviewer's guides were provided. SAS programs for the analyses of the primary and key secondary endpoints (body weight and hunger score) were also provided.

### 3.2 Evaluation of Efficacy

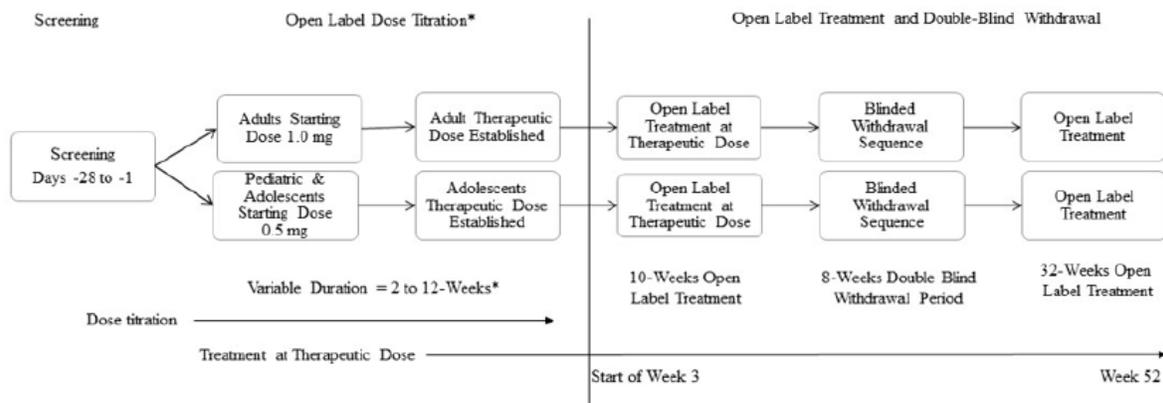
#### 3.2.1 Study Design and Endpoints

Except for the inclusion criteria related to the specific disease (*POMC* vs. *LEPR*), the study design and analysis procedures were identical for the two Phase 3 studies. The common design of the two studies is shown in Figure 1.

It was planned that approximately 10 patients in the pivotal cohort would be enrolled and receive approximately 1 year of setmelanotide at daily doses that had been individually titrated. After 12 weeks of open-label treatment, patients who achieved at least 5 kg weight loss at the end of the open label treatment period (or least 5% weight loss if baseline body weight was <100 kg) continued into a double-blind withdrawal period lasting 8 weeks, inclusive a 4-week placebo treatment period. Although it is stated in the protocol that the onset of the placebo period was variably timed, every subject who entered the withdrawal period in fact received the same

sequence of 4-week setmelanotide followed by 4-week placebo during this period. Next, patients resumed with open label treatment of setmelanotide for an additional 32 weeks.

**Figure 1 Design of the Phase 3 Studies**



\*The last 2 weeks of the open-label dose titration phase in which the therapeutic dose for an individual patient was established was considered the first 2 weeks of open-label treatment. Patients subsequently received an additional 10 weeks of active treatment in the open-label treatment phase for a total combined duration of 12 weeks before transitioning into the double-blind withdrawal phase.

The efficacy analyses of the Phase 3 studies used the following two analysis populations:

- The Full Analysis Set (FAS) consisted of all subjects who received at least 1 dose of study medication and had a baseline and at least 1 post-baseline efficacy assessment performed for the primary endpoint.
- The Designated Use Set (DUS) consisted of subjects who receive any of the study drug injections, demonstrate  $\geq 5\text{kg}$  weight loss or 5% of body weight is  $< 100\text{kg}$  at baseline over the 12-week open label treatment period, and proceed into the double-blind, placebo withdrawal period.

The primary objective was to demonstrate statistically significant and clinically meaningful effects of setmelanotide on percent body weight change at the end of 1 year of treatment in patients with *POMC* (or *LEPR*) deficiency obesity. The primary efficacy endpoint was the proportion of patients in the FAS who demonstrated at least 10% weight reduction at approximately 1 year compared to baseline. The key secondary endpoints were:

1. Percent change from baseline in body weight at appropriately 1 year in the DUS
2. Percent change from baseline in weekly average “most hunger” score at approximately 1 year in the DUS and age  $\geq 12$  years
3. Proportion of patients in the FAS and age  $\geq 12$  years who achieved at least 25% decrease in weekly average “most hunger” score from baseline at approximately 1 year

### 3.2.2 Statistical Methodologies

Formal statistical hypothesis testing was performed on the primary and key secondary endpoints at 1-sided, 0.05 level of significance.

The primary endpoint, at least 10% weight loss compared to baseline in 1 year, was analyzed in the FAS population. It was compared to a historical reference rate of 5% of responders. A 90% confidence interval (CI) for the proportion of responders was obtained using the Clopper-Pearson (exact) method. Statistical significance is met if the lower bound of the CI larger than 5%. At least 3 responders out of 10 subjects is needed to achieve statistical significance.

The continuous key secondary endpoints (percent change from baseline in body weight, weekly average “most hunger”) were analyzed in the DUS population, using a linear mixed model with a fixed term for time and baseline measurement of weight or hunger score and a random effect for subjects. A compound symmetry covariance matrix was employed. The statistical reviewer performed additional analyses of the continuous endpoints using the FAS population. In statistical reviewer’s analyses, an ANCOVA model was used which included measurements from the final visit at 1 year as the outcome and baseline as a covariate.

The proportion of patients who reach at least 25% hunger improvement was also compared to a reference rate of 5% of responders. It was analyzed in the  $\geq 12$  years old patients in the FAS population via an exact binomial test, similar to the analysis of the primary endpoint.

There was no missing data for Study 012. For Study 015, the applicant imputed missing values related to study drug as 0 change from baseline, namely baseline observation carried forward (BOCF), and imputed missing values unrelated to study drug using linear extrapolation, with time as a linear factor in the imputation model. The statistical reviewer performed additional sensitivity analyses for Study 015: (1) impute all missing data as BOCF, which is considered a conservative approach, since all subjects with missing values were regarded as non-responders (2) impute missing values due to adverse event as BOCF and impute missing values unrelated to study drug using multiple imputation (monotone regression). Due to the large number of visits, the visits were grouped as (V3, V4, V5) (V6, V7, V8) (V9, V10, V11, V12). Averages were taken among the visits within each group and were used in the imputation model together with baseline values. The three subjects who did not enter the withdrawal period were not included in imputation. For analyses of the binary endpoints, continuous body weights or hunger scores at 1 year were converted to binary values. Asymptotic standard errors for proportions were used in application of Rubin’s rule.

A pre-specified hierarchical testing procedure was used to control Type I error. After statistical significance was achieved for the primary endpoint, the three key secondary endpoints were tested in the order stated in Section 3.2.1.

### 3.2.3 Patient Disposition, Demographic and Baseline Characteristics

Subject dispositions were shown in Table 1. In Study 012, one subject was labeled as discontinued the study due to lack of efficacy. However, the subject only discontinued treatment early and had no missing data for body weight and hunger score measurements at 1 year. In Study 015, one subject discontinued the study at Week 33 due to death from injuries sustained in

an automobile accident, which was considered unrelated to study drug. Another subject was withdrawn from the study early at Week 9 due to adverse event (AE) probably related to study drug. In total, 2 subjects had missing data for body weight and 3 subjects had missing data for hunger score at 1 year.

Subject demographics were shown in **Table 2**. There were 5 male and 5 females in Study 012, and 3 males and 8 females in Study 015. Majority of the patients were white, and all except one patient were from USA.

**Table 1 Patient Dispositions**

Dispositions	Study 012 (Pivotal Cohort)	Study 012 (Supplemental Cohort)	Study 015 (Pivotal Cohort)	Study 015 (Supplemental Cohort)
<b>Enrolled</b>	10	4	11	2
<b>Treated</b>	10	4	11	2
<b>FAS<sup>1</sup></b>	10	3	11	2
<b>DUS<sup>2</sup></b>	9	2	7	1
<b>Safety Set<sup>3</sup></b>	10	4	11	2
<b>Completed Trial, n(%)<sup>4</sup></b>	9 (90)	0	9 (81.8)	0
<b>Withdrew from Trial, n(%)<sup>4</sup></b>	1 (10)	1 (25)	2 (18.2)	0
<b>Missing Data for Body Weight or Hunger Score at 1 Year, n(%)<sup>4</sup></b>	0	NA	3 (27.3)	NA

1. Full Analysis Set: definition in Section 3.2.2

2. Designated Use Set: definition in Section 3.2.2

3. Safety set consists of subjects who receive any of the study drug injections and have at least one post-dose safety assessment.

4. Percentages are calculated based on FAS.

Source: Statistical Reviewer's Analyses

**Table 2 Patient Demographics-Pivotal Cohort**

Characteristics	Study 012 (N=10)	Study 015 (N=11)
<b>Age</b>		
Mean (SD)	18.4 (6.2)	23.7 (8.39)
Min, Max	11, 30	13, 37
<b>Sex, n(%)</b>		
Male	5 (50)	3 (27.3)
Female	5 (50)	8 (72.7)
<b>Race, n(%)</b>		
White	7 (70)	10 (90.9)
Other	3 (30) <sup>1</sup>	1 (9.1) <sup>2</sup>
<b>Ethnicity, n(%)</b>		
Hispanic Or Latino	1 (10)	0
Not Hispanic Or Latino	8 (80)	11 (100)
Unknown	1 (10)	0
<b>Country, n(%)</b>		
USA	1 (10)	0
Non-USA	9 (90)	11 (100)

1. The 3 other races in Study 012 include 1 Arab, 1 Moroccan and 1 NA.
2. The 1 other race in Study 015 is South Asian.

Source: Statistical Reviewer’s Analyses

### 3.2.4 Results and Conclusions

The primary objective was met in both phase 3 studies, based on the applicant’s analyses (Table 3). 8 out of 10 patients in Study 012 and 5 out of 11 patients in study 015 achieved at least 10% weight loss after 1 year treatment of setmelanotide, demonstrating statistical significance. The two sensitivity analyses conducted by the statistical reviewer, including a conservative analysis that considered all missing values as non-responders, gave the same conclusion (Table 4).

The three key secondary endpoints also achieved statistical significance. Mean percent change in body weight from baseline to 1 year was significantly different from 0 in both the FAS and DUS populations and in both studies (Table 5). There was slightly greater mean percent reduction in body weight in the DUS population than in the FAS population as expected, since the DUS population excluded patients who did not show early weight reduction. Consistent with results of the primary endpoint, the effect of setmelanotide on body weight appeared to be greater in the *POMC* deficiency patients (study 012) compared to the *LEPR* deficiency patients (study 015). When treatment with setmelanotide was withdrawn in the subjects in the DUS population at round 16 weeks, there appeared to be an increase in body weight in all those subjects (Figure 2, Figure 3). Reinitiation of treatment with setmelanotide resulted in resumed weight loss in most subjects. The timing of the increase and decrease in body weight matched the starting and ending of the 4-weeks of placebo in the double-blind withdrawal period (Figure 4, Figure 5).

Mean percent change in weekly average of daily “most hunger” score from baseline to 1 year was also significantly different from 0 in both FAS and DUS populations and in both studies (Table 6). 4 out of 8 patients in Study 012 and 7 out of 11 patients in study 015 achieved at least 25% improvement in hunger score after 1 year treatment of setmelanotide, demonstrating statistical significance (Table 7). The two sensitivity analyses of Study 015, including a conservative analysis that considered all missing values as non-responders, gave the same conclusion (Table 8). Statistical reviewer’s analyses for the hunger score endpoints classified one additional subject in Study 015 as non-responder but did not alter the conclusions from the applicant’s analyses. The effect of the withdrawal period and reinitiation of treatment with setmelanotide on hunger score was observed in some but not all of the patients in the DUS population. Unlike the gradual decrease in body weight over time, the hunger score measures in individual subjects fluctuated with a high variance, and the trend was less clear in individual patients (graphs now shown). Mean percent change in hunger score did show an obvious increase during the 4-weeks of placebo period in both studies (Figure 6, Figure 7).

**Table 3 Primary endpoint: Proportion of Patients Achieving at Least 10% Weight Loss at 1 Year - FAS**

	<b>Study 012 N=10</b>	<b>Study 015 N=11</b>
Number (%) achieving $\geq 10\%$ weight loss at 1 year	8(80)	5(45.5) <sup>1</sup>
90% CI <sup>2</sup>	(49.3, 96.3)	(20.0, 72.9)

95% CI <sup>2</sup>	(44.4, 97.5)	(16.8, 76.6)
One-sided p-value <sup>3</sup>	<0.0001	0.0001

1. Two subjects with missing value for body weight at 1 year: one with AE was considered non-responder and the other was considered responder based on linear extrapolation.
2. From the Clopper-Pearson (exact) method
3. From exact binomial test, testing the null hypothesis: Proportion =5%.

Source: Clinical Summary of Efficacy Tables 4 and 5, verified by Statistical Reviewer.

**Table 4 Sensitivity analyses for Primary Endpoint - FAS - Study 015**

	Sensitivity Analysis 1 <sup>1</sup> N=11	Sensitivity Analysis 2 <sup>2</sup> N=11
Number (%) achieving $\geq$ 10% weight loss at 1 year	4 (36.4)	(44.8)
90% CI	(13.5, 65.0)	(19.9, 69.7)
95% CI	(10.9, 69.2)	(15.1, 74.5)
One-sided p-value	0.002	0.004

1. All subjects with missing body weight measurement at 1 year (n=2) were considered non-responders.
2. One subject who discontinued the study early due to AE was considered non-responder. The other subject who died from car accident was imputed using multiple imputation and analyzed using Rubin's rule.

Source: Statistical Reviewer's Analyses

**Table 5 Key Secondary Endpoint 1: Mean Percent Change in Body Weight at 1 Year**

	Study 012 - FAS N=10	Study 015 - FAS N=11	Study 012-DUS N=9	Study 015-DUS N=7
Mean percent change in body weight at 1 year (LS mean) <sup>1</sup>	-23.1	-9.8	-25.6	-12.8
90% CI	(-30.2, -16.1)	(-14.8, -4.9)	(-29.9, -21.2)	(-19.3, -6.3)
95% CI	(-31.9, -14.4)	(-15.7, -4.0)	(-31.0, -20.1)	(-20.5, -5.0)
One-sided p-value <sup>2</sup>	<0.0001	0.0005	<0.0001	0.0006

1. Linear model contains baseline body weight as a covariate.  
Two subjects in Study 015 with missing body weight at 1 year: one subject with AE (non-DUS) was imputed as 0 change from baseline. The other subject who die from car accident (DUS) was imputed using multiple imputation and analyzed using Rubin's rule.
2. Testing the null hypothesis: mean percent change=0

Source: Statistical Reviewer's Analyses

**Table 6 Key Secondary Endpoint 2: Mean Percent Change in Weekly Average of Daily 'Most Hunger' Score at 1 Year - Age $\geq$ 12 Years**

	Study 012 - FAS N=8	Study 015 - FAS N=11	Study 012-DUS N=7	Study 015-DUS N=7
Mean percent change in	-31.2	-31.0	-27.1	-43.8

weekly average “most hunger” score at 1 year (LS mean) <sup>1</sup>				
90% CI	(-49.0, -13.3)	(-49.4, -12.6)	(-42.6, -11.5)	(-61.5, -26.2)
95% CI	(-53.6, -8.7)	(-53.0, -9.0)	(-46.9, -7.2)	(-64.9, -22.8)
One-sided p-value <sup>2</sup>	0.007	0.003	0.009	<0.0001

1. Linear model contains baseline weekly average ‘most hunger’ score.  
Three subjects in Study 015 with missing hunger score at 1 year: Two subjects (non-DUS) were imputed as 0 change from baseline. One subject who die from car accident (DUS) was imputed using multiple imputation and analyzed using Rubin’s rule.
  2. Testing the null hypothesis: mean percent change=0
- Source: Statistical Reviewer’s Analyses

**Table 7 Key Secondary Endpoint 3: Proportion of Patients Achieving  $\geq 25\%$  Improvement in Weekly Average of Daily ‘Most Hunger’ Score - Age $\geq 12$  Years; FAS**

	<b>Study 012 N=8</b>	<b>Study 015 N=11</b>
Number (%) achieving $\geq 25\%$ improvement in weekly average ‘most hunger’ score	4 (50)	7 (63.6) <sup>1</sup>
90% CI <sup>2</sup>	(19.3, 80.7)	(35.0, 86.5)
95% CI <sup>2</sup>	(15.7, 84.3)	(30.8, 89.1)
One-sided p-value <sup>3</sup>	0.0004	<0.0001

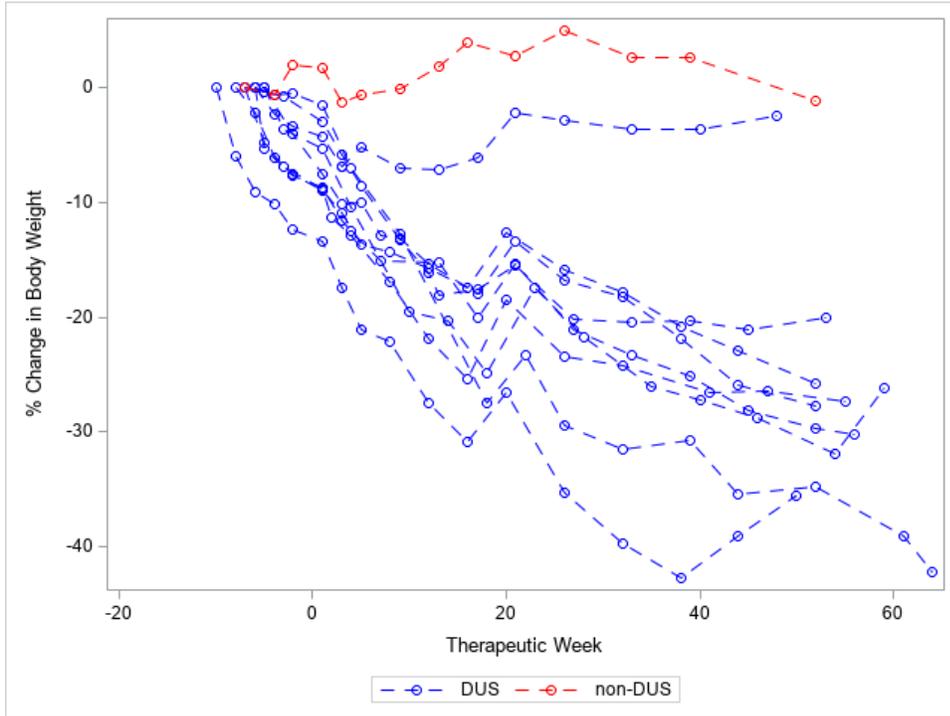
1. Three subjects with missing value for hunger score at 1 year: Two subjects (non-DUS) were imputed as 0 change from baseline. One subject who die from car accident (DUS) was considered responder based on linear extrapolation.
  2. From the Clopper-Pearson (exact) method
  3. From exact binomial test, testing the null hypothesis: Proportion =5%.
- Source: Statistical Reviewer’s Analyses

**Table 8 Sensitivity analyses for Key Secondary Endpoint 3 - FAS - Study 015**

	<b>Sensitivity Analysis 1<sup>1</sup> N=11</b>	<b>Sensitivity Analysis 2<sup>2</sup> N=11</b>
Number (%) achieving $\geq 25\%$ improvement in weekly average ‘most hunger’ score	6 (54.6)	(62.6)
90% CI	(27.1, 80.0)	(38.2, 87.0)
95% CI	(23.4, 83.3)	(33.5, 91.7)
One-sided p-value	<0.0001	<0.0001

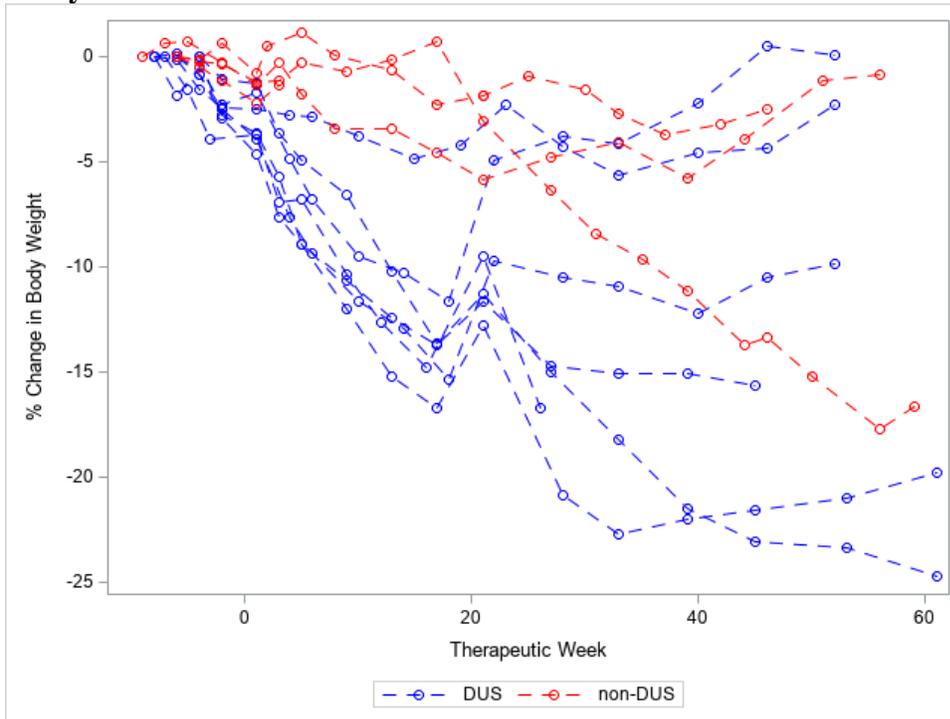
1. All subjects (n=3) with missing hunger score measurement at 1 year were considered non-responders.
  2. Three subjects in Study 015 with missing hunger score at 1 year: Two subjects (non-DUS) were imputed as 0 change from baseline. One subject who die from car accident (DUS) was imputed using multiple imputation and analyzed using Rubin’s rule.
- Source: Statistical Reviewer’s Analyses

**Figure 2 Percent Change in Body Weight from Baseline in Individual Patients–FAS– Study 012**



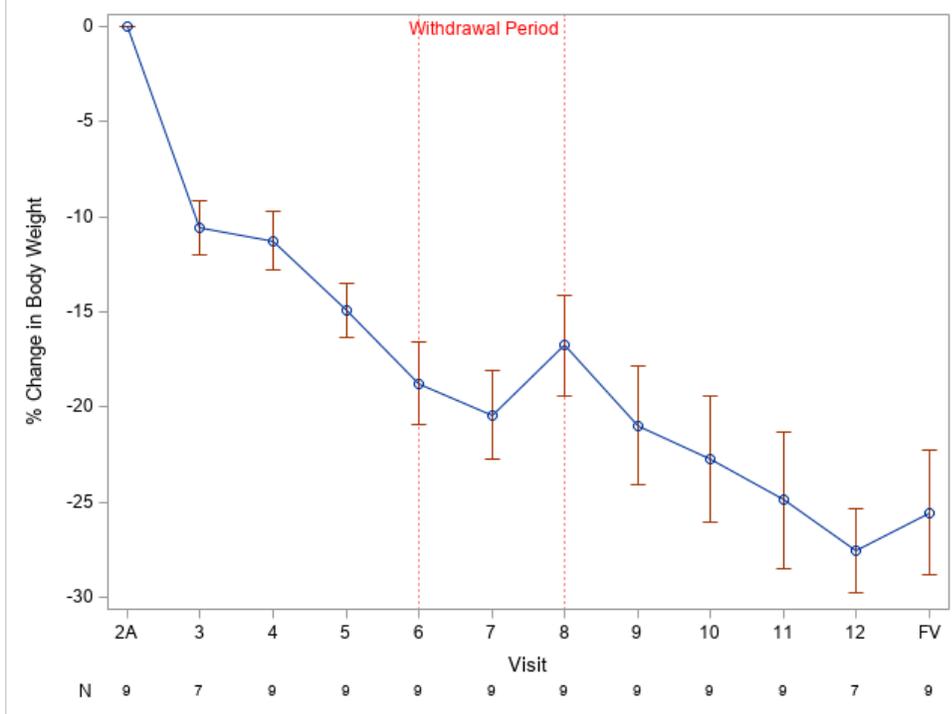
Source: Statistical Reviewer's Analyses

**Figure 3 Percent Change in Body Weight from Baseline in Individual Patients– FAS– Study 015**



Source: Statistical Reviewer's Analyses

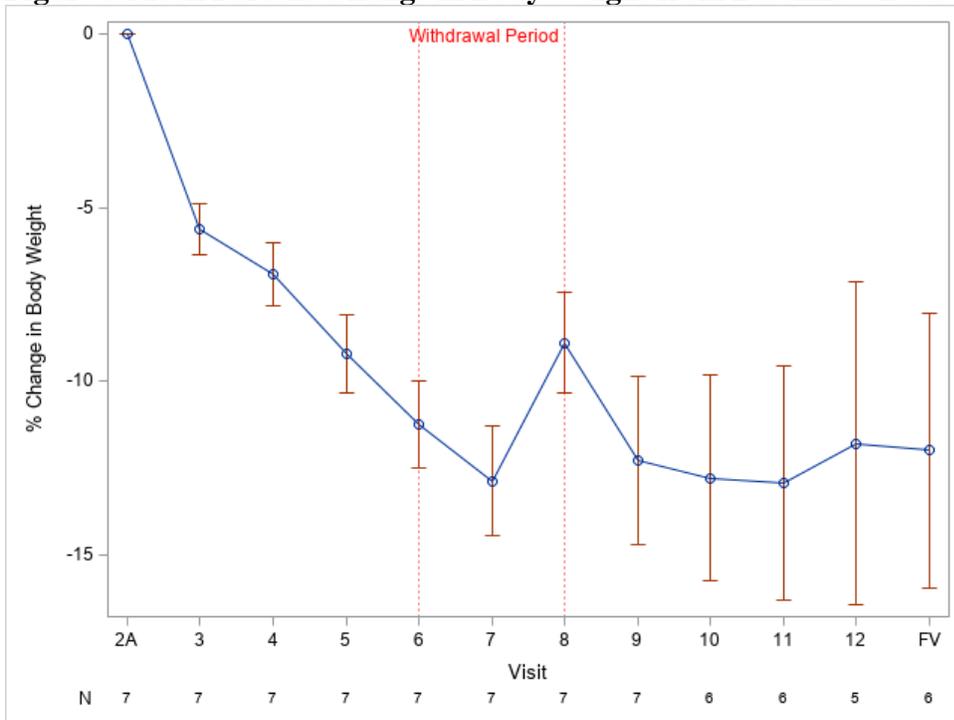
**Figure 4 Mean Percent Change in Body Weight from Baseline– DUS – Study 012**



1. Error bars represent standard errors. N represents the number of subjects with observed values.

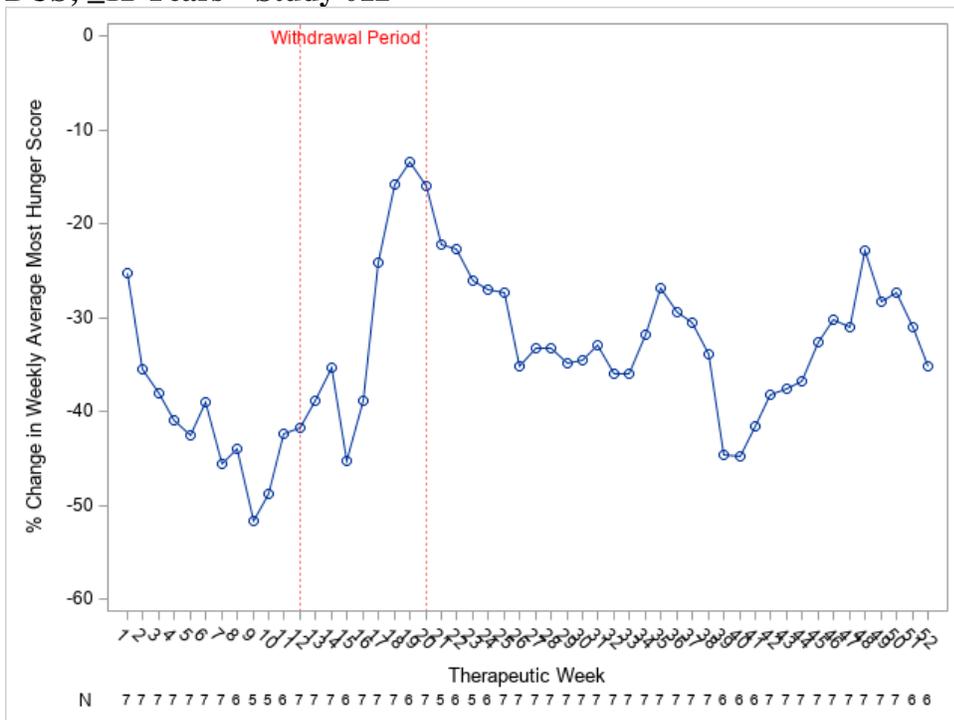
Source: Statistical Reviewer's Analyses

**Figure 5 Mean Percent Change in Body Weight from Baseline<sup>1</sup>– DUS – Study 015**



1. Error bars represent standard errors. N represents the number of subjects with observed values.  
Source: Statistical Reviewer’s Analyses

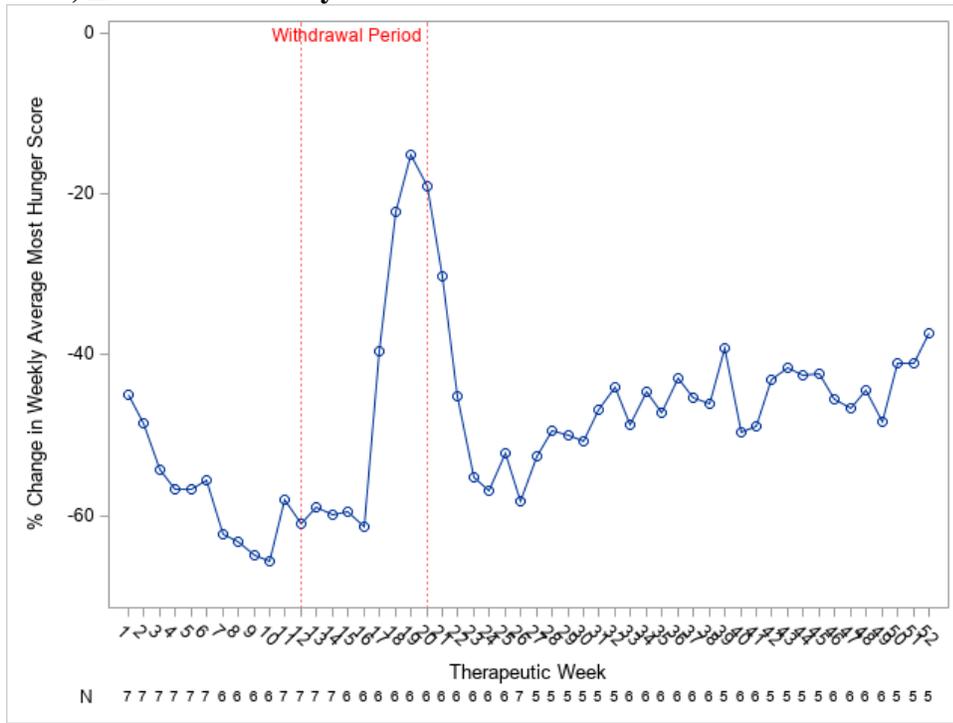
**Figure 6 Mean Percent Change in Weekly Average “Most Hunger” Score from Baseline<sup>1</sup>– DUS; ≥12 Years – Study 012**



1. N represents the number of subjects with observed values.

Source: Statistical Reviewer's Analyses

**Figure 7 Mean Percent Change in Weekly Average “Most Hunger” Score from Baseline1–DUS; ≥12 Years – Study 015**



1. N represents the number of subjects with observed values.

Source: Statistical Reviewer's Analyses

### 3.3 Evaluation of Safety

Analyses on safety events were reviewed by Dr. Ovidiu Galescu in the medical division. There does not appear to be any major safety issue.

### 3.4 Benefit Risk Assessment

Setmelanotide appears to have a positive benefit-risk profile in the *POMC* and *LEPR* deficiency obesity patients who have no other therapeutic option.

## 4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

### 4.1 Gender, Race, Age, and Geographic Region

The primary endpoint, percentage of subjects with LH suppression at Week 24, was assessed by subgroups, and presented as descriptive statistics in Table 9. Due to the very small sample size in each study, the proportion of responders in the subgroups can vary a lot by chance.

**Table 9 Subgroup analysis of the primary endpoint - FAS**  
**% Achieving  $\geq 10\%$  Weight Loss at 1 Year**

	<b>Study 012</b> <b>(N=10)</b>	<b>Study 015</b> <b>(N=11)<sup>1</sup></b>
<b>Sex, % (n/N)</b>		
Female	80 (4/5)	25 (2/8)
Male	80 (4/5)	100 (3/3)
<b>Race, % (n/N)</b>		
White	85.7 (6/7)	50 (5/10)
Non-White	66.7 (3/4)	0 (0/1)
<b>Age, % (n/N)</b>		
< 18 years	83.3 (5/6)	33.3 (1/3)
$\geq 18$ years	75 (3/4)	50 (4/8)

1. Two subjects with missing value for body weight at 1 year: one with AE was considered non-responder and the other was considered responder based on linear extrapolation.

Source: Statistical Reviewer's Analyses

## 5 SUMMARY AND CONCLUSIONS

### 5.1 Statistical Issues

#### 5.1.1 Lack of Control Arm

Both phase 3 studies lacked a parallel control arm. In order to draw statistical inference, 5% historical control response rate was assumed in the null hypothesis for the primary endpoint. Based on the supportive document submitted by the applicant, the available data (Kuehnen, 2016) suggested that 0% of *POMC* or *LEPR* deficiency patients would demonstrate at least 10% weight loss in a single year without any treatment. In addition, historical data have been collected from patients in the two studies (12 patients in *POMC* and 12 patients in *LEPR*) and provided 315 individual patient-years in total. Among them, there were only 6 (~2%) occurrences with more than 10% weight loss in one year, and 5 out of the 6 were associated with surgical interventions. Figure 8 and Figure 9 showed the historical weight change in these patients. These results suggest the assumed 5% control response rate in the null hypothesis is reasonable.

The withdrawal period allowed each patient to serve as their control. The fact that all the subjects in the DUS population showed increase in body weight during the 4-weeks of double-blind placebo period and most of them resumed weight loss after the reinitiation treatment of setmelanotide (Figure 2, Figure 3) further suggested that the weight loss in these subjects was caused by treatment with setmelanotide.

The lack of a control arm is more problematic for the hunger score endpoints. (b) (4)

The effect of the withdrawal period and reinitiation of treatment with setmelanotide on hunger score was observed in some subjects in the DUS population, providing some support to the effect of setmelanotide on the hunger endpoints. We are convinced that setmelanotide has some effect on hunger score, but without historical control data it is uncertain how much of the change from baseline at 1 year was caused by treatment with setmelanotide. Moreover, the COA team had

difficulty confirming the construct validity of the instrument due to the small sample size of the studies.

### 5.1.2 Missing Data

There was no missing data for body weight and hunger score at 1 year in Study 012. For Study 015, two subjects had missing body weight and three subjects had missing hunger score at 1 year. Since the study conclusions are robust to the conservative sensitivity analyses where all the missing values are imputed as 0 change from baseline, we do not have much concern about the missing data.

For one subject who had missing value for hunger score and did not show weight loss at 1 year, the applicant considered the subject as a responder for hunger score based on linear extrapolation. We think it is more appropriate to impute this subject using BOCF, since the subject only had early hunger score measurements before 20 weeks and did not show weight loss at 1 year.

## 5.2 Collective Evidence

The primary objective was met in both Phase 3 studies: 5 out of 10 (80%, 95% CI: 44.4%, 97.5%) *POMC* deficiency patients in Study 012, and 5 out of 11 (45.5%, 95% CI: 16.8%, 76.6%) *LEPR* deficiency patients in Study 015 achieved  $\geq 10\%$  weight loss from baseline at 1 year. The comparison to historical control data of the population and the historical data from these subjects provided support to the effect of setmelanotide on body weight. The key secondary endpoints also achieved statistical significance. Mean percent change in weekly average of daily “most hunger” score from baseline to 1 year was significantly different from 0 in both studies. The effect of the withdrawal period on hunger score was observed in some subjects in the DUS population (Figure 6, Figure 7). These results, taken together, provided support to the effect of setmelanotide on the hunger score endpoints. However, the lack of historical control data for hunger score made it difficult to quantify this effect. The uncertain construct validity for the instrument made it difficult to interpret the results.

## 5.3 Conclusions and Recommendations

This NDA is approvable from statistical point of view. My statistical review of the efficacy results suggests support for the weight reduction claim (b) (4)

## 5.4 Labeling Recommendations

The results of the continuous endpoints in the proposed product label were based on the DUS population. Since the DUS population excluded subjects who did not show early weight loss, it tends to overestimate the treatment effect. We recommend using the results from the FAS population for all the endpoints including the continuous endpoints. We also recommend presenting 95% CI instead of (b) (4) % CI for all the results in Section 14.

It is difficult to quantify the effect of setmelanotide treatment on the hunger score endpoints, due to the lack of historical control data. Moreover, the uncertain construct validity for the instrument made it difficult to interpret the results. We leave to the clinical and COA teams to decide whether the hunger score endpoints can be included in the label.

APPENDICES

Figure 8 Longitudinal Profiles of the Collected Historical Weight (kg) Versus Age (years)-Study 012

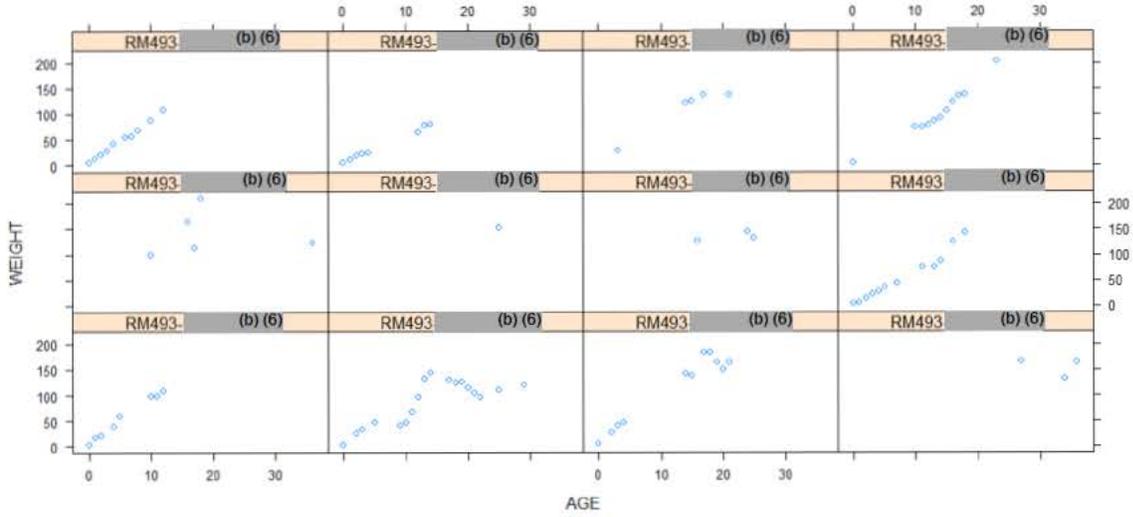
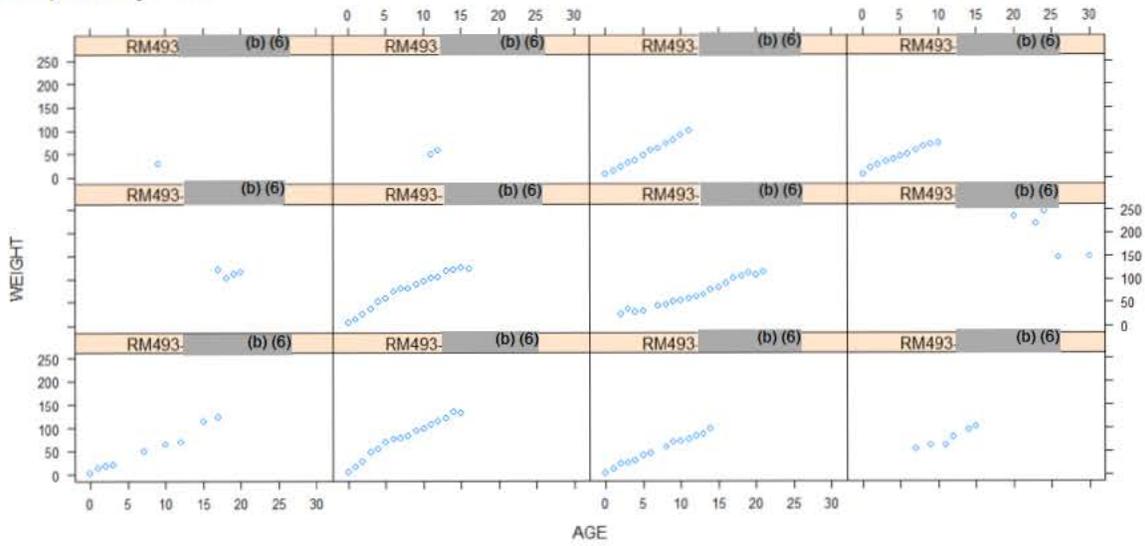


Figure 9 Longitudinal Profiles of the Collected Historical Weight (kg) Versus Age (years)-Study 015



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**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.**  
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