Rhythm Pharmaceuticals

Topline Results from Phase 3 Trials of Setmelanotide in POMC and LEPR Deficiency Obesity

August 2019

Forward Looking Statements

This presentation contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including statements regarding Rhythm's expectations for 2019 and 2020, estimated addressable patient populations, anticipated timing for enrollment, design and completion of clinical trials, the results of clinical trials, the FDA's or EMA's review of those results, the timing for filing of an NDA, the release of results of clinical trials, and Rhythm's strategy, prospects and plans. Statements using word such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward looking statements. Our forward-looking statements are based on current beliefs and expectations of our management team that involve risks, potential changes in circumstances, assumptions and uncertainties. Any or all of the forward-looking statements may turn out to be wrong, or be affected by inaccurate assumptions we might make or by known or unknown risks and uncertainties. Our statements about the results and conduct of our clinical trial could be affected by the potential that there are changes in the data or interpretation of the data by the FDA or EMA, whether the results will be deemed satisfactory by the FDA or EMA (for example, we describe the results of the trial as positive and the FDA or EMA may disagree with that characterization), and whether additional studies will be required or other issues will arise that will delay submission of our NDA or negatively impact acceptance, review and approval of setmelanotide by the FDA or EMA; and our statements about the potential commercial opportunity could be affected by the potential that our product does not receive regulatory approval, does not receive reimbursement by third party payors, or a commercial market for the product does not develop because of any of the risks inherent in the commercialization of pharmaceutical products. For all these reasons, actual results and developments could be materially different from those expressed in or implied by our forward-looking statements. All forward looking statements are subject to risks detailed in our filings with the U.S. Securities and Exchange Commission, including the Company's Annual Report on Form 10-K and our Quarterly Reports on Form 10-Q. You are cautioned not to place undue reliance on these forward-looking statements, which are made only as of the date of this press release. We undertake no obligation to publicly update such forward-looking statements to reflect subsequent events or circumstances.

Positive Topline Results from Pivotal Phase 3 Trials in POMC and LEPR Deficiency Obesities

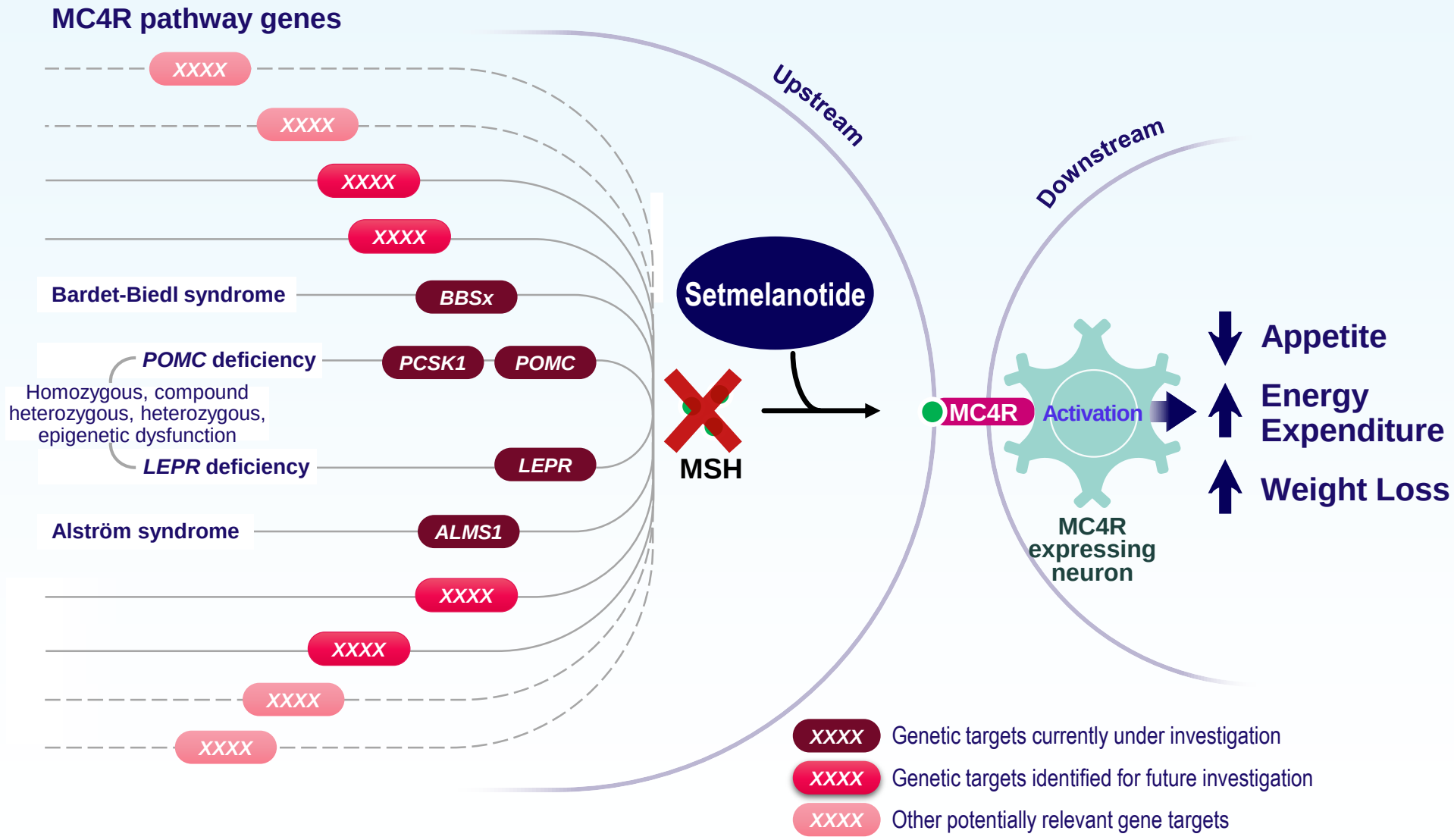
Both studies met primary and key secondary endpoints, with **statistically significant** and **clinically meaningful** results in reductions of weight and hunger

- POMC: 8/10 participants met greater than 10% weight loss threshold ($p<0.0001$)
- LEPR: 5/11 participants met greater than 10% weight loss threshold ($p=0.0001$)
- During placebo withdrawal, participants experienced substantial, consistent increases in weight and hunger
- 17 of 19 eligible participants will be participating in the extension study to continue setmelanotide treatment

Safety consistent with prior clinical experience; setmelanotide generally well-tolerated

NDA on-track for 4Q19-1Q20 submission

Setmelanotide is a Targeted Therapy that Restores the Impaired MC4R Pathway



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Summary of Efficacy Endpoints: POMC

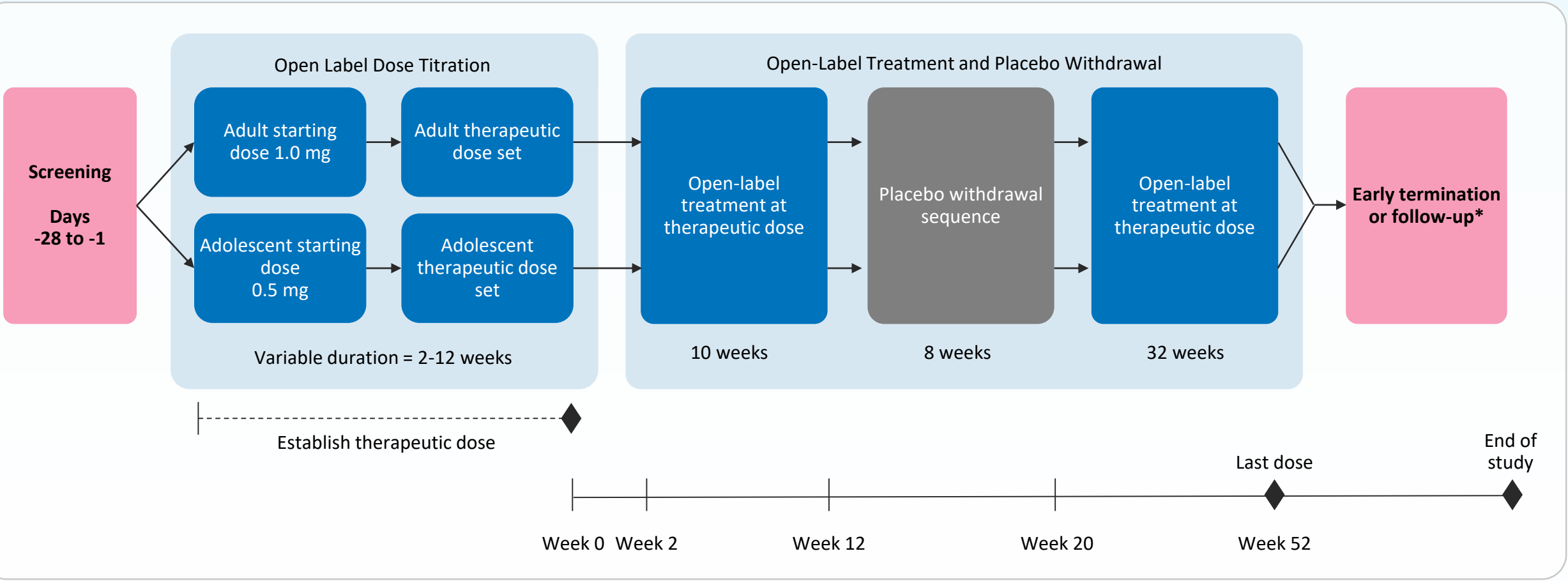
Primary: Proportion of Participants Achieving at Least 10% Change in Body Weight	**80.0%** p<0.0001
Key Secondary: Mean Percent Change from Baseline in Body Weight	**-25.4%** p<0.0001
Key Secondary: Mean Percent Change from Baseline in Most Hunger Rating	**-27.8%** p=0.0005
Key Secondary: Proportion of Participants with 25% Reduction in Hunger	**50.0%** p=0.0004

Summary of Efficacy Endpoints: LEPR

Primary: Proportion of Participants Achieving at Least 10% Change in Body Weight	**45.5%** p=0.0001
Key Secondary: Mean Percent Change from Baseline in Body Weight	**-12.5%** p<0.0001
Key Secondary: Mean Percent Change from Baseline in Most Hunger Rating	**-41.9%** p<0.0001
Key Secondary: Proportion of Participants with 25% Reduction in Hunger	**72.7%** p<0.0001

Summary of Phase 3 Results

POMC and LEPR Phase 3 Trials – Trial Design



* Participants eligible to enroll in long-term extension study

POMC Deficiency Obesity

POMC Participant Demographics

Age at Trial Enrollment (years)	
Mean (range)	18.4 (11-30)
<12 years old (n)	2
Gender, M,F	5, 5
Weight (kg)	
Mean	118.7
Range	55.9-186.7
BMI (kg/m^2)	
Mean	40.4
Range	26.6-53.3
Most Hunger (≥12 years old)	
Most hunger in 24 hours	8.0
Range	7.0-9.0

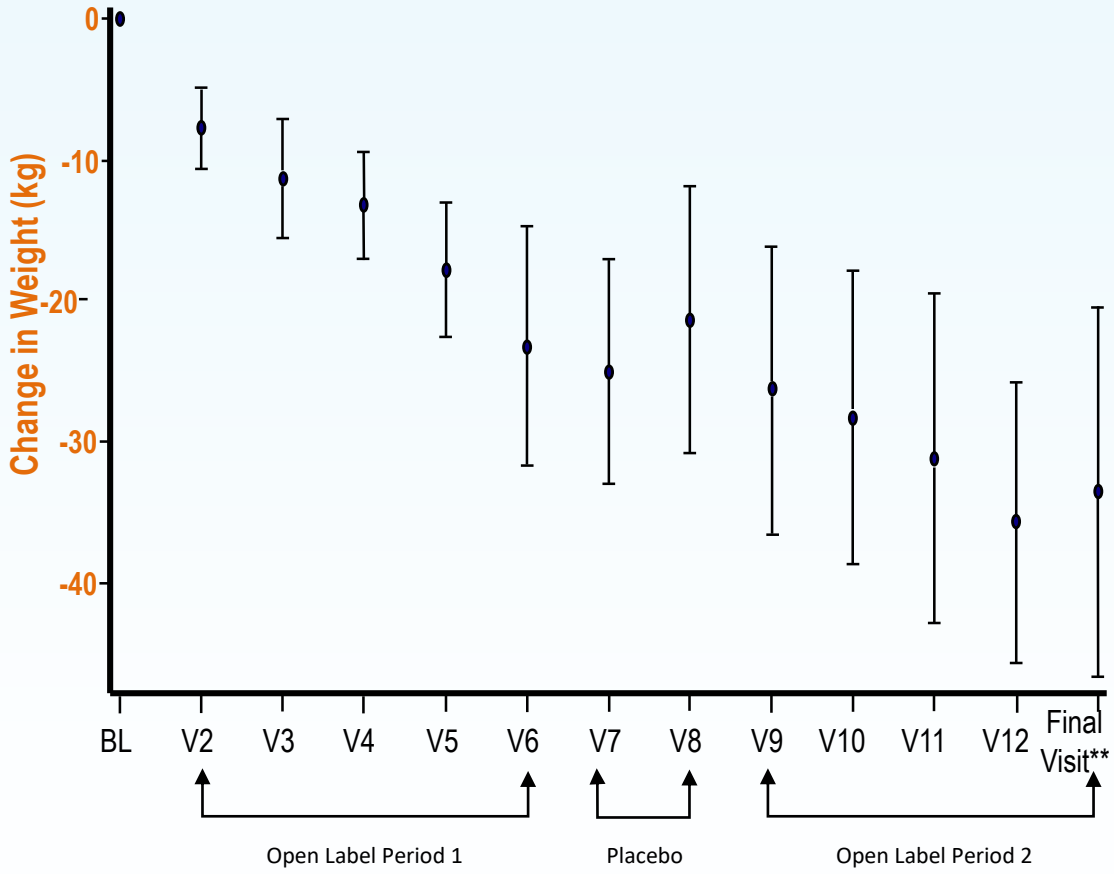
POMC Phase 3 Trial – Topline Results

Endpoint	
Proportion of Participants Achieving at Least 10% Change in Body Weight	**80%** p<0.0001 90% CI (49.31, 96.32)
Mean Percent Change from Baseline in Body Weight (%)*	**-25.4** Range: -35.6 to -2.4 p<0.0001 90% CI (-28.80, -21.98)
Mean Percent Change from Baseline in Most Hunger Rating (%) *†	**-27.8** Range: -72 to -1 p=0.0005 90% CI (-40.58, -14.96)
Proportion of Participants with 25% Reduction in Hunger†	**50%** p=0.0004 90% CI (19.29, 80.71)

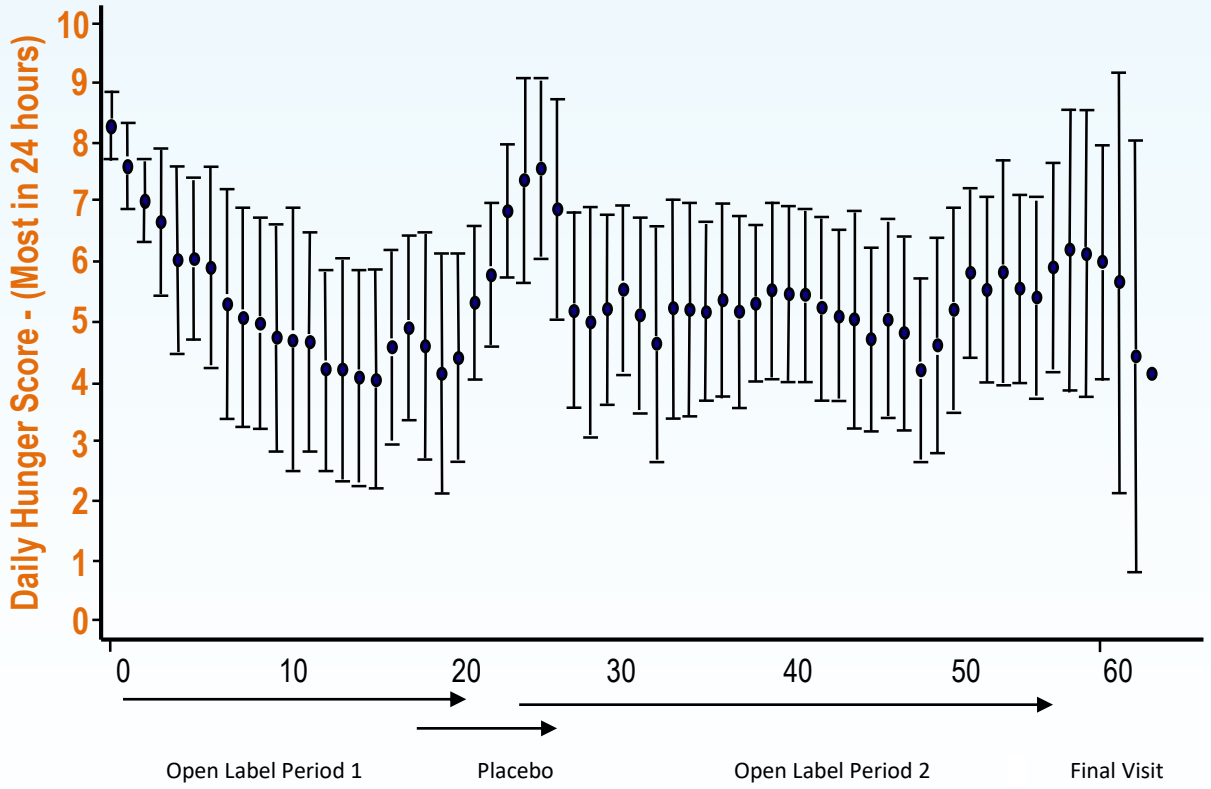
*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;
†, score is based on 0-10 Likert scale from question, “In the last 24 hours, how hungry did you feel when you were the most hungry?” for participants at least 12 years of age

POMC Phase 3 Trial – Change in Weight and Hunger Over 1 Year

Change in Weight*



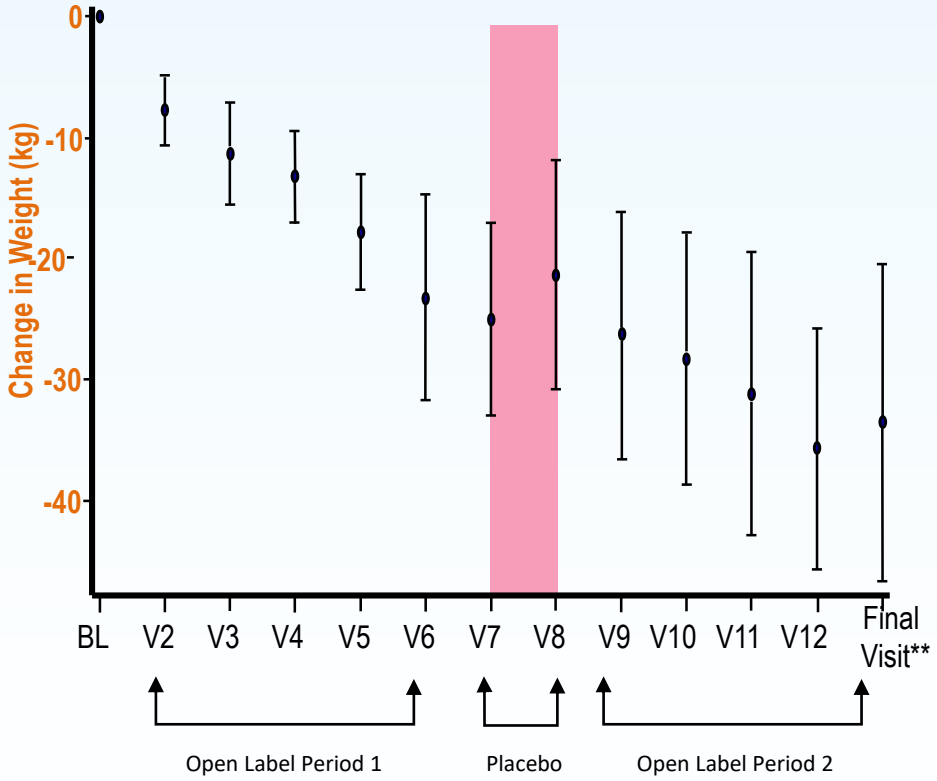
Change in Hunger Score*†



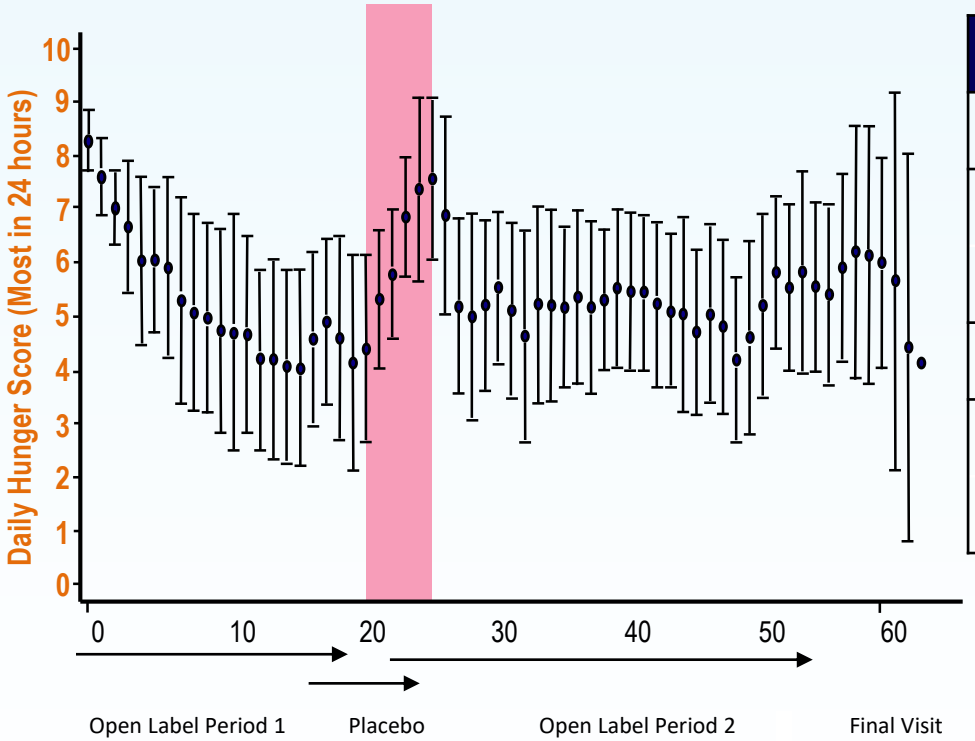
BL, baseline; V, nominal visit; N, number; error bars are confidence intervals (90%)
*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;
†, score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for participants at least 12 years of age
** This was the final nominal visit for all participants, except for one

POMC Phase 3 Trial – Substantial Weight Gain and Hunger Increase During Placebo Withdrawal

Change in Weight*



Change in Hunger Score*†



During Placebo Period:	
Change in weight (kg)	
Mean	+5.5
Range	1.5-10.5
Change in hunger score	
Mean	+2.3
Range	-2.0 to 6.7

BL, baseline; V, nominal visit; N, number; error bars are confidence intervals (90%)
*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;
†, score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for participants at least 12 years of age
** This was the final nominal visit for all participants, except for one

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Taking a Closer Look at POMC

- 8 of the 10 POMC participants achieved the primary endpoint threshold of 10% weight loss vs. baseline
- These individuals achieved between 25.8% – 35.6% weight loss
- Of the participants who did not meet the primary endpoint:
  - One participant had confounding comorbidities making their response difficult to assess
  - One participant had a genetic variant that we later learned may not be a loss of function variant in *POMC*

LEPR Deficiency Obesity

LEPR Participant Demographics

Age at Trial Enrollment (years)	
Mean (range)	23.4 (12-37)
<12 years old (n)	0
Gender, M,F	3, 8
Weight (kg)	
Mean	133.3
Range	89.4-170.4
BMI (kg/m^2)	
Mean	48.2
Range	35.8-64.6
Most Hunger (≥12 years old)	
Most hunger in 24 hours	7.1
Range	5.0-8.0

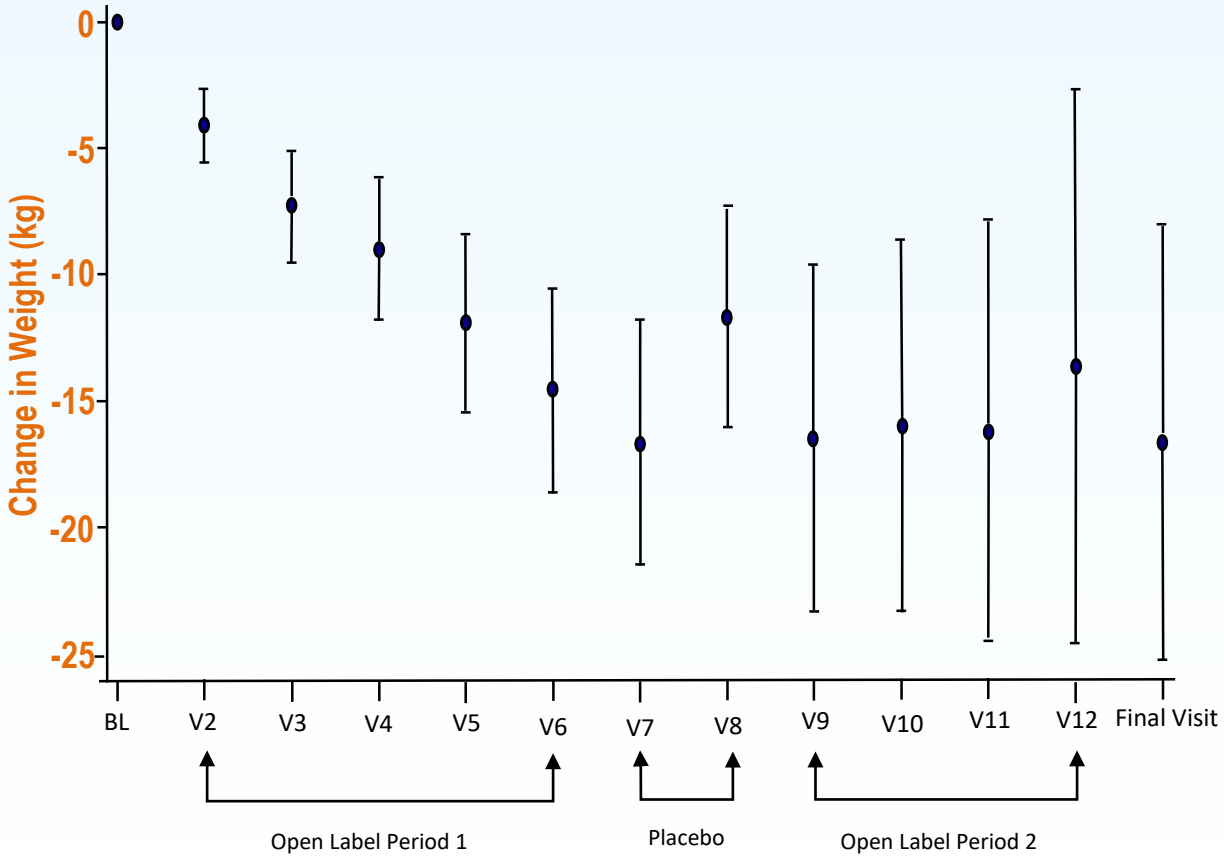
LEPR Phase 3 Trial – Topline Results

Endpoint	
Proportion of Participants Achieving at Least 10% Change in Body Weight	**45.5%** p=0.0001 90% CI (19.96, 72.88)
Mean Percent Change from Baseline in Body Weight (%)*	**-12.5** Range: -23.3 to +0.09 p<0.0001 90% CI (-16.10, -8.83)
Mean Percent Change from Baseline in Most Hunger Rating (%) *†	**-41.9** Range: -67 to 0 p<0.0001 90% CI (-54.76, -29.09)
Proportion of Participants with 25% Reduction in Hunger†	**72.7%** p<0.0001 90% CI (43.56, 92.12)

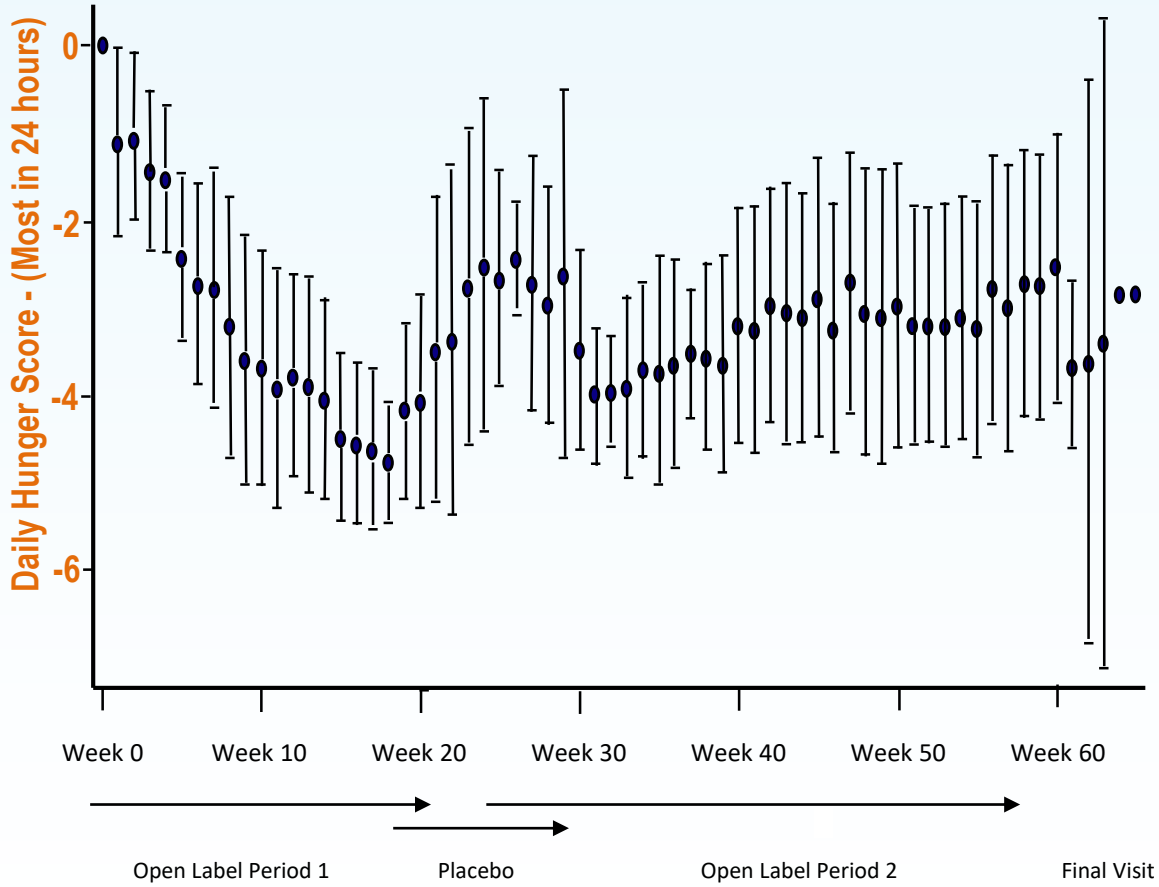
*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;
†, score is based on 0-10 Likert scale from question, “In the last 24 hours, how hungry did you feel when you were the most hungry?” for participants at least 12 years of age

LEPR Phase 3 Trial –Change in Weight and Hunger Over 1 Year*

Change in Weight*



Change in Hunger Score *†



BL, baseline; V, nominal visit; N, number; error bars are confidence intervals (90%)

*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;

†, score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for participants at least 12 years of age

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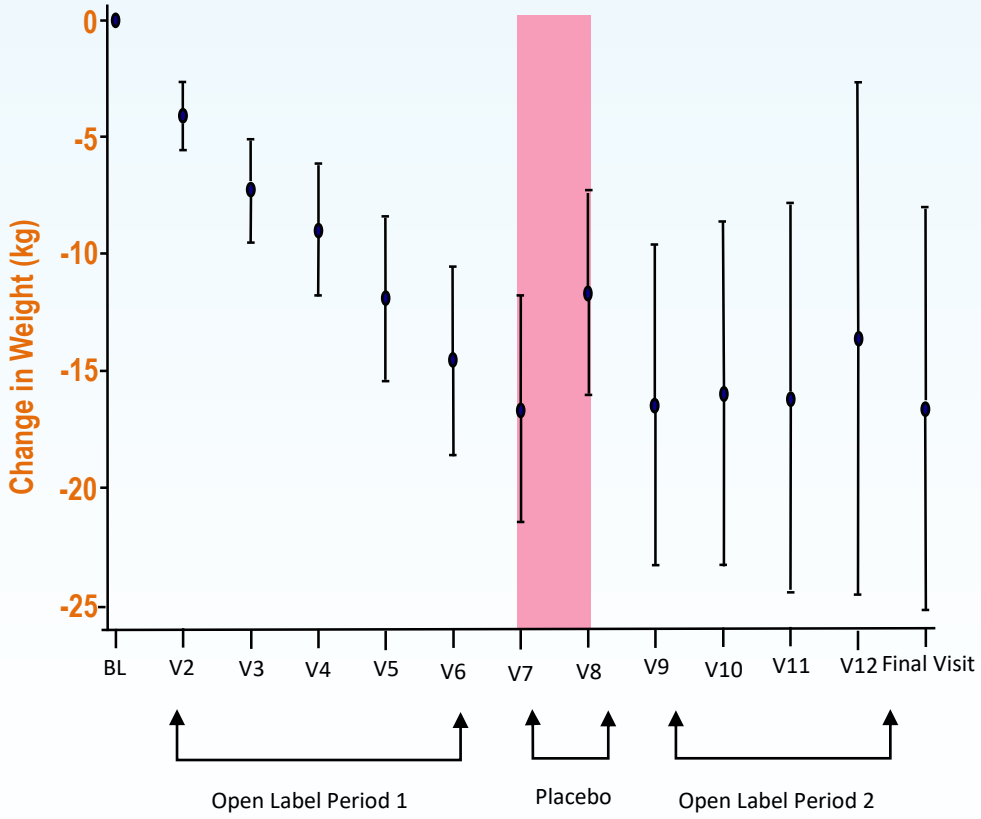
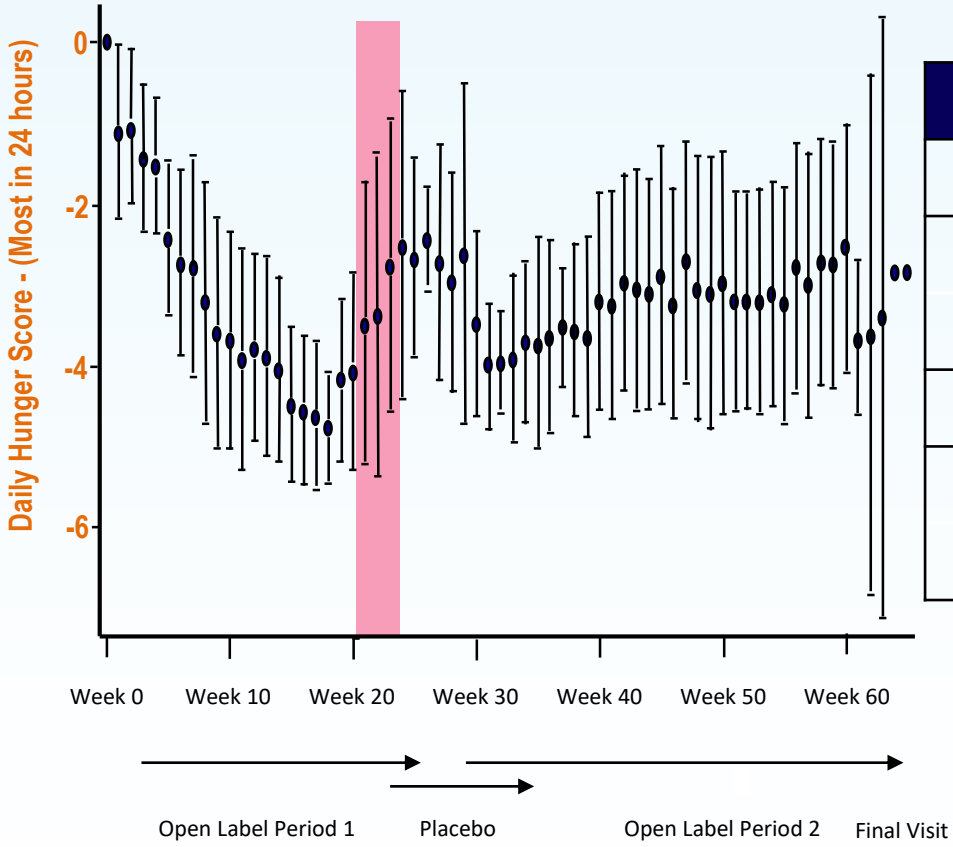
LEPR Phase 3 Trial – Substantial Weight Gain and Hunger Increase During Placebo Withdrawal*

Change in Weight*



Change in Hunger Score *†



During Placebo Period:	
Change in weight (kg)	
Mean	+4.9
Range	2.9-9.0
Change in hunger score	
Mean	+3.1
Range	0 to 7.3

BL, baseline; V, nominal visit; N, number; error bars are confidence intervals (90%)
*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;
†, score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for participants at least 12 years of age

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Taking a Closer Look at LEPR

- 5 of the 11 LEPR participants achieved the primary endpoint threshold of 10% weight loss vs. baseline
- These individuals achieved between 15.2% - 23.3% mean weight loss
- Of the participants who did not meet the primary endpoint:
  - Three participants showed initial meaningful responses but after the placebo period appeared to lose response to setmelanotide:
    - One of these participants missed primary endpoint by achieving a 9.8% weight loss
    - Data for all three participants suggest incorrect dosing
    - All three participants experienced substantial weight gain when they came off drug after study completion and plan to enroll in extension
  - One participant discontinued treatment early in the study due to an AE
  - Two participants had confounding comorbidities making their response difficult to assess

No Safety Concerns and Generally Well-tolerated in POMC and LEPR

- Treatment-emergent related adverse events included injection sites reactions, hyperpigmentation and nausea/vomiting
- One participant withdrew due to mild hypereosinophilia
- No reported setmelanotide-related cardiovascular AEs
- No SAEs related to treatment with setmelanotide
- Non-setmelanotide related SAEs were reported in 8 participants and included depression, pleural effusion, adrenal insufficiency, severe pleuritis, panic attack, death (passenger in motor vehicle accident), suicidal ideation, gastric band removal and cholecystitis. All patients, excluding the death, remained on drug with no interruption of treatment
- Per FDA guidance, the study monitored for depression and suicidality using validated questionnaires. No worsening of depression and no increased risk of suicidal ideation associated with setmelanotide

Rhythm Expects Significant Progress in 2019 and 2020

✓	Updated interim data for HET obesity
✓	Topline data from both POMC and LEPR Phase 3 studies
4Q19	Presentation and publication of full POMC and LEPR Phase 3 results
4Q19-1Q20	Initial NDA submission filings for setmelanotide in POMC and LEPR
2H19	Complete pivotal enrollment in BBS and Alström Phase 3 study
2H19	Update on ongoing efforts to increase participant identification
2H19	Expand Phase 2 basket studies into additional MC4R pathway disorders
2020	Topline data from BBS and Alström Phase 3 study
2020	Additional data in HET obesity


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POMC and LEPR Phase 3 Trials – Statistical Plan

Primary endpoint: Proportion of participants who received at least one dose of setmelanotide and demonstrate at least 10% weight reduction at ~1 year compared to baseline

- Analyzed using an exact binomial test which tests whether the percentage of participants who reach at least **10% loss in body weight** is greater than 5%.
- Natural history suggests that 0% of participants with either POMC or LEPR deficiency obesity would reach the 10% threshold. To be conservative, a 5% prediction was made.
- The identical approach was applied to the key secondary responder analysis for hunger, except that the threshold was 25% reduction in hunger.

Key mean percent change secondary endpoints:

- Mean percent change from baseline for both weight and hunger was analyzed using a linear mixed model for repeated measures analysis of covariance.
- For these analyses, participants were considered evaluable if, at the end of the first open label period, they achieved 5kg of weight loss, or 5% weight loss, if their baseline weight was less than 100 kg.