New Data in MC4R Pathway Heterozygous (HET) Obesity and Next Steps

March 2019

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Executive Summary

Stratifying MC4R pathway heterozygous (HET) patients into cohorts based on genetic variants and believed impact on pathway function

- Estimate >20,000 high-impact loss-of-function (LOF) HET patients in the United States

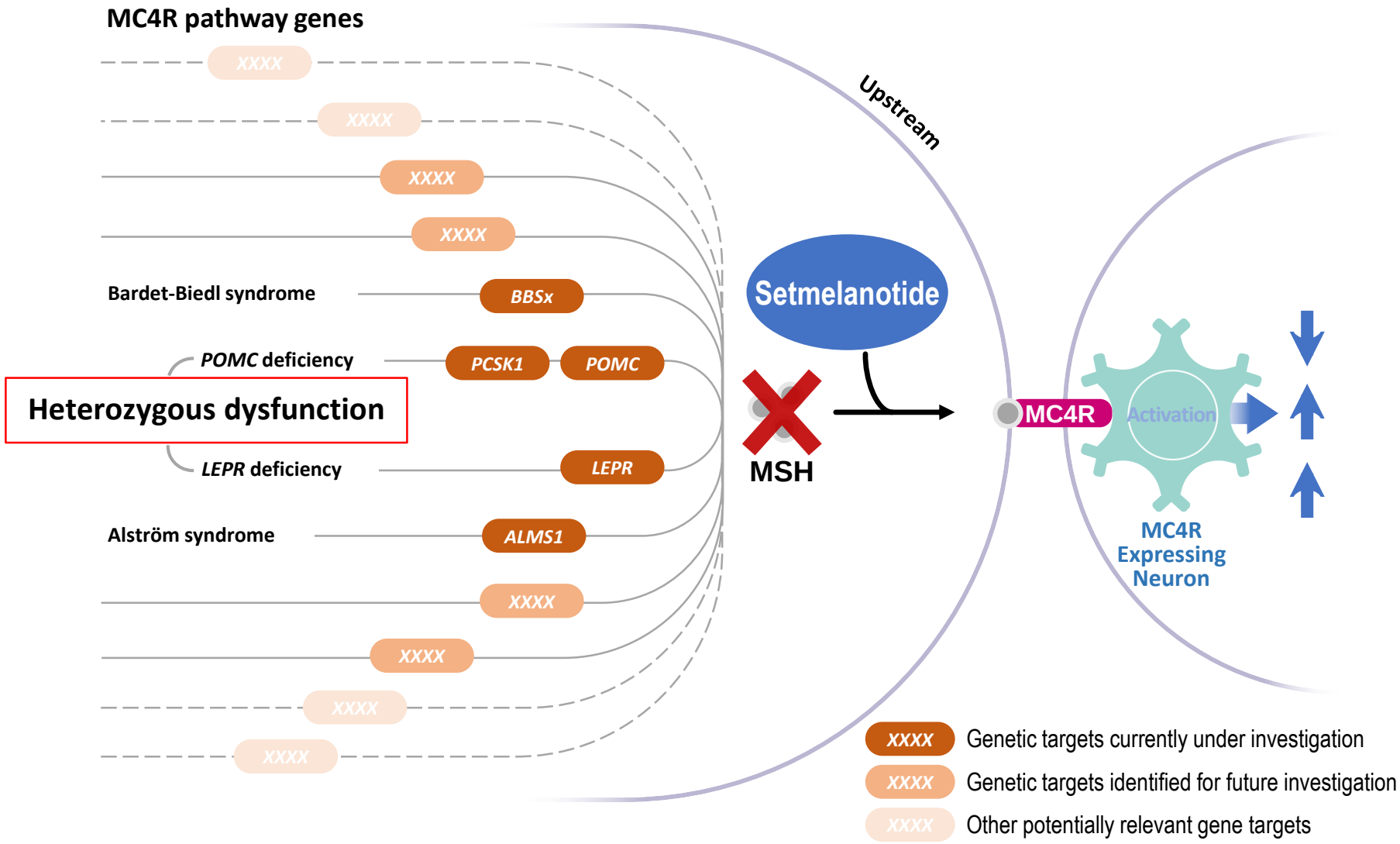
Updated data shows greater, more consistent weight loss in HET patients with high-impact LOF variants

- All four high-impact LOF patients appear setmelanotide-responsive
- Nine patients in other LOF subgroups have more variable responses

Ongoing focus: expanding pool of high-impact variants; identifying and enrolling HET patients in study

Continuing to enroll HET patients in Phase 2 basket study through at least the remainder of 2019

Rhythm Focus: Genetic Defects in the MC4R Pathway



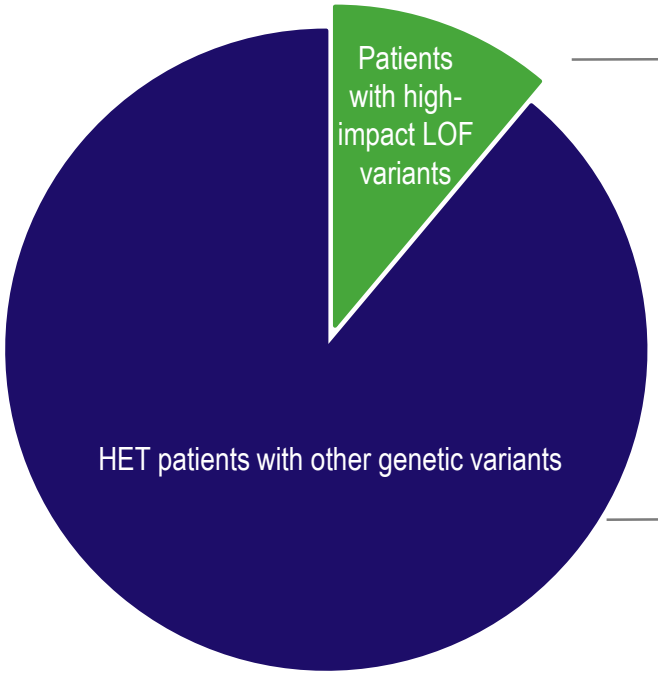
Defining MC4R Pathway Heterozygosity

Genotype	Wildtype	Homozygote	Heterozygote
			
Definition	No genetic variant[1]	The same loss-of-function genetic variant present on both copies of a gene	One loss-of-function genetic variant present on one copy of a gene
Phenotype	No POMC deficiency obesity	e.g. POMC deficiency obesity[2]	e.g. POMC heterozygous obesity

[1]A genetic variant (mutation) is a difference in DNA sequences between an individual and the population; [2]Currently POMC, LEPR, BBS and AS deficiency obesity indications are being studied in pivotal trials

Stratifying HET Patients Based on Genetic Variant: Significant Population

Rhythm estimates >20,000 high-impact LOF patients in U.S.[1]



graph not drawn to scale

Rhythm's Approach

INITIAL SUBGROUP FOCUS:

- **Well-characterized, published high-impact variants, expected to be most responsive to setmelanotide**
  - **Genetic Focus:** Truncations (nonsense); frame shift; splice site variants; as well as well-characterized, high-confidence, published missense variants
  - **Clinical Focus**: HET patients with severe, early-onset obesity and hyperphagia
- **Goal:** Achieve proof-of-concept to support design of pivotal trial

ADDITIONAL SUBGROUPS:

- **Other HET genetic variants:**
  - Uncharacterized missense variants
  - Partial loss-of-function variants
  - Newly discovered variants
  - Less rare variants
- **Composite HET** (more than one variant in more than one gene)
- **Goal:** Better understand HET biology and enlarge potential patient pool

[1]Calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity; High impact HET allele frequency based on Rhythm genetic sequencing (Feb 2019)

All High-Impact LOF Patients Appear Setmelanotide-Responsive

Preliminary data – March 2019

All patients ongoing:

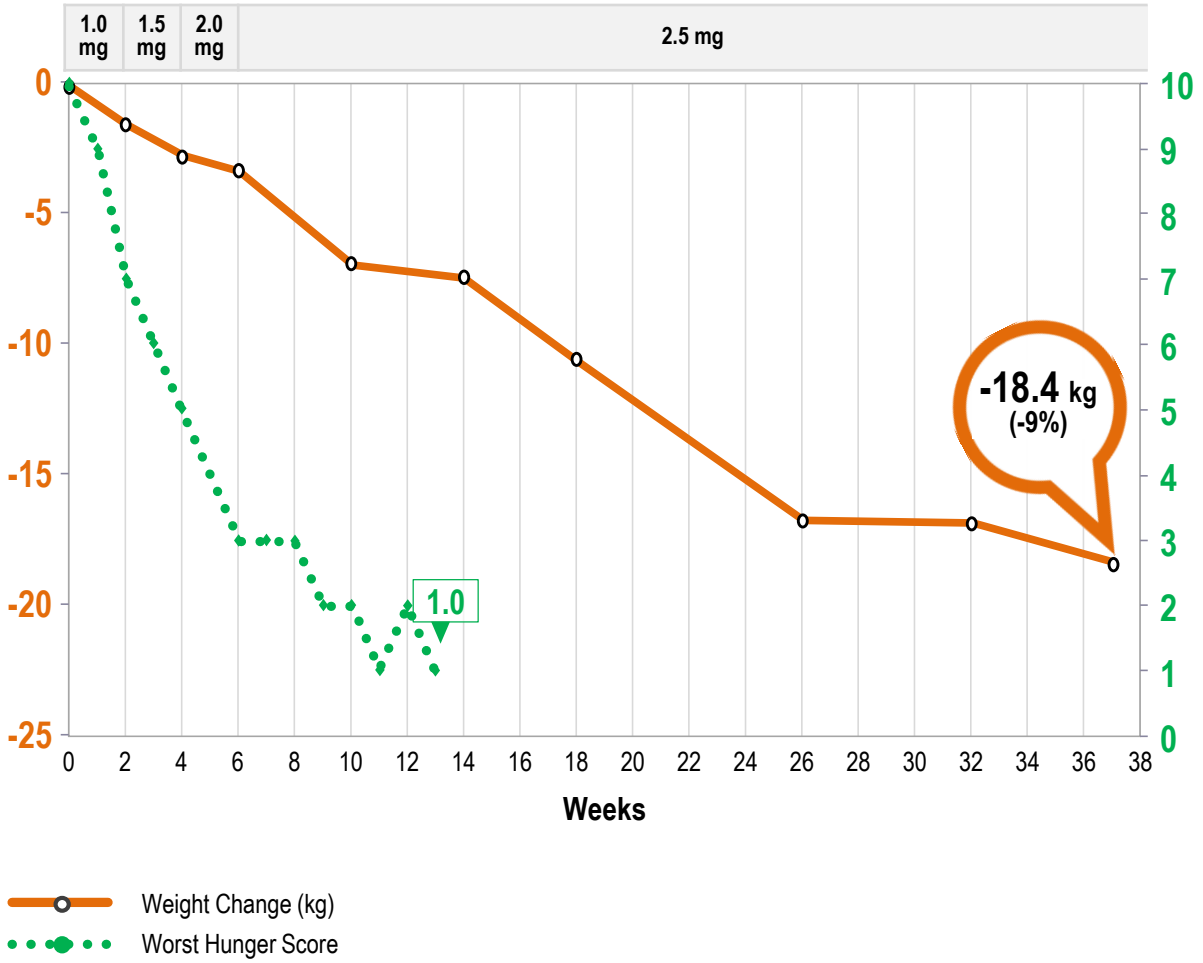
Patient	Total treatment duration[1] (weeks)	Baseline Weight (kg/(lbs))	Weight Loss (kg/(lbs))	Weight loss	Change in Hunger Score (10 pt scale)	Hunger score reduction
1	37	204 (451)	18.4 (40.5)	9.0%	-9	90.0%
2	29	129 (284)	22.3 (49.0)	17.3%	-5	71.4%
3	4	187 (412)	7.1 (15.6)	3.8%	-4	40.0%

Fourth patient, still very early in dose titration, showing promising weight loss and hunger score decreases

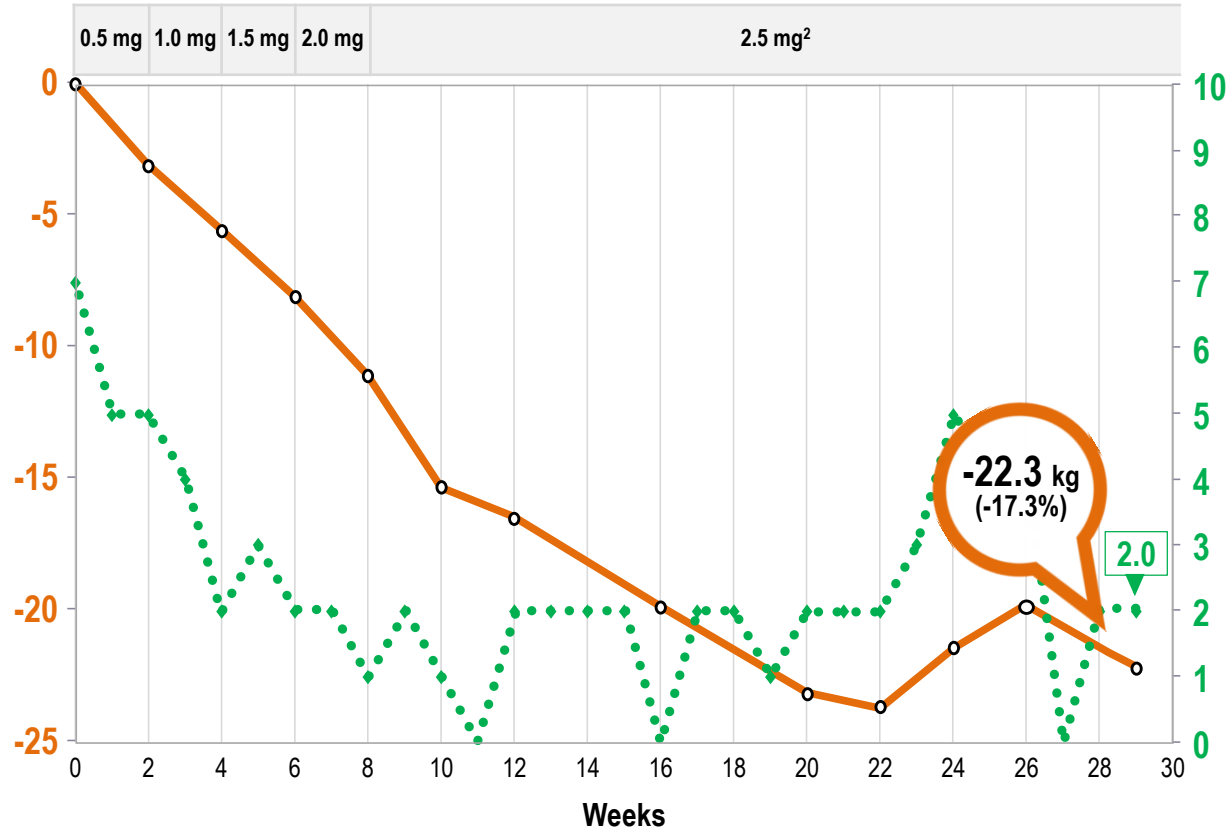
[1]Total treatment duration including any titration period which can last 6-12 weeks. [2]Too early in treatment to provide data, but initial weight and hunger score reductions were noted. Note: these are all new patients since last update.

High-Impact LOF Patients #1 & 2

22 yr old female
Starting weight = 203.8 kg
Starting BMI = 79.6
Starting hunger score (worst) = 10.0 pts[1]



40 yr old female[2]
Starting weight = 128.8 kg
Starting BMI = 41.6
Starting hunger score (worst) = 7.0 pts



[1]For some patients whose site uses paper based methods, hunger data lags in Rhythm's systems. [2]Patient 2 went on per protocol optional withdrawal period from Weeks 22-26.

Patients in Other Subgroups Have More Variable Responses

Five patients ongoing[1]:

Patient	Total treatment duration[2] (weeks)	Baseline Weight (kg/(lbs))	Weight Loss (kg/(lbs))	Weight loss	Change in Hunger Score (10 pt scale)	Hunger score reduction
1	74	150 (330)	12.1 (26.6)	8.0%	-7	78.0%
2	66	147 (323)	7.5 (16.5)	5.1%	-1	20.0%
3	20	118 (259)	15.0 (33.0)	12.8%	-6	75.0%
4	16	106 (232)	7.2 (15.8)	6.9%	-7	70.0%
5	7	150 (330)	4.6 (10.1)	3.0%	NA	NA

Four patients discontinued treatment:

- One patient due to lack of efficacy at 14 weeks[3]
- Three patients with ≤ 4 weeks of total therapy, so efficacy not able to be assessed:
  - Two patients due to AE (tanning, muscle cramps)[3]
  - One patient withdrawn by site for patient non-compliance

[1]Two of these patients were reported in June 2018. [2] Total treatment duration including any titration period, which can last 6-12 weeks. [3]These three patients were reported in June 2018. AE = adverse event

Safety & Tolerability Data Consistent with Prior Experience

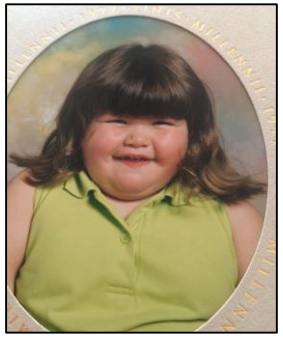
Safety profile for all 13 HET patients:

- Setmelanotide continues to be well-tolerated
- No serious adverse events (AEs) reported
- No new discontinuations due to AEs since those reported in June 2018
- Overall safety profile remains consistent with previous updates

Meet Katy: HET Patient with Severe, Early-Onset Obesity & Hyperphagia

"[My disease] causes extreme unrelenting hunger and excessive eating. As a child…the fridge and food was controlled massively…but nobody could understand that I was desperately hungry and just wanted to stop that feeling."

3 YEARS



11 YEARS, 231 POUNDS

23 YEARS, 450 POUNDS

INFANCY:

"Normal" weight at birth, but begins to rapidly gain weight at 9 weeks

4 YEARS:

Diagnosed with POMC Heterozygous Deficiency Obesity

CHILDHOOD:

Self-isolation and missed school days

Asthmatic, increased pain and pressure on her knees make play and PE difficult

ADOLESCENCE:

Put on anti-depresseants

Numbness and agonizing back pain

Abnormal pubertal development

23 YEARS:

Sleep apnea; some cardiac issues; insulin resistance. Cracked and bleeding skin

Key Imperatives for Execution of HET Development Plan

ADD TO POOL OF HIGH-IMPACT LOF VARIANTS

Screen and classify potential new and uncharacterized variants:

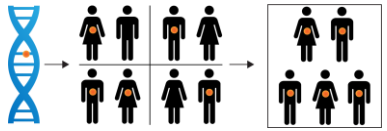
- Computational model for assessing variants
- Biochemical analysis of variants in *POMC*, *PCSK1*, *LEPR*

Rhythm estimates thousands of potential new and uncategorized HET variants in MC4R pathway genes

CONTINUE AND EXPAND GENOTYPING EFFORTS

Through GO-ID and other ongoing genotyping efforts, identify additional patients and new genetic variants tied to MC4R loss of function

ENROLL ELIGIBLE PATIENTS IN BASKET STUDY



- Confirm proof-of-concept in high-impact LOF variants
- Explore impact of setmelanotide in other HET variants
- Inform regulatory strategy in HET obesity and design of pivotal studies

Rhythm Expects Significant Progress in 2019 and 2020

✓	Updated interim data for HET obesity
3Q19	Topline data from both POMC and LEPR Phase 3 studies
4Q19-1Q20	Initial NDA submission filings for setmelanotide in POMC and LEPR
2H19	Complete pivotal enrollment in BBS and Alström Phase 3 study
2019	Update on ongoing efforts to increase patient identification
2019	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

Conclusions

1. Updated data shows promising and consistent weight loss in HET patients with high-impact LOF variants
2. Rhythm believes there is a significant, distinct opportunity for setmelanotide in high-impact HET patients
3. Rhythm is exploring the potential for opportunities among broader HET population
4. Rhythm is progressing multiple efforts to expand pool of high-impact variants, and to identify and enroll additional HET patients in basket study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Scientific Support for HET Contribution to Obesity

Preclinical Data:

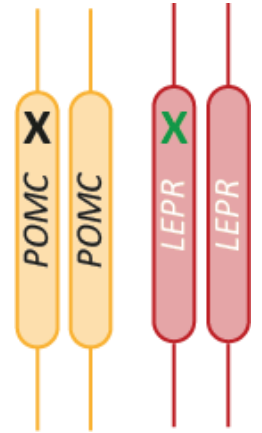
- MC4R pathway **heterozygous (+/-)** mice show intermediate levels of obesity versus knockout and wild-type mice

Clinical and Genetic Evidence:

- The HET population is larger and more complex than the homozygous population
  - Individuals with heterozygous MC4R pathway variants have variable penetrance[1] of obesity
- A comprehensive understanding of impact of variants on obesity limited by variant rarity
- Less rare HET variants are associated with obesity
- Published research includes numerous individual case histories of HET obesity patients with severe, early-onset obesity and hyperphagia

[1]Penetrance: translation of a genetic variant to an obesity/hyperphagia phenotype, or symptomatology

Composite HET: Multiple Impairments of the MC4R Pathway

				
Genotype	Wildtype	Homozygote	Heterozygote	**Composite Heterozygote**
Definition	No genetic variant	The same loss-of-function genetic variant present on both copies of a gene	One loss-of-function genetic variant present on one copy of a gene	**At least one loss-of-function genetic variant in each of two different genes**
Phenotype	No POMC deficiency obesity	e.g. POMC deficiency obesity*	e.g. POMC heterozygous obesity	**e.g. MC4R-pathway composite obesity**

- Strong genetic evidence that composite HET variants impact obesity[1]
- Potential setmelanotide-responsive subgroup of HET obesity from among other HET genetic variants

[1]Ayers, et al. JCEM 2018; 103: 2601–2612.