



**Rhythm Pharmaceuticals:
Targeting upstream MC4R pathway defects to
transform the care of genetic obesity**

Company Presentation - April 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, anticipated timing for enrollment, design and completion of clinical trials, the timing for filing of an NDA, the release of results of clinical trials, expectations regarding the use of cash, 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. Such statements are subject to numerous risks and uncertainties, including but not limited to, our ability to enroll patients in clinical trials, the outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our expenses, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and quarterly reports on Form 10-Q and other reports we file with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this presentation or to update them to reflect events or circumstances occurring after the date of this presentation, whether as a result of new information, future developments or otherwise.

Transforming the Care of Patients with Genetic Obesity

The MC4R pathway is the key pathway regulating weight and hunger. Genetic defects in the MC4R pathway cause insatiable hunger, leading to severe and early-onset obesity

There are currently no effective or approved treatments for people living with rare MC4R pathway disorders

Potential First-in-Class Therapy

Setmelanotide is an MC4R agonist designed to rescue the pathway from genetic defects that occur upstream of MC4R receptor:

- **Dramatic reductions in weight and hunger observed in four rare MC4R pathway disorders:**
 - Awarded FDA Breakthrough Therapy and EMA PRIME designations
 - Pivotal Phase 3 trials ongoing in all four indications
- **Phase 2 development ongoing in additional MC4R pathway disorders:**
 - Promising efficacy in high-impact loss-of function (LOF) HET obesity

Rhythm Engine: Integrated Efforts to Accelerate Growth

- **GO-ID Genotyping Study and TEMPO Registry:** Enable clinical study enrollment, patient identification and exploration of genetic variants tied to MC4R LOF
- **Rhythm Basket Study:** Facilitates rapid enrollment and exploration of setmelanotide's potential in patients with new genetic targets or syndromes tied to the MC4R pathway
- **Pipeline Expansion:** Leverage Rhythm expertise to treat additional disorders

Genetic Disorders of Obesity Impact Every Aspect of Daily Life

Meet Katy: Living with HET Obesity

“It 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:

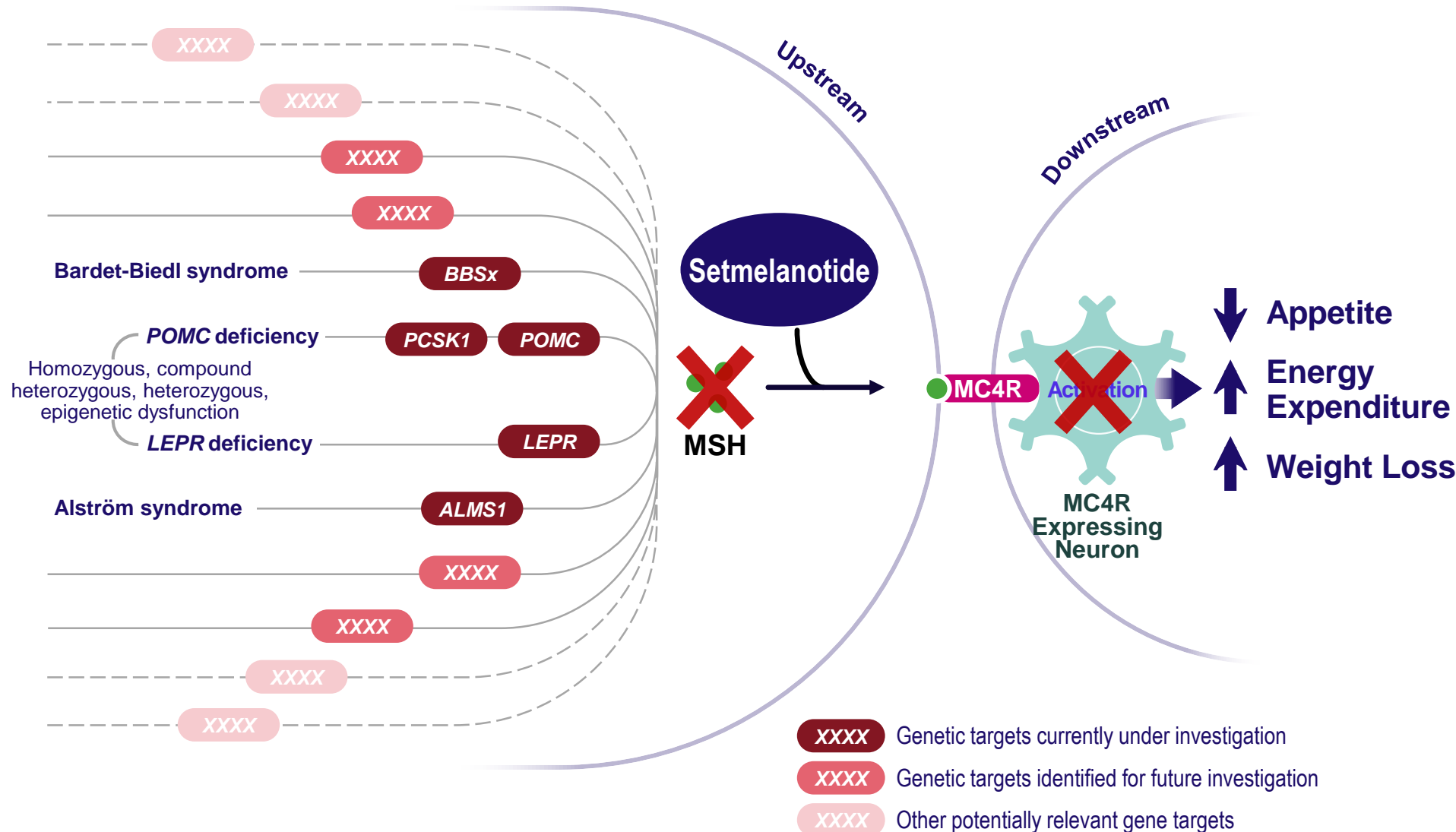
Put on anti-depressants
Numbness and agonizing back pain
Abnormal pubertal development

23 YEARS (CURRENT):

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

The MC4R Pathway Is Responsible for Regulating Energy Balance

MC4R pathway genes





Setmelanotide: Potential First-in-Class Replacement Therapy for MC4R Pathway Disorders

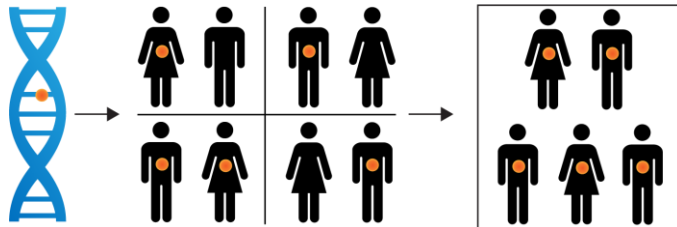
Potent first-in-class MC4R agonist



- Setmelanotide: 8 amino acid peptide with high potency (EC_{50} 0.27nM)
 - Administered by once daily subcutaneous injection
 - Retains the specificity and functionality of the naturally-occurring hormone
- Once-weekly formulation in clinical development
 - Developed in partnership with Camurus
 - Terminal half-life ~123 hours
 - Beginning Phase 2 studies
- Previous clinical trials with approximately 330 patients with obesity demonstrated statistically significant weight loss and favorable tolerability profile
- IP: Composition of matter in all major markets
 - US patent, with possible Hatch-Waxman extension, to 2032
- Highly competitive cost of goods sold

Basket Study: Foundation for Achieving POC in MC4R Pathway Disorders

Phase 2 Basket Study



Designed to facilitate rapid progress to proof of concept (POC) in potential new indications for setmelanotide



3 month POC study phase:

Weight loss, hunger and other metabolic parameters are measured



If significant weight loss and acceptable safety and tolerability is demonstrated

1 year open-label, single-arm, POC extension studies

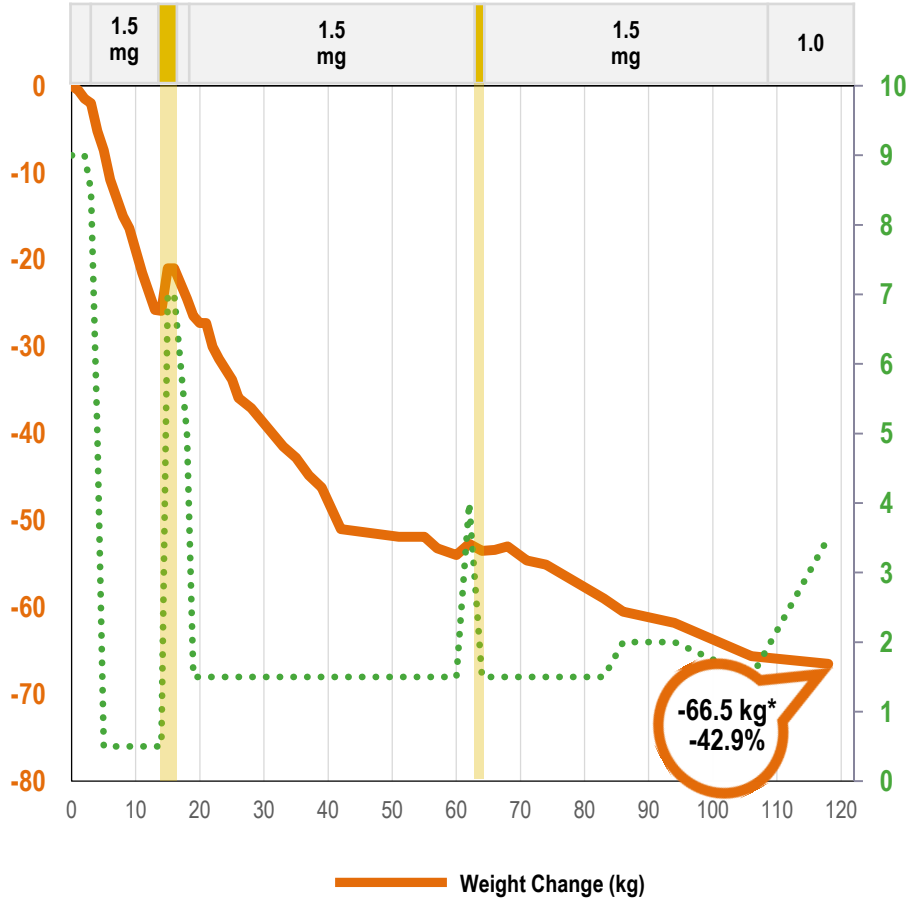
Indications enrolled in Phase 2:

- POC Achieved, Phase 3 initiated:
POMC, LEPR, BBS & Alström Syndrome
- Pre-POC, Phase 2 ongoing:
HET obesity, POMC epigenetic obesity
- New Indications: Additional genetic targets upstream of MC4R

POMC and LEPR Phase 2 Studies: Patients #1

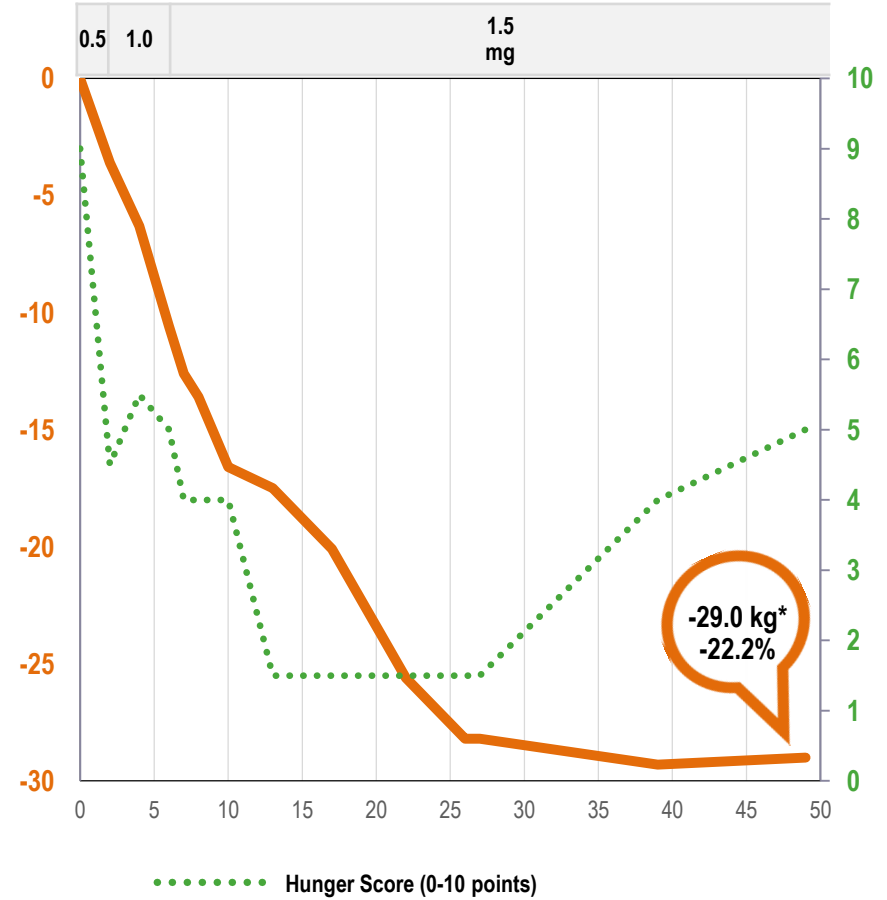
POMC Patient #1⁽¹⁾

20 yr old female
 Starting Weight = 155.0 kg
 Starting BMI = 49.8 kg/m²



LEPR Patient #1⁽²⁾

23 yr old male – LEPR Mutation
 Starting Weight = 130.6 kg
 Starting BMI = 39.9 kg/m²



* Figures represent cumulative weight lost in kgs | Not all patients had similar responses

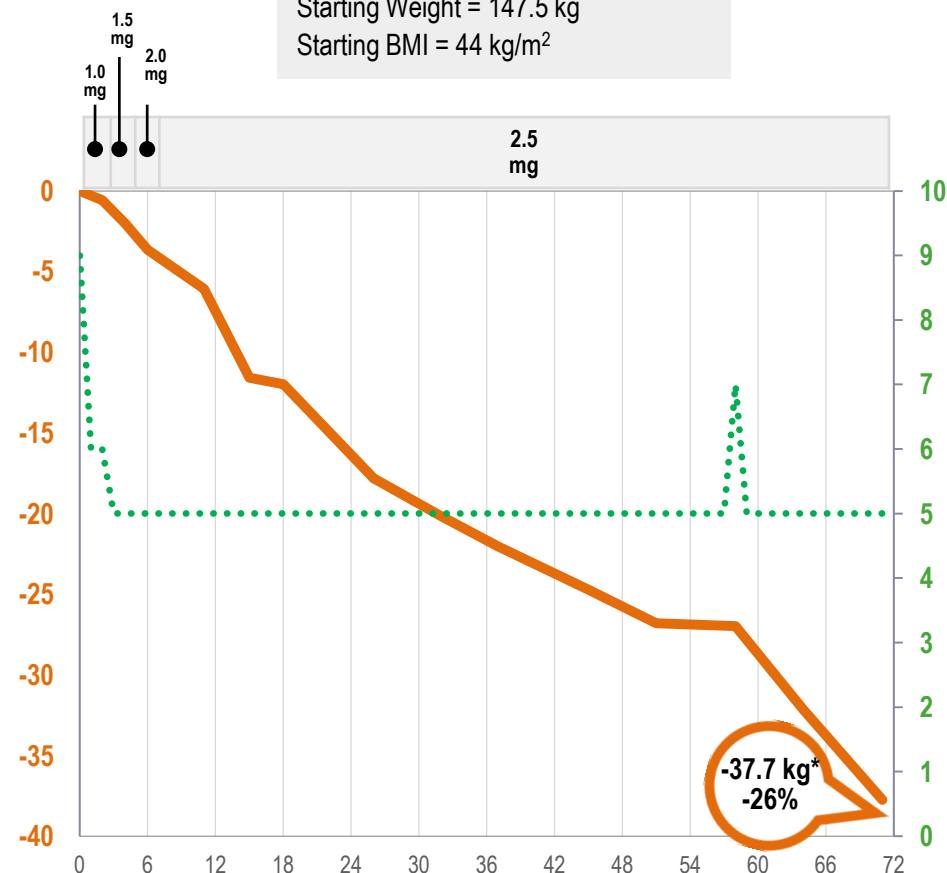
(1) Kühnen, et. al, Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. *N Engl J Med.* July 2016 . Yellow vertical bars represent intervals with dose withdrawal or modifications

(2) Biebermann, et al. MC4R Agonism Promotes Durable Weight Loss in Patients with Leptin Receptor Deficiency. *Nat Med.* 2018 May 7.

BBS and Alström Syndrome Phase 2 Studies: Patients #1

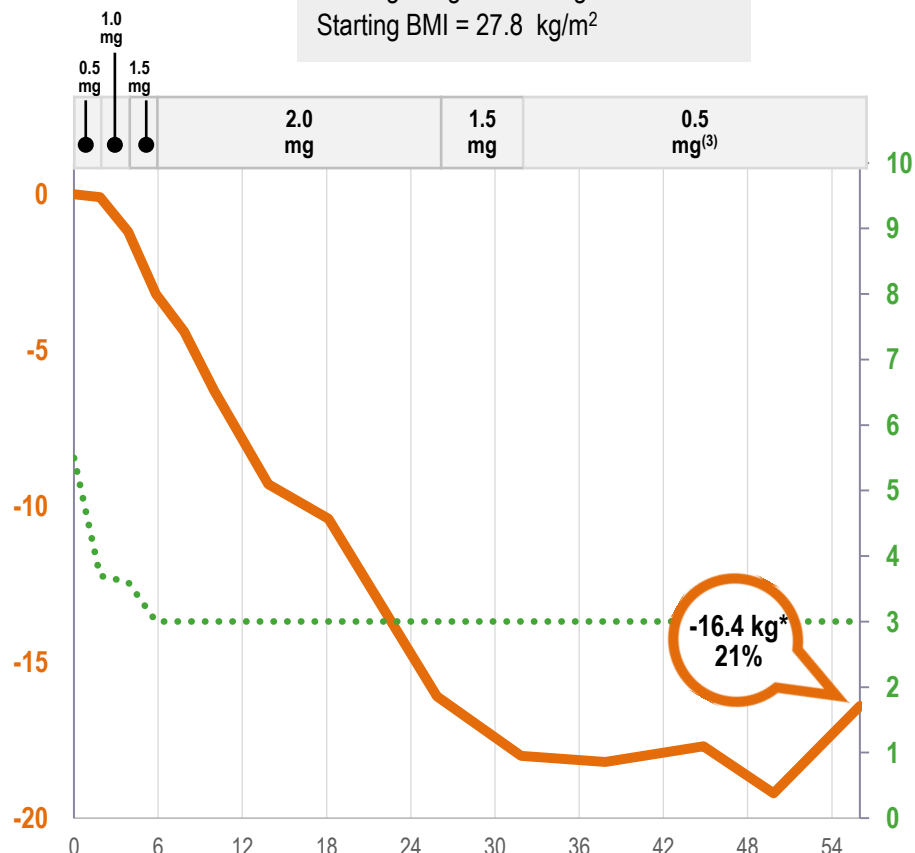
BBS Patient #1⁽¹⁾

25 yr old male - BBS1 Mutation
 Starting Weight = 147.5 kg
 Starting BMI = 44 kg/m²



AS Patient #1⁽²⁾

12 yr old male
 Starting Weight = 78.6 kg
 Starting BMI = 27.8 kg/m²



— Weight Change (kg)

..... Hunger Score (0-10 points)

* Figures represent cumulative weight lost in kgs | Not all patients had similar responses

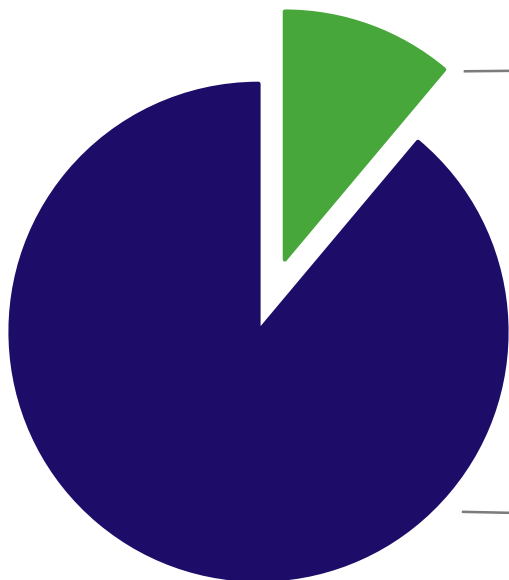
(1) Haws et al. Effect of the Melanocortin-4 Receptor Agonist Setmelanotide on Obesity and Hyperphagia in Individuals Affected by Bardet-Biedl Syndrome. ESPE 2018, Sept. 28, 2018.

(2) Han et al. Effect of Setmelanotide (MC4R Agonist) on Obesity and Hunger in Individuals With Alström Syndrome. ObesityWeek 2018, November 15, 2018.

(3) From week 49 onwards, the dose was lowered to 0.5 mg five times a week

HET Obesity: Stratifying Patients Based on Genetic Variant

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 LOF 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 & 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

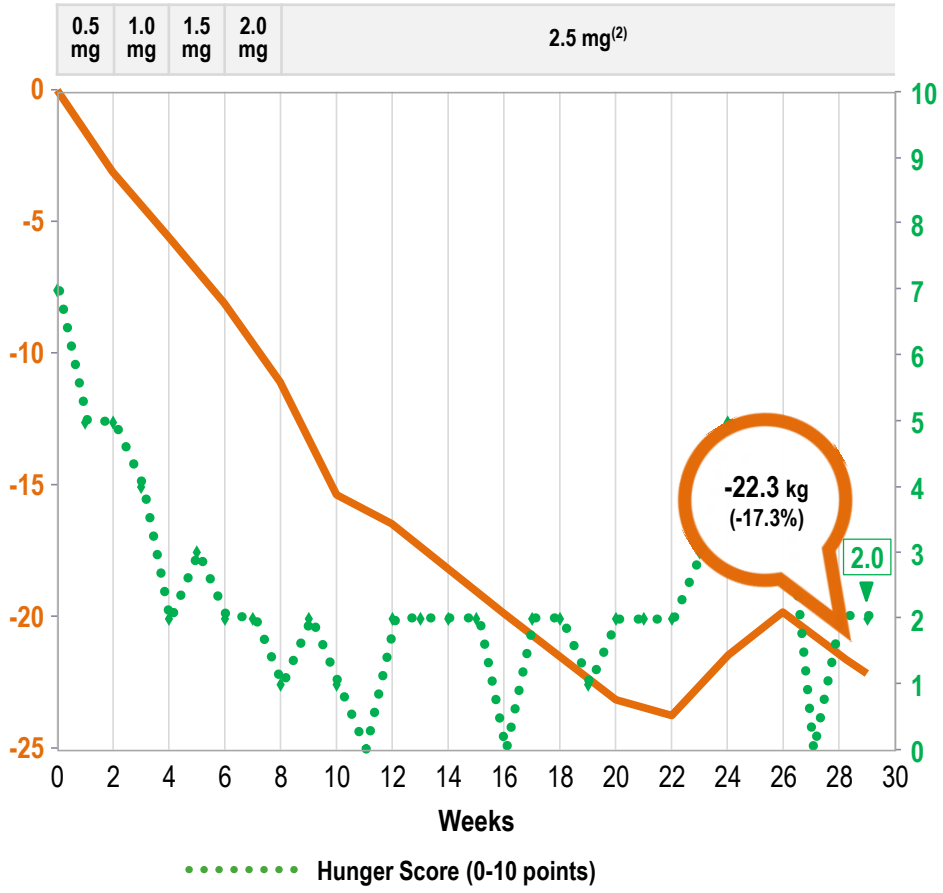
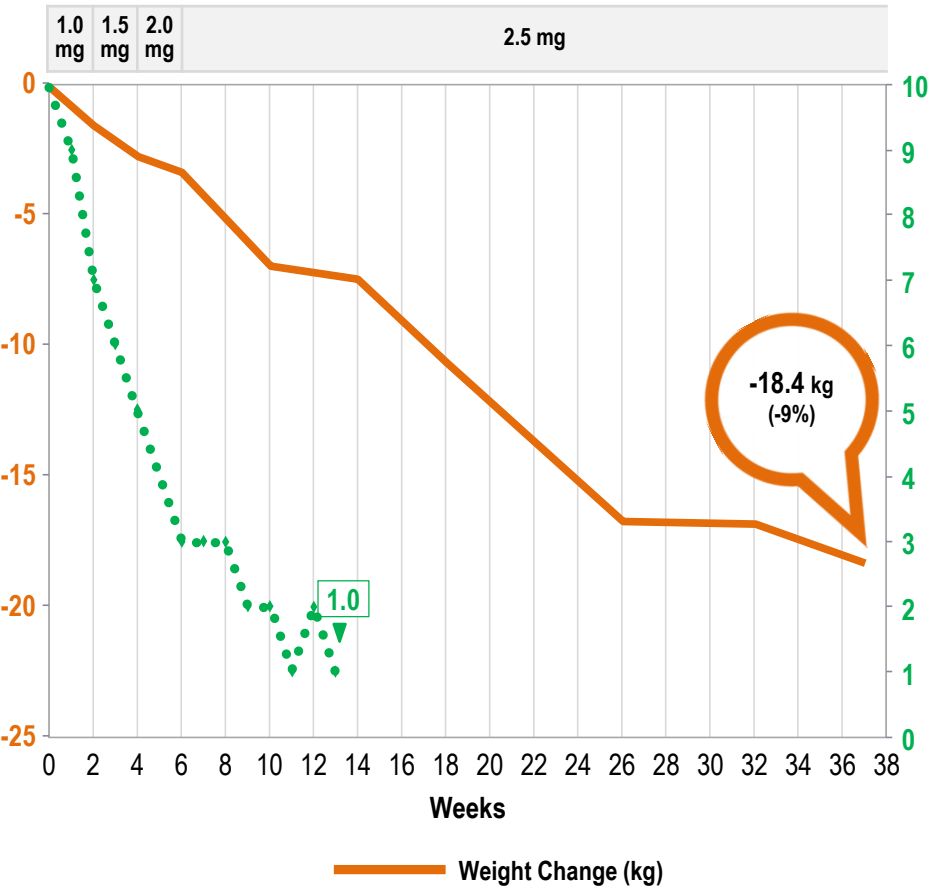
⁽¹⁾Calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity; High impact HET allele frequency based on Rhythm genetic sequencing (Feb 2019)

More Consistent Weight Loss in HET Patients with High-Impact LOF Variants

Four of four patients with high impact LOF variants demonstrating weight and hunger response, compared to more variable responses in HET patients with other LOF variants

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.

Setmelanotide Has Been Generally Well-Tolerated

Safety and Tolerability

Setmelanotide has been evaluated in over 330 patients with obesity, with individual patient treatment duration now exceeding four years

- Setmelanotide has been generally well-tolerated
- Most AEs are mild and non-mechanism based:
 - Mild injection site reactions
 - Darkening of skin (tanning) and skin lesions, mediated by the closely related MC1 receptor (the natural “tanning” receptor)
- Discontinuations are rare; no increase in CV parameters

All pivotal trials share a common design:

- Patients aged ≥ 6
- ~1-year trial duration, with long-term extension
- Dosage: Daily subcutaneous injection
- 1^o endpoint: categorical analysis of responders⁽¹⁾
- Key 2^o endpoints include mean weight loss and hunger measures
- Supplemental patients enrolling beyond pivotal cohorts to generate additional data

POMC and LEPR Phase 3 Trials

- Pivotal cohorts (n~10) fully enrolled for each trial
- Top-line data from both trials expected in 3Q19

BBS/Alström Combined Phase 3 Trial

- Pivotal cohort (n~30), with at least 20 BBS patients and 6 Alström patients
- 14-week placebo-controlled period, followed by completion of active open-label treatment for total duration of ~52 weeks
- Completion of pivotal enrollment expected in 2H19

⁽¹⁾ Percentage of patients who have at least a 10% reduction in body weight at approximately one year.



Building a Community for the Treatment of Rare Genetic Disorders of Obesity

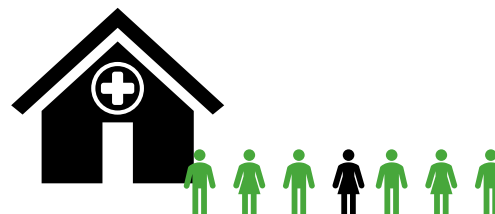
Epidemiology Suggests Significant Market Opportunity

POMC, LEPR Deficiency and HET Obesity: Non-Syndromic Disorders



Patients diagnosed after genetic screening.

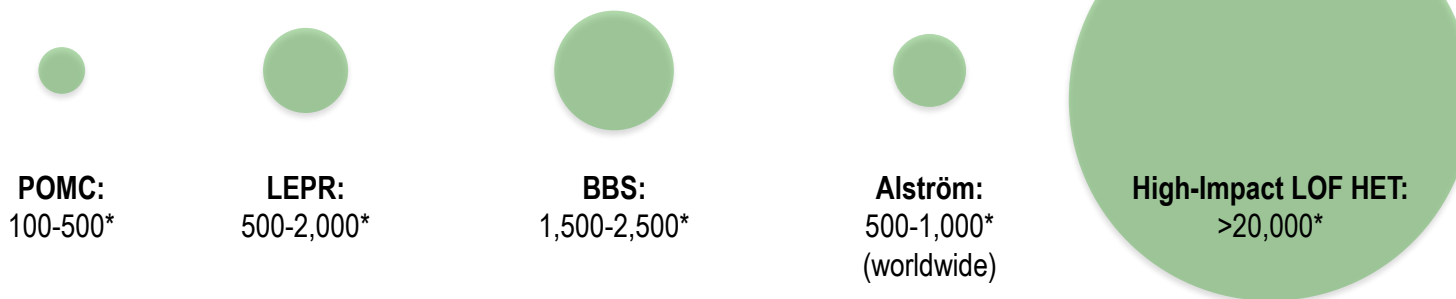
BBS and Alström Syndrome: Syndromic Disorders



Patients often known to the medical system.



CLINICAL EPIDEMIOLOGY (1)



GENETIC EPIDEMIOLOGY (2)

~13,000 individuals in the U.S. with **POMC** or **LEPR** -- a **five-fold increase** over the clinical epidemiology estimate.

* The patient numbers above are based on company estimates

(1) Unless otherwise noted, These numbers reflect U.S. only; Rhythm believes that the addressable patient population in Europe is at least as large as in the U.S.

(2) Ayers et al. [Melanocortin-4 Receptor Pathway Dysfunction in Obesity: Patient Stratification Aimed at MC4R Agonist Treatment](#). *J Clin Endocrinol Metab*. 2018 May 2. doi: 10.1210/jc.2018-00258

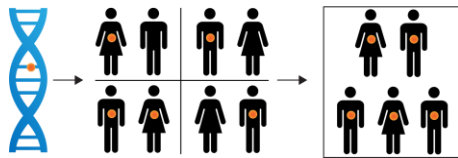
Rhythm Engine to Build Integrated Patient Community



Identifies individuals with rare genetic disorders of obesity who may be eligible for further study and treatment with setmelanotide



Rhythm-Sponsored Phase 2 Basket Study



TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

Designed to facilitate rapid progress to proof of concept in potential new indications for setmelanotide

Commitment to understanding the ongoing impact and burden of disease on patients and their caregivers



Identifies individuals with rare genetic disorders of obesity in order to **increase the frequency of genetic testing** and **shift practice patterns among treating physicians**

- Individuals with obesity ≥ 2 years of age
- Recruitment via HCPs caring for patients with severe obesity
- Expected enrollment of $\geq 9,000$ patients from 140 centers+ worldwide
- Genotyping panel includes over 100 genes associated with genetic obesity
- Individuals identified with MC4R pathway mutations may enroll in future clinical trials, observational trials, or TEMPO registry

Community Building Through the TEMPO Registry

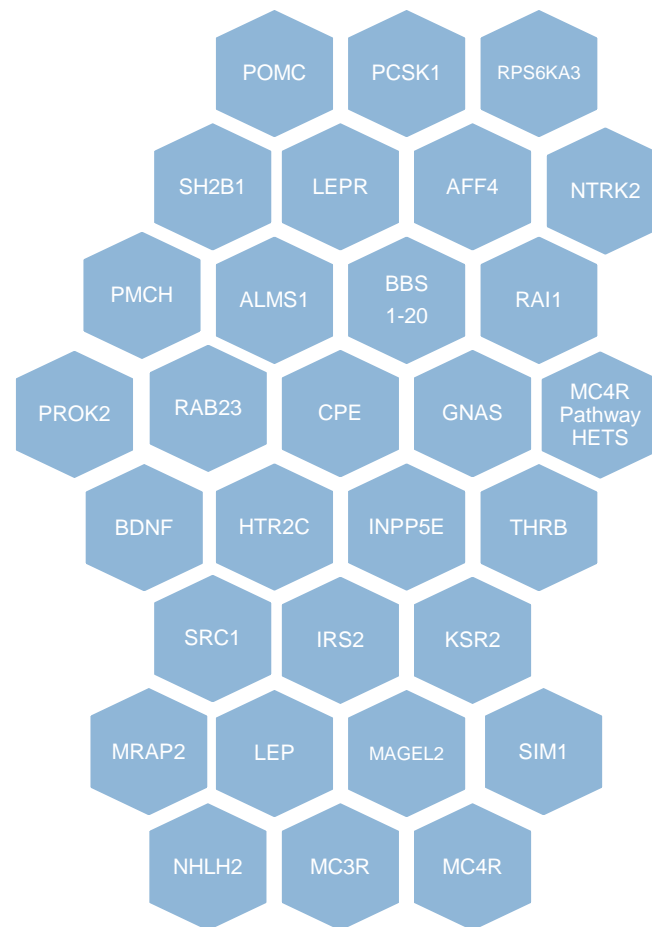


TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

Builds on ongoing collaborations with existing patient registries (e.g. CRIBBS for BBS) to facilitate **better understanding of rare genetic disorders of obesity** in the medical community

- Target enrollment of ~1,000 patients
- Genetic screening through GO-ID
- Potential enrollment in Phase 2 basket studies
- Launched at 57th Annual ESPE Meeting (September 2018)

TEMPO is for individuals with specific variants in the MC4R pathway genes, that include at least one of the following:



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

Living with the Insatiable Hunger and Obesity that Characterize BBS

“As our daughter Lucy grows older, the weight obstacle of BBS looms more ominously before us, hindering much of what we do. Lucy measures most of her activities and much of her happiness around when her next meal is, what food is available where, and it is an overwhelming task to help her take control. Weight affects so much in her life and we are working so hard to fight to give her a more fulfilling life without the confines that obesity presents.”

-Shawni, mother to Lucy, a child living with BBS





Appendix

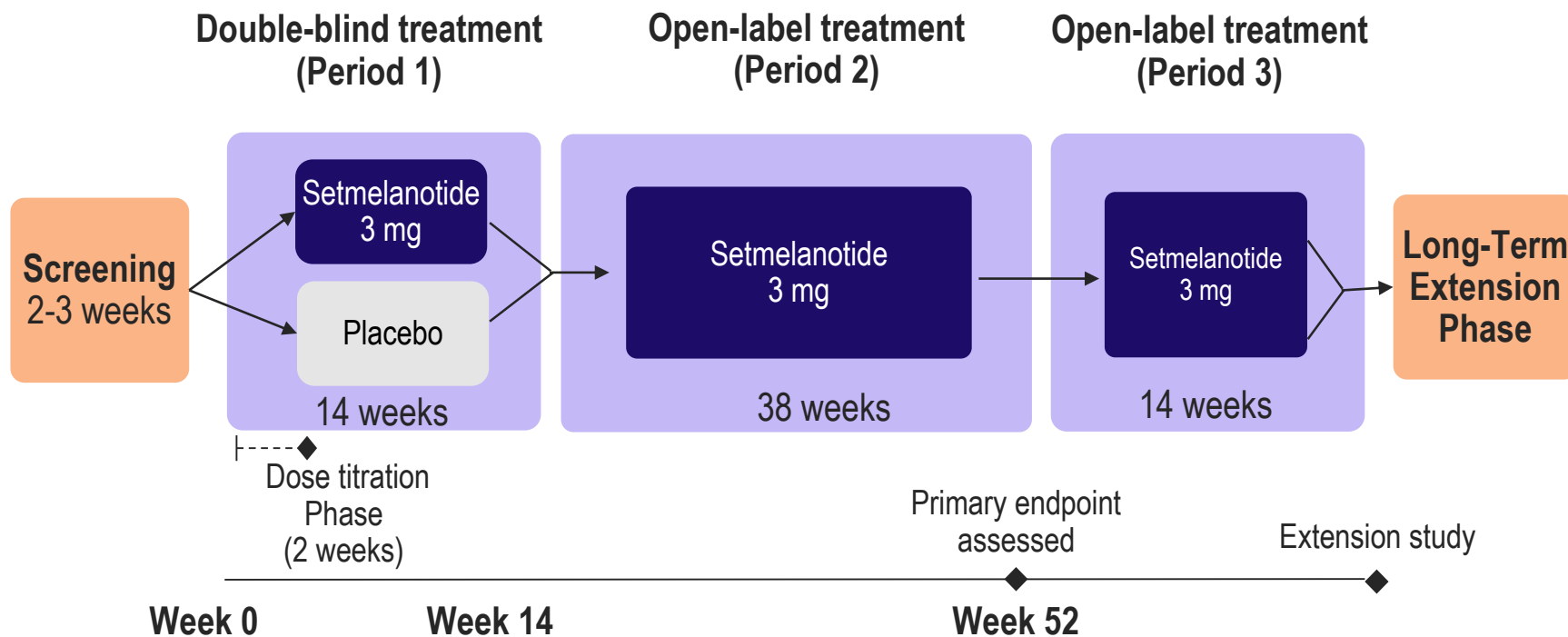
Rhythm Pipeline

Indication	PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3
SETMELANOTIDE				
POMC Deficiency Obesity	▶			
LEPR Deficiency Obesity	▶			
Bardet-Biedl Syndrome	▶			
Alström Syndrome	▶			
MC4R Pathway HET Obesity	▶			
POMC Epigenetic Disorders	▶			
RM-853 (GHRELIN O-ACYLTRANSFERASE INHIBITOR)				
Prader-Willi Syndrome	▶			

Rhythm is currently assessing opportunities to further evaluate setmelanotide in PWS and plans to pursue these in parallel with the development of RM-853.



Bardet Biedl & Alström Syndrome: Phase 3 Study Design



Primary Endpoint: Percentage of patients (12 years of age and older at Week 0) who have at least a 10% reduction in body weight at Week 52

Phase 3 Study Update

Protocol	<ul style="list-style-type: none">■ Final comments from FDA have been incorporated
Study enrollment milestones	<ul style="list-style-type: none">■ <u>First patient with BBS enrolled</u>
Study enrollment goals	<ul style="list-style-type: none">■ Enrollment <u>minimum</u>:<ul style="list-style-type: none">• 20 BBS patients• 6 Alström Syndrome patients
Centers of excellence	<ul style="list-style-type: none">■ Marshfield Clinic Health System<ul style="list-style-type: none">• Bob Haws, MD■ University College London Great Ormand Street Institute of Child Health<ul style="list-style-type: none">• Phil Beales, MD
Confirmed Countries	<ul style="list-style-type: none">■ United States, United Kingdom, Canada, Netherlands, Spain

Phase 2 BBS and Alström Results¹ Support Advancement to Phase 3

	Variant	Sex	Age, years	Treatment, weeks	Weight Change	Hunger Score Reduction
Patient 1	BBS1	Male	25	65	-26% (-37.7 kg)	44%
Patient 2	BBS2	Female	61	55	-15% (-14.5 kg)	86%
Patient 3	BBS10	Female	16	64	-24% (-29.1 kg)	N/A
Patient 4	BBS12	Female	17	50	-24% (-23.1 kg)	83%
Patient 6	BBS5	Female	16	47	-11.2% (-13.7 kg)	66%
Patient 7	BBS4	Female	14	41	-15.5% (-13.7 kg)	21%

- **6 of 9 BBS patients achieved clinically significant weight loss of >10% change from baseline**
 - Patients 6 and 7: Updated data (Jan. 2019) demonstrate longer-term weight loss and hunger score reductions
- **3 patients discontinued treatment**
 - Patient 5 (pediatric patient with BBS1 variant and type 1 diabetes) experienced 53.3% reduction in hunger and reduction in hemoglobin A1c (10.1% to 7.6%) before withdrawing
 - Two patients (one non-genetically confirmed) withdrew due to lack of weight loss

(1) Haws RM et al. Effect of the Melanocortin-4 Receptor Agonist Setmelanotide on Obesity and Hyperphagia in Individuals Affected by Bardet-Biedl Syndrome. ESPE 2018. Abstract RFC6.3. Updated data for pts. 6 & 7 announced by Rhythm in January 2019.

HET Patients in Other Subgroups Have More Variable Responses

Five patients ongoing¹:

	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
Patient 1	74	150 (330)	12.1 (26.6)	8.0%	-7	78.0%
Patient 2	66	147 (323)	7.5 (16.5)	5.1%	-1	20.0%
Patient 3	20	118 (259)	15.0 (33.0)	12.8%	-6	75.0%
Patient 4	16	106 (232)	7.2 (15.8)	6.9%	-7	70.0%
Patient 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 weeks³
- 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

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

Key Imperatives for Execution of HET Development Plan

**ADD TO POOL OF
HIGH-IMPACT LOF
VARIANTS**



Screen and classify potential new and uncharacterized variants:

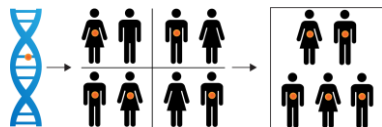
- Computational model for assessing variants
 - Biochemical analysis of variants in *POMC*, *PCSK1*, *LEPR*
- Rhythm estimates thousands of potential new and uncategorized HET variants in MC4R pathway genes*

**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

Scientific Support for HET Contribution to Obesity

Preclinical Data:

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

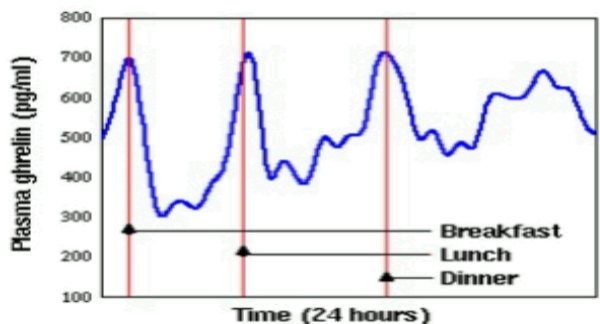
Clinical and Genetic Evidence:

- 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

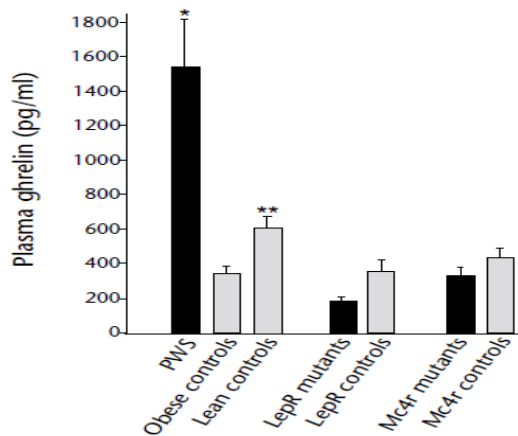
⁽¹⁾Penetrance: translation of a genetic variant to an obesity/hyperphagia phenotype, or symptomatology

RM-853: Potent, Orally Available GOAT Inhibitor for PWS

Ghrelin is tightly correlated with hunger signals throughout the day



People with PWS have higher ghrelin levels



- GOAT is key enzyme involved in producing active ghrelin
- Blocking GOAT results in:
 - Lower levels of active ghrelin, *and*
 - Increased levels of DAG, a ghrelin precursor believed to have independent beneficial effects
- In preclinical studies with high fat-fed mice, RM-853 prevented body weight gain and reduced fat mass, with favorable PK, PD and safety profile
- Development plan complements and expands ongoing efforts
 - RM-853 IND filing expected Q1 2020
 - Still planning to evaluate setmelanotide in PWS, in parallel with development of RM-853
 - Future Phase 2 trial of setmelanotide may evaluate longer durations of treatment, higher doses, younger patients and operational limitations of prior trial
 - Given setmelanotide and RM-853's distinct mechanisms of action, will explore opportunities to evaluate in combination, as there may be complementary effects

Cash expected to be sufficient to Fund Operations into 2H '20

SHARES OUTSTANDING
as of 12/31/2018

34,410,725
(basic share count)
2,616,530
(options granted)

**CASH, CASH EQUIVALENTS AND
SHORT TERM INVESTMENTS**
as of 12/31/2018

\$ 252.1 million

Raised \$163M in net proceeds in June 2018 follow-on offering




rhythm