Rhythm Pharmaceuticals:

Targeting upstream MC4R pathway defects to transform the care of genetic obesity

Company Presentation - January 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 two additional MC4R-pathway disorders**:
  - Preliminary efficacy demonstrated in heterozygous and epigenetic disorders of MC4R pathway

Multiple Avenues to Accelerate Growth

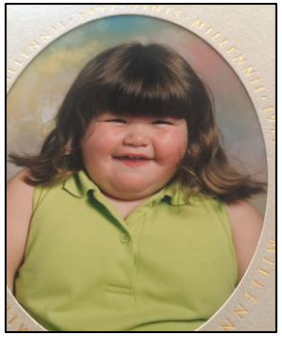
- **GO-ID Genotyping Study and TEMPO Registry**: Enable clinical study enrollment, patient identification and exploration of new genetic variants tied to MC4R loss of function
- **Rhythm Basket Study:** Facilitates rapid enrollment and exploration of setmelanotide's potential in patients with new genetic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

Genetic Disorders of Obesity Impact Every Aspect of Daily Life

Meet Katy: Living with an MC4R Pathway Disorder

"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-depresseants

Numbness and agonizing back pain

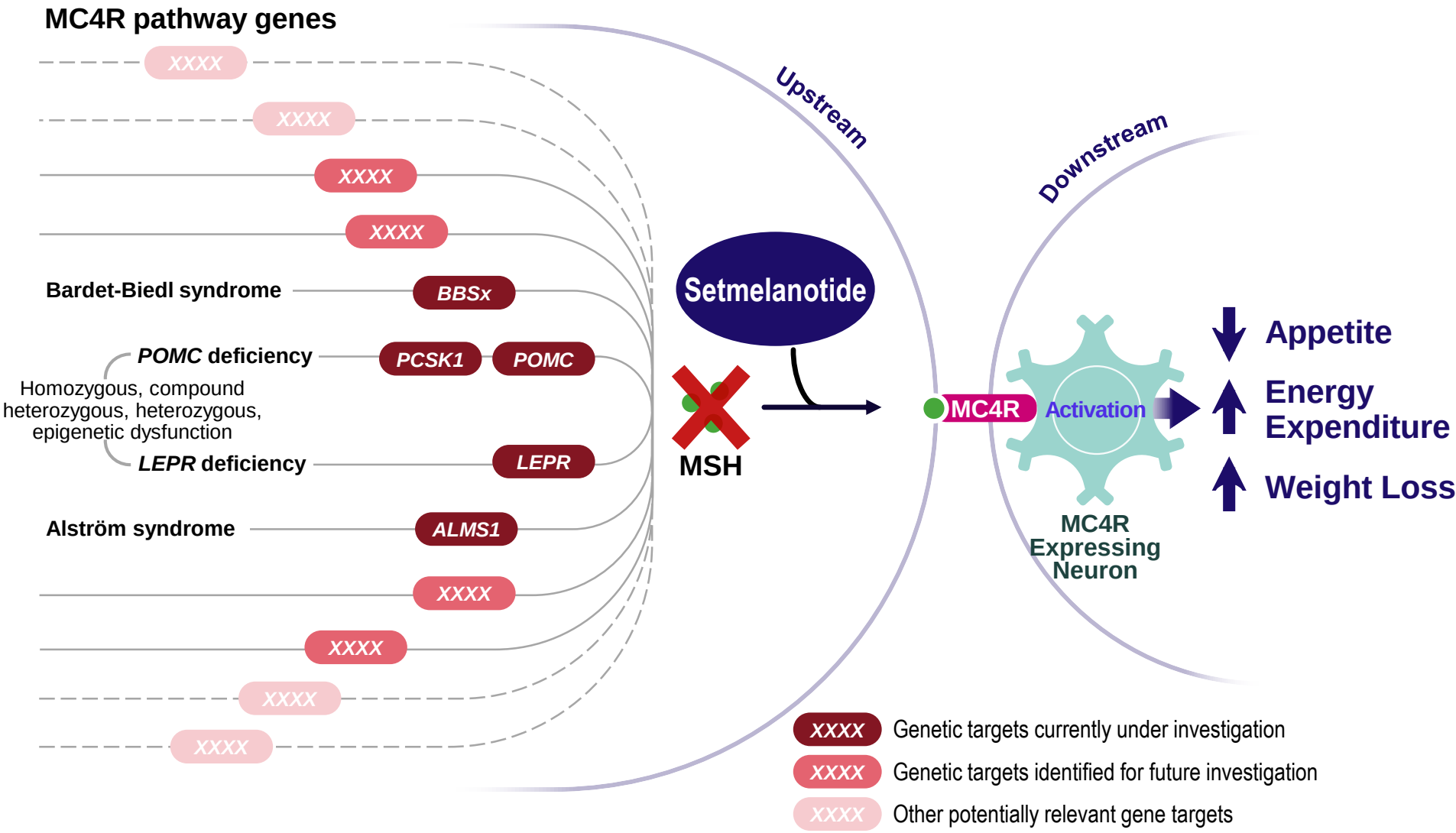
Abnormal pubertal development

23 YEARS (CURRENT):

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

Genetic Defects in the MC4R Pathway Cause Insatiable Hunger and Obesity

Setmelanotide Rescues the Impaired MC4R Pathway



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

Overview of Setmelanotide

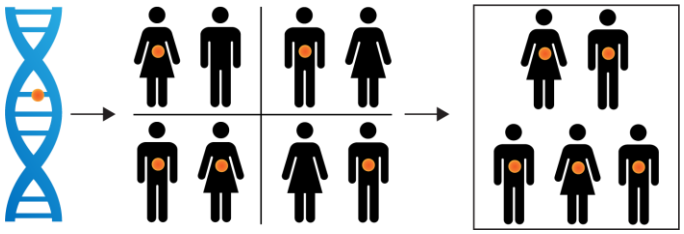
Potent first-in-class MC4R agonist

- *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
- Previous clinical trials with approximately 300 obese patients 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

* NOAEL: No-observed-effect-level

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 proof-of-concept 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, proof of concept extension studies

Indications enrolled in Phase 2:

- POC Achieved, Phase 3 initiated:
  POMC, LEPR, BBS & Alström Syndrome
- Pre-POC, Phase 2 ongoing:
  MC4R pathway heterozygous obesity, POMC epigenetic obesity
- New Indications: Additional genetic targets upstream of MC4 receptor

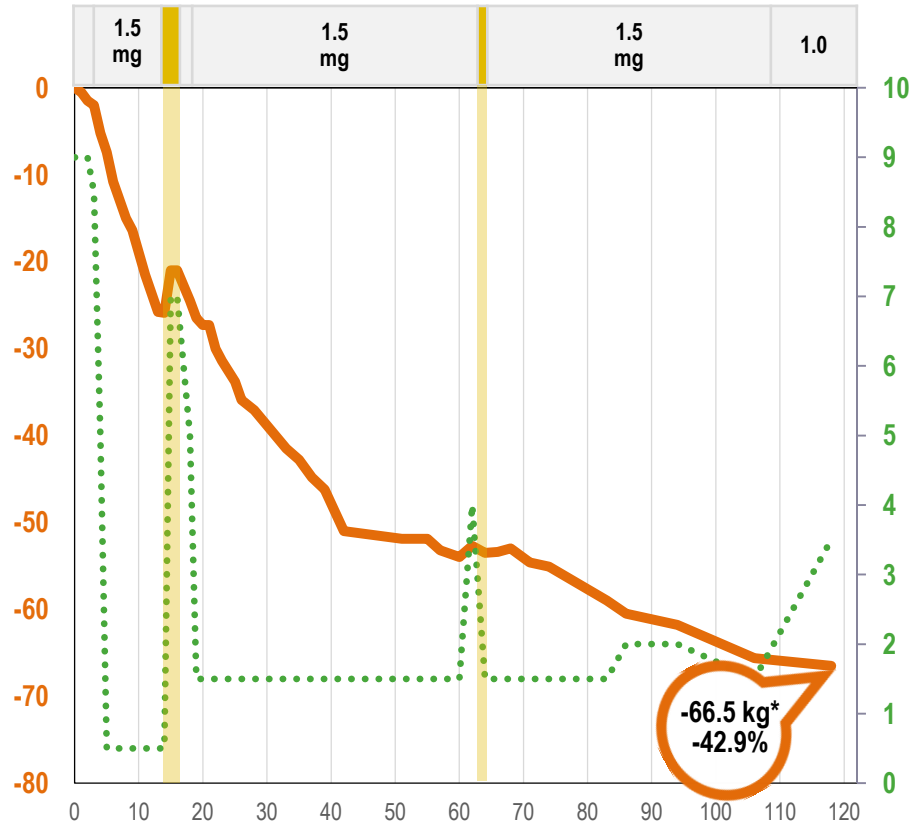
Close coordination with GO-ID Genotyping Study:

- Patients with genetic mutations identified from GO-ID study eligible to enroll in basket study

POMC and LEPR Phase 2 Studies: Patients #1

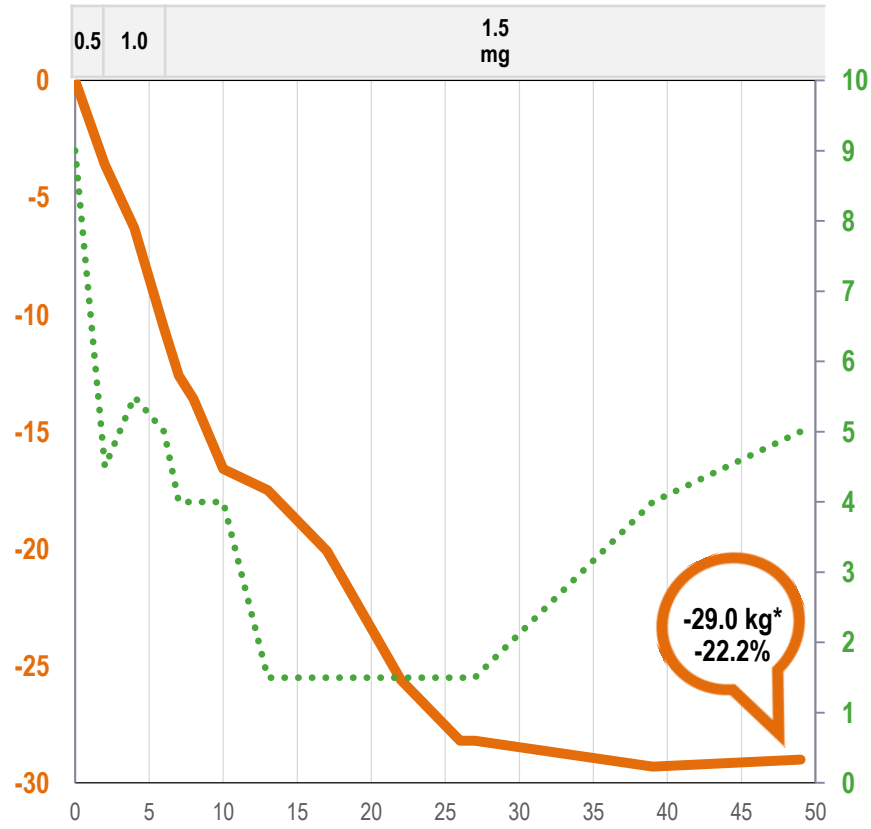
POMC Patient #1[1]

20 yr old female
Starting Weight = 155.0 kg
Starting BMI = 49.8 kg/m^2



LEPR Patient #1[2]

23 yr old male – LEPR Mutation
Starting Weight = 130.6 kg
Starting BMI = 39.9 kg/m^2



Weight Change (kg)

Hunger Score (0-10 points)

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

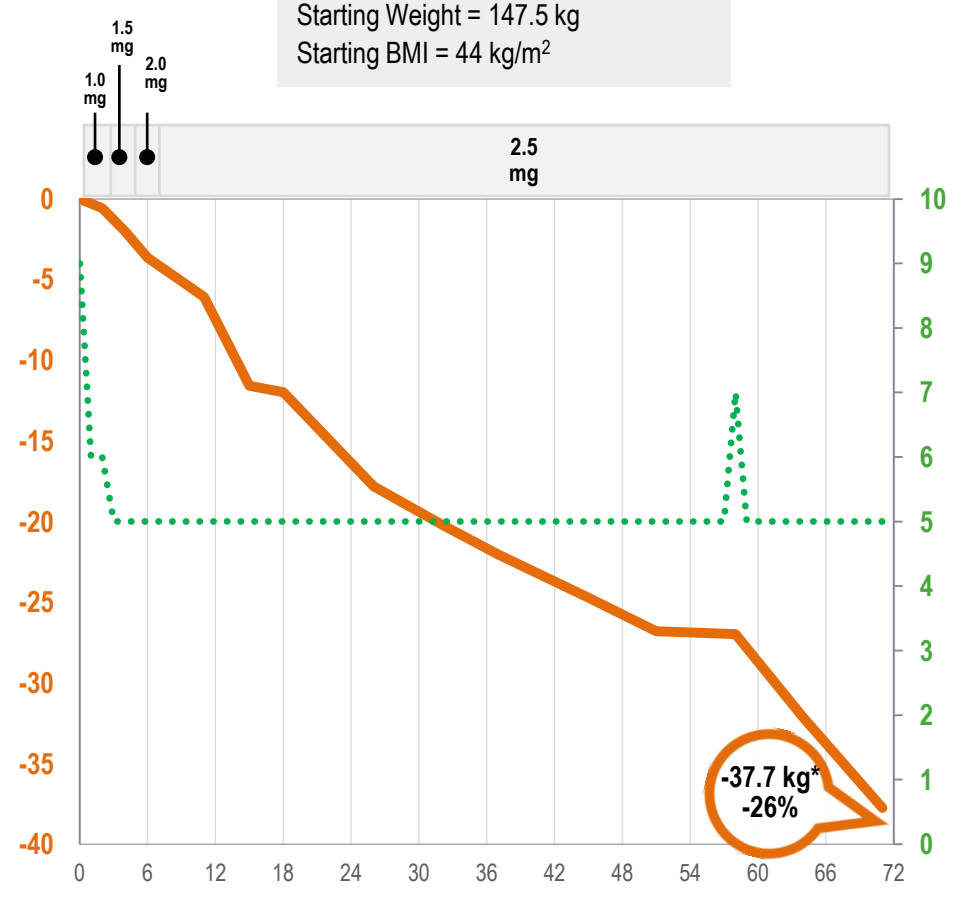
(1) Kühnen, et. al, Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. *N Engl J Med*. July 2016 . *Yellow vertical bars represent intervals with dose withdrawal or modifications*

(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

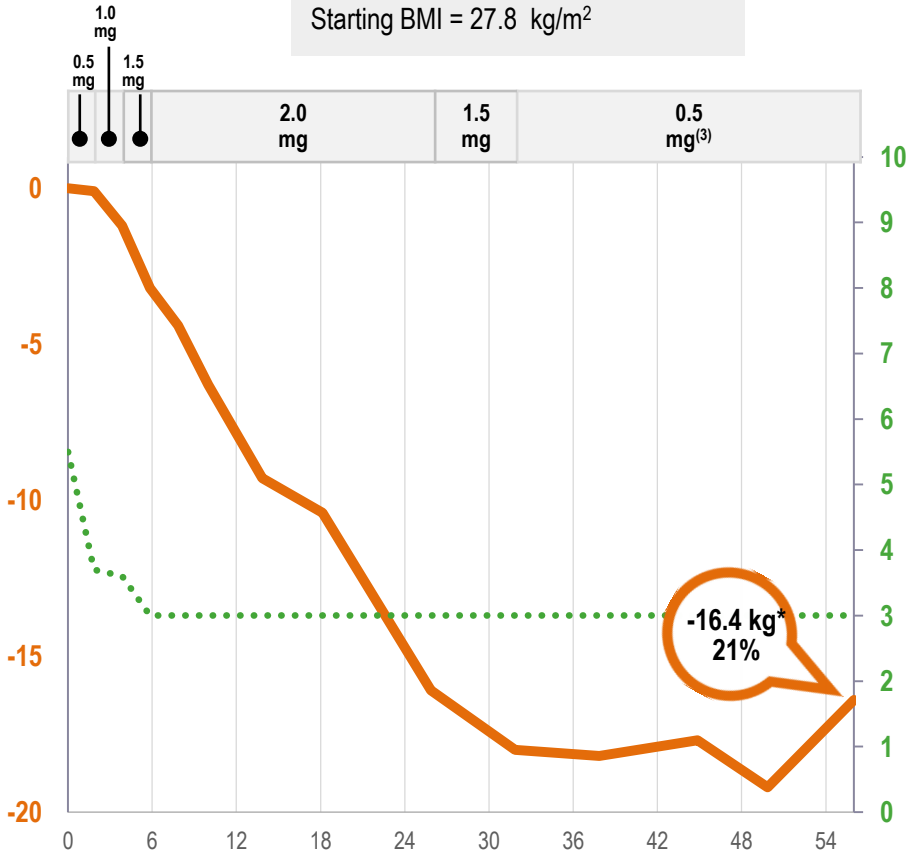
BBS Patient #1[1]

25 yr old male - BBS1 Mutation
Starting Weight = 147.5 kg
Starting BMI = 44 kg/m^2



AS Patient #1[2]

12 yr old male
Starting Weight = 78.6 kg
Starting BMI = 27.8 kg/m^2



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

Phase 2 BBS and Alström Results[1] 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.

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Additional Indications in Phase 2 Basket Study

Heterozygous and Epigenetic Obesity Disorders

- Focus on most debilitated patients
  - ***MC4R pathway heterozygous deficiency:*** one loss of function allele
  - ***POMC epigenetic disorders:*** disease caused by DNA modifications that can change gene expression without altering DNA
- Initial preliminary data as of June 2018:
  - ***MC4R pathway heterozygous deficiency:*** positive initial weight and hunger responses in two evaluable patients
  - ***POMC epigenetic disorders:*** positive initial weight and hunger response in one evaluable epigenetic patient
- Updated interim data expected in *first quarter of 2019*
- Plan to continue enrolling additional patients, in order to better identify those likely to benefit from setmelanotide and inform next steps

Setmelanotide Has Been Generally Well-Tolerated

Safety and Tolerability

Setmelanotide has been evaluated in over 300 obese subjects

- 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

Ongoing Pivotal Phase 3 Trials in POMC, LEPR and BBS/Alström

All pivotal trials share a common design:

- Patients aged ≥ 6
- ~1-year trial duration, with long-term extension
- Dosage: Daily subcutaneous injection
- 1º endpoint: categorical analysis of responders[(1)]
- Key 2º 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.

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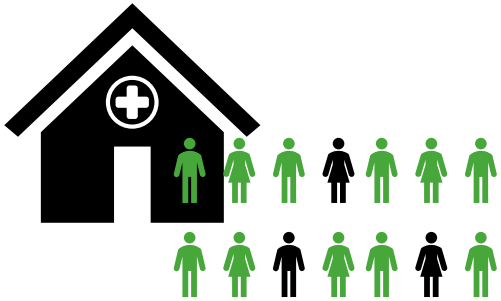
Building a Community for the Treatment of Rare Genetic Disorders of Obesity

Epidemiology Suggests Significant Market Opportunity

POMC & LEPR Deficiency Obesity:
Non-Syndromic Disorders

Patients diagnosed after genetic screening.

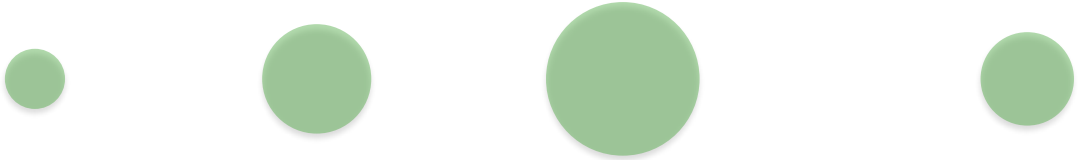
BBS and Alström Syndrome:
Syndromic Disorders



Patients often known to the medical system.
E.g: Over 450 BBS patients enrolled in CRIBBS registry

CLINICAL EPIDEMIOLOGY

Up to 5,000 patients in U.S.(1)



POMC: 100-500* **LEPR:** 500-2,000* **BBS:** 1,500-2,500* **Alström:** 500-1,000 (worldwide)

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) 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. JCEM citation

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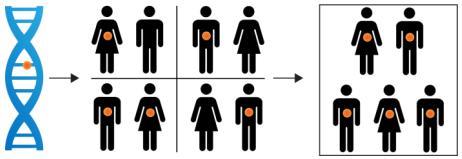
Rhythm-Sponsored Initiatives to Expand Addressable Patient Population

GO ID genotyping

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



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

TEMPO

TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

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

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GO-ID Genotyping Initiative

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

- Genotyping study of individuals with obesity ≥2 years of age
- Recruitment via outreach to HCPs caring for patients with severe obesity
- Expected enrollment of ≥ 9,000 patients from more than 140 centers worldwide
- Genotyping panel includes over 100 genes associated with genetic obesity
- Individuals identified with mutations in MC4R pathway genes may be enroll in future clinical trials, observational trials, or TEMPO registry
- Goal: Increase the frequency of genetic testing and shift practice patterns among treating physicians

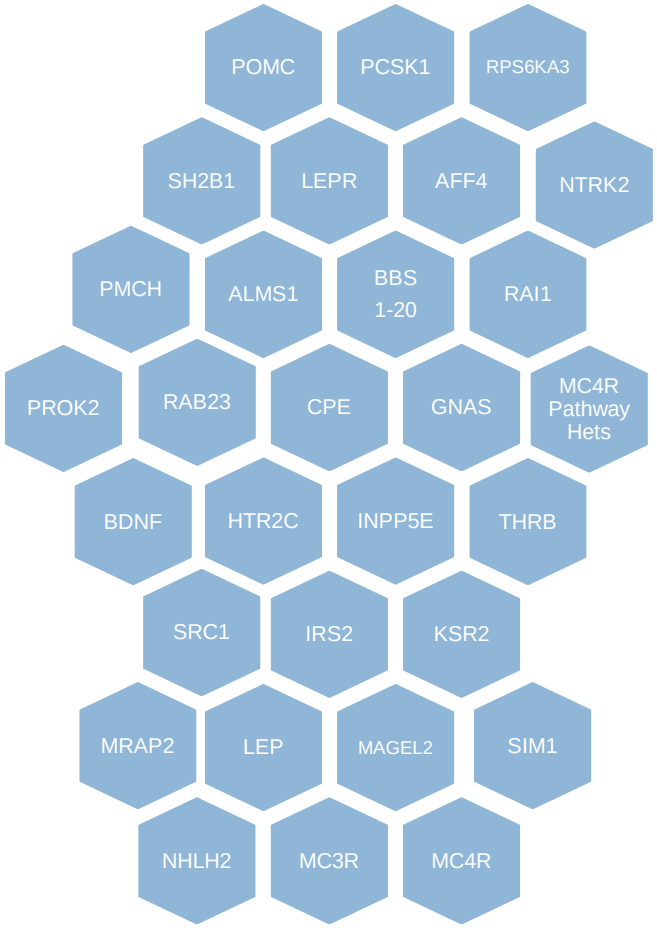
Community Building Through the TEMPO Registry

TEMPO

TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

- Commitment to understanding the ongoing impact and burden of disease on patients and their caregivers
  - Facilitates enhanced understanding of these conditions in the medical community
  - Builds upon ongoing collaborations with existing patient registries (e.g., CRIBBS for BBS)
- Target enrollment of ~1,000 patients
- Genetic screening through GO-ID
- Potential enrollment in Basket study

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



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Rhythm Achieved Key Milestones in 2018

- ✓ Completed enrollment in POMC & LEPR Phase 3 trials
- ✓ Announced updated positive Phase 2 BBS & Alström results
- ✓ Breakthrough Therapy and EMA Prime designation expanded to include BBS & Alström
- ✓ Enrolled first patient in pivotal Phase 3 study in BBS & Alström
- ✓ Advanced Phase 2 trials of MC4R pathway heterozygous deficiency and epigenetic disorders
- ✓ Launched TEMPO registry to gather information about people affected by rare genetic disorders of obesity
- ✓ In-licensed RM-853, potential therapy for Prader-Willi
- ✓ Completed follow-on offering, extending expected cash runway to second-half of 2020

Rhythm Expects Significant Growth in 2019 and 2020

1Q19	Updated interim data for MC4R pathway heterozygous and epigenetic obesity disorders
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

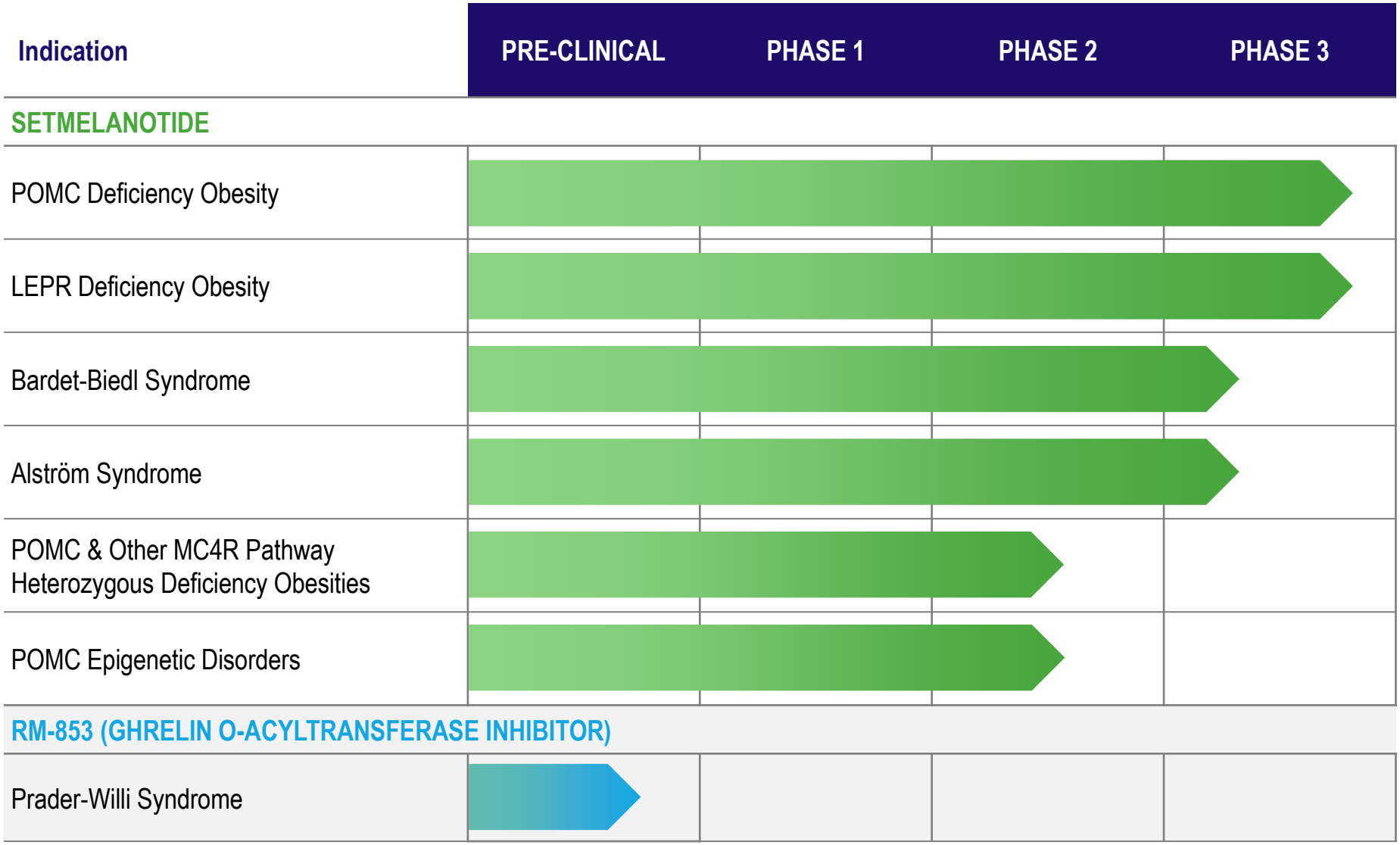
Living with the Insatiable Hunger and Obesity that Characterize BBS

"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

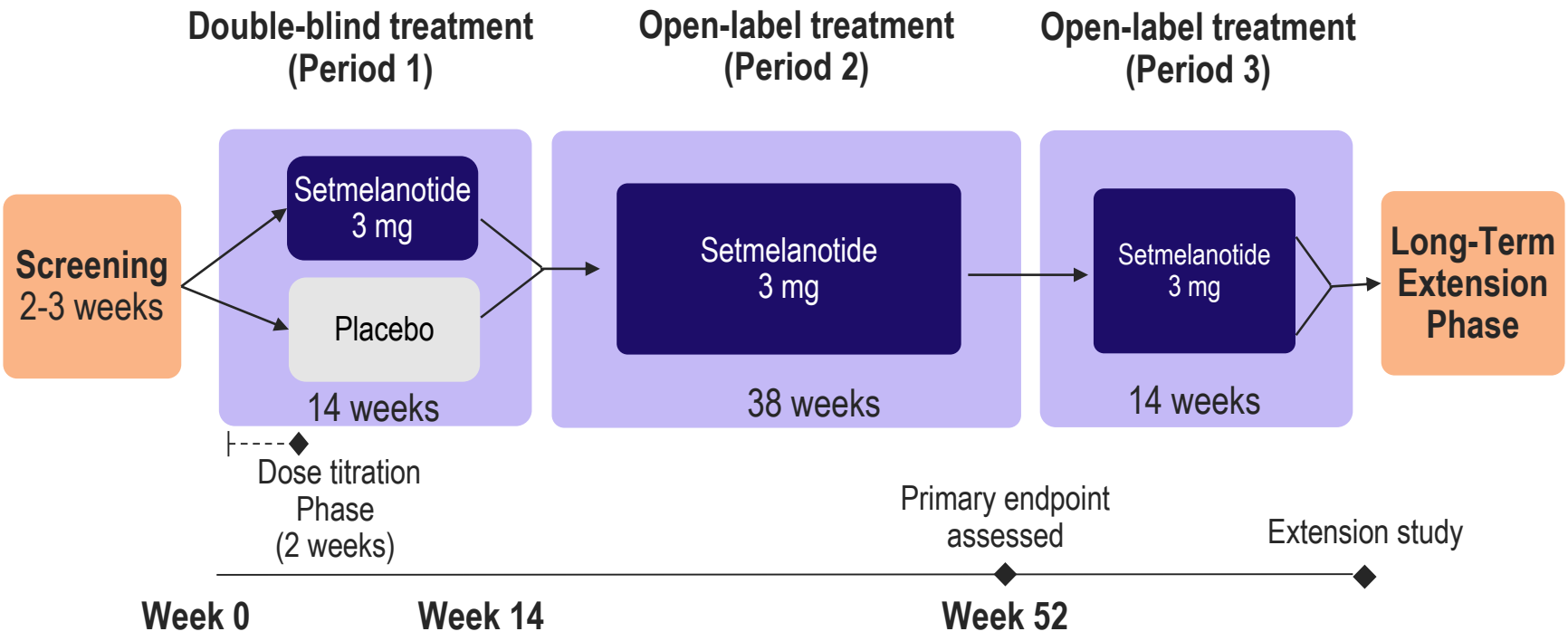
Appendix

Rhythm Pipeline



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



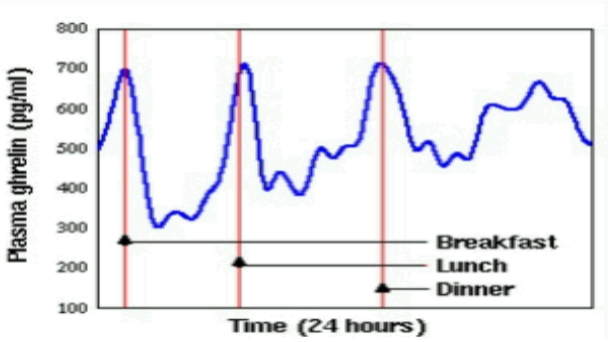
Primary Endpoint: Percentage of patients (12 years of age and older at Week 0) who have at least a 10% reduction in body weight at Week 52

Phase 3 Study Update

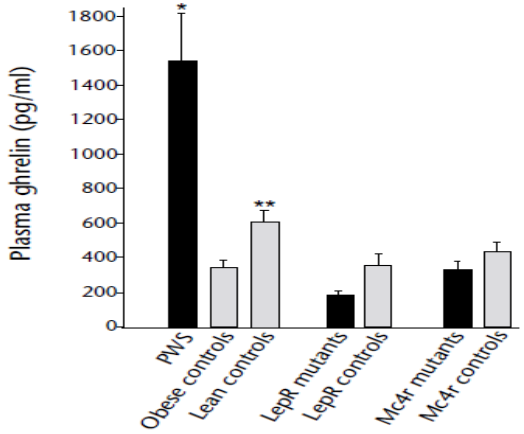
Protocol	▪ Final comments from FDA have been incorporated
Study enrollment milestones	▪ **First patient with BBS enrolled**
Study enrollment goals	▪ Enrollment **minimum**: • 20 BBS patients • 6 Alström Syndrome patients
Centers of excellence	▪ Marshfield Clinic Health System • Bob Haws, MD ▪ University College London Great Ormand Street Institute of Child Health • Phil Beales, MD
Confirmed Countries	▪ United States, United Kingdom, Canada, Netherlands, Spain

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 9/30/2018*	CASH, CASH EQUIVALENTS AND SHORT TERM INVESTMENTS *as of 9/30/2018*
34,382,525 (basic) 36,857,315 million (fully-diluted)	$ 272.4 million

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

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