UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **January 10, 2020**

RHYTHM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-38223**	**46-2159271**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification Number)

222 Berkeley Street
12th Floor
Boston, MA 02116
(Address of principal executive offices, including Zip Code)

Registrant's telephone number, including area code: **(857) 264-4280**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	RYTM	The Nasdaq Stock Market LLC (Nasdaq Global Market)

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter). Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01 Regulation FD Disclosure.

Rhythm Pharmaceuticals, Inc. (the "Company") will discuss information in the attached presentation during meetings with investors in San Francisco, California beginning Monday, January 13, 2020 through Thursday, January 16, 2020 to coincide with the 38th Annual J.P. Morgan Healthcare Conference. A copy of the materials is furnished as Exhibit 99.1 to this Current Report on Form 8-K. The Company undertakes no obligation to update, supplement or amend the materials attached hereto.

The information contained in this Item 7.01 and in the accompanying Exhibit 99.1 shall not be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing, unless expressly incorporated by specific reference to such filing. The information in this Item 7.01 and the exhibit hereto shall not be deemed to be "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or otherwise subject to the liabilities of that section or Sections 11 and 12(a)(2) of the Securities Act of 1933, as amended.

Item 9.01 Financial Statements and Exhibits.

Exhibit No.	Description
99.1	Company Presentation dated January 2020

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

RHYTHM PHARMACEUTICALS, INC.

Date: January 10, 2020

By: /s/ Hunter Smith
Hunter Smith
Chief Financial Officer

Rhythm Pharmaceuticals

Targeting MC4R pathway and transforming the care of patients with rare genetic disorders of obesity

January 2020

Rhythm PHARMACEUTICALS

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 2020, anticipated timing for enrollment, our sufficiency of cash, design and completion of clinical trials, the timing for filing of an NDA, MAA and other similar filings, the release of results of clinical trials, and expectations regarding Rhythm's financial position, strategy, prospects and plans. Statements using words 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 impact of management departures and transitions, 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.

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):

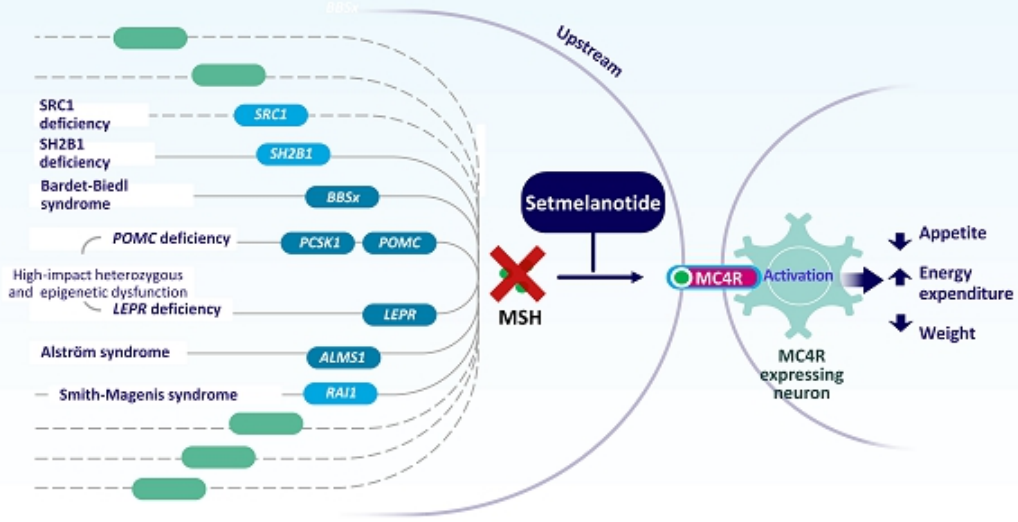
Sleep apnea; some cardiac issues; insulin resistance. Cracked and bleeding skin

Rhythm's Focus in 2020 is Expanding the Opportunity for Setmelanotide in Rare Genetic Disorders of Obesity

1	Secure **FDA approval** for POMC or LEPR deficiency obesities
2	Deliver on the potential of setmelanotide to patients with **Bardet-Biedl and Alström syndromes** and advance disease understanding ahead of **pivotal Phase 3 data**
3	Establish proof-of-concept in **new indications** currently in **Phase 2 Basket Study**
4	Drive disease understanding through **genetic sequencing** and community building

Setmelanotide has Potential to Address Multiple MC4R Pathway Disorders

Addresses MC4R pathway by replacing MSH stimulating hormone



Genetic targets in Phase 3 | Genetic targets added to Phase 2 Basket study Sept, 2019 | Other potentially relevant gene targets

Rhythm PHARMACEUTICALS

MC4R Pathway Disorders: Genetic or Syndromic Diagnosis

Genetically-identified

Patients diagnosed after genetic screening

- **POMC** deficiency obesity ~100-500 U.S. patients*
- **LEPR** deficiency obesity ~500-2,000 U.S. patients*
- **HETs** POMC and LEPR heterozygous obesity ~20,000 U.S. patients*
- **SRC1** deficiency obesity ~23,000 U.S. patients*
- **SH2B1** deficiency obesity ~24,000 U.S. patients*
- **MC4R** deficiency obesity** ~10,000 U.S. patients*

Clinically-identifiable, syndromic

Patients often known to the medical system

- **Bardet-Biedl** syndrome ~2,500 U.S. patients*
- **Alström** syndrome ~500 U.S. patients*
- **Smith-Magenis** syndrome ~2,400 U.S. patients*

Pivotal Indications
Phase 2 indications

*Based on company estimates; Images are for illustrative purposes only and not intended to imply or suggest actual prevalence estimates or patient identification yields.
** Estimated prevalence of U.S. patients with addressable variants of the MC4R.

POMC and LEPR Deficiency Obesities

Secure FDA approval for
POMC or LEPR deficiency obesities

Setmelanotide Met all Primary and Key Secondary Endpoints in Phase 3 Trials for POMC and LEPR

Demonstrated statistically significant and clinically meaningful reductions of weight and hunger

POMC Phase 3 Topline*			
80% p<0.0001	**-25.4%** p<0.0001	**-27.8%** p=0.0005	**31.9kg 70.2lbs**
>10% weight loss	mean weight reduction	mean hunger score reduction	mean weight loss in 1 year

LEPR Phase 3 Topline*			
45.5% p<0.0001	**-12.5%** p<0.0001	**-41.9%** p<0.0001	**16.7kg 36.8lbs**
>10% weight loss	mean weight reduction	mean hunger score reduction	mean weight loss in 1 year

Substantial, consistent **increases in weight and hunger during placebo withdrawal period**

18 of 19 eligible participants **continuing on setmelanotide** in the extension study

NDA submission expected by the end of **1Q 2020**

MAA submission expected in **2Q 2020**

*Data announced by Rhythm in August 2019 and presented at The Obesity Society annual meeting during ObesityWeek in November 2019.

Bardet-Biedl & Alström Syndromes

Deliver on the potential of setmelanotide to patients with Bardet-Biedl and Alström syndromes and advance disease understanding ahead of pivotal Phase 3 data

Strong Phase 2 Data in BBS Shows Substantial Weight Loss and Hunger Control at ~Two Years, Supporting Advancement into Phase 3

Gene	Treatment, weeks	Weight Change from Baseline	Hunger Score Change from Baseline
BBS1	123	**-36.7%**	-33%
BBS2	119	**-15%**	-71%
BBS10	121	**-28%**	-100%*
BBS12	108	**-25%**	67%
BBS5	83	**-10.8%**	-38%
BBS4	73	**-17.9%**	-14%**

Data announced by Rhythm in September 2019.

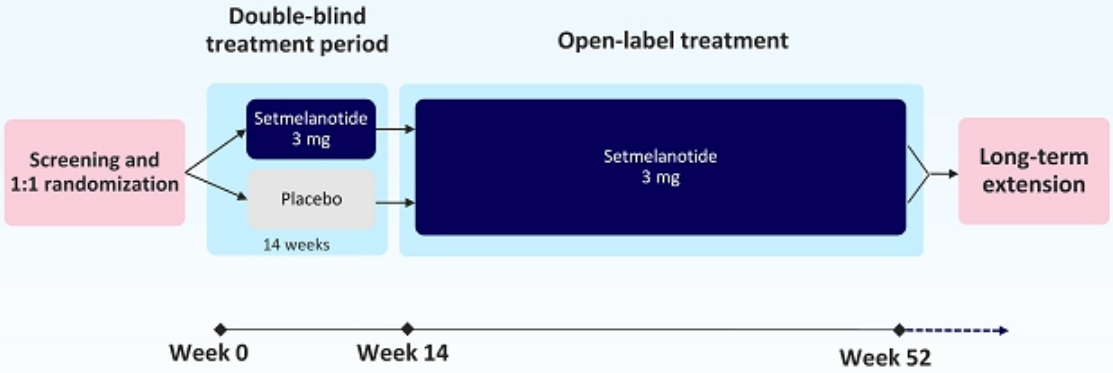
- Six of nine patients responded - all maintain weight loss at ~two years
- Mean percent weight reduction of responders = **22.2%** after ~two years on therapy
- Three patients discontinued treatment†
- Seven of nine patients enrolled in long-term extension study

*Pt. has cognitive impairment, so Food Problem Diary (FPD) score maintained by caregiver; **Pt. did not have baseline hunger measure. The first score was a 7, which was not recorded until after the patient had received treatment. Current score is a 6.; † 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. Patient subsequently entered long-term extension study; Two patients (one non-genetically confirmed) withdrew due to lack of weight loss.

Bardet Biedl & Alström Syndromes Phase 3 Trial: Enrollment in Pivotal Cohort Complete

Pivotal cohort:
- 32 BBS patients
- 6 Alström syndrome patients

Enrolling patients in supplemental cohort



Primary Endpoint: Proportion of patients (>12 years of age) who have at least a 10% reduction in body weight.

Partnering with the Patient Community to Build Awareness and Disease Understanding

Ongoing relationships with patient advocacy groups to drive awareness, disease understanding and build support for regulatory pathway

- Bardet-Biedl Syndrome Foundation
- BBS Family Foundation
- BBS UK
- Alström Syndrome UK
- Alström Syndrome International (ASI)

Existing patient cohorts allow for better understanding of the clinical course of the disease

- CRIBBS registry includes 550 patients as of December 2019
- ASI maintains country-level patient records
- Large cohorts of BBS patients known in France, UK, Germany and more

CMO Murray Stewart at the 2019 9th Alström Syndrome International Family Conference and Scientific Symposium

Engaging with Physicians to Advance Disease Understanding for BBS and Alström Syndrome

Rhythm **field medical teams** have engaged with **more than 275 physicians** in the U.S. and EU who are involved in the diagnosis and management of BBS and Alström syndrome.

500 – 870*

Identified patients in the **United States** who are being treated for BBS or Alström syndrome

1,200 – 1,725*

Identified patients in **Europe** who are being treated for BBS or Alström syndrome

Rhythm GOLD Academy: 20 faculty members have trained **more than 750 providers** on rare genetic disorders of obesity facilitating management of severe obesity and hunger.

*Assessment of numbers of patients relies on HCP recall, which may result in over or under reporting

Rhythm Engine & Basket Study

Establish proof-of-concept in new indications

Rhythm Engine is the Foundation of Future Growth through Patient Finding and Clinical Development

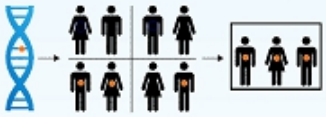
GO ID genotyping

UNCOVERING RARE OBESITY
Sponsored genetic testing program

Biobanks

101-gene panel

Phase 2 Basket Study

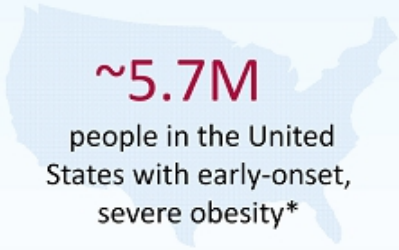


Six indications

TEMPO
TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

Approximately 5.7M People in the U.S. Have Severe, Early-onset Obesity

Rhythm is focused on patients who have rare genetic variants in the MC4R pathway



~5.7M
people in the United States with early-onset, severe obesity*

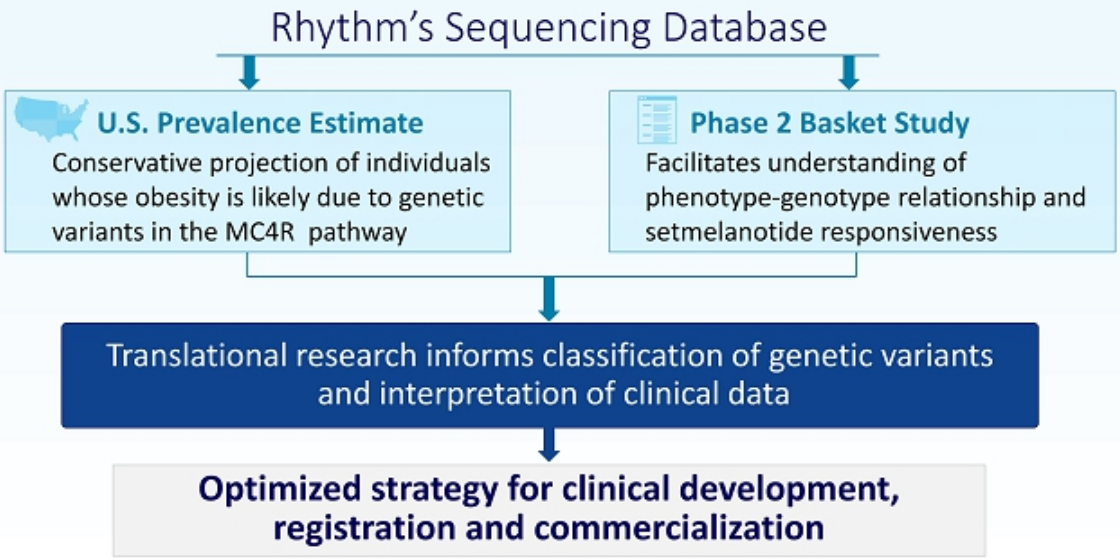
Rhythm has sequenced
13,567**
individuals with severe obesity

1,584 or 11.7%
of these individuals have rare variants making them potentially eligible for
Rhythm's Phase 2 Basket Study

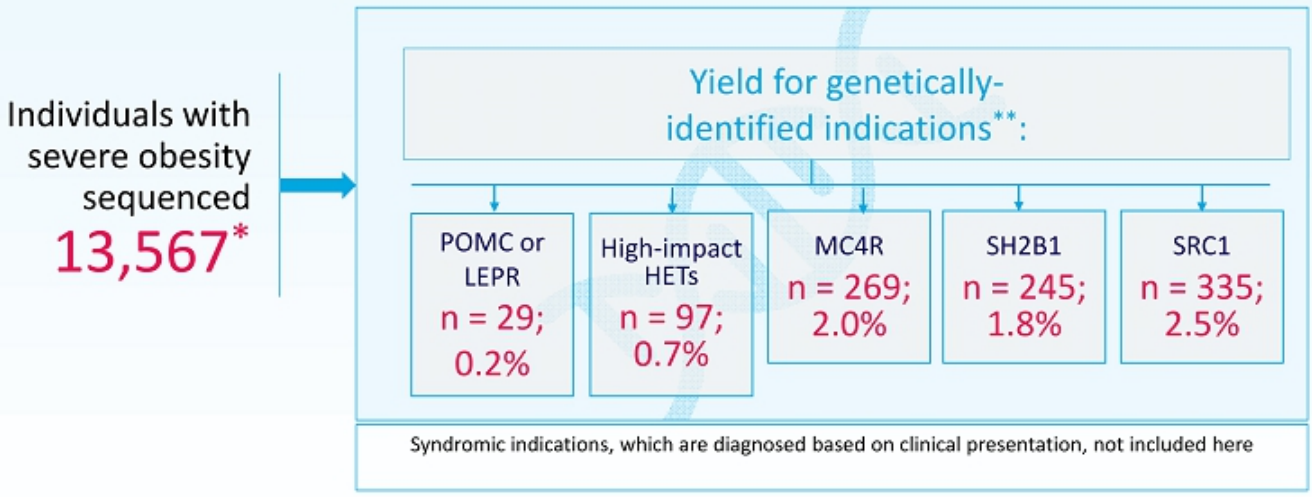
Rhythm is initially studying 10 rare genetic disorders of obesity, estimated to affect upwards of 85,000 people in the United States

*These calculations assume a U.S. population of 327 million, of which 1.7% have early-onset, severe obesity (Hales et al in Jama – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016);
** As of June 2019; sequencing efforts are ongoing.

Rhythm's Approach Enables Deep Understanding of Rare Genetic Disorders of Obesity and Optimizes Registration/Commercial Strategy



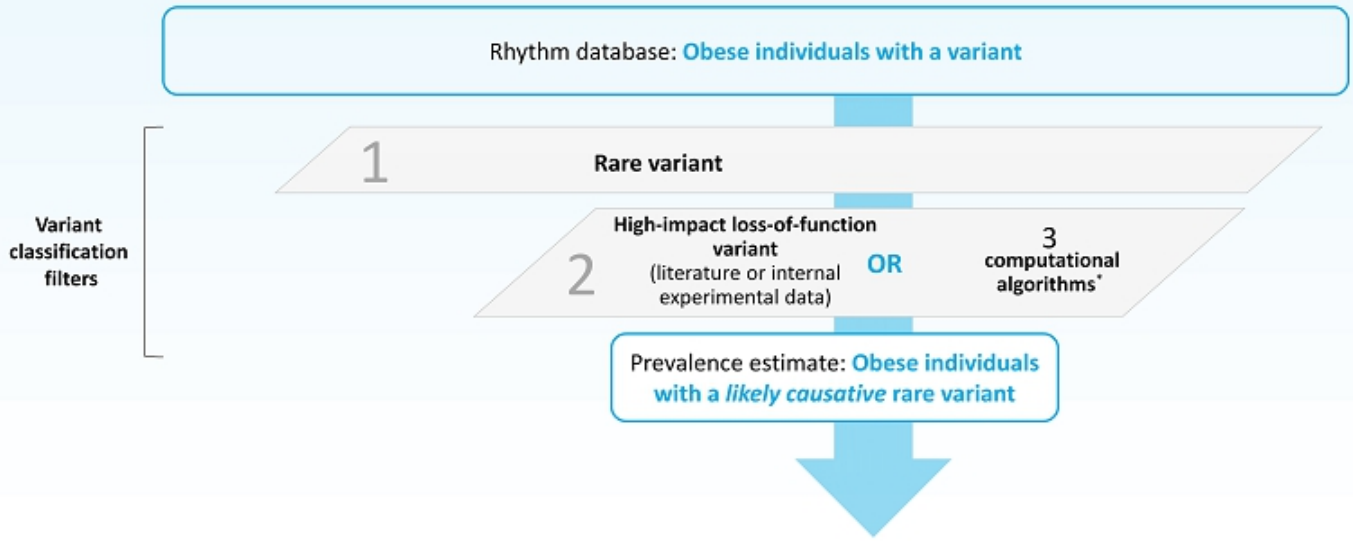
Sequencing Yield for Genetically-identified Indications Points to Significant Opportunity



* As of June 30, 2019; sequencing efforts are ongoing.
**Basket yield includes 683 individuals with other variants; some patients have more than one variant.

Translating Rhythm Sequencing Data to U.S. Prevalence Estimates

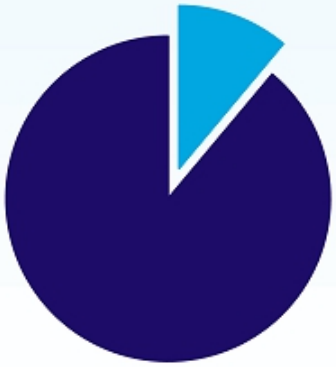
Most stringent criteria for variant classification to establish baseline estimates of US prevalence



*PolyPhen: Adzhubei IA, et al. Nat Methods 7(4):248-249 (2010); SIFT: Vaser R, et al. Nat Protocol 4:1073-1081 (2009); Mutation Taster: Schwarz JM, et al. Nat. Methods 11(4):361-362 (2014)

Stratifying Patients Based on Loss of Function (LOF) Variant – HET Example

U.S. prevalence approximately **1 million** for individuals with heterozygous POMC or LEPR variants, and **>20,000** high-impact LOF patients in U.S.*



graph not drawn to scale

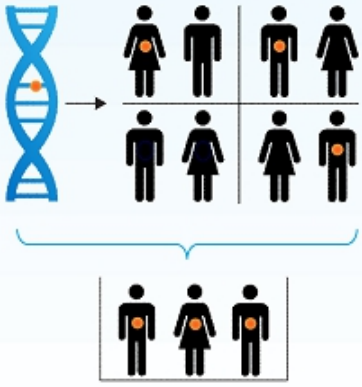
- Patients present with severe, early-onset obesity and hyperphagia
- Basket Study cohorts stratified by impact of variant on pathway function
- High-impact LOF variants expected to be most responsive to setmelanotide
- Other cohorts will clarify potential setmelanotide treatable populations
- Data update expected in 2020

* 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)

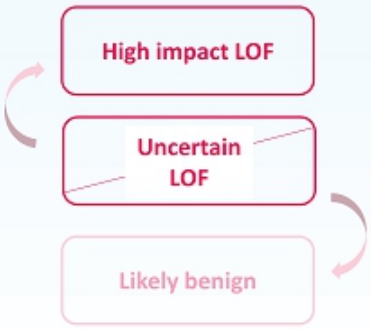
Basket Study Key to Proof of Concept, Advancing Indications to Phase 3

Enrolling Multiple Cohorts in Each Indication

- Improve understanding of interplay of genetic variation and MC4R pathway function
- Aim for seamless integration with sequencing efforts
- Rapid proof-of-concept in new indications
- Delivers pivotal indications into phase 3 trials

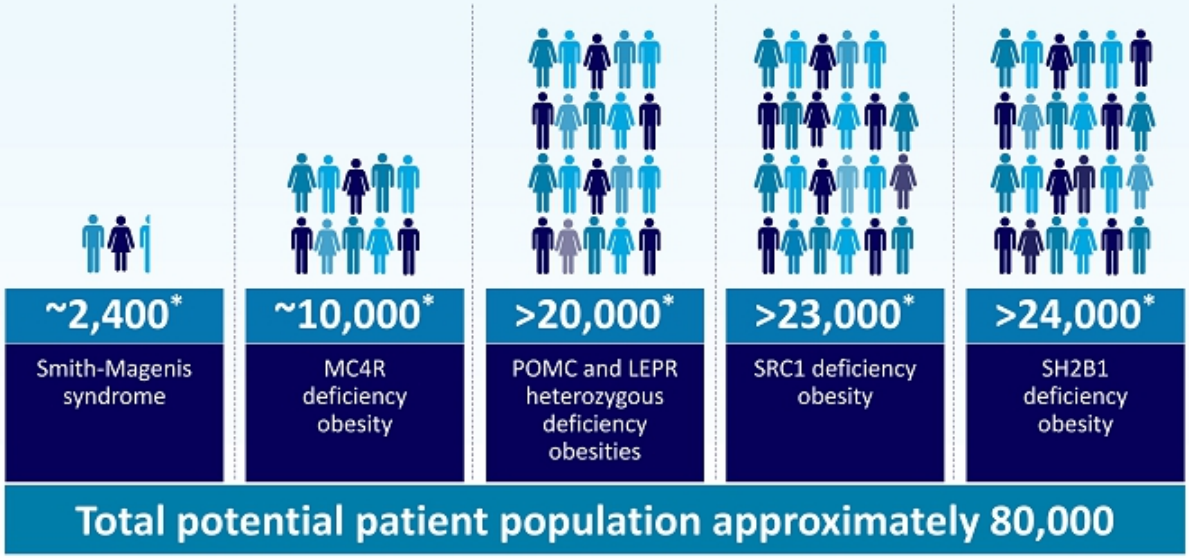


Cohort stratification



Images are for illustrative purposes only and not intended to imply or suggest actual prevalence estimates or patient identification yields.

Phase 2 Basket Study Indications Have Significant Patient Populations



* Company estimates calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity (Hales et al in JAMA – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016); Allele frequency based on Rhythm genetic sequencing (June 2019)

Setmelanotide Generally Well-tolerated Across Development Program

Setmelanotide has been evaluated in more than 400 patients with obesity, with individual patient treatment duration now exceeding four years

Setmelanotide has been generally well-tolerated

Most AEs are mild:

- Mild injection site reactions
- Darkening of skin (tanning) and skin lesions, mediated by the closely related MC1 receptor (the natural "tanning" receptor)
- Nausea/vomiting: mild and early in treatment

Discontinuations are rare; no increase in CV parameters

- In POMC and LEPR pivotal trials, setmelanotide was not associated with significant changes to blood pressure or heart rate

Patient experience with setmelanotide*

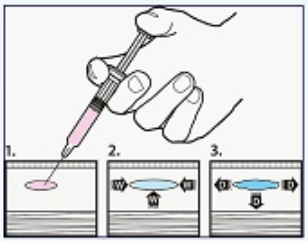
Duration on therapy	# of patients
< 1 year	**> 420**
> 1 year	**42**
> 2 years	**16**
> 3 years	**3**
> 4 years	**2**

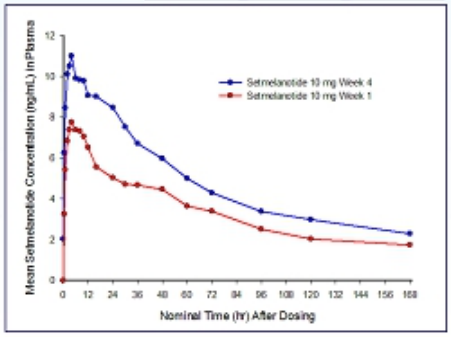
* Estimates as of November 2019, inclusive of patients likely randomized to treatment in certain double-blinded clinical studies.

Setmelanotide Once-weekly Subcutaneous Injection in Development

Update expected in 2020 on clinical development

- Setmelanotide delivered through gel-like depot with slow diffusion
  - Mean pharmacokinetic half-life of 123 hours
  - Formulation intended to be more patient-friendly
- Currently being evaluated in more than 70 healthy obese volunteers
  - Trial includes daily cohort receiving doses higher than those used in Phase 3 pivotal trials
  - Designed to evaluate pharmacokinetics, pharmacodynamics, safety after three months on investigational drug
- Partnership with Camurus AB leveraging FluidCrystal® technology





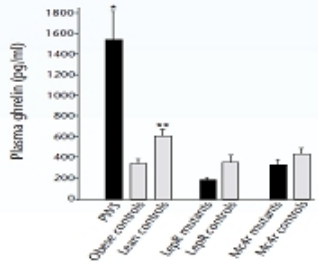
RM-853: Potent, Orally Available GOAT Inhibitor for Prader-Willi Syndrome (PWS)

IND filing for RM-853 expected in 2020

- Ghrelin O-Acyltransferase (GOAT) is key enzyme involved in producing active ghrelin
- Blocking GOAT results in:
  - Lower levels of active ghrelin, *and*
  - Increased levels of des-acyl-ghrelin (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 in 2020
  - Plan to explore potential of setmelanotide and RM-853 combination in PWS

Ghrelin is tightly correlated with hunger signals throughout the day

People with PWS have higher ghrelin levels



Rhythm Achieved Key Milestones in 2019

- ✓ Announced positive topline data from POMC and LEPR pivotal Phase 3 trials: met all primary and key secondary endpoints
- ✓ Announced positive updated data from Phase 2 Basket Study in BBS and Alström syndrome
- ✓ Completed pivotal enrollment in BBS and Alström syndrome Phase 3 study
- ✓ Announced promising data in HET obesity and strategy for further development
- ✓ Expanded Phase 2 Basket Study into four additional MC4R pathway disorders
- ✓ Announced yield of 11.7% from genetic sequencing of 13,567 individuals with severe obesity
- ✓ Launched *Uncovering Rare Obesity* to increase access to genetic testing
- ✓ Established GOLD Academy to support patient identification and community building efforts
- ✓ Completed follow-on offering, extending expected cash runway through at least the end of 2021

Rhythm Expects Transformational Progress in 2020

1 First potential approval for setmelanotide in POMC or LEPR deficiency obesities

1Q: NDA submission

2Q: MAA submission

2 Bardet-Biedl and Alström syndromes Phase 3

4Q or 1Q21: Topline data from Phase 3 trial

3 New indications

2020: Proof-of-concept data in HET patients and one or more additional rare genetic disorders of obesity

2020: Clinical development update for once-weekly formulation

2020: Filing of investigational new drug application for RM-853 for Prader-Willi Syndrome

U.S. Prevalence Estimates Suggest >85,000 Patients with MC4R Pathway-driven Rare Genetic Disorders of Obesity

Pivotal Indications = > 5,000
- POMC deficiency obesity
- LEPR deficiency obesity
- Bardet-Biedl syndrome
- Alström syndrome

HETs: > 20,000*
- POMC and LEPR heterozygous deficiency obesities

New indications > 60,000
- SRC1 deficiency obesity
- SH2B1 deficiency obesity
- Smith-Magenis syndrome
- MC4R deficiency obesity

* Company estimates calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity (Hales et al in JAMA – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016); Allele frequency based on Rhythm genetic sequencing (June 2019); Company also estimates that EU prevalence is similar for each indication.

Cash Expected to be Sufficient to Fund Operations Through at Least End of 2021

SHARES OUTSTANDING *as of 9/30/2019*	*34,578,564 (basic share count)*
CASH, CASH EQUIVALENTS AND SHORT-TERM INVESTMENTS *as of 9/30/2019*	$ 162.4 million

Raised $161.3M in estimated net proceeds in October 2019 follow-on offering of 9.3 million shares of common stock

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

Strong Leadership Team with Broad Biopharma Experience

				
Keith M. Gottesdiener, MD *Chief Executive Officer*	**Hunter Smith** *Chief Financial Officer*	**Nithya Desikan** *Chief Commercial Officer*	**Murray Stewart, MD** *Chief Medical Officer*	**Simon D. Kelner** *Chief Human Resources Officer*
MERCK	Celgene	Johnson & Johnson Biogen	novelion THERAPEUTICS gsk	MERCK teva
10-plus marketed products and NDAs 200-plus INDs	*Financial leadership for Otezla® ; 20-plus years in finance, M&A, capital markets*	*15-plus marketed products and NDAs 7 commercial launches*	*20-plus marketed products and NDAs 10-plus INDs*	*25-plus years global HR leadership experience in biopharma*

Setmelanotide: Investigational MC4R agonist

FDA Breakthrough Therapy Designation

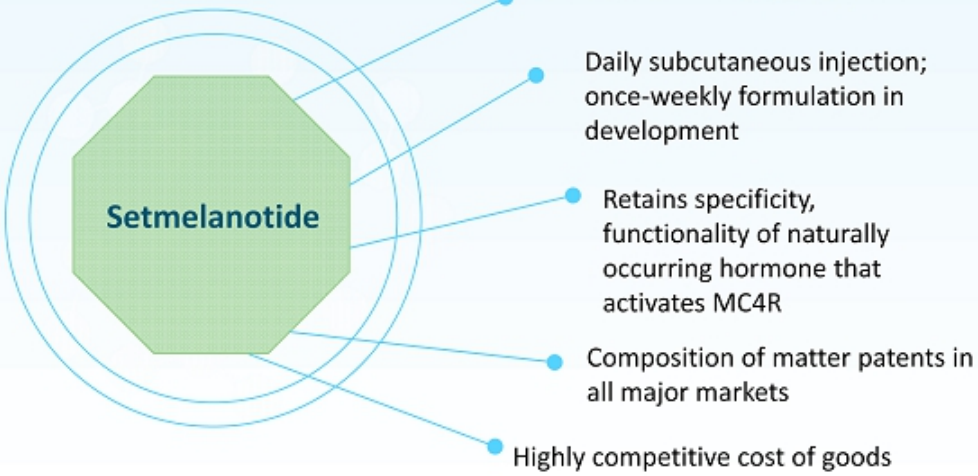
- POMC deficiency obesity
- LEPR deficiency obesity
- Bardet-Biedl syndrome
- Alström syndrome

FDA Orphan Drug Designation

- POMC deficiency obesity
- LEPR deficiency obesity
- Bardet-Biedl syndrome

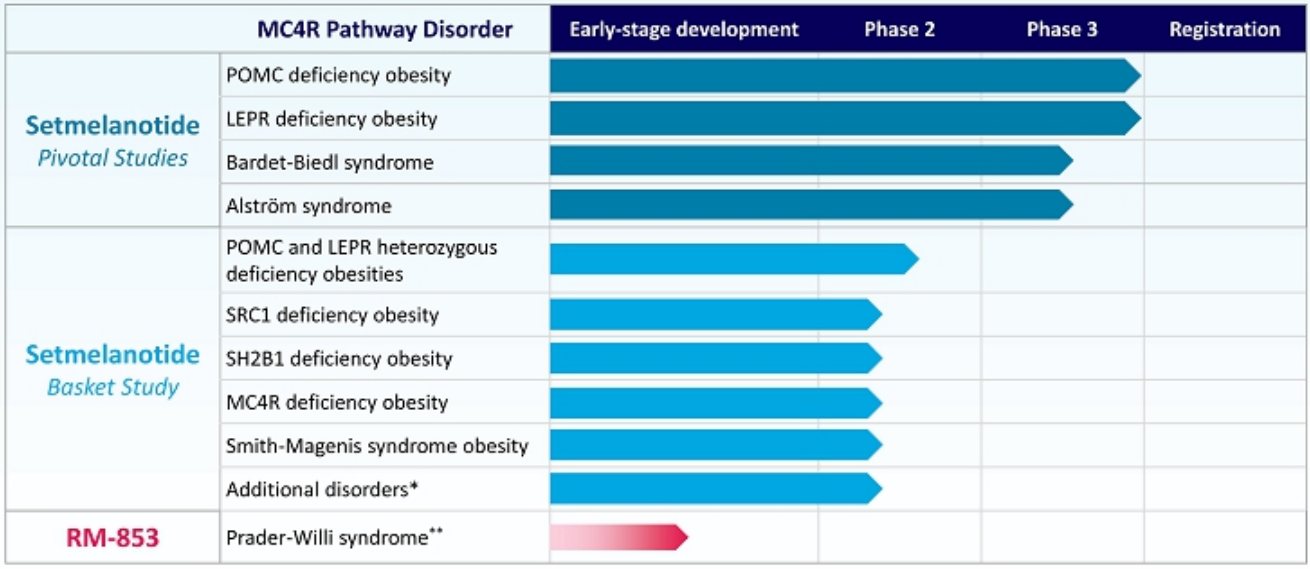
EMA PRIME Designation

- For treatment of obesity and control of hunger associated with deficiency disorders of the MC4R pathway



POMC, pro-opiomelanocortin; LEPR, leptin receptor

Rhythm Pipeline Focused on MC4R Pathway Disorders



** Rhythm is currently assessing setmelanotide in additional disorders, including POMC epigenetic disorders and LEP and CPE deficiency obesity, as part of investigator-initiated protocols within the basket study. Given the recent discovery of these rare disorders of the MC4R pathway, there is currently limited or no genetic sequencing or epidemiology data that defines prevalence. However, Rhythm believes that these are rare disorders which may be setmelanotide-responsive.*

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

BBS and Alström Syndrome Pivotal Trial Statistical Approach

Primary endpoint	Three key secondary endpoints (after ~52 weeks of treatment)		
Proportion of patients (≥12 years old) who achieve ≥10% reduction in body weight after ~52 weeks of treatment	Proportion of patients (≥12 years old) who achieve a ≥25% improvement in daily hunger score	Body weight percent change from baseline in patients ≥ 12 years old	Daily hunger score percent change from baseline in patients ≥ 12 years old
• Primary: Based on an exact binomial test, at a 1-sided 0.05 significance level; A 2-sided 90% CI will be calculated using the exact Clopper-Pearson method. The statistical criterion corresponds to the 2-sided 90% CI for setmelanotide of the response rate excluding 10% (i.e., lower bound of the CI >0.10)		• Based on a one-sample t-test with assumed mean percent change from baseline of zero, at a 1-sided 0.05 significance level. • As in the POMC/LEPR pivotal trials, these percent change analyses to be conducted on pivotal patients who achieve at least 5 kg (or 5% if <100 kg) weight loss after 14 weeks of active setmelanotide treatment	

- Historical control response rate of 10% responders is used as a comparator for primary endpoint and responder key secondary endpoint, in the Full Analysis Set
- All prespecified primary and key secondary analyses are performed on the pooled BBS and Alström syndrome pivotal patient population
- Power Statement: A sample size of 7 patients provides ~95% power at 1-sided alpha of 0.05 and ~91% power at 1-sided alpha of 0.025, to yield a statistically significant difference, assuming the Phase 2 Basket Study 66% response for weight loss
- Although these data suggest that powering the study for the primary endpoint will require a minimal number of patients (N<10), the size of the trial is also a function of the rarity of BBS and Alström syndrome and a desire to better understand the effect of setmelanotide in these patient populations. Hence, at least 20 BBS and at least 6 Alström syndrome patients were planned to be enrolled in the study (N=38 were actually enrolled in the pivotal cohort)
- Rhythm proposed Statistical Analysis Plan; not all elements reviewed by FDA

POMC and LEPR Phase 3 Trials Achieve Statistically Significant and Clinically Meaningful Results in Reductions of Weight and Hunger

POMC Phase 3 Results

Endpoint	Result
Proportion of Participants Achieving at Least 10% Change in Body Weight	80% p<0.0001
Mean Percent Change from Baseline in Body Weight*	-25.4 % p<0.0001
Mean Percent Change from Baseline in Most Hunger Rating *†	-27.8% p=0.0005
Proportion of Participants with 25% Reduction in Hunger†	50% p=0.0004
Participants Aged ≥19 years Mean Percent Change from Baseline in BMI (n=4)	-22.33% p=0.056
Participants Aged <19 years Mean Percent Change from Baseline in BMI z-score (n=6)	-49.18% p=0.007

LEPR Phase 3 Results

Endpoint	Result
Proportion of Participants Achieving at Least 10% Change in Body Weight	45.5% p=0.0001
Mean Percent Change from Baseline in Body Weight*	-12.5% p<0.0001
Mean Percent Change from Baseline in Most Hunger Rating *†	-41.9% p<0.0001
Proportion of Participants with 25% Reduction in Hunger†	72.7% p<0.0001
Participants Aged ≥19 years Mean Percent Change from Baseline in BMI (n=8)	-10.59% p=0.01
Participants Aged <19 years Mean Percent Change from Baseline in BMI z-score (n=3)	-13.35% p=0.12

These data were presented as part of the Company's topline data disclosure on Aug. 7, 2019, and as late-breaking presentations during ObesityWeek 2019.

*, 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
Data were presented during late-breaking research forum at the 37th Annual Meeting of The Obesity Society at ObesityWeek® 2019.

Rhythm PHARMACEUTICALS

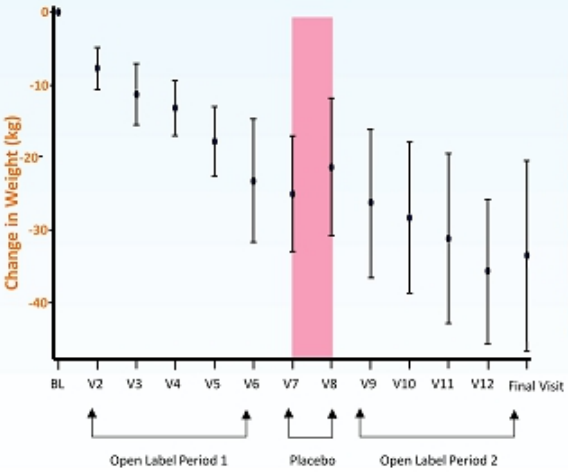
Taking a Closer Look at POMC

- 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*

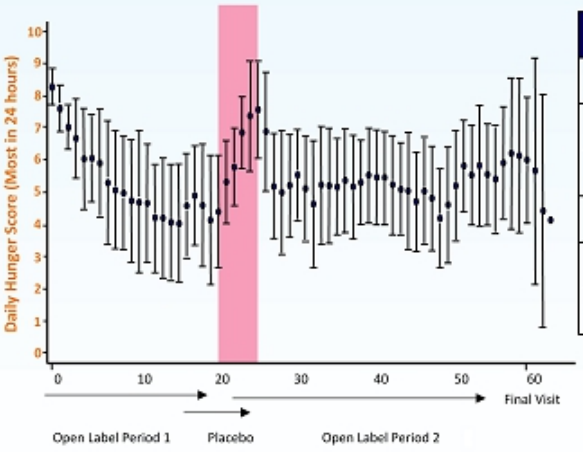
These data were presented as part of the Company's topline data disclosure on Aug. 7, 2019.

POMC Phase 3 Trial – Change in Weight and Hunger Over 1 Year with 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	+2.2
Range	2.0 to 9.86

These data were presented as part of the Company's topline data disclosure on Aug. 7, 2019.

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

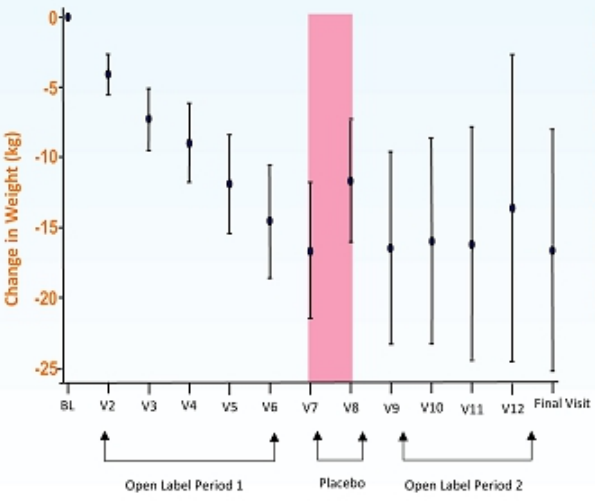
Taking a Closer Look at LEPR

- 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% 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

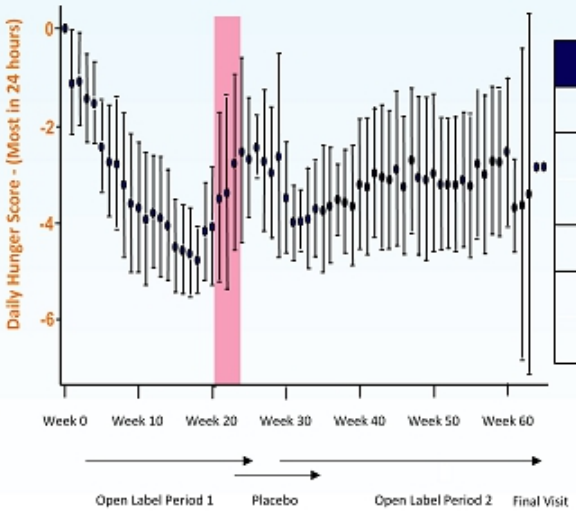
These data were presented as part of the Company's topline data disclosure on Aug. 7, 2019.

LEPR Phase 3 Trial – Change in Weight and Hunger Over 1 Year with 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	2.9-9.3
Change in hunger score	
Mean	+3.1
Range	4.0 to 10.0

These data were presented as part of the Company's topline data disclosure on Aug. 7, 2019.

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

POMC and LEPR Participant Demographics – Phase 3 Trials

POMC Deficiency Obesity

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/m²)	
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

LEPR Deficiency Obesity

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/m²)	
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

Updated Phase 2 Data in Alström Syndrome*

Age at enrollment/ Sex	Baseline Weight (kg)	Treatment, weeks	% Weight Change from Baseline	% Hunger Score Change from Baseline†
12/M	78.6	95	**-20%**	-25%
15/F	70.7	84	**1%**	-38%
16/F	91.6	68	**-6%**	0%

- Patient 1 has reached healthy body weight
- Patient 3 maintaining weight and reduced hunger – HbA1c decreased by 3% from 11% to 8%
- All 3 continuing patients plan to enter long-term extension trial

*As previously disclosed, patient 2 (data not shown) discontinued at ~14 weeks; **Updated data announced by Rhythm in September 2019.**

Phase 2 Data in HET Patients Based on LOF Variant

All high-impact LOF patients appear setmelanotide-responsive; other subgroups have more variable responses

	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
High-Impact LOF Group	37	204 (451)	18.4 (40.5)	9.0%	-9	90.0%
	29	129 (284)	22.3 (49.0)	17.3%	-5	71.4%
	4	187 (412)	7.1 (15.6)	3.8%	-4	40.0%
Other Subgroups	74	150 (330)	12.1 (26.6)	8.0%	-7	78.0%
	66	147 (323)	7.5 (16.5)	5.1%	-1	20.0%
	20	118 (259)	15.0 (33.0)	12.8%	-6	75.0%
	16	106 (232)	7.2 (15.8)	6.9%	-7	70.0%
	7	150 (330)	4.6 (10.1)	3.0%	NA	NA

High-Impact LOF Group:

- All patients ongoing; fourth patient, still very early in dose titration, showing promising weight loss and hunger score decreases.

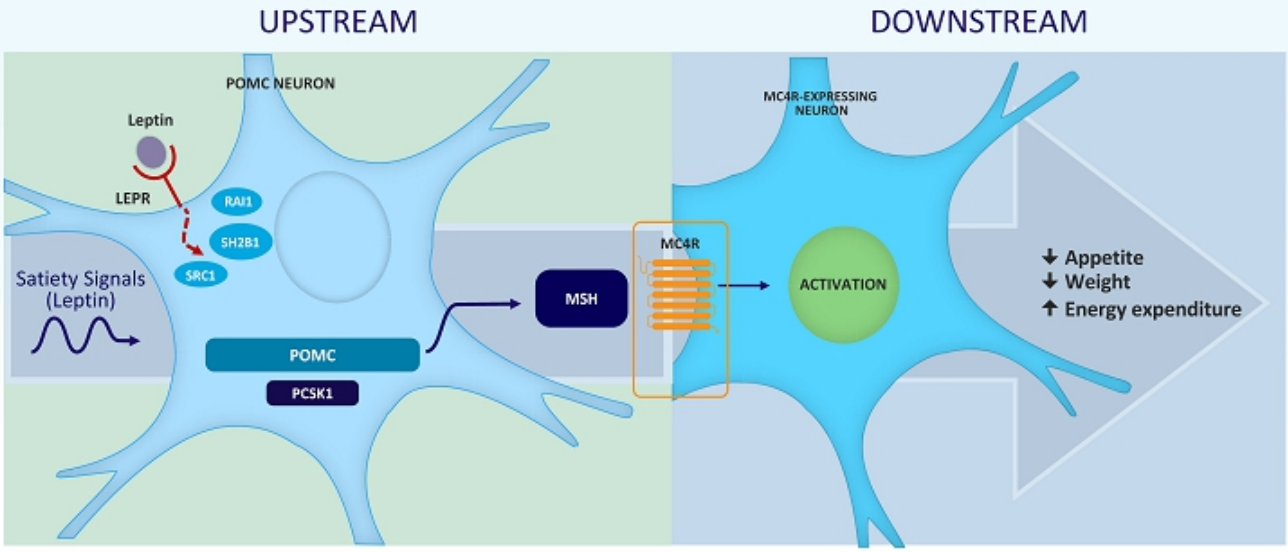
Other Subgroups:

- Five patients ongoing[1]
- 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] and one patient withdrawn by site for patient non-compliance.

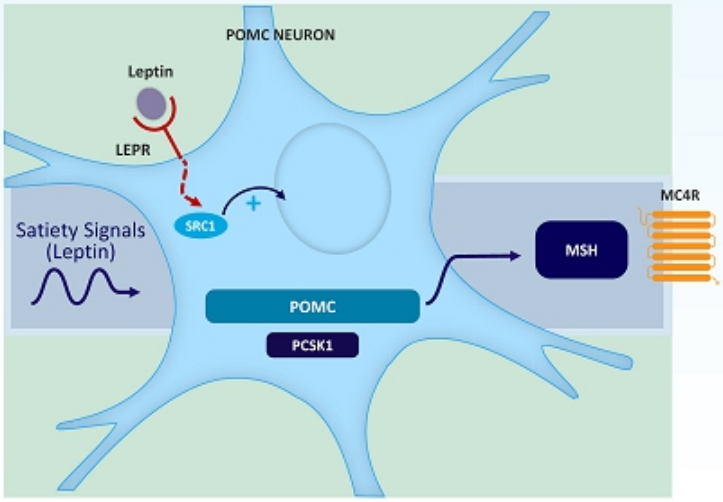
[1]Two of these patients were reported in June 2018. [2]Total treatment duration including any titration period, which can last 6-12 weeks. [3]These three patients were reported in June 2018. AE = adverse event

These data were presented in March 2019.

New MC4R Pathway Indications Based on Supported Scientific Rationale



SRC1 is a Transcriptional Coactivator that Drives POMC Expression



Pathway Relevance: **Drives POMC Expression**

- Transcriptional coactivator activated downstream of LEPR
- Found in POMC neurons

Autosomal Dominant

- Obesity arises due to heterozygous gene variants

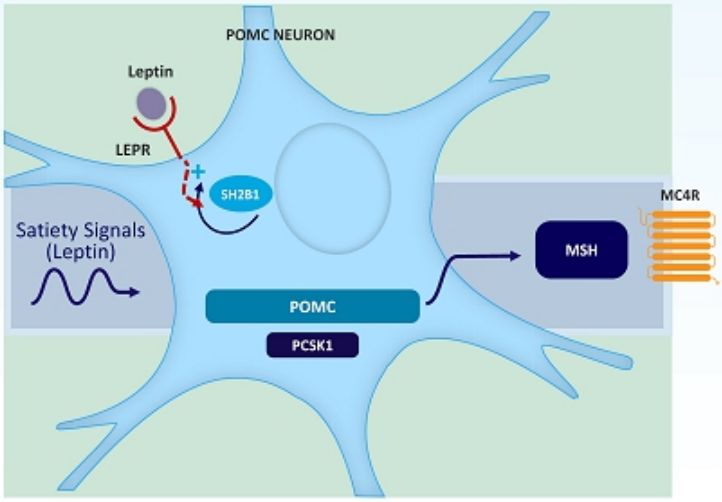
Clinical Presentation

- Early onset obesity and hyperphagia
- Hyperleptinemia

Citations

- Yang et al 2019, Nat Comm. 10, Article 1718

SH2B1 is an Adapter Protein that Regulates LEPR Activity



Pathway Relevance: **Regulates LEPR activity**

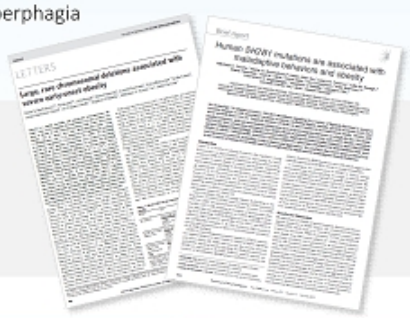
- Adapter protein
- Found in POMC neurons

Autosomal Dominant

- Obesity arises due to heterozygous gene variants or chromosomal deletions

Clinical Presentation

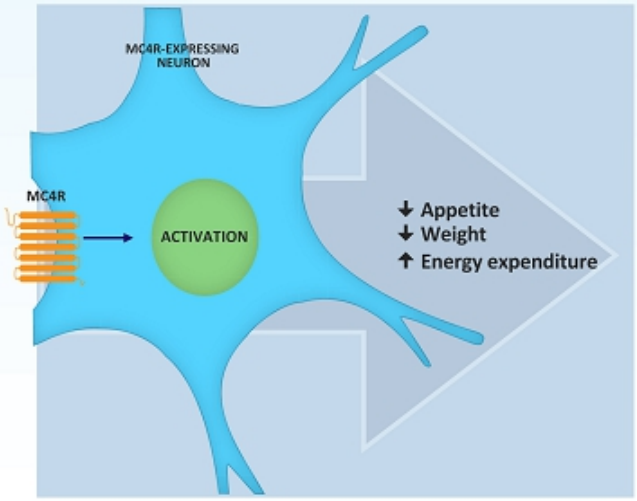
- Early onset obesity and hyperphagia
- Hyperinsulinemia



Citations

- Doche et al 2011, JCI, 122; 4732
- Ockukova et al 2010, Nature, 463; 666

MC4R: Receptor for POMC Ligand MSH



Pathway Relevance: **Receptor for POMC ligands**

- Required for satiety effects of α/β-MSH

Autosomal Dominant

- Obesity arises due to heterozygous gene variants

Clinical Presentation

- Early onset obesity and hyperphagia

Setmelanotide

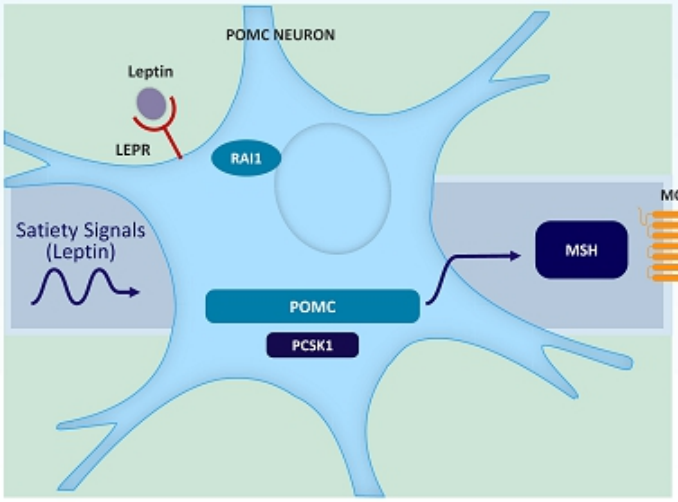
- Pharmacological target for setmelanotide
- Rhythm conducted small, 4-week PhIb study in MC4R deficiency obesity
- Rhythm biochemical studies indicate that setmelanotide can address specific MC4R variants
- Current indication is focused on addressable MC4R variant carriers

Citations

- Farooqi et al 2003, NEJM, 348; 1085
- Collett et al 2017, Molecular Metabolism, 6; 1321

Rhythm PHARMACEUTICALS

Smith-Magenis Syndrome: RAI1 Affects POMC Expression



Pathway Relevance: Decreased Pathway Function Upstream of MC4R

- Causal gene is RAI1
- Transcription factor for a number of pathway genes

Autosomal Dominant

- Gene variants and chromosomal deletions

Clinical Presentation

- Adolescent obesity and hyperphagia
- Sleep disturbance, cognitive impairment, craniofacial anomalies, low energy expenditure

Citations

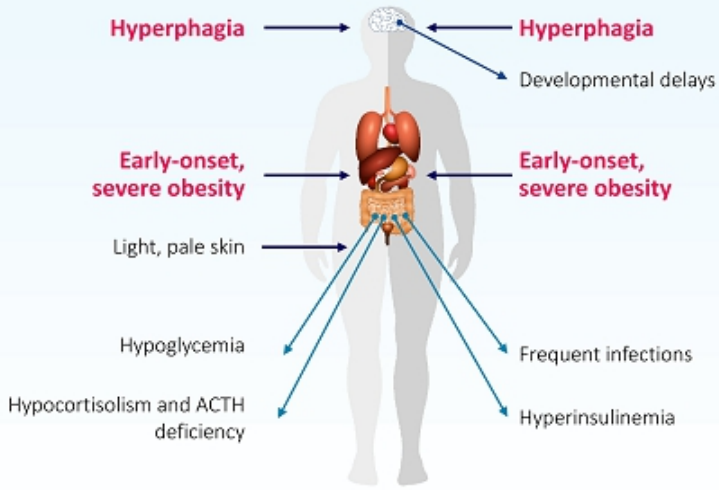
- Edelman et al 2007, Clin Genet; 71: 540–550
- Burns et al 2010, Hum. Mol. Gen; 19; 4026

POMC and LEPR Deficiency Obesities Characterized by Early-onset Obesity, Unrelenting Hunger

POMC Deficiency Obesity

Results from loss-of-function homozygous or biallelic variants in the POMC gene

U.S. prevalence estimated to be 100 to 500 patients



LEPR Deficiency Obesity

Results from loss-of-function homozygous or biallelic variants in the LEPR gene

U.S. prevalence estimated to be 500 to 2,000 patients

No approved therapies

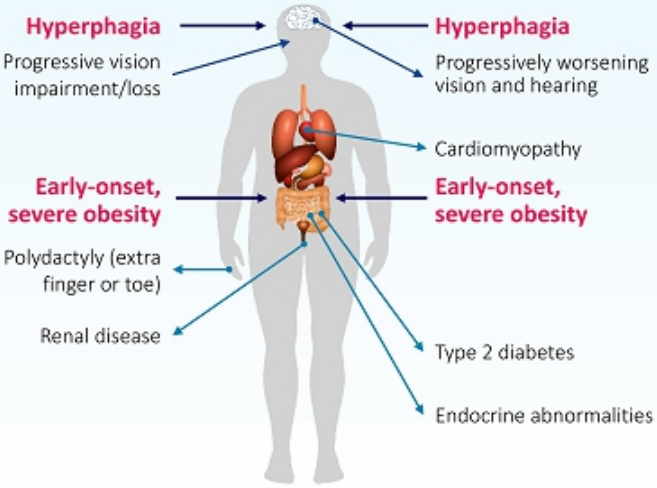
Rhythm PHARMACEUTICALS

Bardet-Biedl and Alström Syndromes Associated with Severe Obesity and Hunger

Bardet-Biedl syndrome[1]

Rare ciliopathy disorder resulting from genetic variants within **BBS family of genes**

U.S. prevalence estimated to be **2,500** patients



Alström syndrome[2,3]

Rare ciliopathy disorder associated with **ALMS1 mutation**

U.S. prevalence estimated to be **500** patients

References: 1. Forsythe E, Beales PL. Bardet-Biedl Syndrome. 2003 Jul 14 [Updated 2015 Apr 23]. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1363/. **2.** Marshall JD et al. *Curr Genomics*. 2011;12(3):225-235. **3.** Marshall JD et al. Alström Syndrome. 2003 Feb 7 [Updated 2012 May 31]. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1267/.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