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): **September 25, 2019**

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:

- o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
- o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
- o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
- o 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 x

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. x

Item 7.01 Regulation FD Disclosure.

On September 25, 2019, Rhythm Pharmaceuticals, Inc. (the "Company") issued the attached press release providing an update on its research and development efforts and providing updated data for its Phase 2 Basket trial. Further, the Company reviewed a slide presentation during a webcast on September 25, 2019. Copies of the press release and the presentation slides are furnished as Exhibits 99.1 and 99.2, respectively, to this Current Report on Form 8-K and a replay of the webcast will be available on the Company's website at www.rhythmtx.com under "Investors & Media" for 30 days following the event. 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 Exhibits 99.1 and 99.2 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 exhibits 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	Press release dated September 25, 2019.
99.2	Company Presentation dated September 2019.

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: September 25, 2019

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

Rhythm Pharmaceuticals Provides Update on Research and Development Programs

— Four new MC4R pathway obesity indications added to Phase 2 Basket Study and enrolling patients —

— Genetic sequencing of 13,567 individuals with severe obesity yields 11.7 percent (1,584 individuals) who have a rare genetic variant within MC4R pathway eligible for Phase 2 Basket Study —

— Sequencing results supports ultra-rarity of POMC and LEPR deficiency obesity —

— Sequencing results suggest U.S. prevalence estimates for four new indications of greater than 60,000 —

— Updated data from continuing patients with Bardet-Biedl syndrome in Phase 2 Basket trial demonstrate 22.2 percent mean weight loss following approximately two years on therapy —

— Rhythm R&D event in New York City; Live webcast begins at 8:15 a.m. today —

Boston, MA — September 25, 2019 — Rhythm Pharmaceuticals, Inc. (Nasdaq:RYTM), a biopharmaceutical company aimed at developing and commercializing therapies for the treatment of rare genetic disorders of obesity, today will announce an update on its Research & Development (R&D) programs, genetic sequencing efforts and patient finding initiatives at its R&D event in New York City.

During the event, the Company will provide a comprehensive overview of the four new melanocortin-4 receptor (MC4R) pathway-driven disorders that it has added to its Phase 2 Basket Study, as well as updated U.S. prevalence estimates for all of the MC4R pathway-driven rare genetic disorders of obesity for which it is currently evaluating setmelanotide. The Company also will share updated data from its Phase 2 Basket Study of setmelanotide in Bardet-Biedl syndrome (BBS) and Alström syndrome and provide details on ongoing community building and patient-finding efforts related to those two indications. Together, the presentations will highlight how the Rhythm Engine is working to discover disease-causing genetic variants and sequence patients to identify those living with MC4R pathway-driven disorders of obesity and potentially provide these patients with the first disease-modifying therapeutic option.

“In collaboration with partners, patients and health care providers, Rhythm is advancing toward our goal of changing the paradigm for rare genetic disorders of obesity,” said Keith Gottesdiener, M.D., Chief Executive Officer of Rhythm. “We are committed to advancing the science underlying MC4R-pathway obesity disorders and expanding our clinical development and community-building efforts. Through these initiatives, we aim to provide patients with severe obesity and unrelenting hunger a potential new therapeutic option, and to equip physicians and caregivers with the knowledge and resources to better manage these disorders.”

Expansion of the Rhythm Basket Study into Four Additional Indications

Rhythm is expanding its Phase 2 Basket Study into four new indications: SRC1 deficiency obesity, SH2B1 deficiency obesity, MC4R deficiency obesity and Smith-Magenis syndrome obesity. The Company is evaluating setmelanotide for the treatment of severe obesity and unrelenting hunger, or hyperphagia, associated with these diseases.

- ***SRC1 deficiency obesity*:** SRC1 is a transcriptional coactivator that drives pro-opiomelanocortin (POMC) expression.
- ***SH2B1 deficiency obesity*:** SH2B1 is an adapter protein that regulates leptin receptor (LEPR) activity.
- ***MC4R deficiency obesity:*** The MC4R is the receptor for POMC ligands, and is responsible for the satiety effects of α/β-MSH. The Company plans to focus its development efforts on patients with potentially rescuable variants in the MC4R.
- ***Smith-Magenis syndrome (SMS) obesity**:* SMS is caused by dysfunction of the RAI1 gene, a transcription factor for a number of MC4R pathway genes, which affects POMC expression.

“We are taking an exciting step toward our foundational goal of translating our understanding of the MC4R pathway into treatments for people living with rare genetic disorders of obesity,” said Alastair Garfield, Ph.D., Vice President of Translational Research and Development of Rhythm. “Leveraging our extensive scientific expertise, genetic sequencing initiatives and variant interpretation capabilities, we selected additional rare genetic disorders of obesity to include in our Phase 2 Basket Study, each with a strong scientific tie to the MC4R pathway and, we believe, a larger target population than certain other indications that we are currently evaluating in clinical trials. We look forward to evaluating setmelanotide in these indications in the months and years ahead. We are also committed to continuing to probe the numerous other MC4R pathway genes that may be implicated in rare genetic disorders of obesity and may provide additional opportunities for setmelanotide.”

Genetic Sequencing Provides Updated U.S. Prevalence Estimates for Genetically-identified MC4R Pathway-driven Indications

Rhythm has been collaborating with partners to advance its own initiatives to sequence individuals living with early-onset, severe obesity to uncover more rare genetic disorders of obesity, and develop a better understanding of those disorders currently under study in its pivotal trials and Phase 2 Basket Study. As of June 2019, the Company collected samples from 13,567 individuals with severe obesity, and those samples have yielded 11.7 percent, or 1,584 genetically-identified individuals, who have a rare genetic variant of the MC4R pathway and who may be eligible for inclusion in Rhythm’s Phase 2 Basket Study or Rhythm’s pivotal Phase 3 trials.

Rhythm’s genetic sequencing results have identified samples from 29 patients with POMC or LEPR deficiency obesity. This result supports that these conditions are ultra-rare, even among the portion of the population with severe, early-onset obesity. These results are consistent with Rhythm’s clinical epidemiology estimates of 100-500 POMC deficiency obesity and 500-2,000 LEPR deficiency obesity patients living in the U.S.

Additionally, Rhythm believes the sequencing yield in this cohort supports the Company’s prior estimates of greater than 20,000 people living with high-impact heterozygous obesity of the *POMC, PCSK1* or *LEPR* genes in the U.S.

For the genetically-defined MC4R pathway indications that the Company has not previously included in prior clinical trials, the Company applied well-established functional and computational filtering processes to refine this yield and provide estimated U.S. prevalence(1):

Indication	Estimated U.S. Prevalence
SRC1 deficiency obesity	>23,000
SH2B1 deficiency obesity	>24,000
MC4R deficiency obesity	>10,000

Syndromic conditions, such as SMS, BBS and Alström syndrome, are often clinically identified and confirmed by genetic testing. Rhythm estimates that there are greater than 2,400 people living with severe obesity and SMS in the U.S.

Update on Clinical Data from Phase 2 Basket Study in BBS and Alström Syndrome, and Community Building and Patient-Finding Efforts in these Two Indications

Rhythm provided an update on data from its Phase 2 Basket Study of setmelanotide in patients with BBS and Alström syndrome. As previously disclosed in January 2019, six of nine enrolled patients with BBS showed weight loss of greater than 10 percent on setmelanotide treatment. As of August 2019, all of these patients either continued to maintain, or increased, their weight loss following approximately two years of treatment, with a mean weight reduction of 22.2 percent. Additionally, five of six patients continued to show a substantial decrease in hunger from baseline.

In patients with Alström syndrome, the three patients on treatment at the Company's last update in November 2018 have continued on treatment. One of these patients has demonstrated 20 percent weight loss and a 25 percent reduction in hunger score at greater than one year. One patient has not lost weight but has demonstrated a 38 percent decrease in hunger and improved diabetes control at greater than one year, and the third patient achieved 6 percent weight loss without a change in hunger. All three patients plan to continue setmelanotide therapy in the long-term extension trial.

"Rhythm is working to build a community to better understand the substantial, long-term burden of rare genetic and syndromic disorders of obesity on the lives of patients and their families. Both BBS and Alström syndrome are typically diagnosed via clinical presentation, which requires an informed healthcare-provider community, capable of recognizing and managing the care of these patients," said Nithya Desikan, Chief Commercial Officer of Rhythm. "We believe we may have identified nearly one third of the estimated BBS and Alström patients living in the U.S., providing a foundation as we continue to enroll our pivotal Phase 3 trial in BBS and Alström syndrome, and begin to build the infrastructure to support the potential commercialization of setmelanotide in these indications."

Webcast Information:

The live audio webcast of today's R&D event can be accessed under "Events & Presentations" in the Investors & Media section of the Company's website at www.rhythmtx.com. A replay of the webcast will be available on the Rhythm website for 30 days following the event.

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(1) SRC1 and SH2B1 deficiency obesity epidemiology estimates include patients with high-impact loss-of-function variants, screened through three computational algorithms applied for newly-observed variants. 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); allele frequency based on Rhythm genetic sequencing (June 2019).

About Rhythm

Rhythm is a biopharmaceutical company focused on the development and commercialization of therapies for the treatment of rare genetic disorders of obesity. The company recently announced positive topline results from pivotal Phase 3 clinical trials of setmelanotide, its MC4R agonist, in patients with POMC deficiency obesity and LEPR deficiency obesity, and Rhythm expects to share the full data in forthcoming publications and medical meeting presentations. The company plans to complete its first rolling new drug application (NDA) submission to the U.S. Food and Drug Administration in the fourth quarter of 2019 or the first quarter of 2020. Rhythm is also evaluating setmelanotide in a pivotal Phase 3 study in patients with Bardet-Biedl syndrome and Alström syndrome, and expects to complete enrollment in the second half of 2019. The company is leveraging the Rhythm Engine — comprised of its Phase 2 basket study, TEMPO Registry, GO-ID genotyping study and Uncovering Rare Obesity program — to improve the understanding, diagnosis and potentially the treatment of rare genetic disorders of obesity. For healthcare professionals, visit www.UNcommonObesity.com for more information. For patients and caregivers, visit www.LEADforRareObesity.com for more information. The company is based in Boston, MA.

Forward-Looking Statements

This press release 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 anticipated timing for enrollment of patients in clinical trials and submission of an NDA, its ongoing efforts related to patient identification, estimates of treatable patient populations, the timing of the release of results of clinical trials, the efficacy of setmelanotide in patients with POMC deficiency obesity, LEPR deficiency obesity, Bardet-Biedl Syndrome, Alström Syndrome, POMC heterozygous deficiency obesity, or POMC epigenetic disorders, as well as new indications that we may pursue. 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 design and outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, and 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 release or to update them to reflect events or circumstances occurring after the date of this release, whether as a result of new information, future developments or otherwise.

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Rhythm Research and Development Event

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 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, estimates of treatable patient populations, the efficacy of setmelanotide in patients with new indications, 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.

Today's Agenda

Introductions

Hunter Smith, Chief Financial Officer

Welcome and Overview

Keith Gottesdiener, M.D., Chief Executive Officer

Science Behind New Indications

Alastair Garfield, Ph.D., Vice President of Translational Research and Development

Update on Epidemiology Estimates

Keith Gottesdiener, M.D., Chief Executive Officer

Rhythm Engine, Basket Study and Update on Phase 2 Bardet-Biedl Syndrome Patients

Murray Stewart, M.D., Chief Medical Officer

Bardet-Biedl and Alström Syndromes Community Building and Patient Finding

Nithya Desikan, Chief Commercial Officer

Closing Remarks and Q&A

Welcome

Keith Gottesdiener, M.D.
Chief Executive Officer

Welcome to Rhythm's Fall 2019 R&D Event

4 new indications being added to Phase 2 Basket Study

Growing database now with sequences of

13,567

people with early-onset, severe obesity

Sequencing yield and updated **epidemiology** for pivotal and basket indications

Rhythm Engine and what it's designed to accomplish

Progress in programs for **Bardet-Biedl and Alström syndromes**

Rhythm Achievements on the Road to Changing the Paradigm with a Much-needed Therapy for Rare Genetic Disorders of Obesity

Translational Research and Genetics

- Added **high-impact heterozygous (HET)** obesity to **Basket Study** and presented preliminary clinical data demonstrating consistent weight and hunger responses
- Launched **Uncovering Rare Obesity**, a free genetic testing program
- Launched **TEMPO** registry and **GO-ID** trial

Clinical Advancement

- Secured **Breakthrough Therapy** and **EMA PRIME** designations for POMC, LEPR, BBS & Alström
- Achieved **positive Phase 2** Bardet-Biedl & Alström syndromes results
- Enrolled first patient in pivotal Phase 3 study in BBS & Alström
- **Completed enrollment in** POMC Phase 3 trial
- Completed enrollment in LEPR **Phase 3 trial**
- Initiated Phase 2 trial for **once-weekly** formulation of setmelanotide
- **Met all primary and key secondary endpoints** for weight loss and reduction in hunger in **POMC and LEPR Phase 3 trials**

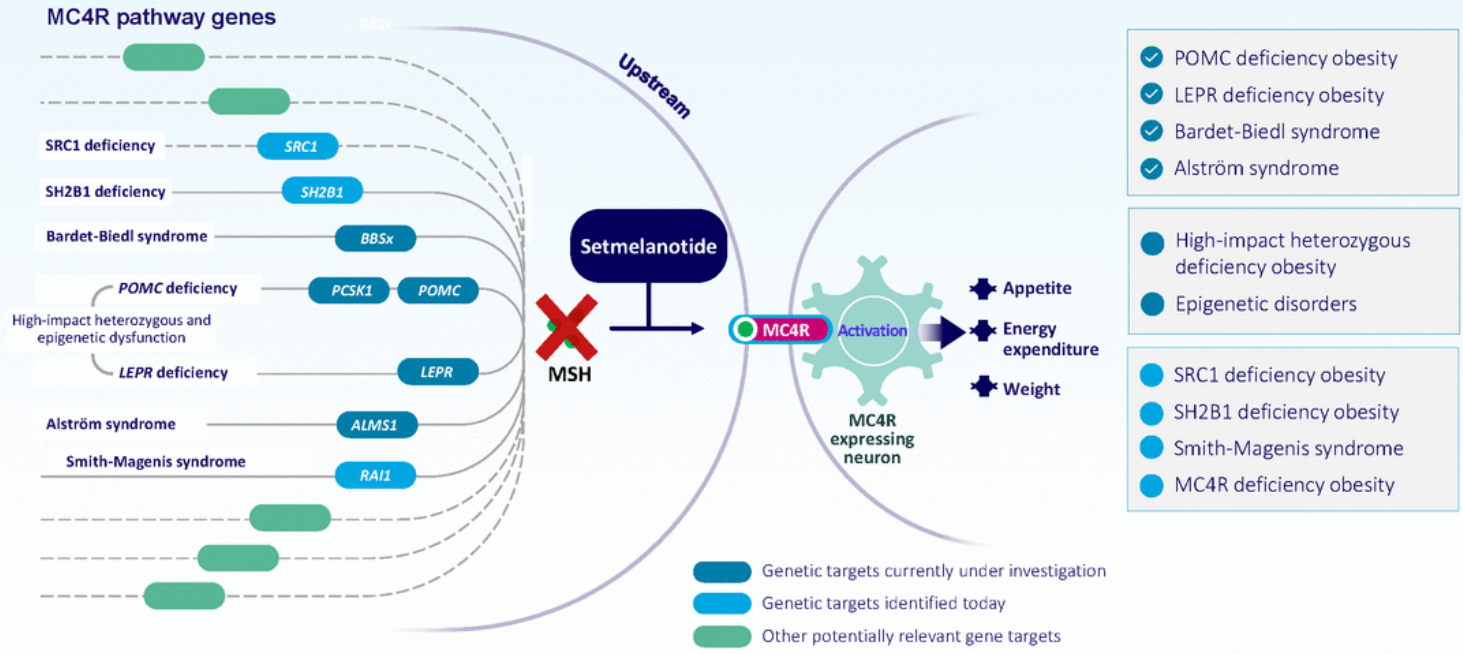
Expand Basket Study and provide update on genetic sequencing and patient finding

Today's Focus is on New Indications and Patient Finding

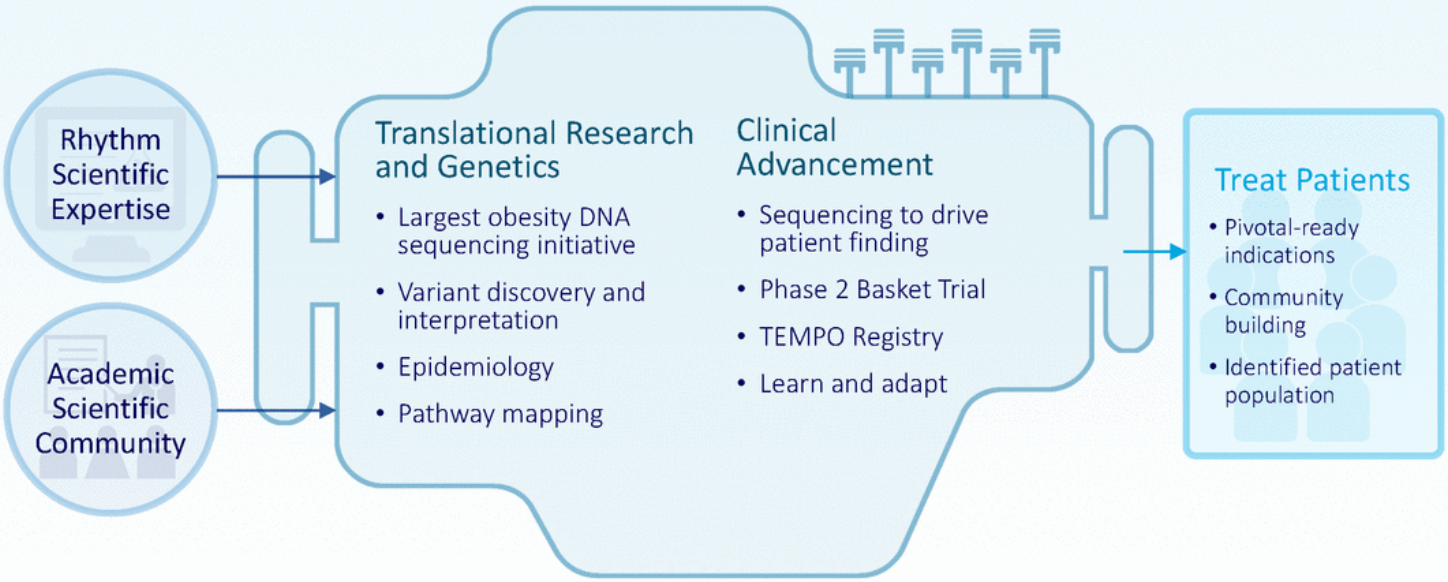
These Rhythm initiatives remain on track

- POMC and LEPR deficiency obesities pivotal data and registration
  - Presentations of data at major medical meeting expected during 4Q2019
  - U.S. New Drug Application submission on track to be completed 4Q2019/1Q2020
- High-impact HETs progressing in Rhythm Basket Study; update coming in 2020
- Commercialization approach for POMC/LEPR - 1H2020

Setmelanotide has Potential to Address Multiple Genetic Disorders that Disrupt MC4R Pathway Function



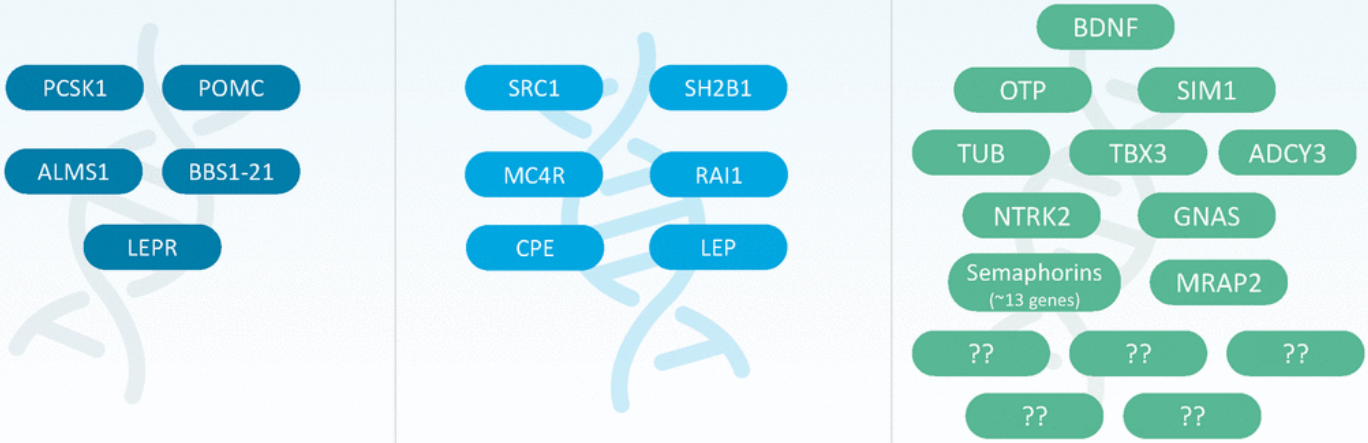
Rhythm Engine Drives Understanding and Treatment of Rare Genetic Disorders of Obesity



Science Behind New Indications

Alastair Garfield, Ph.D., Vice President of
Translational Research and Development

Numerous MC4R Pathway Genes Implicated in Rare Genetic Disorders of Obesity



MC4R Pathway Disorders: Genetic or Syndromic Diagnosis

Genetically-identified

POMC, LEPR deficiency obesities; High-impact HETs

Patients diagnosed after genetic screening

- SRC1 deficiency obesity
- MC4R deficiency obesity
- SH2B1 deficiency obesity

Clinically-identifiable, syndromic

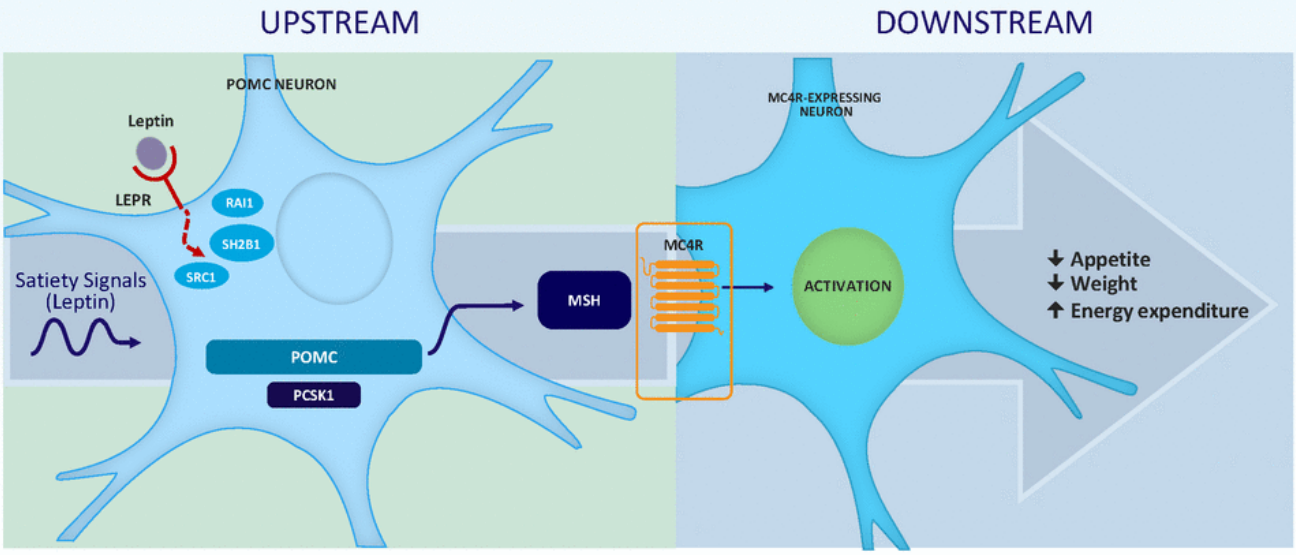
BBS and Alström syndrome

Patients often known to the medical system

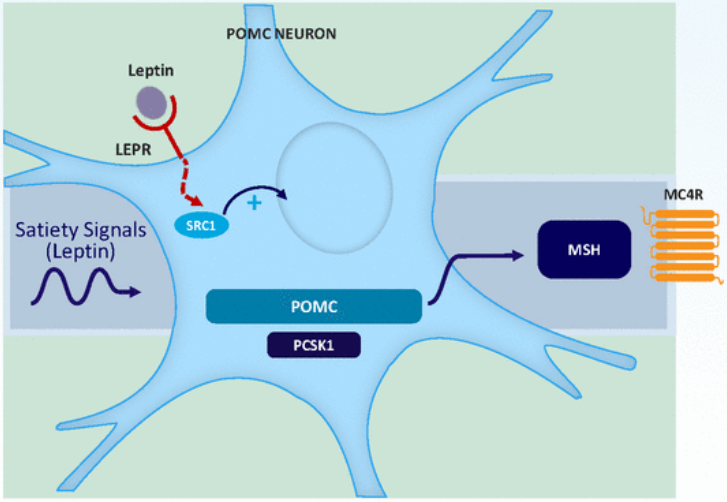
- Smith-Magenis syndrome

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

New MC4R Pathway Indications Based on Proven 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

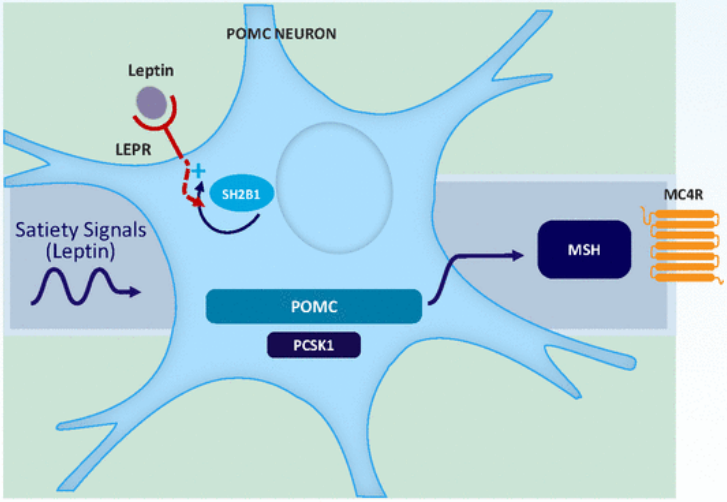
- Early onset obesity and hyperphagia
- Hyperleptinemia

Citations

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


Steroid receptor coactivator-1 modulates the function of Pomc neurons and energy homeostasis

SH2B1 is an Adapter Protein that Regulates LEPR Activity



Pathway Relevance: **Regulates LEPR activity**

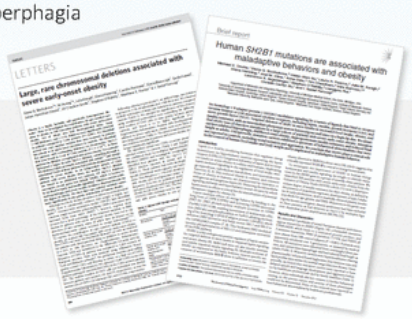
- Adapter protein
- Found in POMC neurons

Autosomal Dominant

- Obesity arises due to heterozygous gene variants or chromosomal deletions

Clinical Presentation

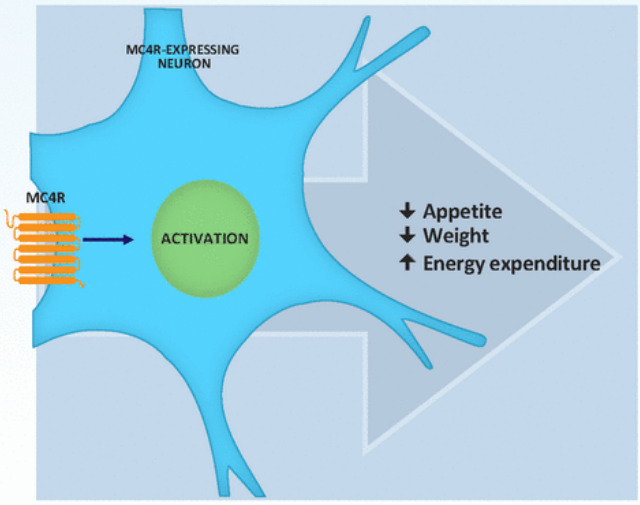
- Early onset obesity and hyperphagia
- Hyperinsulinemia



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

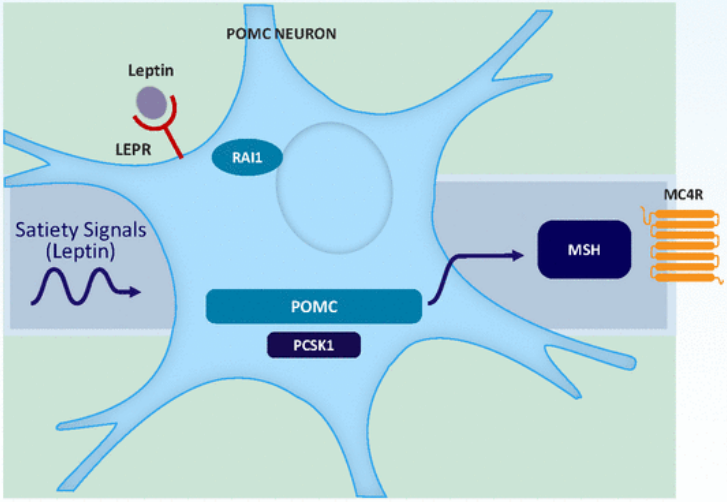
- Pharmacological target for setmelanotide
- Rhythm conducted small, 4-week PhIb study in MC4R deficiency obesity
- Rhythm biochemical studies indicate that setmelanotide can rescue specific MC4R variants
- Current indication is focused on rescuable MC4R variant carriers

Citations

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

Rhythm PHARMACEUTICALS

Smith-Magenis Syndrome Obesity: RAI1 Affects POMC Expression



Pathway Relevance: Decreased Pathway Function Upstream of MC4R

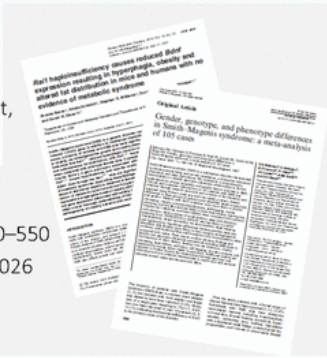
- Causal gene is RAI1
- Transcription factor for a number of pathway genes

Autosomal Dominant

- Gene variants and chromosomal deletions

Clinical Presentation

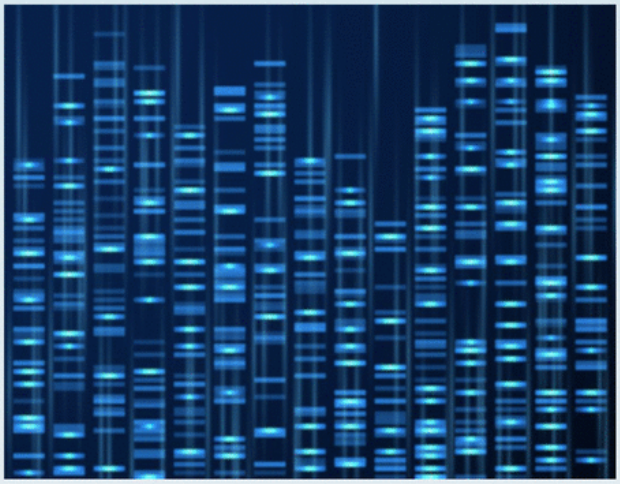
- Adolescent obesity and hyperphagia
- Sleep disturbance, cognitive impairment, craniofacial anomalies, low energy expenditure



Citations

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

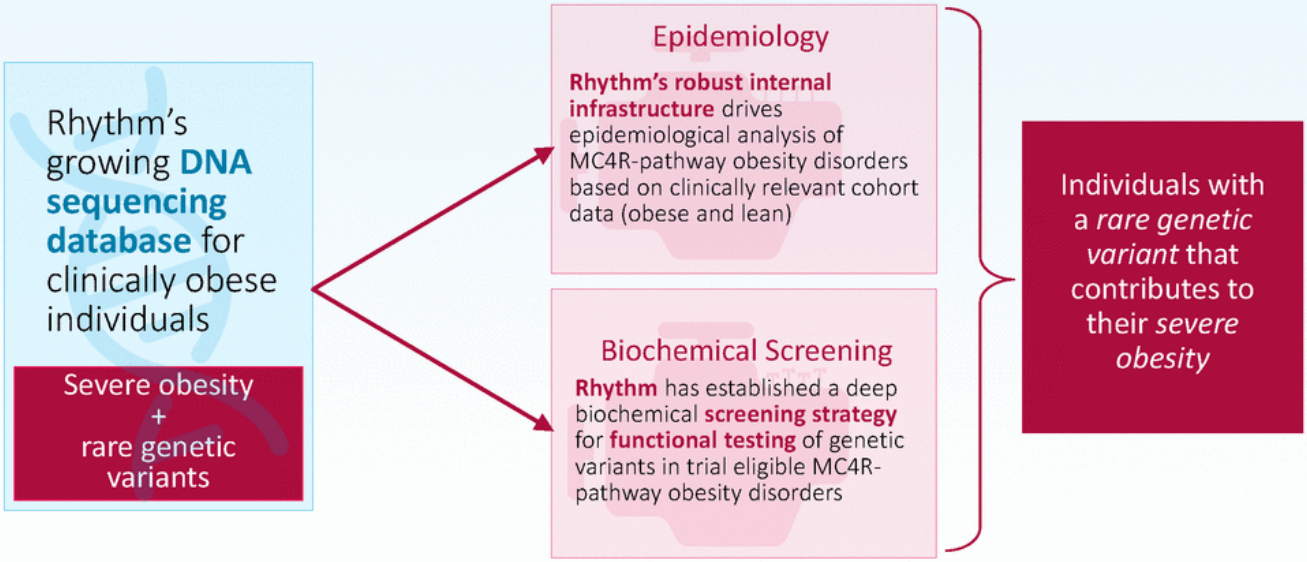
Leveraging Sequencing Data to Build a Better Understanding of Genetics Underlying Obesity



101 Gene Panel for Obesity

- Clinically relevant obesity genes
- Research based genes
- Not all associated with MC4R pathway

There's an Art to the Science of Rhythm's Genotyping Strategy



Epidemiology Estimates for MC4R Pathway-driven Disorders

Keith Gottesdiener, M.D.
Chief Executive Officer

Building the Largest Genetic Database for Severe Obesity

Clinical Characteristics:

Early-onset obesity

Obesity is severe

BMI> 40* as adults

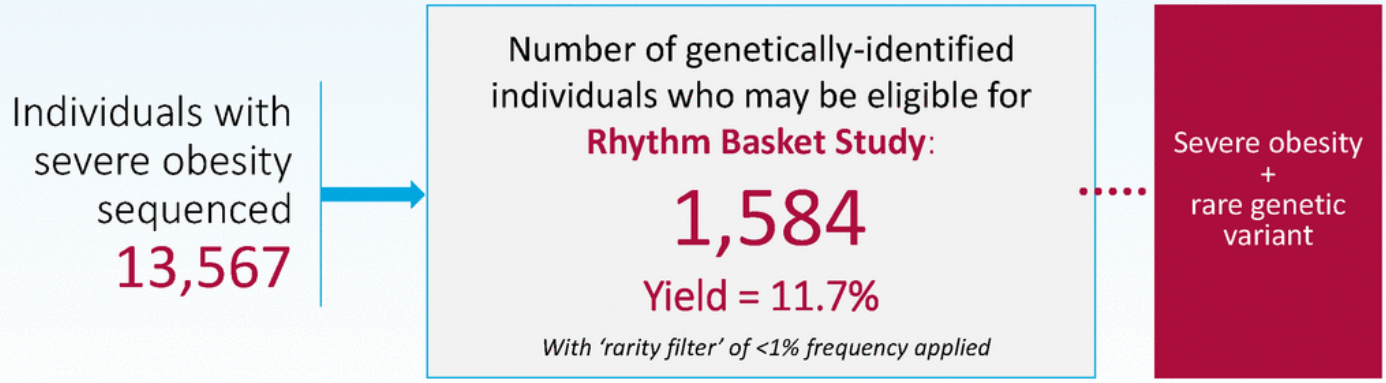
Rhythm's growing database has

13,567

samples**

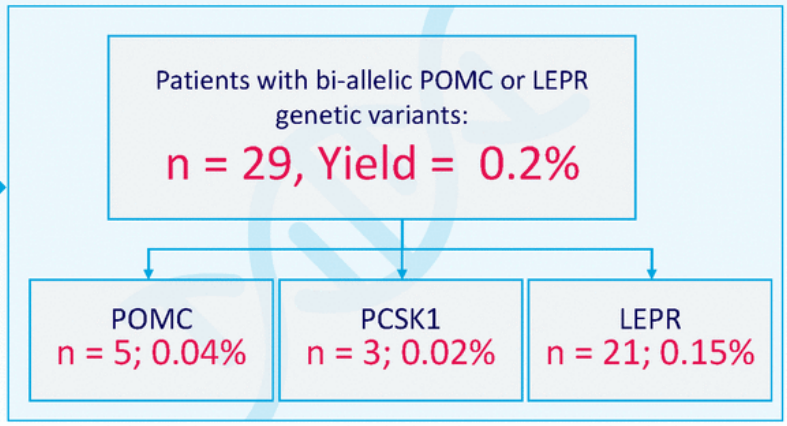
* For children under 12, included those who are 1.4 X 95th percentile for weight; ** As of June 2019.

Sequencing Focused on Genetically-identified Rare Disorders of Obesity



Sequencing Yield Supports Ultra-rare Populations in POMC and LEPR Deficiency Obesities

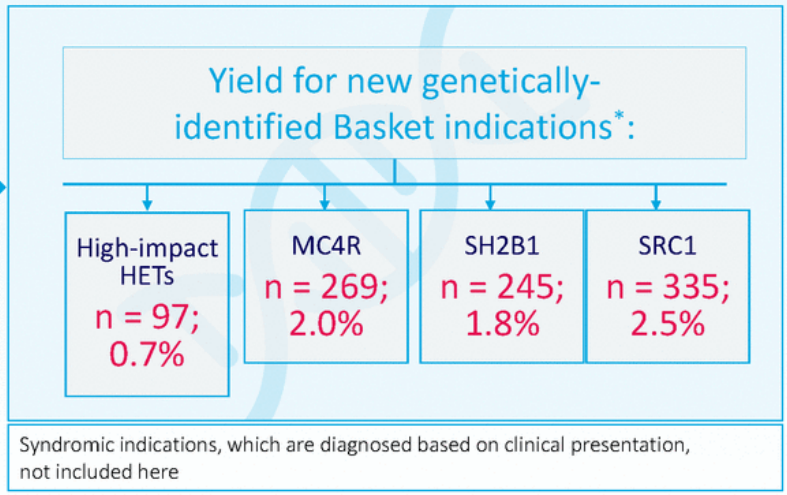
Individuals with severe obesity sequenced
13,567



Consistent with Rhythm's U.S. clinical epidemiology estimates of 100-500 for POMC deficiency obesity and 500-2,000 for LEPR deficiency obesity

Sequencing Yield for New Basket Indications Points to Significant Opportunity

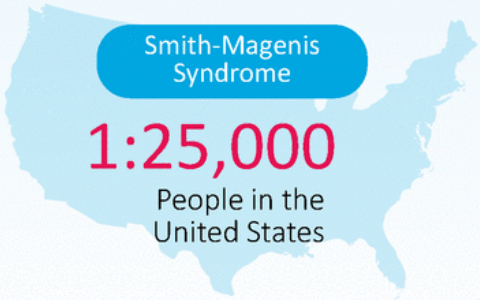
Individuals with severe obesity sequenced
13,567



Syndromic indications, which are diagnosed based on clinical presentation, not included here

*Basket yield includes 683 individuals with other variants; some patients have more than one variant.

Obesity Affects a Meaningful Portion of Patients with Smith-Magenis Syndrome



10%
of patients have RAI1 variants

90%
of patients have 17p11.2 chromosomal deletion

U.S. epidemiology estimate of SMS patients living with severe obesity:

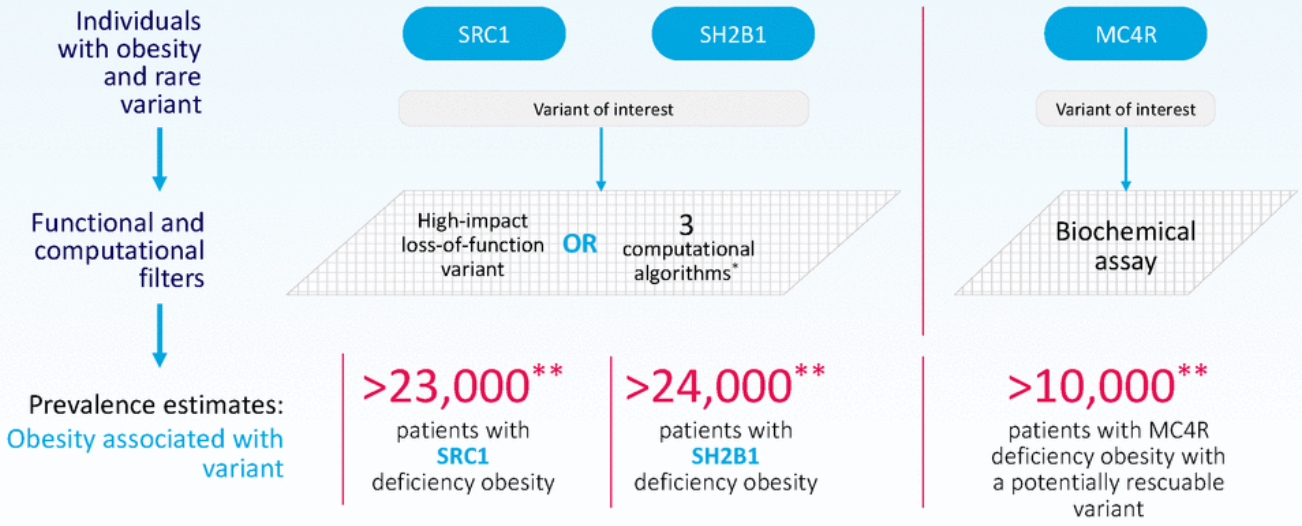
67%
of SMS patients with RAI1 variant live with obesity*

13%
of SMS patients with 17p11.2 deletion live with obesity*

U.S. epidemiology estimate of SMS patients living with severe obesity	> 2,400

* Elsea and Girirajan, European Journal of Human Genetics, 16;412-421 (2008)

Translating Rhythm Sequencing Data to U.S. Prevalence Estimates



***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 J.M., et al. Nat. Methods 11(4):361-362 (2014) ** 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)

U.S. Prevalence Estimates for MC4R Pathway-driven Rare Genetic Disorders Obesity

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

High-impact HETs: > 20,000*

Pivotal indications: up to 5,000*
POMC deficiency obesity
LEPR deficiency obesity
Bardet-Biedl syndrome
Alström syndrome

* 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.

Rhythm Engine and the Basket Study

Murray Stewart, M.D., Chief Medical Officer

Rhythm Engine: Identifying Patients, Discovering Diseases and Advancing a Therapy

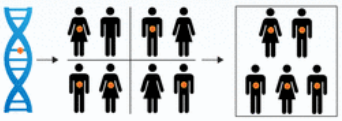
GO ID genotyping

UNCOVERING RARE OBESITY

Sponsored genetic testing program

Biobanks

Phase 2 Basket Study



TEMPO

TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

Uncovering Rare Obesity Program Broadens Access to Genetic Testing and Facilitates Diagnosis of Rare Genetic Disorders of Obesity

Raise Awareness

Elevate awareness and increase suspicion of rare genetic disorders of obesity (RGDO)

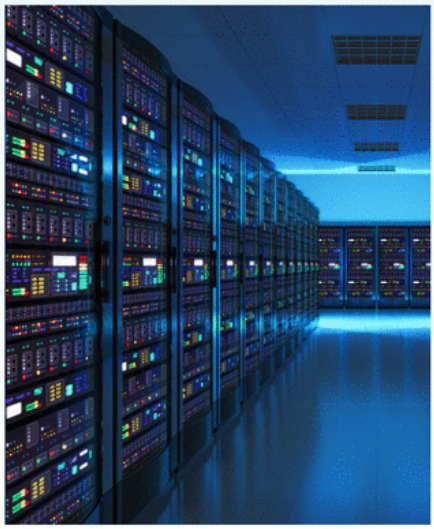
Increase Frequency of Genetic Testing

Providing simple and efficient genetic testing program

Improve Access to Genetic Testing

Offering no-cost genetic testing option

Biobanks Providing Large Data Sets for Patient Identification and Furthering Disease Understanding



Established collaborations with

9

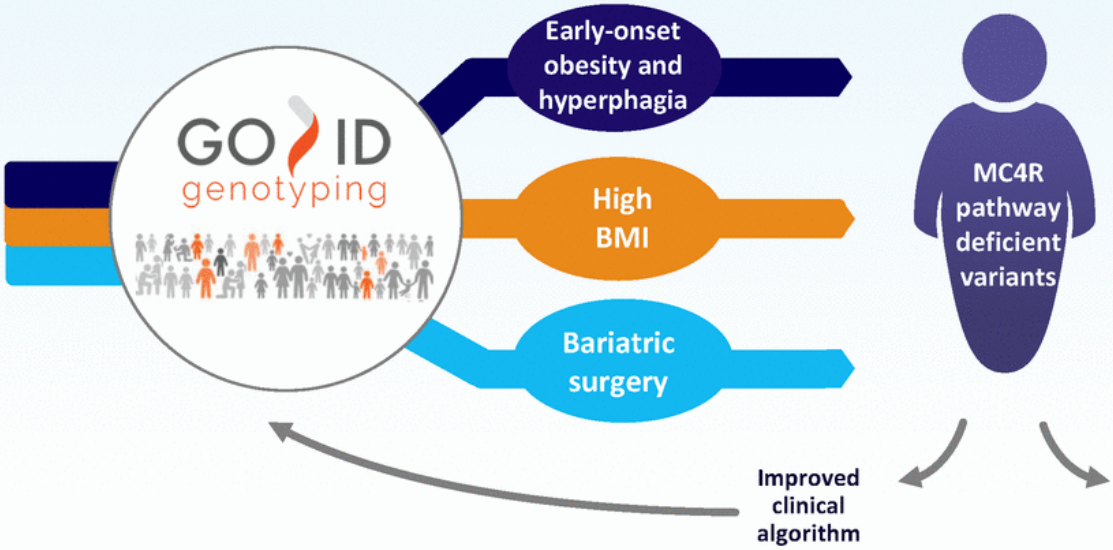
well-known biobanks giving Rhythm access to sequencing data from

23,000

individuals with severe obesity

- Identification of eligible patients for potential trial enrollment and treatment
- Data for variant characterization
- Evaluation of clinical features that may be predictive of genotypes of interest

GO-ID Driving Genetic Testing and Patient Finding while Evaluating and Enriching Distinct Patient Subsets



81 sites

9 countries

Significant overlap with Basket Study

Community Building Through the TEMPO Registry

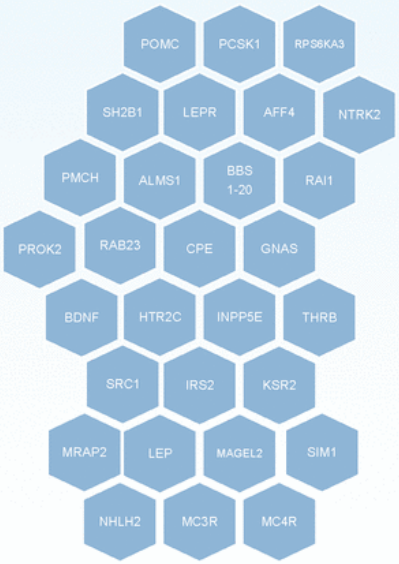
TEMPO

TRACING THE EFFECT OF THE MC4R PATHWAY IN OBESITY

Designed to complement existing patient registries (e.g. CRIBBS for BBS) and to facilitate **better understanding of rare genetic disorders of obesity** in the medical community

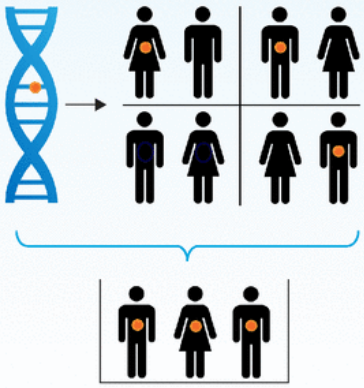
- Target enrollment of ~1,000 patients
- Genetic screening through GO-ID
- Potential enrollment in Phase 2 basket studies

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



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

- 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



- Multiple cohorts of HETs patients enrolled
- Enrolling patients in new indications

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

Updated Phase 2 Data in BBS Show Continued Responses at ~Two Years

	Gene	Treatment, weeks	Weight Change from Baseline	Hunger Score Change from Baseline
Patient 1	BBS1	123	**-36.7%**	-33%
Patient 2	BBS2	119	**-15%**	-71%
Patient 3	BBS10	121	**-28%**	-100%*
Patient 4	BBS12	108	**-25%**	67%
Patient 6	BBS5	83	**-10.8%**	-38%
Patient 7	BBS4	73	**-17.9%**	-14%**

- Six of nine pts 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
  - 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. Pt subsequently entered long-term extension study
  - Two patients (one non-genetically confirmed) withdrew due to lack of weight loss

*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.

Updated Phase 2 Data in Alström Syndrome Show Variable Responses

	Age at enrollment/ Sex	Baseline Weight (kg)	Treatment, weeks	% Weight Change from Baseline	% Hunger Score Change from Baseline†
Patient 1	12/M	78.6	95	**-20%**	-25%
Patient 3*	15/F	70.7	84	**1%**	-38%
Patient 4	16/F	91.6	68	**-6%**	0%

- Patient 1 showed strongest response and HCP started decreasing the dose after 32 weeks of treatment; currently 0.5 mg/day and 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

Community Building and Patient Finding

Nithya Desikan, Chief Commercial Officer

Community Building Off and Running

Disease Journey

- Reducing barriers to diagnosis

Advocacy Relations

- Building relationships with multiple advocacy groups in US and EU

Established Registries

- CRIBBS (Bardet-Biedl syndrome registry)
- Large cohorts of known patients

Field Medical Outreach

- GOLD academies building awareness and community
- Field team members connecting with HCPs

Mapping the BBS Patient Journey to Diagnosis and Beyond

Working to Reduce Barriers to Diagnosis


Solomon, Living with BBS

Variability:
Variability of presentation and progression of the disease

Initial concerns dismissed:
Caregivers collect "proof" to raise HCP suspicion

Medical Team:
Specialists brought in as symptoms increase and worsen with no coordinated care

Specialists may include:
Pediatricians, ENTS, ophthalmologist, endocrinologist, nephrologist and/or therapist

Discovering BBS:
Happens by chance for most via an encounter with someone familiar with BBS; or someone diagnosed with it.

Patient Advocacy Collaborations Advance Common Mission to Improve Lives of Patients, Families Affected by Bardet-Biedl, Alström Syndromes

- Increase disease awareness and reduce barriers to diagnosis
- Gain feedback on clinical trial design and materials
- Support pathway to regulatory approval

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

Bardet Biedl Syndrome Foundation

BBS UK
Bardet-Biedl Syndrome UK

Alström Syndrome UK
Strength for today, hope for the future

ASI
Alström Syndrome International

Community Building: Genetic Obesity Leadership and Network Development

GOLD Academy
Genetic Obesity Leadership Development

Launched in 2019 to educate health care providers, develop management strategies and build a peer-to-peer network

Established education modules on rare genetic disorders of obesity, hyperphagia, clinical characteristics, potential diagnosis and management strategy

20
GOLD Academy faculty

20
programs completed or in process

>500
Health care providers have or are expected to participate

Patient Finding Efforts have Resulted in Many Identified Patients with BBS and Alström syndrome*

Field Medical teams survey of physicians confirms original prevalence of estimates for Bardet-Biedl, Alström syndromes

Estimated Clinical Epidemiology

2,500 in U.S.

2,500 in EU

Bardet-Biedl syndrome

500 in U.S.

500 in EU

Alström syndrome

Rhythm Physician Interactions

224

physicians who treat BBS patients

93

physicians who treat patients with Alström syndrome

BBS Patients Identified

500-800* in U.S.

1,000 - 1,500* in EU

Patients with Alström Syndrome Identified

50-70* in U.S.

200-225* in EU

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

Conclusion

Rhythm Expects Significant Progress in 2019 and 2020

✓	Updated interim data for HET obesity
✓	Positive topline data from both POMC and LEPR Phase 3 studies
✓	Expand Phase 2 basket studies into four additional MC4R pathway disorders
2H19	Complete pivotal enrollment in BBS and Alström Phase 3 study
4Q19-1Q20	Initial NDA submission for setmelanotide in POMC and LEPR
2020	Additional data in high impact HETs obesity and additional Basket indications
2020	Topline data from BBS and Alström Phase 3 study

Rhythm Is Transforming the Care for Patients with Rare Genetic Disorders of Obesity Driven by deficiencies within the MC4R Pathway

Discovering MC4R pathway disorders that cause obesity and identifying patients

Rhythm has expanded the Basket Study into **4 new indications**, all with strong scientific ties to the MC4R pathway

Sequencing has improved our understanding of:

- **POMC and LEPR**
- **New indications**, for which the estimated prevalence is substantial

Significant progress in Bardet-Biedl and Alström syndromes programs

- Patients in Phase 2 trial showing deepening of response over longer-term
- Patient finding efforts are exceeding expectations

Rhythm Engine is executing on a scientific approach to identifying patients with rare genetic disorders of obesity related to the MC4R pathway


Rhythm
PHARMACEUTICALS

Setmelanotide has Potential to Address Multiple Genetic Disorders that Disrupt MC4R Pathway Function