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): **March 28, 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)

500 Boylston Street, 11th 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))

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 March 28, 2019, Rhythm Pharmaceuticals, Inc. (the "Company") issued the attached press release regarding interim clinical data and expected 2019 and 2020 milestones. Further, the Company reviewed a slide presentation during a conference call on March 28, 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. 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 March 28, 2019.
99.2	Company Presentation dated March 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: March 28, 2019

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

Rhythm Pharmaceuticals Announces Promising Clinical Data in MC4R Pathway Heterozygous Obesity and Strategy for Further Development

— Stratifying Enrollment of MC4R Pathway Heterozygous (HET) Patients in Phase 2 Basket Study Based on Loss-of-Function (LOF) Variants—
— Preliminary Data Show Consistent Weight Loss and Decreases in Hunger Observed in Patients with High-Impact LOF Variants —
— Management to Host Conference Call at 8:30 am ET Today —

Boston, MA — March 28, 2019 — Rhythm Pharmaceuticals, Inc. (Nasdaq:RYTM), a biopharmaceutical company focused on the development and commercialization of therapeutics for the treatment of rare genetic disorders of obesity, today announced updated interim data from its ongoing Phase 2 basket study of setmelanotide in melanocortin-4 receptor (MC4R) pathway heterozygous (HET) obesity. In addition, the company unveiled plans to continue evaluating setmelanotide in HET obesity, with patients enrolled into cohorts based on their loss-of-function (LOF) variants.(1) This decision is based primarily on clinical results, which show a more consistent treatment benefit in patients with higher-impact LOF variants.

“We are committed to advancing setmelanotide as swiftly as possible, with the goal of addressing the severe, early-onset obesity and relentless hunger experienced by people living with rare genetic disorders of obesity,” said Keith Gottesdiener, M.D., Chief Executive Officer of Rhythm. “Today’s announcement marks an important milestone in our efforts to assess the full range of setmelanotide’s potential applications. As part of our work to better understand the biological underpinnings of rare genetic disorders of obesity, we have identified a wide spectrum of heterozygous LOF variants and believe there is a relationship between LOF variant and impact on pathway function. This belief is corroborated by the new clinical data announced today, as patients with high-impact LOF variants experienced a more consistent and greater response to setmelanotide. The data also provide a compelling strategy for further development. We look forward to pursuing proof-of-concept in HET patients with high-impact LOF variants, while exploring setmelanotide’s potential benefit in patients with other variant subgroups and leveraging our genotyping engine to accelerate HET patient identification broadly.”

HET obesity is caused by the mutation of one of two genetic copies of a gene in the MC4R pathway and can include patients with heterozygous mutations in genes such as *POMC*, *PCSK1* and *LEPR*. While there are numerous individual case histories of HET patients with severe, early-onset obesity and hyperphagia, HET patients have variable penetrance of obesity. Variable penetrance of disease in patients with heterozygous variants is a phenomenon observed in many genetic disease states. In patients with HET obesity, Rhythm believes this variability may be driven by the type of LOF variant, with higher-impact LOF variants more substantially impairing MC4R pathway function and, therefore, increasing the likelihood of developing hyperphagia and, subsequently, severe obesity.

Rhythm’s clinical development efforts are initially focused on achieving proof-of-concept in patients with well-characterized, high-impact LOF variants. Patients with these variants can present clinically with the same severe, early-onset obesity and hyperphagia characteristic of other rare genetic disorders of obesity. Rhythm estimates a prevalence of upwards of 20,000 severely obese people living with high-impact LOF variants in the United States. Rhythm will also explore setmelanotide’s potential in cohorts of HET patients with other genetic variants, in order to drive understanding of HET biology and identify additional people who may be setmelanotide-responsive.

New Clinical Data from Phase 2 Basket Study in HET Obesity

Today, Rhythm announced preliminary data from 13 HET patients who were treated with setmelanotide, including four patients with high-impact LOF variants and nine patients with other LOF variants:

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(1) A genetic variant is a difference in DNA sequences between an individual and the population.

- All four patients with high-impact LOF variants remain on therapy, including two patients who have been on treatment for more than 29 weeks. (2) The first patient, who entered the study weighing 451 pounds, lost 40.5 pounds (nine percent body weight) and experienced a hunger score decrease of 90 percent after 37 weeks of treatment with setmelanotide. The second patient, who entered the study weighing 284 pounds, lost 49 pounds (17.3 percent body weight) and experienced a hunger score decrease of 71.4 percent after 29 weeks of treatment. The two additional patients have been on treatment for a short duration and are showing promising weight loss and hunger score decreases during dose titration.
- Five of nine patients with other LOF variants remain on therapy, with treatment durations ranging from seven to 74 weeks. This includes the two responding patients on whom Rhythm reported data in June 2018. Across these five patients, one experienced a clinically-meaningful weight loss of greater than 10 percent, three experienced weight loss between five and eight percent, and one has been on treatment for a short duration and it is too early to assess response to therapy. Among the four response-evaluable patients, hunger score decreases ranged from 20 to 80 percent.
- Four of nine patients with other LOF variants discontinued treatment, including one patient who was discontinued due to lack of efficacy (previously reported in June 2018). The other three patients were discontinued following less than four weeks on therapy and therefore efficacy could not be evaluated. This includes the two patients on whom Rhythm reported in June 2018, both discontinued due to adverse events (AEs). In addition, one patient was withdrawn by the site for patient non-compliance.

Consistent with prior clinical experience, setmelanotide continues to be well-tolerated. There were no serious AEs reported and no new discontinuations due to AEs since those reported in June 2018.

Clinical Development Plans in HET Obesity

Rhythm plans to continue enrolling HET patients in its Phase 2 basket study in cohorts stratified by LOF variant. In addition to pursuing proof-of-concept in high-impact LOF variants, Rhythm also plans to explore setmelanotide's potential in additional patient cohorts, including patients with partial LOF or newly-characterized variants, patients with more common variants, and patients with composite HET variants. Rhythm expects patient enrollment to continue at least through the remainder of 2019, with updated data to follow in 2020. Rhythm anticipates that these data will help inform the most appropriate strategy to support the potential registration and approval of setmelanotide for the treatment of setmelanotide-responsive subgroups of HET obesity.

In parallel, Rhythm intends to further ongoing efforts to better understand HET obesity and facilitate patient identification. In order to add to the pool of high-impact variants, Rhythm is undertaking a comprehensive effort to screen and classify new and uncharacterized variants in the MC4R pathway, using both computational models for assessing variants and biochemical analysis of variants in *POMC*, *PCSK1*, and *LEPR* to assess functional impact. Rhythm estimates that there are thousands of potential new and uncharacterized HET variants in MC4R pathway genes. Additionally, the company plans to leverage the Rhythm Engine, a portfolio of programs including the GO-ID genotyping study, the TEMPO Registry and the Phase 2 basket study, to identify patients who may be eligible for treatment with setmelanotide, rapidly enroll eligible patients in the ongoing trial, and better characterize the ongoing impact and burden of disease on patients and their caregivers.

Upcoming Milestones Across Broader Setmelanotide Development Program

Rhythm is advancing its development program for setmelanotide toward key 2019 and 2020 milestones. The company expects to:

- Announce topline data from its ongoing pivotal Phase 3 trials in patients with pro-opiomelanocortin (POMC) deficiency obesity and leptin receptor (LEPR) deficiency obesity in the third quarter of 2019 and, if positive,

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(2) Total treatment duration as reported always includes any titration period, which can last 6-12 weeks before reaching a therapeutic dose.

submit concurrent New Drug Application filings to the U.S. Food and Drug Administration in the fourth quarter of 2019 or early 2020.

- Complete enrollment in its combined pivotal Phase 3 trial in Bardet-Biedl syndrome (BBS) and Alström syndrome in the second half of 2019, and to report topline data in 2020.
- Expand its ongoing Phase 2 basket study into additional MC4R pathway disorders in 2019, while continuing to enroll patients with POMC epigenetic disorders.

Conference Call Information

Rhythm Pharmaceuticals will host a live conference call and webcast at 8:30 a.m. ET today to discuss these clinical data and review its strategy for further development in HET obesity. The conference call may be accessed by dialing (844) 498-0570 (domestic) and (409) 983-9726 (international) and referring to conference ID 7579267. A webcast of the conference call will be available in the Investors section of the Rhythm website at ir.rhythmtx.com. The archived webcast will be available on Rhythm's website approximately two hours after the conference call and will be available for 90 days following the call.

About Setmelanotide

Setmelanotide is a potent, first-in-class, MC4R agonist in development for the treatment of rare genetic disorders of obesity. Setmelanotide activates MC4R, part of the key biological pathway that independently regulates energy expenditure and appetite. Variants in genes within the MC4R pathway are associated with unrelenting hunger and severe, early-onset obesity. Rhythm is currently developing setmelanotide as a replacement therapy for patients with monogenic defects upstream of MC4R, for whom there are no effective or approved therapies. The FDA has granted Breakthrough Therapy designation to setmelanotide for the treatment of obesity associated with genetic defects upstream of the MC4 receptor in the leptin-melanocortin pathway, which includes POMC deficiency obesity, LEPR deficiency obesity, BBS and Alström syndrome. The European Medicines Agency has also granted PRIority MEdicines (PRIME) designation for setmelanotide for the treatment of obesity and the control of hunger associated with deficiency disorders of the MC4R pathway.

About Rhythm Pharmaceuticals

Rhythm is a biopharmaceutical company focused on the development and commercialization of therapies for the treatment of rare genetic disorders of obesity. Rhythm is currently evaluating the efficacy and safety of setmelanotide, the company's first-in-class MC4R agonist, in Phase 3 studies in patients with POMC deficiency obesity, LEPR deficiency obesity, BBS, and Alström syndrome. Rhythm is dedicated to improving the understanding of severe obesity that results from specific genetic disorders. 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 expectations regarding its estimates of patient population, its efforts to identify patients, anticipated timing for enrollment and design of clinical trials, anticipated timing for submission of New Drug Application filings, and timing of the release of results of clinical trials. Statements using word such as "expect", "anticipate", "believe", "may", "will", "plans" 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, 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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Exhibit 99.2

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

March 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, estimated addressable patient populations, anticipated timing for enrollment, design and completion of clinical trials, the timing for filing of an NDA, the release of results of clinical trials, 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.

Executive Summary

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

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

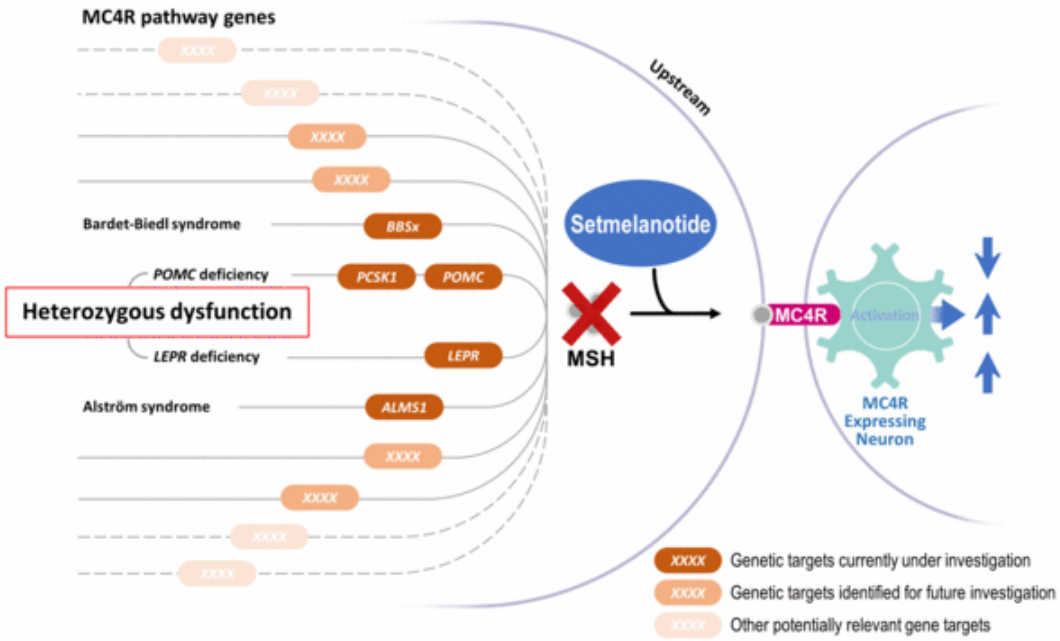
Updated data shows greater, more consistent weight loss in HET patients with high-impact LOF variants

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

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

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

Rhythm Focus: Genetic Defects in the MC4R Pathway



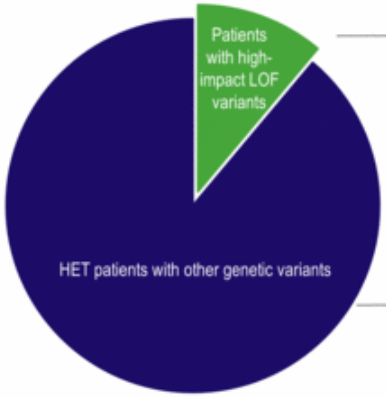
Defining MC4R Pathway Heterozygosity

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

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

Stratifying HET Patients Based on Genetic Variant: Significant Population

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



graph not drawn to scale

Rhythm's Approach

INITIAL SUBGROUP FOCUS:

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

ADDITIONAL SUBGROUPS:

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

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

All High-Impact LOF Patients Appear Setmelanotide-Responsive

Preliminary data – March 2019

All patients ongoing:

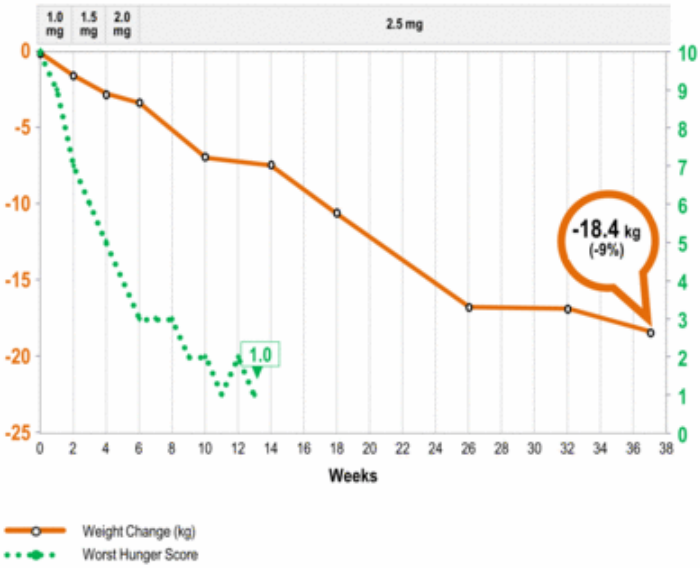
Patient	Total treatment duration[1] (weeks)	Baseline Weight (kg/(lbs))	Weight Loss (kg/(lbs))	Weight loss	Change in Hunger Score (10 pt scale)	Hunger score reduction
1	37	204 (451)	18.4 (40.5)	9.0%	-9	90.0%
2	29	129 (284)	22.3 (49.0)	17.3%	-5	71.4%
3	4	187 (412)	7.1 (15.6)	3.8%	-4	40.0%

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

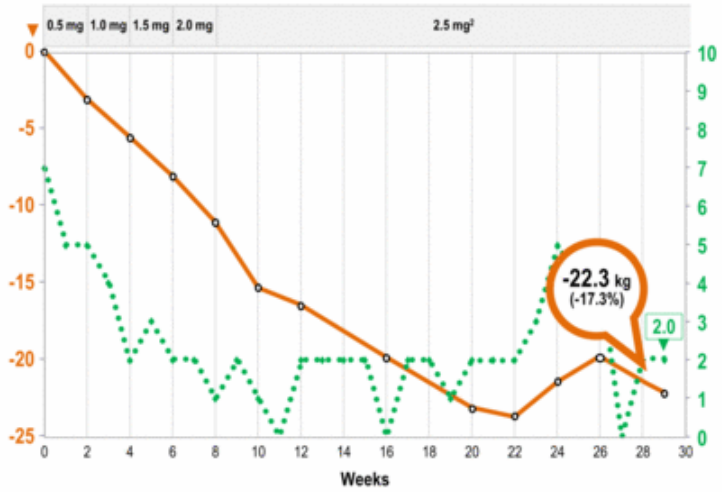
[1]Total treatment duration including any titration period which can last 6-12 weeks. [2]Too early in treatment to provide data, but initial weight and hunger score reductions were noted. Note: these are all new patients since last update.

High-Impact LOF Patients #1 & 2

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



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



Weight Change (kg)
Worst Hunger Score

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

Patients in Other Subgroups Have More Variable Responses

Five patients ongoing[1]:

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

Four patients discontinued treatment:

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

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

Safety & Tolerability Data Consistent with Prior Experience

Safety profile for all 13 HET patients:

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

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

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

3 YEARS

11 YEARS, 231 POUNDS

23 YEARS, 450 POUNDS

INFANCY:

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

4 YEARS:

Diagnosed with POMC Heterozygous Deficiency Obesity

CHILDHOOD:

Self-isolation and missed school days

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

ADOLESCENCE:

Put on anti-depresseants

Numbness and agonizing back pain

Abnormal pubertal development

23 YEARS:

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

Key Imperatives for Execution of HET Development Plan

ADD TO POOL OF HIGH-IMPACT LOF VARIANTS

Screen and classify potential new and uncharacterized variants:

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

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

CONTINUE AND EXPAND GENOTYPING EFFORTS

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

ENROLL ELIGIBLE PATIENTS IN BASKET STUDY

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

Rhythm Expects Significant Progress in 2019 and 2020

✓	Updated interim data for HET obesity
3Q19	Topline data from both POMC and LEPR Phase 3 studies
4Q19-1Q20	Initial NDA submission filings for setmelanotide in POMC and LEPR
2H19	Complete pivotal enrollment in BBS and Alström Phase 3 study
2019	Update on ongoing efforts to increase patient identification
2019	Expand Phase 2 basket studies into additional MC4R pathway disorders
2020	Topline data from BBS and Alström Phase 3 study
2020	Additional data in HET obesity

Conclusions

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

Preclinical Data:

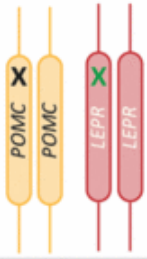
- MC4R pathway **heterozygous (+/-)** mice show intermediate levels of obesity versus knockout and wild-type mice

Clinical and Genetic Evidence:

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

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

Composite HET: Multiple Impairments of the MC4R Pathway

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

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

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