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): **February 2, 2021**

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) (Zip Code)

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

N/A
(Former name or former address, if changed since last report)

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.

On February 2, 2021, Rhythm Pharmaceuticals, Inc. (the "Company") posted a corporate slide presentation in the "Investors & Media" portion of its website at ir.rhythmtx.com. A copy of its current corporate slide presentation is attached to this Current Report on Form 8-K as Exhibit 99.1. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.1.

The information contained in Item 7.01 of this Form 8-K (including Exhibit 99.1 attached hereto) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly provided by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following exhibit relating to Item 7.01 shall be deemed to be furnished, and not filed:

Exhibit No.	Description
99.1	Corporate Slide Presentation of Rhythm Pharmaceuticals, Inc. dated February 2, 2021
104	Cover Page Interactive Data File (embedded within the inline XBRL document)

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: February 2, 2021

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

Rhythm Pharmaceuticals

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

February 2021

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 without limitations statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, anticipated timing for enrollment and release of our clinical trial results, the timing for filing of NDA, MAA or other similar filings, our goal of changing the paradigm for the treatment of rare genetic disorders of obesity, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, and strategy, prospects and plans, including regarding the commercialization of setmelanotide. 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, the impact of the COVID-19 pandemic on our business operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, 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.

Living with Early-onset, Severe Obesity and Hyperphagia

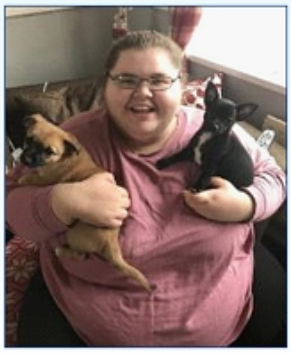
Hallmark Symptoms of Rare Genetic Diseases of Obesity

Adalissa and Solomon with their siblings (unaffected)

"They are constantly, all day long saying they are hungry and asking what's for the next meal and what are we eating the next day. We keep a menu planned and if we deviate from that menu it's a disaster."

"We have had to put locks on our cupboards and fridge and freezer to protect them from themselves!"

*– Olivia, Mother of Adalissa and Solomon, siblings diagnosed with **BBS***



Katy, at 23 years old, 450 pounds

"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."

*- Katy, diagnosed with **POMC heterozygous deficiency obesity***

Our mission:

Change the Paradigm for the Treatment of Rare Genetic Diseases of Obesity

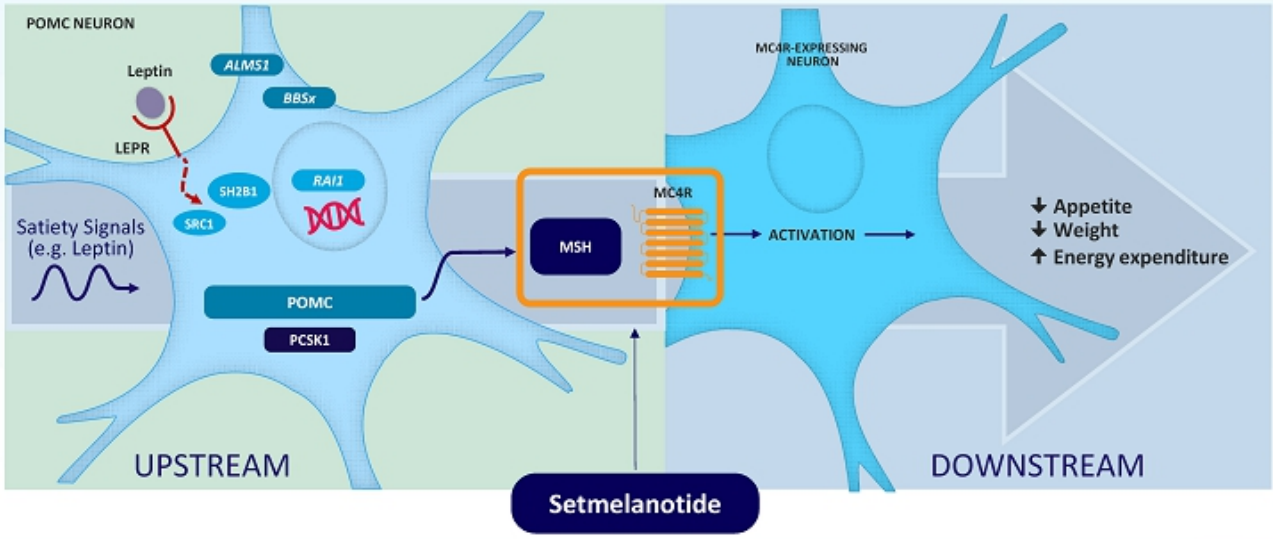
Classic Rare Disease Challenges Apply to Genetic Obesities

- Lost in the system
- Little knowledge
- Little awareness
- No tools or testing
- No treatment

Worst case: *An irritation. It's your fault. Eat less, exercise more.*

MC4R Pathway Biology is Clear and Strong: Regulates Hunger, Caloric Intake, and Energy Expenditure, and, Consequently, Body Weight

Setmelanotide can redress MC4R pathway impairment contributing to early-onset, severe obesity



Rhythm Pipeline Focused on MC4R Pathway Diseases

		Disease	Phase 2	Phase 3	Regulatory Submission	Approved
IMCIVREE™ (setmelanotide) injection		Obesity due to POMC, PCSK1 or LEPR deficiency*			EU	U.S.
Setmelanotide	Bardet-Biedl and Alström syndromes					
	Weekly formulation		Initiate 2H21			
	MC4R Pathway Studies	Phase 3 MC4R Pathway Study: HETs, SRC1, SH2B1	Initiate 2H21			
		Phase 2 Basket Study: HETs, SRC1, SH2B1, MC4R-rescuable, Smith-Magenis syndrome	New data 1H21			
		Phase 2 Exploratory Pathway Basket Study: Variants in 31 genes	Initiate 2H21			
		Pediatric Study	Initiate 2H21			
		Hypothalamic obesity	Initiate 1H21			

* Indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance.

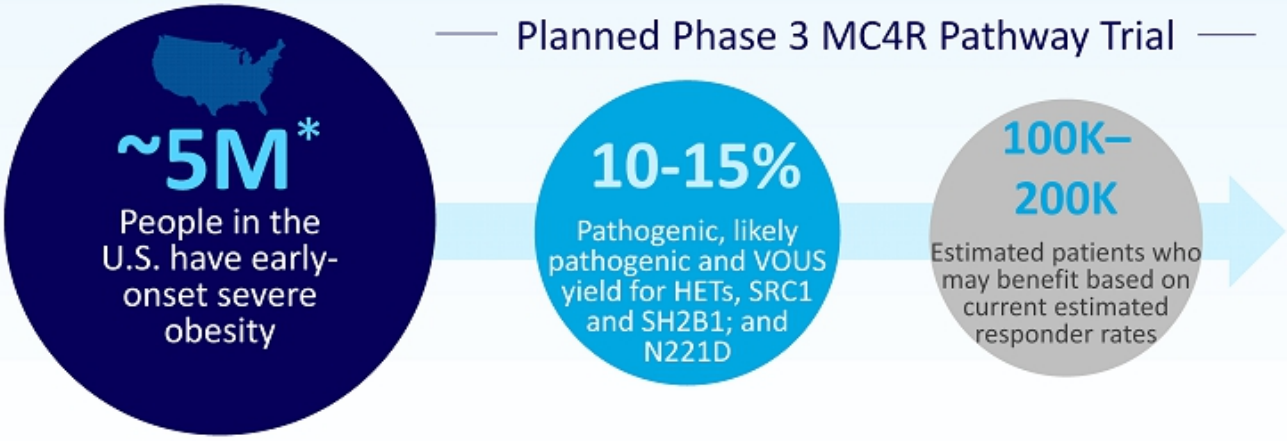
Rare Genetic Diseases of Obesity Associated with the MC4R Pathway Represent a Significant Opportunity

IMCIVREE™ (setmelanotide) injection	Obesity due to POMC, PCSK1 or LEPR deficiency	~600 – 2,500*
Bardet-Biedl syndrome		~1,500-2,500*
Alström syndrome		~500-1,000*
HETs	HETs (POMC, PCSK1 or LEPR) heterozygous deficiency obesity	100,000 – 200,000*
SRC1 or SH2B1 deficiency obesity		
MC4R-rescuable deficiency obesity		~10,000**
Hypothalamic obesity		1,700-3,400***
MC4R Pathway (31 additional genes)		TBD

LEPR, leptin receptor, POMC, pro-opiomelanocortin; MC4R, melanocortin-4 receptor.

* Estimated prevalence of U.S. patients based on company estimates; ** Estimated prevalence of U.S. patients with addressable variants of the MC4R; *** RYTM believes a portion of these patients may be setmelanotide responsive; Estimated prevalence of craniopharyngioma in the United States is 3400-6800 (Garnet et al, 2007), and approximately 50-55% these patients develop severe obesity post tumor resection and experience rapid weight gain in first 6-12 months. (Zacharia, 2012)

Total Potential Addressable Market for Five Genes in U.S. Exceeds 100K



* 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018[1]); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017)

Now Approved in the United States; Initial Commercialization in 1Q21

IMCIVREE™
(setmelanotide) injection

Obesity due to POMC, PCSK1 deficiency	~100-500*
Obesity due to LEPR deficiency	~500-2,000*

Approved by the U.S. FDA for chronic weight management in people with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as:

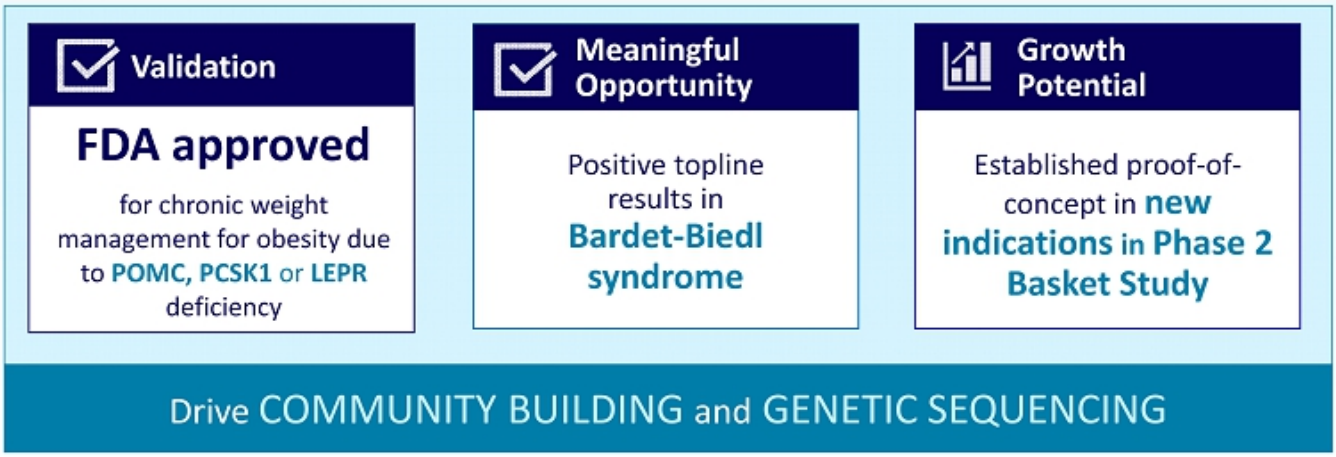
- **Pathogenic;**
- **Likely pathogenic;**
- **Variant of uncertain significance (VOUS)**

* Estimated prevalence of U.S. patients based on company estimates.

Bardet-Biedl Syndrome

Phase 3 Update

Working to Change the Paradigm for the Treatment of Rare Genetic Diseases of Obesity



Phase 3 Bardet-Biedl and Alström Syndromes Trial Met Primary and All Key Secondary Endpoints

Setmelanotide achieved statistical significance and delivered clinically meaningful weight loss and hunger reduction

Phase 3 Topline Data (n=31[a])

34.5%[b]	**-6.2%**	**-30.8%**	**60.2%**
p=0.0024	**p<0.0001**	**p<0.0001**	**p<0.0001**
≥10% weight loss	mean weight reduction	mean hunger score reduction	≥25% reduction in worst hunger

All primary endpoint responders were BBS patients.

As presented on Dec. 22, 2020, reflecting data cut-off of Dec 2. 2020. [a]Study participants older than 12 counted in full analysis set for primary and key secondary endpoints; Five participants were younger than 12, and two participants older than 12 discontinued during placebo-controlled period prior active therapy. [b]Response rate estimated based on imputation methodology discussed with FDA.

A Closer Look at Patients with Bardet-Biedl Syndrome

28 BBS
Patients included in primary analysis set

- Mean actual weight loss: **-8.7 kg**
- Mean percentage weight loss: **- 7.5%**
- 15 of 28 were adults

11 BBS (38.1%)[a]
patients achieved **≥10%** weight loss:

- Mean actual weight loss: **-17.2 kg**
- Mean percentage weight loss: **- 14.7%**
- 8 of 11 were adults

53% of adult BBS patients (8/15) achieved ≥10% weight loss

73% of adult BBS patients (11/15) had ≥5% weight loss

U.S. and EU regulatory submissions for BBS planned for 2H2021

As presented on Dec. 22, 2020, corporate conference call, reflecting data cut-off of Dec 2. 2020. [a]Response rate estimated based on imputation methodology discussed with FDA.

Setmelanotide and BMI-Z Scores for Pediatric BBS Patients in Phase 3 Trial

- BMI-Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child age and sex.
- Setmelanotide achieved statistically significant and clinically meaningful improvements in BMI-Z scores in pediatric patients with obesity due to POMC, PCSK1 or LEPR deficiency.
- Setmelanotide achieved statistically significant and clinically meaningful improvements in BMI-Z scores in pediatric patients with BBS (predefined exploratory endpoint).

BMI-Z Score or BMI standard deviation score: Number of Standard Deviations from Median BMI by Child Age and Sex

At 2 years of age, the patient's BMI was 38.7 kg/m^2

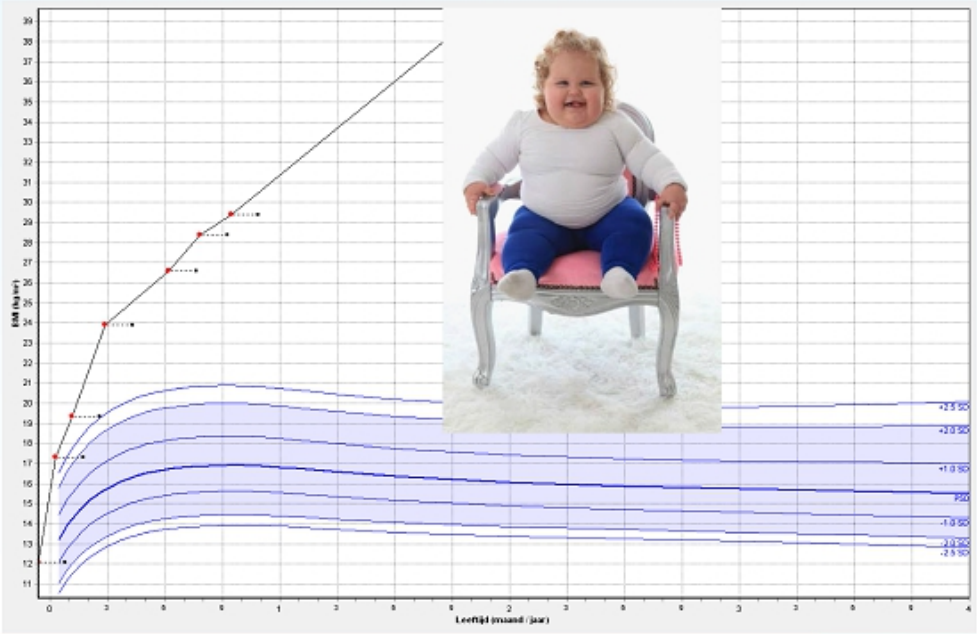
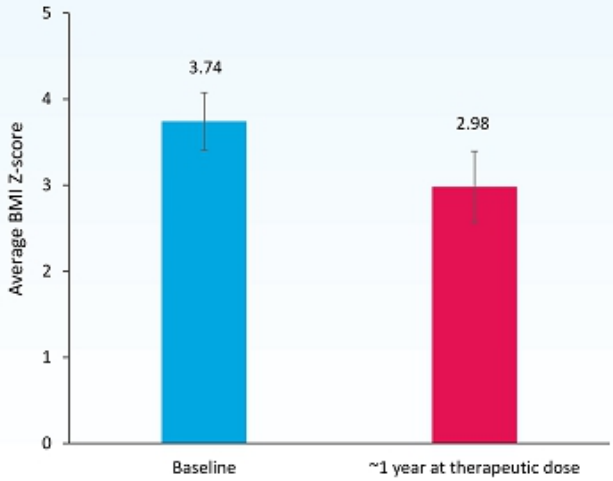


Chart adapted from Kleinendorst et al 2017
Data on file. Image used with permission.

Setmelanotide was Associated with Reductions in BMI-Z Score in Participants with BBS (<18 Years Old) Over ~1 Year at Therapeutic Dose

Participants aged <18 years (n=16)

Mean change from baseline: -0.76
Mean % change from baseline: -24.48%; (P=0.0006)



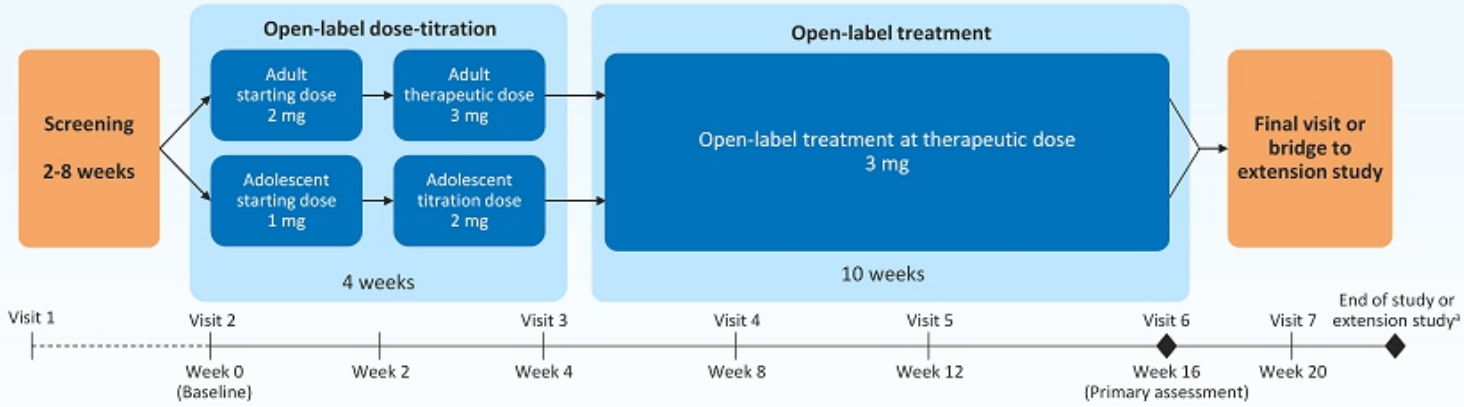
BMI, body mass index. Error bars are the standard error of the mean, which was calculated by dividing the standard deviation by the square root of n.

Phase 2 Basket Study Results

2021 Highlights: Delivered on Proof of Concept in Basket Indications with Significant Market Opportunity

- Rhythm's largest data readout from five genetic cohorts with 65 patients
- Proof of concept achieved in five MC4R pathway genes
- U.S. target patient population across these five genes expanded to 100K-200K
- Largest known genetic obesity database of approximately 37,500 individuals
- Support of our approach for gene selection and variant classification
- Two new trials planned for MC4R pathway diseases in a total of 36 genes

Phase 2 Basket Study Evaluated Response at Three Months of Therapy



[a]Final visit at week 20 for patients not enrolling in a separate extension study.

HETs Patient Demographics – Full Analysis Set

Baseline Characteristics	HETs patients (N=35)
Mean age (years) at enrollment (SD)	39 (18)
Range	15, 68
Female	68.6%
Male	31.4%
Mean weight lbs (SD)	315.9 (65.7)
Range lbs	210, 459
Mean weight kg (SD)	143.3 (29.8)
Range kg	95, 208
BMI Mean kg/m^2 (SD)	50, (9)
Range	35, 79
Failed bariatric surgery	5

Hets, POMC/PCSK1/LEPR heterozygous deficiency obesity; SD, standard deviation.

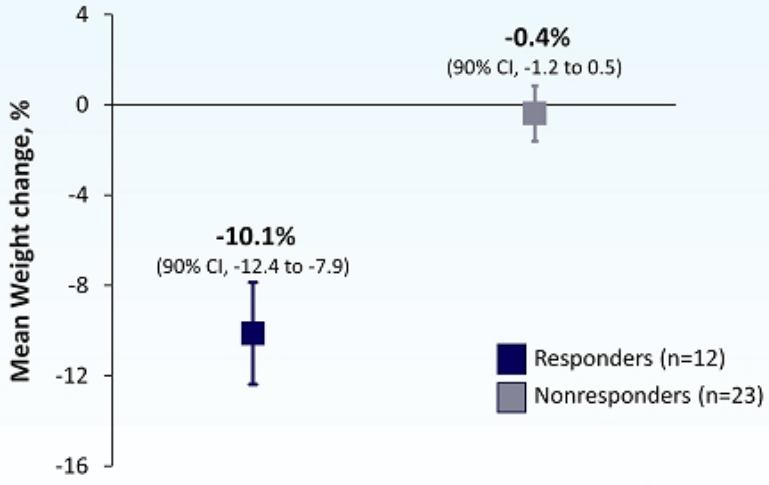
Response Rate and Weight Loss at Month 3 (Overall)
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

34.3% of patients (12/35) achieved the primary endpoint of ≥5% weight loss from baseline at Month 3*

	Baseline	Month 3	Percent change from baseline
Mean (SD) body weight: Overall (n=35)	**143.3 kg** (29.8)	**138.1 kg** (30.7)	**-3.7%** (5.6)
Mean (SD) body weight: Responders (n=12)	**144.7 kg** (32.6)	**130.7 kg** (33.5)	**-10.1%** (4.4)

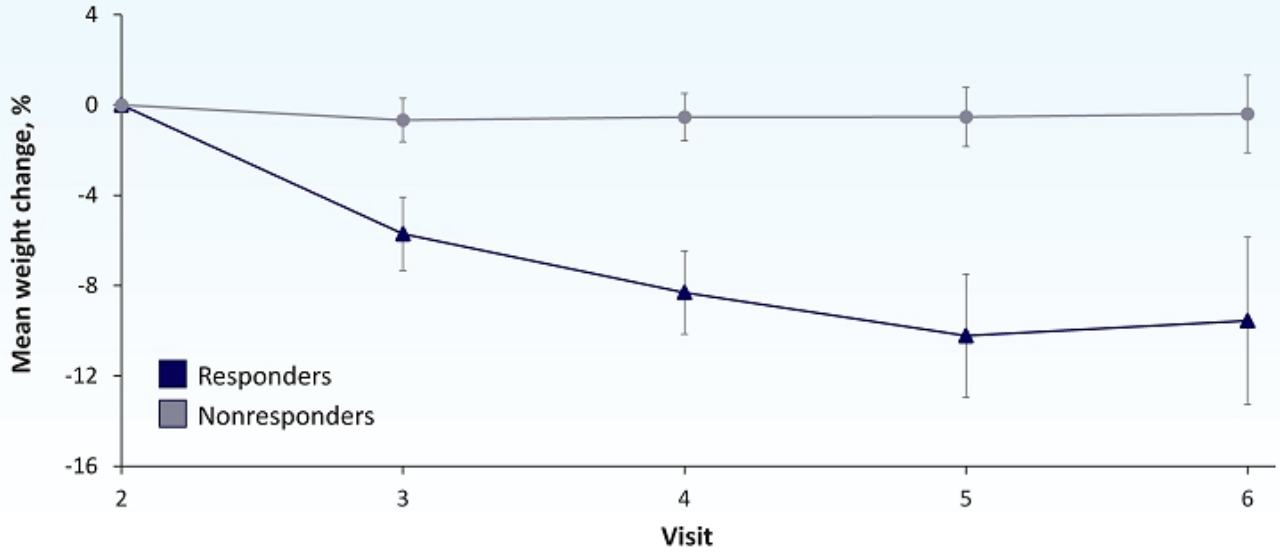
* Data include six patients who withdrew early, last observed value carried forward, as of Dec. 17, 2020.

Response Rate and Weight Loss at Month 3 (Responder/Nonresponder)
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity



Data as of Dec. 17, 2020; Error bars represent the 90% confidence interval.

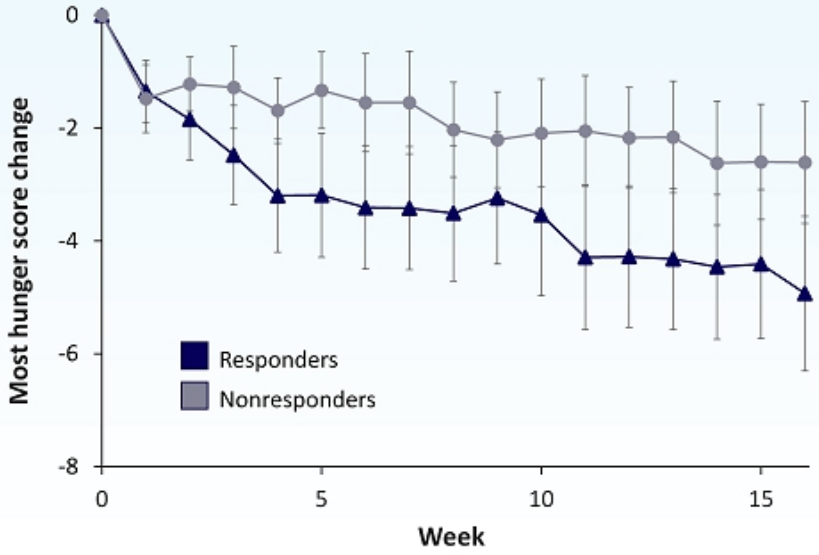
Percent Weight Loss Over Time
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity



Data as of Dec. 17, 2020; Error bars represent the 90% confidence interval.

Change in Most Hunger Score at Month 3 and Over Time
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

	Mean change in most hunger score at Month 3
Responders (n=12)	**-4.5 (90% CI -5.7, -3.2)**
Nonresponders (n=23)	**-2.3 (90% CI -3.2, -1.5)**



Data as of Dec. 17, 2020; Responder is defined by Month 3 weight loss; CI, confidence interval; Error bars represent the 90% CI.

Weight Loss at Month 3 by ACMG Subgroup
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

	Responders, n (%)[a]	Nonresponders, n (%)
Pathogenic/likely pathogenic (n=8)	4 (50.0)	4 (50.0)
Variant of uncertain significance (n=19)	4 (21.1)	15 (78.9)
N221D (n=8)	4 (50.0)	4 (50.0)

Data as of Dec. 17, 2020; CI, confidence interval; ACMG, American College of Medical Genetics. [a]Achieved the threshold of ≥5% weight loss from baseline at Month 3.

SRC1 and SH2B1 Patient Demographics – Completers Set

Baseline Characteristics	SRC1 (N=13)	SH2B1 (N=17)
Mean age (years) at enrollment (SD)	32 (18)	30 (15)
Range	12, 66	12, 60
Female	77%	58%
Male	23%	41%
Mean weight lbs (SD)	258 (44)	272 (60)
Range lbs	168, 313	161, 357
Mean weight kg (SD)	117 (20)	123 (27)
Range kg	76, 142	73, 162
BMI Mean kg/m^2 (SD)	44 (6)	44 (9)
Range	34, 55	32, 68
Failed bariatric surgery	4	5

Completers Set excludes 15 patients who withdrew early due to COVID-related issues, AEs, or lost to follow-up; and 12 ongoing patients who had not reached 12 weeks of therapy. A majority of patients who withdrew early experienced weight loss.

Data cutoff date of Dec. 17, 2020.

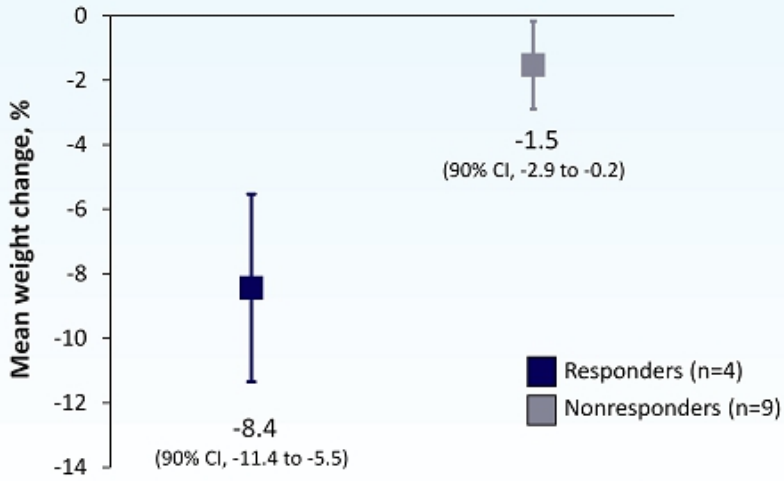
Response Rate and Weight Loss at Month 3 (Overall)
SRC1 Deficiency Obesity – Completers Set

30.8% of patients (4/13) achieved the primary endpoint of ≥5% weight loss from baseline at Month 3

	Baseline	Month 3	Percent change from baseline
Mean (SD) body weight: Overall (n= 13)	**117.1 kg** (20.3)	**112.6 kg** (18.5)	**-3.7%** (4.0)
Mean (SD) body weight: Responders (n=4)	**116.6 kg** (29.1)	**106.4 kg** (24.6)	**-8.4%** (2.5)

Interim data as of Dec. 17, 2020.

Response Rate and Weight Loss at Month 3 (Responder/Nonresponder)
SRC1 Deficiency Obesity – Completers Set



Data as of Dec. 17, 2020; Error bars represent the 90% confidence interval.

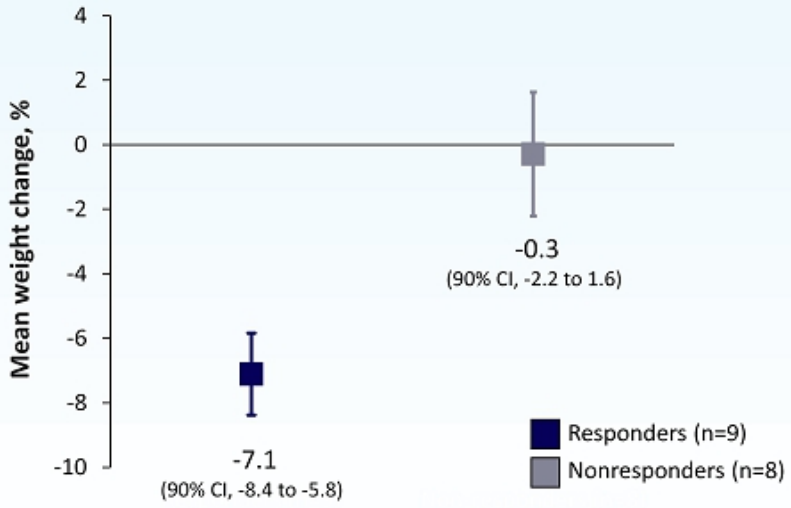
Response Rate and Weight Loss at Month 3 (Overall)
SH2B1 Deficiency Obesity – Completers Set

52.9% of patients (9/17) achieved the primary endpoint of ≥5% weight loss from baseline at Month 3

	Baseline	Month 3	Percent change from baseline
Mean (SD) body weight: Overall (n=17)	**123.4 kg** (27.4)	**118.6 kg** (27.3)	**-3.9%** (4.2)
Mean (SD) body weight: Responders (n=9)	**123.6 kg** (28.1)	**114.8 kg** (26.4)	**- 7.1%** (2.1)

Interim data as of Dec. 17, 2020.

Response Rate and Weight Loss at Month 3 (Responder/Nonresponder)
SH2B1 Deficiency Obesity – Completers Set



Data as of Dec. 17, 2020; Error bars represent the 90% confidence interval.

Setmelanotide Generally Well-tolerated Across Development Program

Setmelanotide has been evaluated in 590 patients with obesity, with some individual patient treatment duration now exceeding five years

Setmelanotide has been generally well-tolerated

Most AEs are mild:

- Mild injection site reactions
- Hyperpigmentation and skin lesions, mediated by the closely related MC1 receptor
- Nausea/vomiting: mild and early in treatment

Discontinuations are rare; no increase in CV parameters

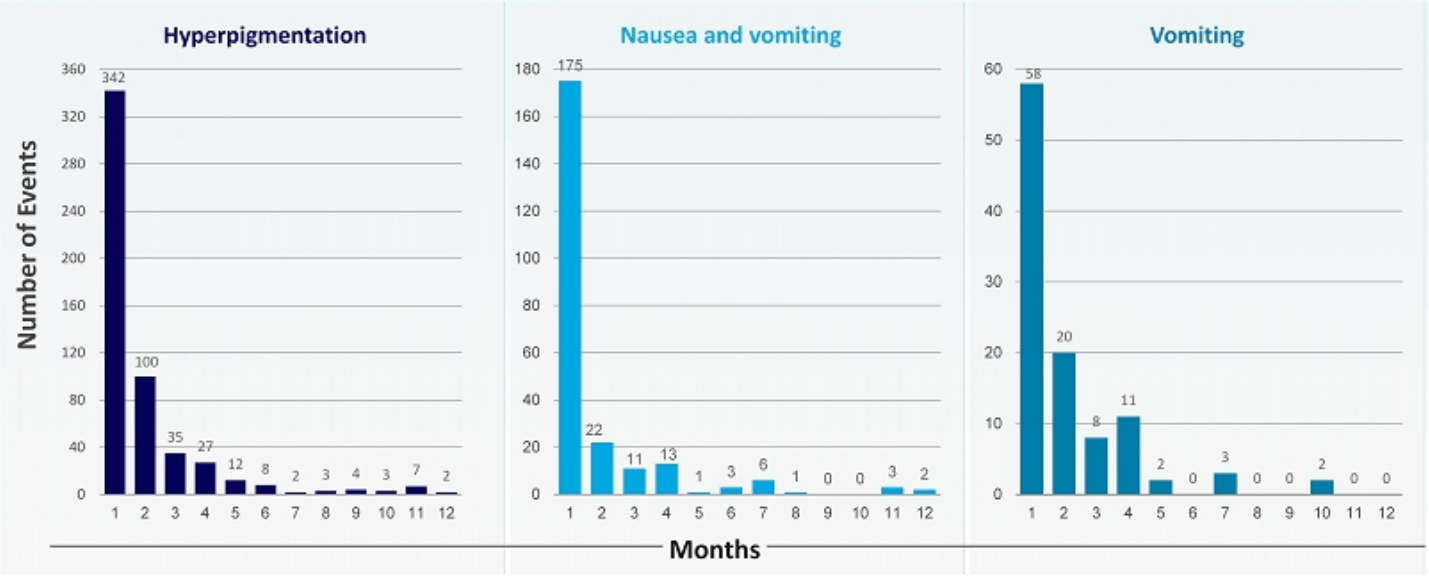
- In POMC and LEPR pivotal trials, setmelanotide was not associated with significant changes to blood pressure or heart rate

Patient experience with setmelanotide*

Duration on therapy	# of patients
< 1 year	**515**
> 1 year	**75**
> 2 years	**29**
> 3 years	**10**
> 4 years	**2**
> 5 years	**1**

* Estimates as of November 2020, inclusive of patients likely randomized to treatment in certain double-blinded clinical studies; does not include subjects in studies evaluating once-weekly formulation.

Safety: Hyperpigmentation, Nausea and Vomiting Events Occurred Early in Treatment



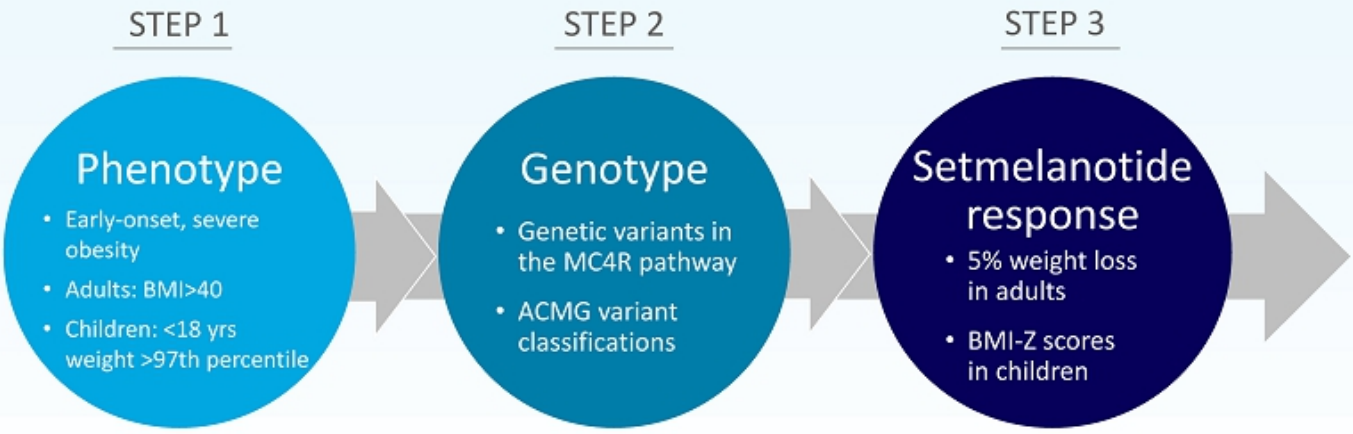
Safety data as of Nov. 10, 2020; Months defined as 30-day periods.

Setmelanotide Achieves Proof of Concept in HETs, SRC1 and SH2B1

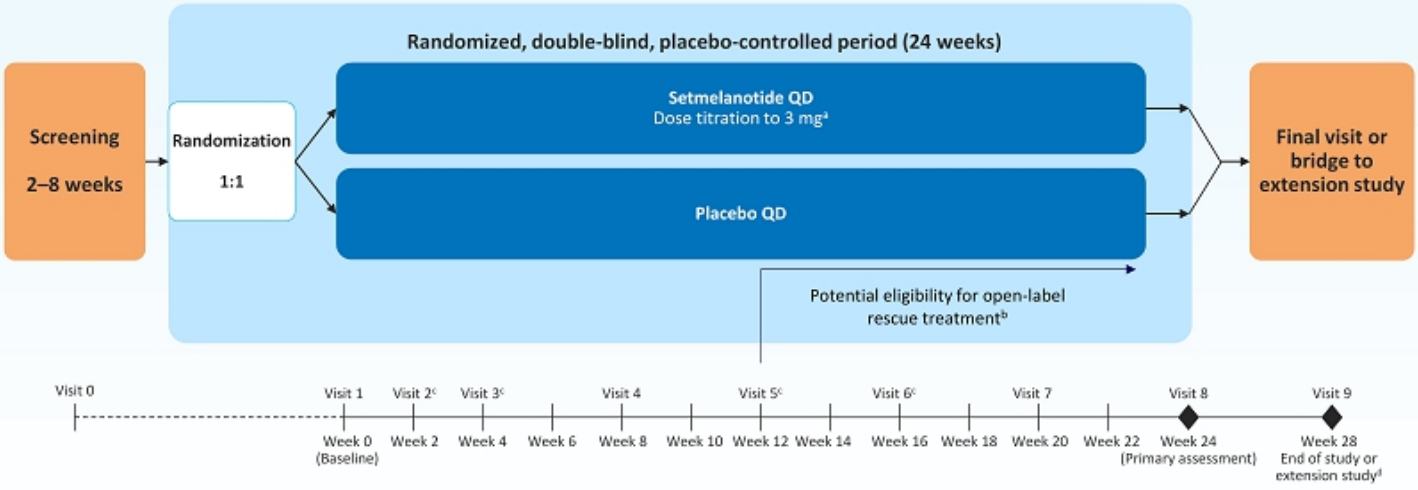
- Overall: Approximately 35% of patients responded with ≥5% weight loss at 12 weeks
- Strong separation between responders and non-responders validates three-step approach
- Responders mean weight loss of 10% for HETs, 8% for SRC1 and 7% SH2B1
- Enhanced responder rate seen within cohorts stratified by ACMG variant classification
- N221D represents potential expansion opportunity
- Setmelanotide is generally well tolerated in these populations

Future Clinical Plans

Targeted but Simple Approach to Treating Obesity

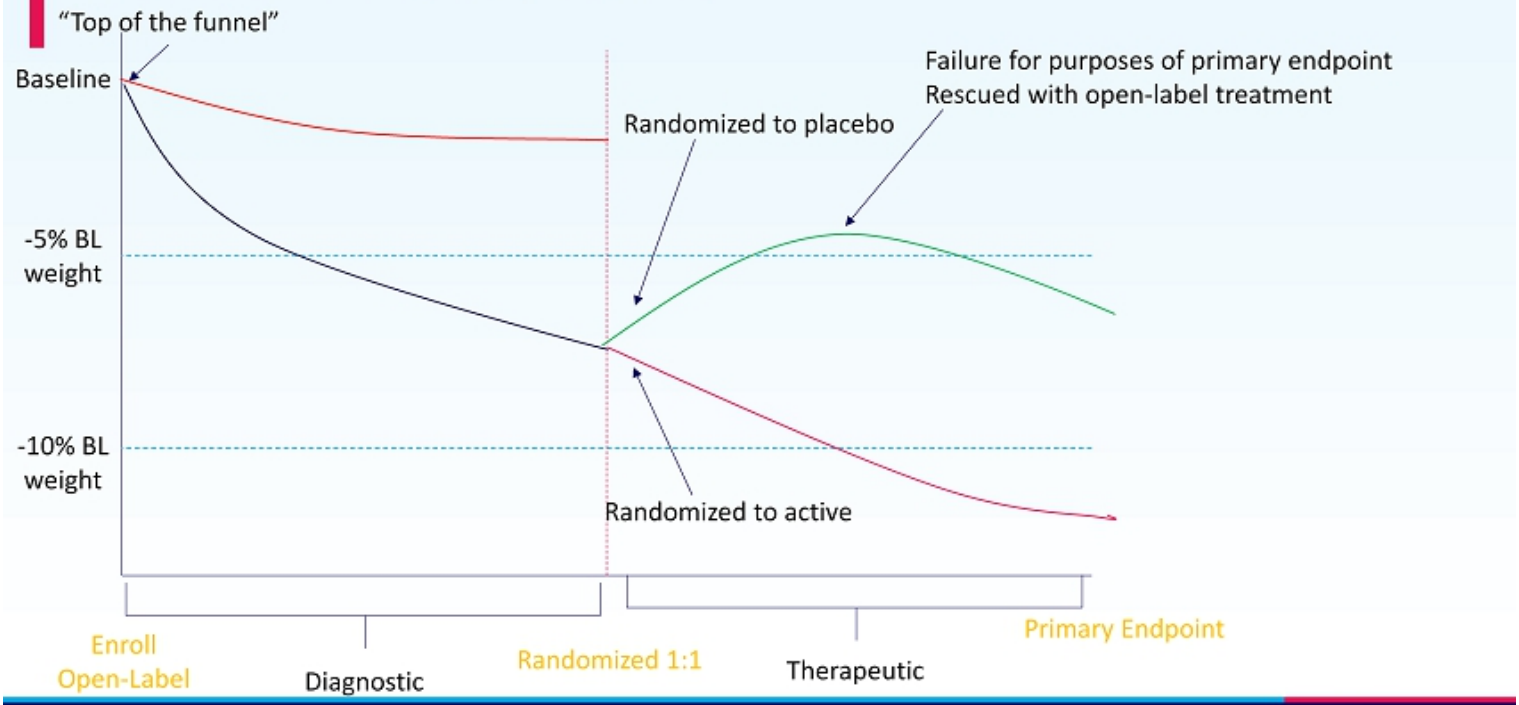


Phase 3 Basket Study Designed to Evaluate Response Compared to Placebo After 24 Weeks of Treatment



[a]For patients ≥12 years old, initial dose of 2 mg for 14 days, followed by 3 mg for the remainder of the study. For patients 6 to <12 years old, initial dose of 1 mg for 7 days, followed by 2 mg for 7 days, followed by 3 mg for the remainder of the study. [b]A patient may be eligible for open-label setmelanotide treatment if experiencing body weight increase ≥5% from baseline, or by investigator decision based on best medical interest of the patient. [c]Virtual study visit. [d]Final visit at Week 28 for patients not enrolling in a separate extension study.
QD, once daily.

Phase 2 MC4R Pathway Exploratory Study



Transformational Progress Expected in 2021

	1H 2021
✓	Proof-of-concept data in HET patients, SRC1 and SH2B1 deficiency obesities
✓	Update on genetic sequencing and epidemiology data
	IMCIVREE commercially available in U.S. for POMC, PCSK1 and LEPR deficiency obesities
	Initiate Phase 2 trial in hypothalamic obesity
	Initial data from Phase 2 Basket study in MC4R-rescuable patients
	Full data analyses from pivotal Phase 3 trial in BBS and Alström syndrome
	2H 2021
	EU decision on POMC, PCSK1 and LEPR MAA
	U.S. and EU regulatory submissions for BBS
	Initiate trial in pediatric patients aged 2-6 years old
	Initiate pivotal MC4R Pathway trial in HET patients, SRC1 and SH2B1 deficiency obesities
	Initiate exploratory MC4R Pathway Basket Study in 31 additional genes
	Initiate registrational trial for weekly formulation

Rhythm Leadership – Strong Team with Broad Biopharma Experience

					
David Meeker, MD *Chair, President and Chief Executive Officer*	**Hunter Smith** *Chief Financial Officer*	**Yann Mazabraud** *Executive Vice President, Head of International*	**Jennifer Chien** *Executive Vice President, Head of North America*	**Murray Stewart, MD** *Chief Medical Officer*	**Simon Kelner** *Chief Human Resources Officer*
SANOFI GENZYME	Celgene	SANOFI GENZYME trevi THERAPEUTICS	SANOFI GENZYME Krystal	novelion THERAPEUTICS gsk	MERCK teva
25-plus years; focus on rare genetic disease treatments, including Aldurazyme®, Fabrazyme® and Myozyme®	*Financial leadership for Otezla®; 20-plus years in finance, M&A, capital markets*	*20 years leading global commercial strategy in rare diseases*	*More than 20 years leading global commercial strategy in rare diseases*	*20-plus marketed products and NDAs 10-plus INDs*	*25-plus years global HR leadership experience in biopharma*


Rhythm®
PHARMACEUTICALS