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): **April 6, 2022**

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 April 6, 2022, Rhythm Pharmaceuticals, Inc. (the "Company") posted a corporate slide presentation in the "Investors & Media" portion of its website at ir.rhythmtx.com to reflect certain updates to clinical trial plans. 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 April 6, 2022
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: April 6, 2022

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

April 2022

Forward Looking Statements

This presentation contains certain forward-looking statements within the meaning of the Private Securiti
Reform Act of 1995, and that involve risks and uncertainties, including without limitation statements reg
potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipate
initiation of clinical trials and release of clinical trial data and our expectations surrounding potential reg
submissions, approvals and timing thereof, our business strategy and plans, including regarding commer
setmelanotide, the application of genetic testing and related growth potential, expectations surrounding
market opportunity for our product candidates, the sufficiency of our cash, cash equivalents and short-te
investments to fund our operations, and strategy, prospects and plans, including regarding the commerci
setmelanotide. Statements using words such as "expect", "anticipate", "believe", "may" and similar term
forward-looking statements. Such statements are subject to numerous risks and uncertainties, including
limited to, our ability to enroll patients in clinical trials, the outcome of clinical trials, the impact of comp
ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and report
liquidity and expenses, the impact of the COVID-19 pandemic on our business and operations, including
studies, clinical trials and commercialization prospects, and general economic conditions, and other risks
detailed from time to time in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and
we file with the Securities and Exchange Commission. Except as required by law, we undertake no obligat
any revisions to the forward-looking statements contained in this presentation or to update them to refle
circumstances occurring after the date of this presentation, whether as a result of new information, futu
developments or otherwise.

Transforming Care of Patients with Rare Genetic Diseases of Ob

IMCIVREE® (setmelanotide) injection

FDA-approved in November 2020

EC marketing authorization received July 2021

Commercial availability in U.S. meeting expectations and market access advancing in key **international markets**

Poised to deliver on **Bardet-Biedl** in the near-term: **PDUFA June 16, 2022**

Clinical deve
meaningfully
address
patient pop

Early-onset, Hyperphagia and Severe Obesity Have a Significan on Patients with Bardet-Biedl Syndrome and their Families

"My weight is my biggest challenge, and it affects every aspect of my activities. When I'm hungry, I can't stop it because I don't have the from my stomach to my brain."

Izzy, who was diagnosed with BBS when she was

"The most prevalent issue in Izzy's life and our family's life."

Leigh, Izzy's mom.

BORN WITH:

Born with bradidactyl, tracheomalacia, small heart murmur and an unexplained fever

2 MONTHS OLD:

Excessive weight gain becoming noticeable

3 YEARS OLD:

Surgery to correct large chiari malformation

BY 4 YEARS OLD:

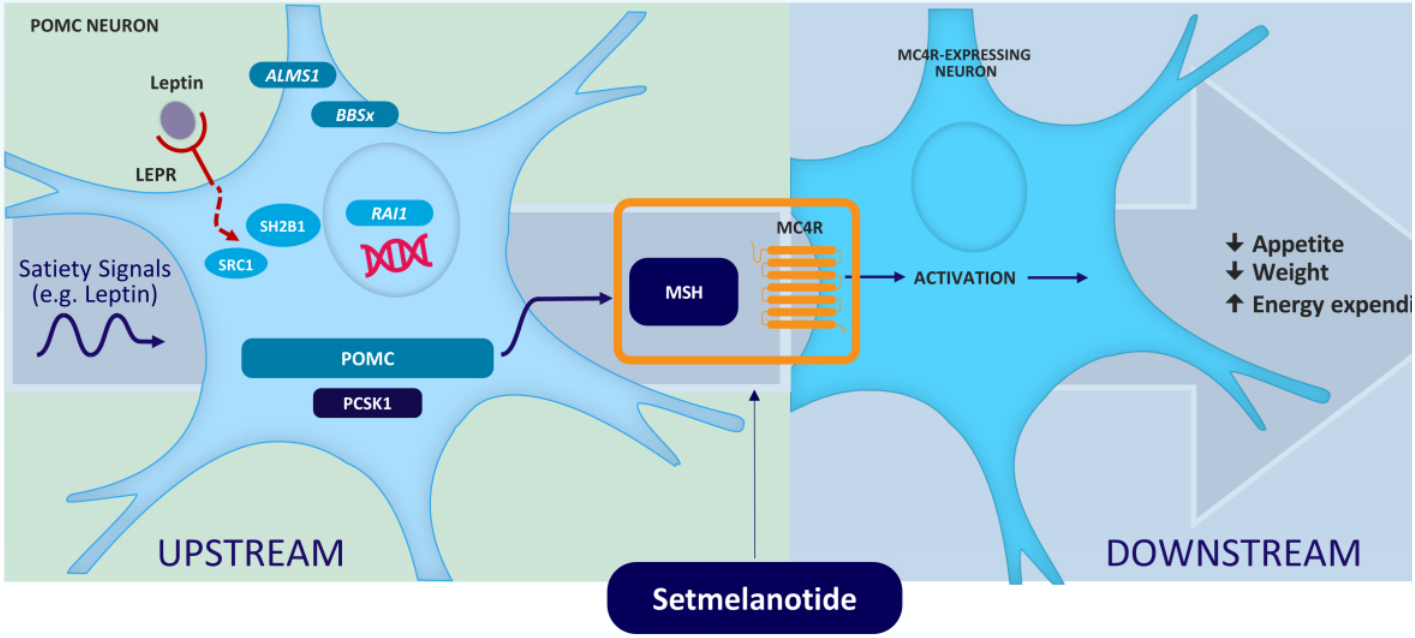
Seen by 15 doctors in six different states

4 ½ YEARS O

Ophthalmo retinitis pi plus hyper severe obe diagnosis

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

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



Executing on Gene-by-gene Strategy to Expand Reach of Setme

Genes Approved	U.S. and EU Regulatory Submissions Filed	Genes in Clini Developmer	
		EMANATE Phase 3	DA Ph
POMC	BBS (*all*)	POMC	
PCSK1	ALMS1	PCSK1	
LEPR		LEPR	ad gene to pa
(biallelic)		SRC1	
		SH2B1	
		(heterozygous or s allele variants	

Setmelanotide lifecycle advancements

Pediatric patients (2-6 years old) and weekly formulation

Clinical Development Programs Designed to Expand the Setme Opportunity

Now approved

600 – 2,500**

IMCIVREE® (setmelanotide) injection

Obesity due to POMC, PCSK1 or LEPR deficiency

Potential U.S. launch in mid-2022£

2,000 – 3,000**

Bardet-Biedl and Alström syndromes

Clinical development expansio

Phase 3 EMANATE Trial

Four independent sub-studi

6,000†	**Heterozygous POMC/PCSK1**
4,000†	**Heterozygous LEPR deficien**
20,000†	**SRC1 deficiency**
23,000†	**SH2B1 deficiency**

Phase 2 DAYBREAK Trial — Exploring an addit **10 genes**

** Estimated prevalence of U.S. patients based on company estimates; does not include ex-U.S. prevalence estimates.

† Estimated U.S. patients based on population* with early-onset, severe from setmelanotide based on Rhythm sequencing results and current e does not include ex-U.S. prevalence estimates.

* 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018ǂ); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017); £ U.S. and EU regulatory subm syndrome filed in September and October 2021, respectively. € Planned EMANATE trial would include patients with variants classified as pathogenic, likely pathogenic or of uncertain significance, and patients with N221D variant;

Bardet-Biedl Community is Established and Patients are Ide

U.S. prevalence estimated to be

1,500 to **2,500** patients

More than **600** individuals living with BBS are enrolled in **CRIBBS registry**

Estimated European prevalence estimated to b

~2,500 patients

More than **1,500** individuals identified in **EU4 + UK** at ~20 academic medical centers w >40 BBS patients

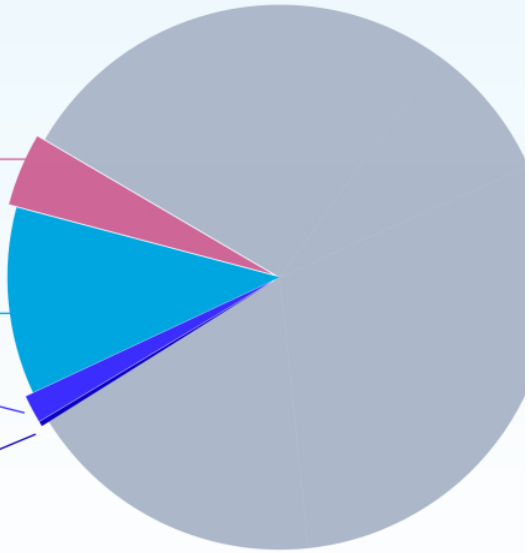
URO: >20%Sequenced Individuals with Severe Obesity Carr in MC4R Pathway Genes Targeted for EMANATE, DAYBREAK

5.1% of individuals sequenced eligible for **EMANATE**

13.1% of individuals sequenced eligible for **DAYBREAK**

1.96% of individuals who were sequenced may carry biallelic variants in one of 22 BBS genes or the *ALMS1* gene up to **0.34%**

carried variants considered pathogenic or likely pathogenic



* Represents a weighted yield from 8,599 URO samples collected as of July 12, 2021. Prior to May 2021, Rhythm's URO panel tested for variants in 40 obesity-related genes, including 11 genes eligible for the DAYBREAK or EMANATE trials; d those 11 genes is available in all 8,599 samples. Rhythm launched URO 2.1/3.0 in early May 2021, which now sequences 79 obesity-related genes and the 16p11.2 chromosomal region, including 25 additional DAYBREAK/EMANATE genes. on all 79 genes (including all 36 DAYBREAK/EMANATE genes) was available for 788 patients and used to calculate a weighted yield across the total study population

Synergistic Strategy Drives Patient Identification for Clinical Trials and Commercialization

Community Building

- Disease state education and awareness
- Field teams
- HCP education programs
- Digital outreach efforts

Genetic Sequencing

- Uncovering Rare Obesity
- Genetic counseling services

3 Potentia

IMCIV
(setmelanotide

Six clinica trials in 2

Future cli trials

Rhythm Leadership – Strong Team with Broad Biopharma Expe

David Meeker, MD
Chair, President and Chief Executive Officer

SANOFI GENZYME

25-plus years; focus on rare genetic disease treatments, including Aldurazyme®, Fabrazyme® and Myozyme®

Hunter Smith
Chief Financial Officer

Celgene

20-plus years in finance, M&A, capital markets; financial leadership for Otezla®

Linda Shapiro Manning, MD, PhD
Chief Medical Officer

novo nordisk® MERCK Boehringer Ingelheim

20-plus years in obesity medicine as an HCP and industry leader

Jennifer Chien
Executive Vice President, Head of North America

SANOFI GENZYME Krystal

20-plus years leading global commercial strategy in rare diseases

Yann Mazabraud
Executive Vice President, Head of International

SANOFI GENZYME trevi THERAPEUTICS

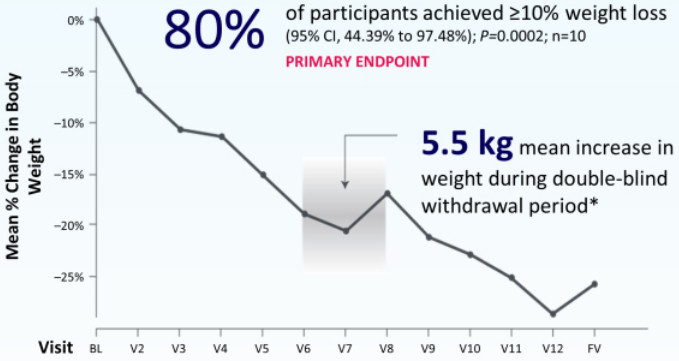
20-plus years leading global commercial strategy in rare diseases

IMCIVREE® (setmelanotide)

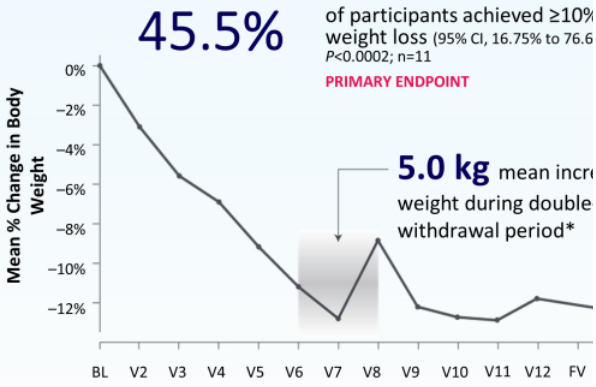
Commercial availability in U.S. meeting expectations and market access advancing in key international markets

U.S. and EU Approvals of IMCIVREE Based on Phase 3 Data fro Studies Conducted in Obesity due to POMC, PCSK1 or LEPR De

POMC/PCSK1



LEPR



Supplemental patients:

- 100% of POMC (n=4) and LEPR (n=4) supplemental patients achieved >10% weight loss*

Long-term extension study:

- 12 of 15 eligible POMC patients enrolled *
- 12 of 15 eligible LEPR patients enrolled *

PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; V, visit; FV, final visit. **Reference:** IMCIVREE Prescribing Information; * Data as of Nov. 16, 2020 cutoff as presented on Dec. 2 call.

IMCIVREE Launch

First three quarters of IMCIVREE commercial availability:

- $3.2M revenue in 2021
- Positive coverage decisions, reimbursement and access
- Continued focus on HCP engagement
- Patient Services and Corporate Accounts teams in place and making a difference

INITIAL PATIENT EXPERIENCE:

38 year old:
Went from being constantly distracted by hunger to forgetting to eat

11 year old:
Mom said: "See, this is not your fault."

International Market Access: First Commercial Sales Expected i Germany and France in Second Quarter 2022

Germany

- **Commercial launch** anticipated in Q2 2022
- IMCIVREE exempted by Federal Joint Committee (G-BA) from **Annex II** (Lifestyle products)

France

- **Paid early access** granted by Haute Autorité de Santé (HAS)
- **First sales** anticipated in Q2 2022
- **Fast-track** procedure obtained
- **Reimbursement dossier** submitted

United Kingdom

- Selected for Highly Specialized Technology evaluation; Po initial NICE Committee meeting in December 2021

Italy

- Reimbursement dossier submitted to Italian Medicines A 2021

Spain

- Reimbursement dossier ready for submission; Agency of Medical Devices (AEMPS) issued positive Therapeutic Pos with no restriction to label

The Netherlands

- Reimbursement dossier submitted

Israel

- Patients identified for named patient sales; Reimburseme ongoing

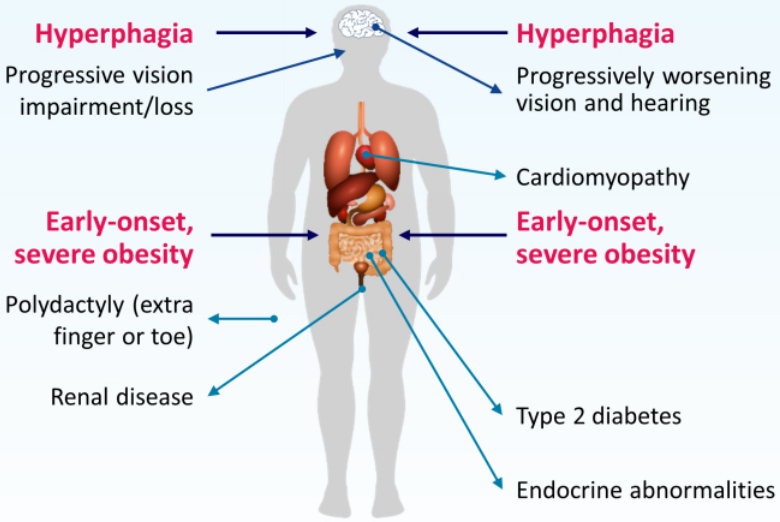
Bardet-Biedl and Alström Syndrome

Poised to deliver on
Bardet-Biedl in the near-term

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

Bardet-Biedl syndrome[1]

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



Alström

Rare cilio
associate
mu

"Critical to treat obesity, absolutely critical!" – PCP[4]

References: 1. Forsythe E, Beales PL. Bardet-Biedl Syndrome. 2003 Jul 14 [Updated 2015 Apr 23]. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1363/. **2.** Marshall JD et al. *Curr Genomics*. 2011;12(3):225-235. **3.** Marshall JD et al. Alström Syndrome. 2003 Feb 7 [Updated 2012 May 31]. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1267/. **4.** From market reserach interviews.

Hyperphagia's Severe Impact on Lives of Patients with BBS and their Caregivers

> *…I constantly felt like I was failing…. because if I did not give her extra food, then I felt terrible for denying her that when I knew she felt like she was starving, and if I did give it to her, I felt like I was slowly killing her and causing her health problems."*

Caregiver

> *We had to put locks on the fridge at one point to kind of keep her from eating cheeses."*

Caregiver

> *I was eating pretty much whatever, whenever and wasn't able to stop myself from eating or sneaking food in the middle of the night."*

Patient

> *She couldn't do as well in s because she was thinking what was in her lunchbox she was going to get at lu*

Caregiver

> *…At one point, [~2 yea found where the white and was able to pull th out of the pantry and j down and was eating f*

Excerpted from in-depth qualitative interviews with patients with BBS and/or their caregivers who were participating in an open-label extension study of setmelanotide.

Vast Majority of BBS Patients* had Clinically Meaningful Respor Setmelanotide at One Year on Therapy in Pivotal Study

Phase 3 trial achieved all predefined primary and key secondary endpoints

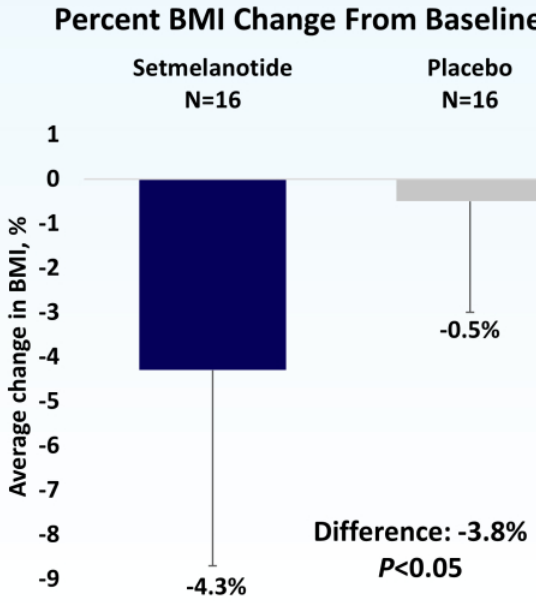
Adults ≥ 18 years old (n=15)		Patients younger than 18 (r
46.7% (7/15) had **≥10% weight reduction**	**60%** (9/15) had **≥5% weight reduction**	**85.7%** (12/14**) had a **reduction in BMI-Z ≥0.2**
–9.1% mean % **change in BMI**		**–9.5%** mean % **change in**

*A total of 28 patients were older than 12 years old and included in the primary analysts set, 15 adults and 13 patients between the ages of 12 and 18; ** One patient was younger and therefore not evaluable in for the primary endpoint; As presented on Dec. 22, 2020, corporate conference call, reflecting data cut-off of Dec 2. 2020, and as presented at The E Meeting in March 2021.

Phase 3 Trial: Setmelanotide Led to Significant BMI Reducti Patients with BBS Versus Placebo at Week 14

14-week placebo-controlled data

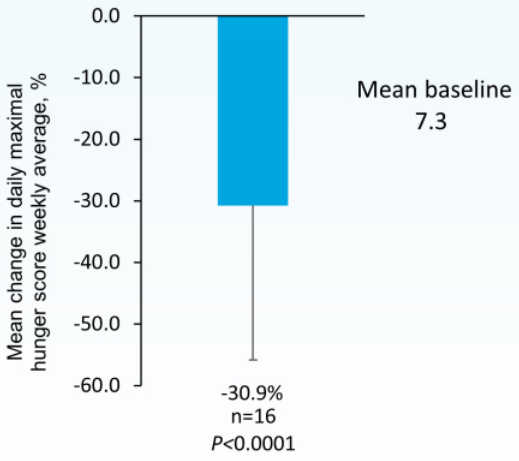
Patients with BBS treated with setmelanotide achieved an average BMI reduction of **−1.5 kg/m²** **(−3.8%)** at Week 14 compared with patients on placebo who saw ***negligible weight loss*** (*P*<0.05)

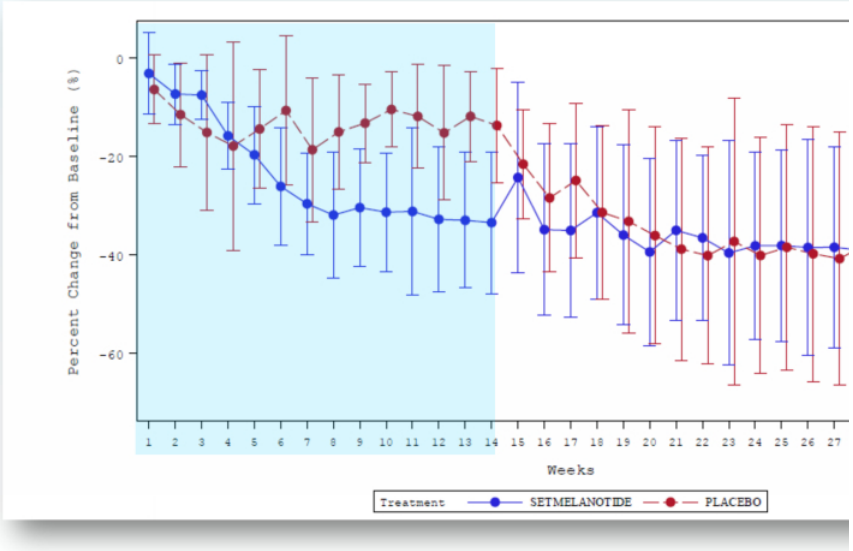


As presented at ESPE 2021 – 59th Annual European Society for Paediatric Endocrinology Meeting, September 2021.

Phase 3 Trial: Setmelanotide Achieved Clinically Meaningful Reduct Hunger in Adults and Children with BBS at Week 52

Data show separation in hunger reduction during placebo period foll group reaching treatment levels rapidly after crossover; all patien crossed over to treatment at week 14.





Daily most hunger score weekly average percent change from placebo-controlled period baseline by week among participants without cognitive impairment who were 12 years old or older

U.S. and EU Regulatory Submissions for BBS and Alström Syndr Recently Completed

Pivotal Phase 3 trial met all primary and key secondary endpoints*

sNDA Accepted by U.S. FDA; Assigned PDUFA target date of June 16, 2022

CHMP recommendation o Type II Variation Application anticipated ir June 2022**

*All patients who met the primary endpoint defined as more than 10 percent weight loss had BBS and none had Alström syndrome.
**Rhythm withdrew Alström syndrome from EMA regulatory submission.

Rhythm Continues to Advance to BBS Commercial Launch

Unmet need in BBS

- Hyperphagia
- Severe obesity
- Co-morbidities
- Current disease management strategies don't work

Solution

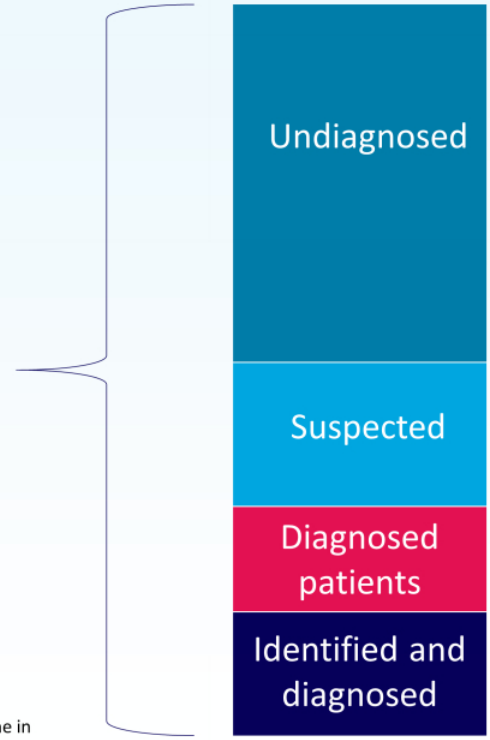
- Address root cause
- Hunger reduction
- Weight loss
- Established safety profile

Rhythm is ready launch in BBS

- Commercial foundation estab
- Experienced commercial team place
- >350 patients alr identified

Roadmap to Identifying Patients with BBS

U.S. prevalence estimated to be
1,500 to **2,500**
patients*



>35
Identifie
diagno
patie

* Company estimate based on published prevalence estimates of one in 100,000 in North America.

Clinical Development

Meaningful Expansion of Addressable Patient Population

Clinical Programs Designed to Achieve Label Expansion on Trac

	Patient Population	Phase 2	Phase 3	Market Au
IMCIVREE™ (setmelanotide) injection	POMC, PCSK1 or LEPR deficiency	✓	✓	✓ U
Setmelanotide *daily formulation*	Bardet-Biedl syndrome (BBS) or Alström syndrome	✓	✓	PDUFA tar Type II Vari
	Pediatrics (age 2 to <6 years); biallelic POMC, PCSK1 or LEPR deficiency or BBS	---	●	
	Heterozygous POMC/PCSK1/LEPR SRC1, SH2B1	Basket Study ✓	Emanate Obesity and Hunger Clinical Trial ○	
	Additional 10 genes with very strong MC4R pathway relevance	Daybreak Obesity and Hunger Clinical Trial ●		
	Hypothalamic obesity	●		
Setmelanotide *weekly formulation*	Biallelic or heterozygous POMC, PCSK1 or LEPR deficiency or BBS		Switch Study ●	
	BBS		*De novo* Study ○	

✓ Denotes study complete, ● Denotes study underway; ○ Denotes planned study

*Rhythm withdrew Alström syndrome from EMA regulatory submission.

EMANATE and DAYBREAK Studies to Drive Significant Expansion Setmelanotide's Potential Addressable Market

Phase 3 EMANATE Trial€

Four independent sub-studies

6,000†	**Heterozygous POMC/PCSK1 deficiency**
4,000†	**Heterozygous LEPR deficiency**
20,000†	**SRC1 deficiency**
23,000†	**SH2B1 deficiency**

Phase 2 DAYBREAK Trial Exploring an additional **10 genes**

Emanate

Obesity and Hunger Clinical Trial

Daybre

Obesity and Hunger

† Estimated U.S. patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results, current estimated responder rates and that 1.7% of the US population (328M; 2019 US cens onset obesity (Hales et al 2018ǂ); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017); £ U.S. and EU regulatory submissions for BBS and Alström syndrome filed in September and October 2021, re trial would include patients with variants classified as pathogenic, likely pathogenic or suspected pathogenic;

Proof of Concept in HETs, SRC1 and SH2B1 Established in Explorato 2 Basket Study with Clinically-meaningful Weight Loss at Month 3

HETs Obesity

POMC/PCSK1/LEPR Heterozygous Deficiency

34.3%

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

Responses to setmelanotide were maintained through 6 and 9 months

SRC1 Deficiency Obesity

30%

of patients **(9/30)** achieved the primary endpoint of **≥5% weight loss** or **≥0.15 reduction in BMI Z score** from baseline at Month 3

SH2B1 Deficie Obesity

42.9%

of patients **(15/35)** the primary endp **≥5% weight lo ≥0.15 reduction i score** from base Month 3

Phase 3 EMANATE 3 Trial to Evaluate Setmelanotide Across Fou Genetic Subtypes; First Patient Enrolled

Four independent sub-studies: allows for independent data readouts and potential registrations

Targeted patient populations: Patients with pathogenic, likely pathogenic or suspected pathogenic variants

- **~5.1% patients** with early-onset obesity test positive for eligible variants with Rhythm's URO

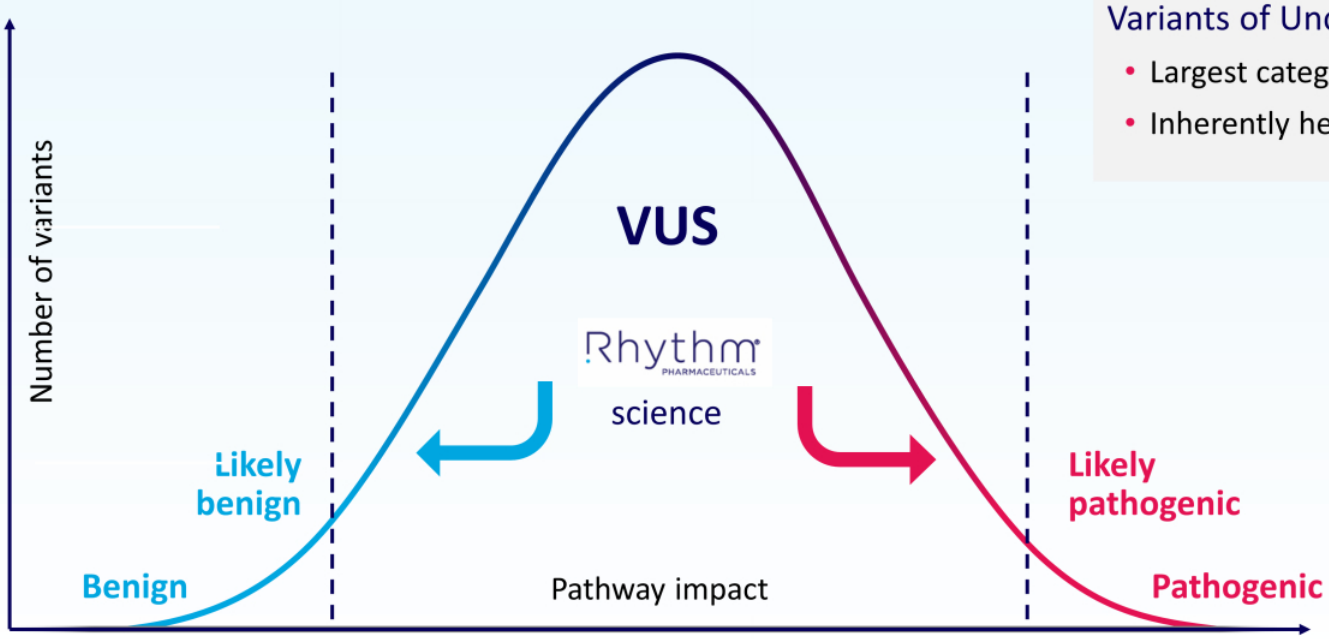
Phase 2 data: supportive of probability of success in each study

Primary Endpoint: BMI better suited to patient population including adults and children

First patient: Enrolled in April 2022

Total Addressable Market: potential of 53,000 patients in the U.S.

ACMG Variant Classification Can Inform MC4R Pathway Deficit a Potentially Setmelanotide Response

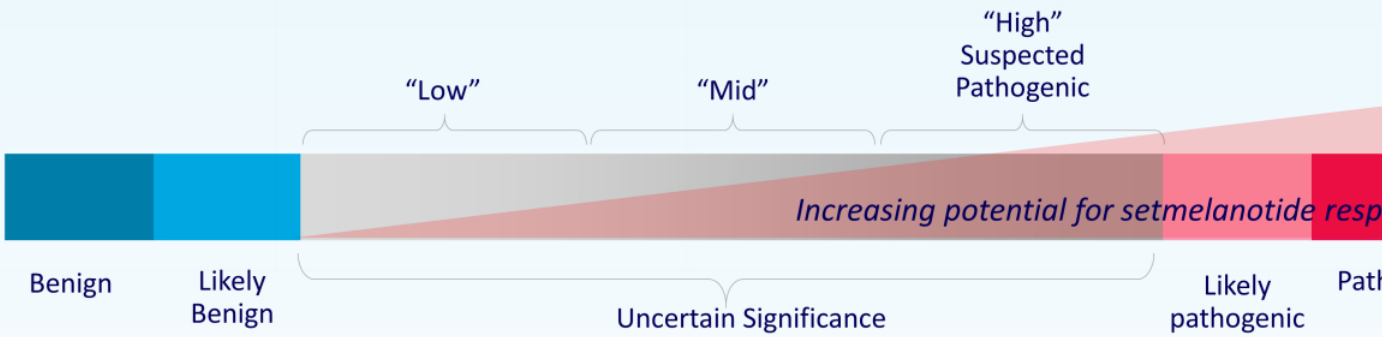


Variants of Uncertain S

- Largest category of ra
- Inherently heterogene

*ACMG Guidelines Richards et al, 2015

Rhythm's Approach to VUS Functional Assessment



Molecular, genetic and clinical characterization of VUS variants to elucidate pathogenicity and likelihood of setmelanotide response

Assessment of setmelanotide in patients with VUS variants to establish genotype-response correlations

Collaboration with g testing labs, clini genetics communit ACMG to accelerat classification and classification of V

Phase 2 Daybreak Trial to Evaluate Setmelanotide Across 10 Ne

Daybreak

Obesity and Hunger Clinical Trial

Relevance to MC4R Pathway: Rhyth
ClinGen-based framework suggests
genes have very strong relevance to
Pathway

Efficient, two-stage trial design

- **16-week, open-label run-in** in allows
signal-seeking in individual gene coh
- **24-week, double-blind treatment** pe
robust proof of concept
- Each genetic cohort can read out ind

First patient: January 2022

Approximately 13.1% of patients wi
onset obesity test positive for DAYB
eligible variants with Rhythm's URO

Phase 2 Daybreak Trial is Evaluating Setmelanotide in 10 Genes Strongest Association with Severe Obesity and MC4R Pathway

Gene	Details
MAGEL2	MAGEL2 knockout mice are hyper-responsive to setmelanotide
KSR2	KSR2 knockout mice treated with MC4R agonist show reduced appetite
SIM1	SIM1 is a transcription factor expressed in MC4R neurons and is associated with sev
PHIP	PHIP variants can disrupt POMC expression and are associated with severe, early-on
TBX3	TBX3 neuronal knockout mice causes abnormal POMC development and obesity
MRAP2	MRAP2 knockout mice treated with MC4R agonist show reduced appetite
HTR2C	HTR2C knockout mice treated with MC4R agonist show reduced appetite
TRPC5	TRPC5 mediates leptin effect of POMC neurons and disruption causes obesity & hyp
PLXNA4	PLXNA4 & SEMA3G are 2 of 13* known genes in the class 3 Semaphorin (SEMA3) pa
SEMA3G	associated with development of hypothalamic neurons that mediate MC4R pathway

* The remaining 11 SEMA3 pathway genes are also listed in DAYBREAK trial protocol but are currently paused for enrollment (together 9 other MC4R pathv
DAYBREAK enrollment for paused genes will be based upon observed response from the initial 10 prioritized genes and resource allocation priorities.

Improved URO with Expanded Gene Panel Launched in July 20

Obese (Class 2)	Obese (Class 3)	Obese (impaired)	
35 – 39.9	40 – 44.9	45 – 49.9	>50

Genetic testing for individuals with BMI >40

URO Utilization as of Dec. 31, 2021

>2,700
U.S. health care providers with pediatric endocrinologists and pediatricians accounting for **>50%**

>13,00
sequence samples

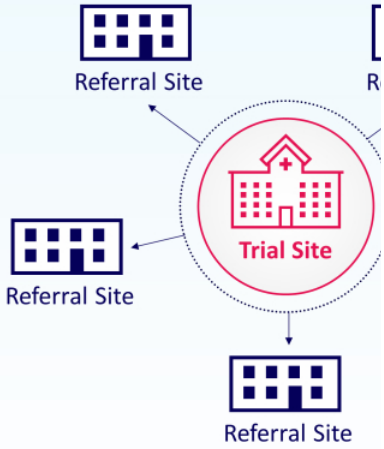
~20%
6 years old and younger | 7

* As identified by Rhythm based

Parallel Operations to Support both EMANATE and DAYBREAK

Site initiations underway

- Approximately 65 trial sites in 14 countries in North America, Europe and the Middle East
- Trial sites to service both EMANATE and DAYBREAK
- Area Development Managers in the field building referral network



Setmelanotide Generally Well-tolerated Across Development P

Setmelanotide has been evaluated in 639 patients with obesity, with some individual patient treatmen 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

Duration on therapy
< 1 year
> 1 year
> 2 years
> 3 years
> 4 years
> 5 years

* Data as of March 8, 2021, inclusiv who received daily or weekly formu setmelanotide.

Continued Transformational Progress Expected in 2022

	1H 2022
✓	Initiate Phase 2 DAYBREAK trial
✓	Initiate Phase 3 “switch study” of weekly formulation
✓	Initiate Phase 3 trial in pediatric patients aged 2-6 years old
✓	Initiate Phase 3 EMANATE trial
	PDUFA target date for BBS and Alström syndrome: June 16, 2022
	Initial data from Phase 2 in MC4R patients
	Initial data from Phase 2 trial in hypothalamic obesity
	Long-term data in BBS; biallelic POMC/PCSK1/LEPR
	CHMP decision on BBS
	2H 2022
	Initiate Phase 3 “*de novo* study” of weekly formulation

Financial Snapshot: Cash Sufficient to Fund Planned Operation
2023

$294.9 Million*
Cash, cash equivalents and short-term investments as of 12/31/2021

Guidance**
cash expected to be sufficient to fund operations into **4Q 2023**

50.2 Million€
Common shares outstanding

Analyst
BofA
Canacc
Cowen; G
Ladenbu
Morg
Needl
We

As disclosed on Form 10-K on March 1, 2022; ** Cash out guidance reflects clinical program changes announced on April 6,2022; € Includes basic and diluted share count; † Analy
brokerage firms known by the company as of January 2022 to have analysts covering the company. This list may not be complete and is subject to change. Analyst opinions, estimate
own and may not represent the opinions, estimates or forecasts of the company.

Appendix

Exclusive Licensing Agreement with RareStone Expected to Exp Reach into Asia

In December 2021, RareStone was granted an exclusive license to develop and commercialize IMCIVREE in China, including mainland China, Hong Kong and Macau

RareStone agreed to:

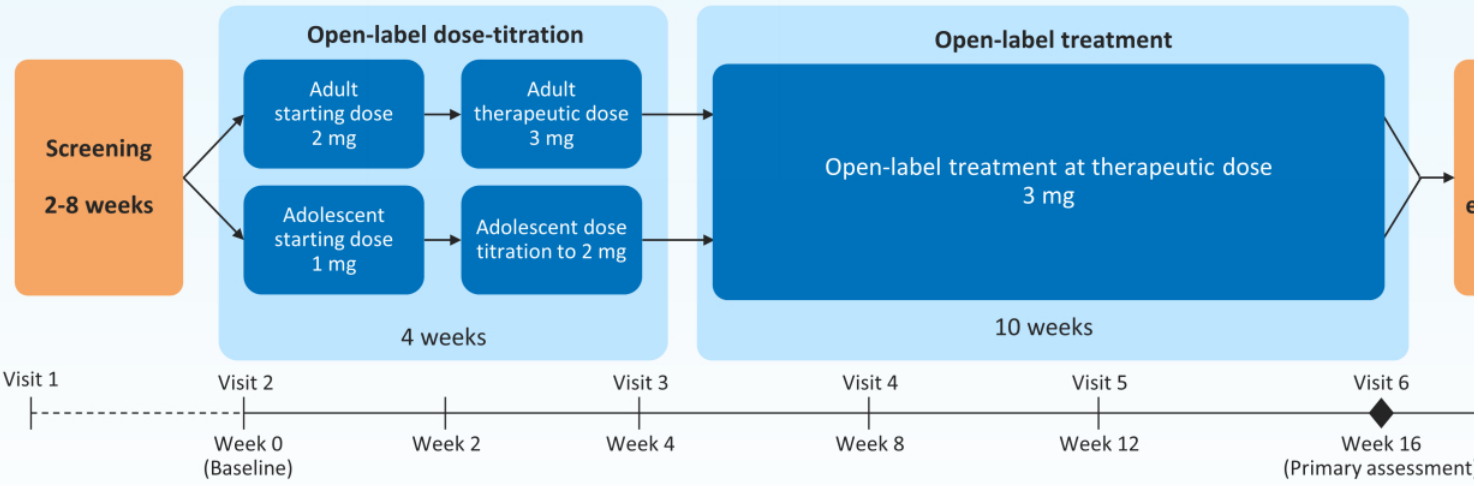
- Seek local approvals to commercialize IMCIVREE for the treatment of obesity and hyperphagia due to and LEPR deficiency, as well as BBS and Alström syndrome
- Fund efforts to identify and enroll patients from China in EMANATE trial

Under the terms of the agreement:

- RareStone made an upfront payment of $7M and issued $5M in equity to Rhythm
- Rhythm eligible to receive development and commercialization milestones of up to $63.5M, as well a payments on annual net sales of IMCIVREE

Results from Exploratory Phase Basket Trial

Phase 2 Basket Study Evaluated Response at Three Months of T



Primary endpoint is the proportion of patients who achieve >5% weight loss at 12 to 16 weeks on th

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

Clinical Characteristics of Patients Enrolled in Exploratory Phase Basket Study

	HETs deficiency obesity Heterozygous POMC, PCSK1 or LEPR	SRC1 deficiency obesity	SH2B1 def obesi
	N=**35**	N=**30**[a]	N=**35**[a]
Mean age (range)	**39 years old** (15 - 68)	**31 years old** (9 - 66)	**31 years o** (8 - 67)
Mean weight	**316 lbs/ 143 kgs**	**270 lbs/ 123 kgs**	**280 lbs/ 127 kgs**
Mean BMI	**50 kg/m²**	**45.4 kg/m²**	**47.2 kg/m**

[a]Patients who received ≥1 dose of study drug and completed baseline assessment

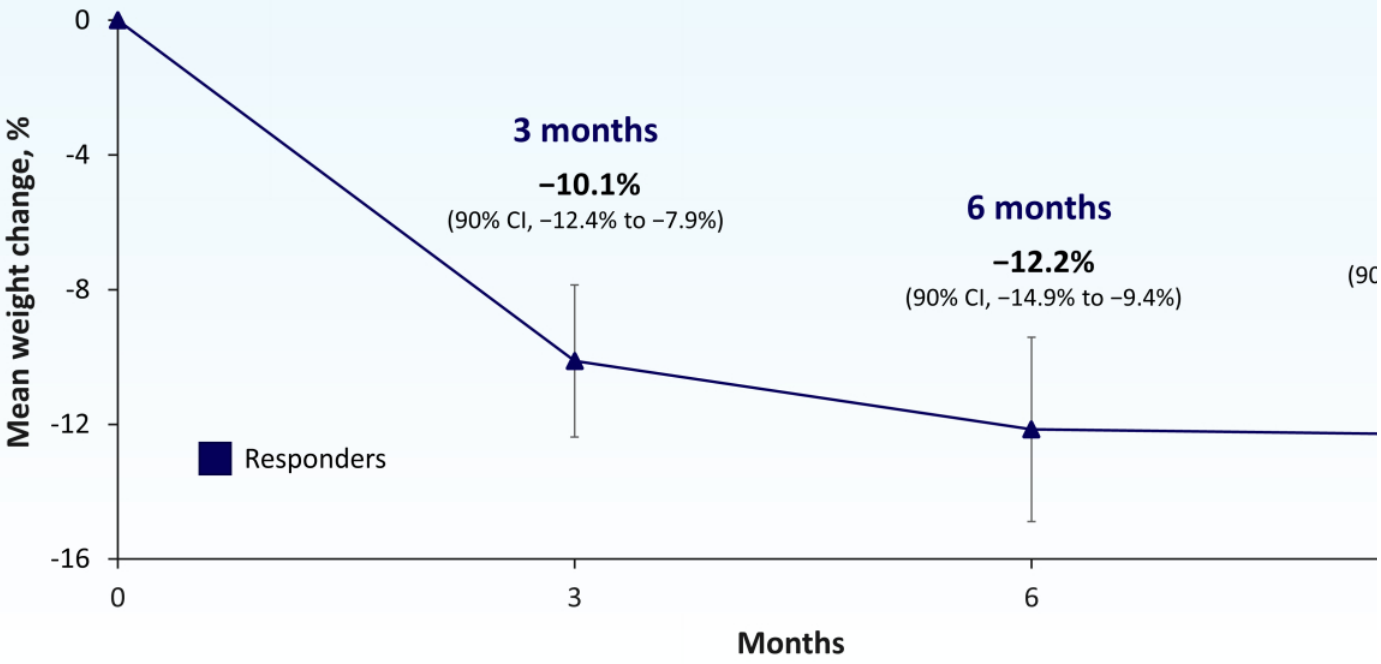
Phase 2 Basket Study: Response Rate and Weight Loss at Mont
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

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

	Baseline	Month 3	Percent chang baseline
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

Long-term Extension Study: Responses to Setmelanotide Were Maintained Th
Months in POMC/PCSK1/LEPR Heterozygous Deficiency Obesity



A responder was defined as having ≥5% weight loss from baseline at Month 3. Data as of December 17, 2020, for Month 3 and as of February 23, 2021, for Months 6 and 9; error bars are the 90% CI. CI, confider

Phase 2 Basket Study: Approximately One-Third of Patients Res Setmelanotide Treatment at Month 3

SRC1 Deficiency Obesity

30% of patients (9/30) achieved the threshold of ≥5% weight loss or ≥0.15 reduction in BMI Z score from baseline at Month 3

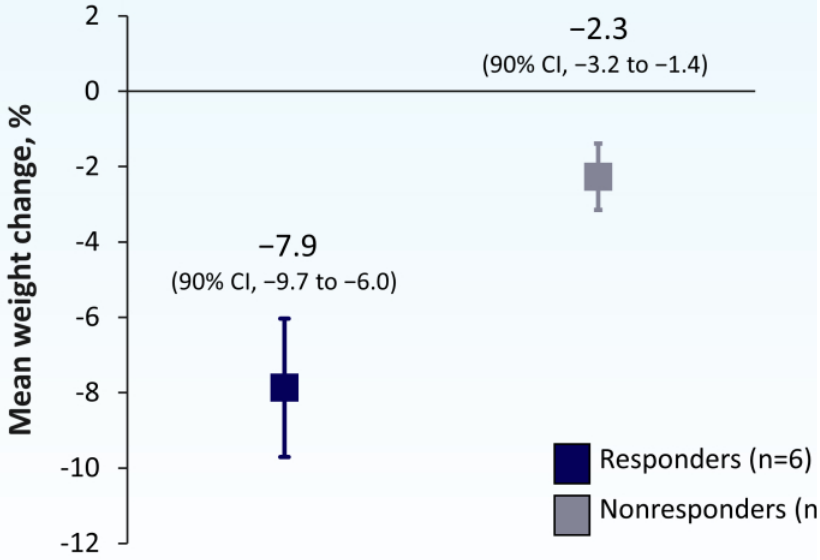
	Responders
≥5% weight loss in those ≥18 years old, n/N (%)	**6/20 (30)**
≥0.15 reduction in BMI Z score in those <18 years old, n/N (%)	**3/10 (30)**

Full analysis set reported. In the Completers' set, 33.3% of patients (7/21) were considered responders, including 33.3% of patients (3/9) ≥18 years old and 33.3% of patients (4/12) <18 years old. A responder w loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Reasons for treatment discontinuation include not wanting to take injections, schedule conflict, adverse event, lack of efficac to the COVID-19 pandemic. BMI, body mass index.

Phase 2 Basket Study: Setmelanotide Decreases Body Weight i with Clear Separation between Responders and Nonresponder

SRC1 Deficiency Obesity

Mean (SD) overall body weight change from baseline of **−4.0%** (3.3%; n=20)

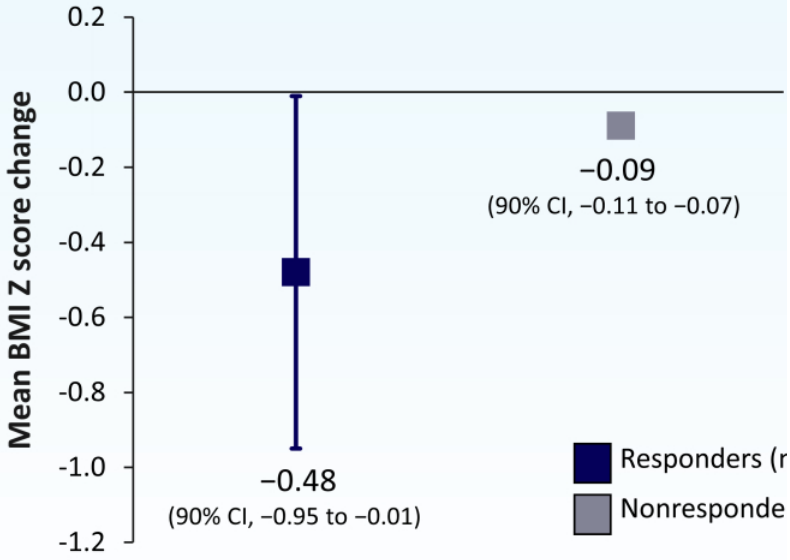


Full analysis set reported. In the Completers' set, mean percent weight change for responders was −8.7% (90% CI, −11.4% to −6.0%; n=4) and for nonresponders was −2.6% (90% CI, −3.8% to −1.3%; n=8). A resp weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% CI. CI, confidence interval; SD, standard deviation

Phase 2 Basket Study: Setmelanotide Decreases BMI Z Score in Chil Adolescents with Clear Separation between Responders and Nonre

SRC1 Deficiency Obesity

Mean (SD) overall BMI Z score change from baseline of **−0.21** (0.23; n=10)



Full analysis set reported. In the completers' set, mean BMI Z score change for responders was −0.48 (90% CI, −0.95 to −0.01; n=3) and for nonresponders was −0.09 (90% CI, −0.11 to −0.07; n=6). A responder w loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% CI. BMI, body mass index; CI, confidence interval

Phase 2 Basket Study: More Than 40% of Patients Respond Setmelanotide Treatment at Month 3

SH2B1 Deficiency Obesity

42.9% of patients (15/35) have achieved the threshold of ≥5% weight loss or ≥0.15 reduction in BMI Z score from baseline at Month 3

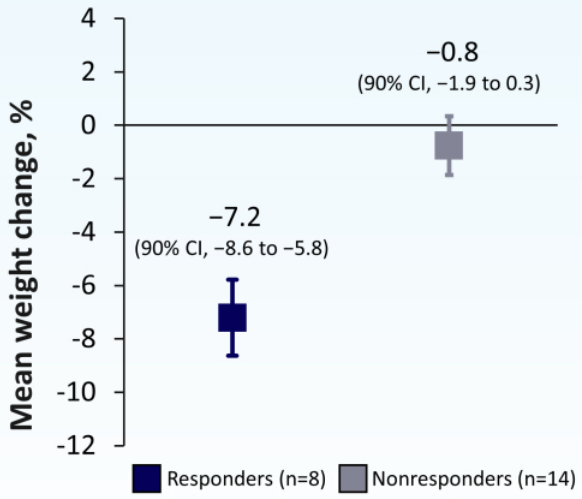
Proportion of patients	Responders
≥5% weight loss in those ≥18 years old, n/N (%)	8/22 (36.4)
≥0.15 reduction in BMI Z score in those <18 years old, n/N (%)	7/13 (53.8)

Full analysis set reported. In the completers' set, 59.1% of patients (13/22) were considered responders, including 53.8% of patients (7/13) ≥18 years old and 66.6% of patients (6/9) <18 years old. A responder v
loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old; BMI, body mass index

Phase 2 Basket Study: Setmelanotide Decreases Body Weight i with Clear Separation between Responders and Nonresponder

SH2B1 Deficiency Obesity

Mean (SD) overall body weight change from baseline of **−3.1%** (3.9%; n=22)



Full analysis set reported. In the Completers' set, in the combined population, mean percent weight change for responders was −7.3% (90% CI, −9.0% to −5.7%; n=7) and for nonresponders was −0.2% (90% CI, - responder was defined as ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% CI. CI, confidence interval; SD, standard deviation

Additional Supporting Slides

Phase 3 Trial in Pediatric Patients Ages 2 to 6 years old Initiated

International one-year, open-label study

Enrollment: 10 patients

- 5 with biallelic POMC, PCSK1 or LEPR deficiency
- 5 with BBS

Primary endpoint: Responder analysis based on proportion of patients who experience a decrease in BMI-Z of ≥0.2

Secondary endpoints: Safety and tolerability

Rare genetic diseases of obesity often present early in life

Phase 3 Trials Evaluating Weekly Formulation of Setmelanotide

Phase 3 randomized, double-blind "switch study" initiated in 4Q 2021

- Enrollment: 30 patients with BBS or biallelic or heterozygous POMC, PCSK1 or LEPR deficiency who have who have on open-label QD setmelanotide treatment for at least 6 months
- Randomized 1:1 for 13 weeks of double-blind administration of QD vs QW, followed by crossover to 13 weeks oper QW for all patients
- Primary endpoint: responder analysis, based on the proportion of patients with no weight gain of 5 percent or gre from baseline to week 13

Phase 3 randomized, double-blind, placebo-controlled "de novo" study of once-weekly (QW) formulati setmelanotide to be initiated in 2H 2022

- Enrollment: 40 setmelanotide-naïve patients with BBS (~60% adults)
- 18 weeks of double-blind administration of QW vs placebo, followed by crossover to 14 weeks of open-label QW administration of setmelanotide for all patients
- Primary endpoint: Mean change in weight compared to placebo

Weekly formulation of setmelanotide designed to improve compliance and ad

Phase 3 EMANATE 3 Trial Comprised of Four Independent Sub-

Design allows for independent data readouts, success in each sub-study and registration for each gene

First patient: 1H 2022

Each sub-study:

- Placebo-controlled: Patients randomized 1:1 (therapy vs. placebo)
- Enrollment: 12-18 months
- Treatment period is 52 weeks

Endpoints

- Primary: Difference in mean percent change in BMI at 52 weeks compared to placebo
- Key secondaries: additional measurements of effect on weight and hunger

1. **POMC/PCSK1***: 86 patients
2. **LEPR***: 86 patients

Stratification:
Suspected patho
pathogenic, path
Age: 6-11, 12-17

3. **SRC1**: 112 patients
4. **SH2B1**: 112 patients

Stratification:
Age: 6-11, 12-17

* Heterozygous

EMANATE Primary Endpoint: Difference in Mean Percent Chang BMI at 52 Weeks Compared to Placebo

Heterozygous POMC/PCSK1 and LEPR sub-studies are 90% powered to show >8% treatment ef placebo

SRC1 and SH2B1 sub-studies are 90% powered to show >7% treatment effect vs. placebo

Assumption to achieve mean treatment effect v placebo:

- The placebo group is not expected to lose weight, even with lifestyle intervention
- The placebo group may even gain 2% over 52 weeks
- Setmelanotide non-responders demonstrate treatment effect (weight loss, BMI reduction) relative to
- Setmelanotide responders anticipated to demonstrate >10% treatment effect at 52 weeks
- Setmelanotide mean treatment effect (weighted responder and non-responder) anticipated to be >8 weeks

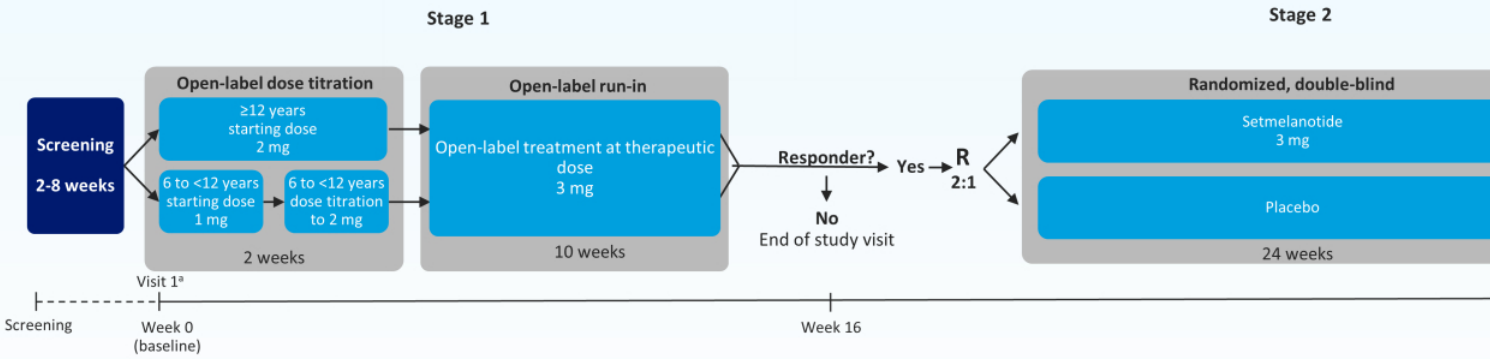
PLP: pathogenic, likely pathogenic or suspected pathogenic

EMANATE Secondary Endpoints to Illustrate Effect on Weight a

Secondary endpoints

- Proportion of patients who achieve at least 5% reduction in BMI at 52 weeks compared to p
- Proportion of patients who achieve at least 10% reduction in BMI at 52 weeks compared to
- Difference in mean change in body weight at 52 weeks in adult patients (age ≥18 years at ba compared to placebo, assessed as change in body weight
- Mean percent change in the weekly average most hunger score at 52 weeks compared to pl
- Mean body weight loss, % body weight loss in responders with ≥5% body weight loss in adu (if ≥18 years at baseline), and a decrease in % of BMI by 3% in pediatric/adolescent patients years at baseline) after 12 weeks compared to placebo
- Mean change in symptoms of hyperphagia and impacts of hyperphagia at 52 weeks compar placebo

Phase 2 DAYBREAK Trial Designed to Evaluate Setmelanotide Th
10 Genes with Strong or Very Strong Relevance to MC4R Pathw



[a]Virtual visit. R, randomization.

DAYBREAK Phase 2 Trial Design and Endpoints Enable Rapid P
Proof of Concept Based on Individual Genes

Primary endpoint is the proportion of patients by gene who enter Stage 2 and are responder compared to placebo

- Responders ≥18 years who achieve 10% or greater body weight reduction from baseline
- Responders <18 years who achieve BMI reduction of > 0.3 from baseline

Secondary endpoints by gene

- Proportion of patients who meet 5% weight loss criteria to enter Stage 2 compared to historic rate of
- Mean change and percent change in body weight in patients ≥18 years of age compared to placebo
- Mean BMI-Z change in patients <18 years of age compared to placebo
- Mean change in waist circumference in patients ≥12 years of age compared to placebo
- Mean % change in weekly average hunger
- Overall safety and tolerability

Other secondaries: physical functioning scores and quality of life measures vs placebo

Phase 3 Trial Setmelanotide Achieved Clinically Meaningful Improve Health-related Quality of Life (HRQOL) in Patients with BBS

85% of patients reported clinically meaningful improvements or preserved non-impaired health related quality of life status

Impact of Setmelanotide on HRQ		
	Adults (≥18 years old)	Childr yea
Patients, n	11	
	IWQOL-Lite total score*	Pe total
Baseline, mean (standard deviation)	74.9 (12.6)	67.2
Change at week 52, mean (SD)	**+12.0 (10.8)**	**+11.**

***Impact of weight on quality of life or IWQOL:** Is a zero to 100 range, with zero being the worst possible and 100 best possible score. A total score increase considered clinically meaningful improvement; Pre-defined ranges are: Impairment: <71.8 = severe, 71.9-79.4 = moderate, 79.5-87.0 = mild, 87.1-94.6 = no
****Pediatric quality of life inventory or PedsQL:** Also zero to 100, with zero being the worst and 100 best possible score. A total score increase of 4.44 or gr considered clinically meaningful. Impairment is defined as a score < 68.2.