UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

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

Date of Report (Date of earliest event reported): **January 9, 2023**

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 January 9, 2023, 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 99.1 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 January 9, 2023
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: January 9, 2023

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

Rhythm Pharmaceuticals

Transforming the lives of patients and their families living with hyperphagia and severe obesity caused by rare MC4R pathway diseases by rapidly advancing care and precision medicines addressing the root cause

January 2023

Forward Looking Statements

This presentation contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, and that involve risks and uncertainties, including without limitation statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipated timing for initiation of clinical trials and release of clinical trial data and our expectations surrounding potential regulatory submissions, approvals and timing thereof, our business strategy and plans, including regarding commercialization of setmelanotide, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, the sufficiency of our cash, cash equivalents and short-term investments to fund our operations, and strategy, prospects and plans, including regarding the commercialization of setmelanotide. Statements using words such as "expect", "anticipate", "believe", "may" 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 liquidity and expenses, the impact of the COVID-19 pandemic on our business and 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.

IMCIVREE® (setmelanotide) injection

First and only **FDA-approved** and **EC-authorized** therapy that targets a root cause of **hyperphagia** and early-onset, **severe obesity**

Strong start to U.S. launch for **Bardet-Biedl syndrome (BBS)**

Achieved access in **eight international markets** in 2022

Expanding **addressable patient population** with robust clinical development program

Rhythm Achieved Key Milestones in 2022, Laying the Groundwork for Continued Momentum Expected in 2023

- ✓ Launched IMCIVREE for BBS in U.S. following FDA approval in June
- ✓ Granted EC marketing authorization for IMCIVREE for BBS; received early access authorization in France
- ✓ Announced positive results from Phase 2 trial in hypothalamic obesity
- ✓ Completed enrollment in Phase 3 trial in pediatric patients
- ✓ Initiated three clinical studies: Phase 3 EMANATE trial, Phase 2 DAYBREAK trial and Phase 3 weekly switch trial
- ✓ Entered non-dilutive RIFA agreement with HealthCare Royalty for up to $100 million
- ✓ Closed $131.2 million public offering

	Study Initiations
2	Pivotal Phase 3 trial in hypothalamic obesity Phase 3 weekly formulation *de novo* trial

	Additional Launches
4+	Germany - BBS Canada – BBS and POMC, LEPR deficiencies The Netherlands and Spain for BBS

	Data Readouts
3	Phase 3 trial in pediatric patients Phase 3 weekly switch trial Preliminary data from Phase 2 DAYBREAK trial

Early-onset, Hyperphagia and Severe Obesity Have a Significant Impact on Patients with MC4R Pathway Diseases and their Families

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

Izzy, who was diagnosed with BBS when she was 5 years old.

"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

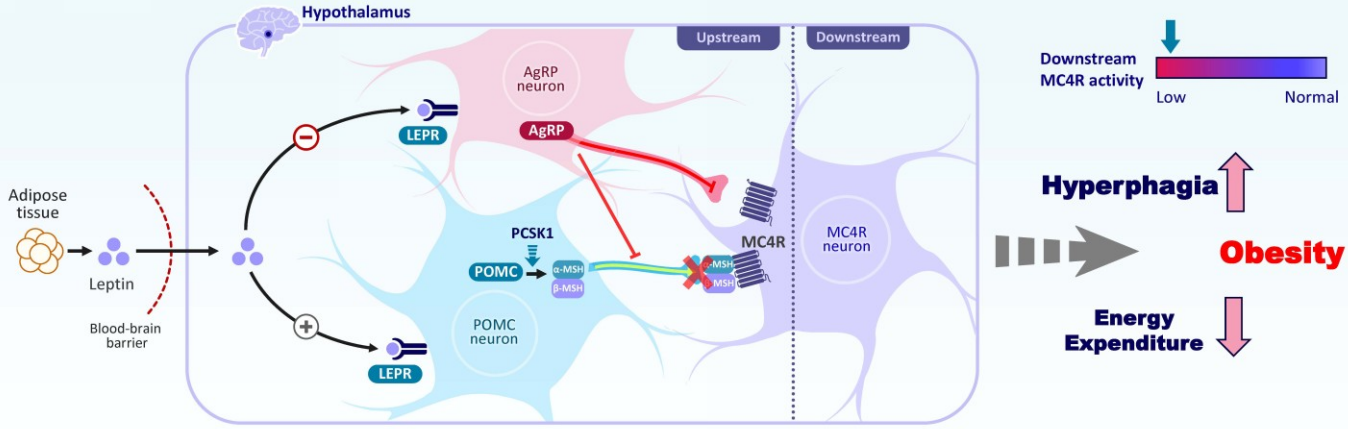
2 MONTHS OLD:
Excessive weight gain becoming noticeable

3 YEARS OLD:
Surgery to correct large chiari malformation

BY 4 YEARS OLD:
Seen by 15 doctors in six different states

4 ½ YEARS OLD:
Ophthalmologist diagnosed retinitis pigmentosa; RP plus hyperphagia and severe obesity led to clinical diagnosis of BBS

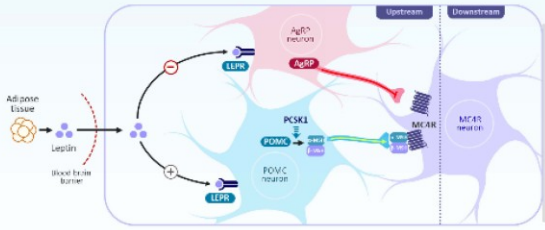
MC4R Pathway Biology is Clear and Strong: Regulates Hunger, Caloric Intake, Energy Expenditure and, Consequently, Body Weight[1-4]



AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Abuzzahab et al. *Horm Res Paediatr.* 2019;91:128-136. **2.** Erfurth. *Neuroendocrinology.* 2020;110:767-779. **3.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732. **4.** Roth. *Front Endocrinol (Lausanne).* 2011;2:49.

Clinical Development Programs Designed to Expand IMCIVREE Label and Overall Opportunity



Approved for:

Bardet-Biedl syndrome and
POMC, PCSK1 and LEPR deficiencies

2,000 – 5,000 patients in the U.S.

Entering Phase 3 in 1H 2023

Hypothalamic obesity

5,000 – 10,000 patients in the U.S.*

Phase 3 EMANATE Trial**

Heterozygous POMC/PCSK1 insufficiency

Heterozygous LEPR insufficiency

SRC1 deficiency

SH2B1 deficiency

53,000 patients in the U.S. †

*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 obesity who may benefit from setmelanotide based on Rhythm sequencing results and current estimated responder rates; does not include ex-U.S. prevalence estimates. Estimate 6,000 with heterozygous POMC/PCSK1 insufficiency; 4,000 with heterozygous LEPR insufficiency, 20,000 with SRC1 deficiency and 23,000 with SH2B1 deficiency . 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018‡); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017)

** EMANATE trial includes patients with variants classified as pathogenic, likely pathogenic or of uncertain significance.

Rhythm Leadership – Strong Team with Broad Biopharma Experience

				
David Meeker, MD *Chair, President and Chief Executive Officer*	**Hunter Smith** *Chief Financial Officer*	**Jennifer Chien** *Executive Vice President, Head of North America*	**Yann Mazabraud** *Executive Vice President, Head of International*	**Joe Shulman** *Chief Technology Officer*
SANOFI GENZYME	Celgene	SANOFI GENZYME Krystal	SANOFI GENZYME trevi THERAPEUTICS	Ra Pharma novelion THERAPEUTICS
25-plus years; focus on rare genetic disease treatments, including Aldurazyme®, Fabrazyme® and Myozyme®	*20-plus years in finance, M&A, capital markets; financial leadership for Otezla®*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years experience leading CMC, supply chain planning and quality assurance and control*

Bardet-Biedl Syndrome

FDA approval in June 2022

EC authorization in September 2022

Bardet-Biedl Community is Established and Patients are Identified

U.S. prevalence estimated to be

1,500 to **2,500**

patients

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

Continued Momentum Across First Full Quarter of Launch

>120* BBS prescriptions

>80* unique prescribers

>40* Approvals for reimbursement

*Cumulative as of September 30, 2022

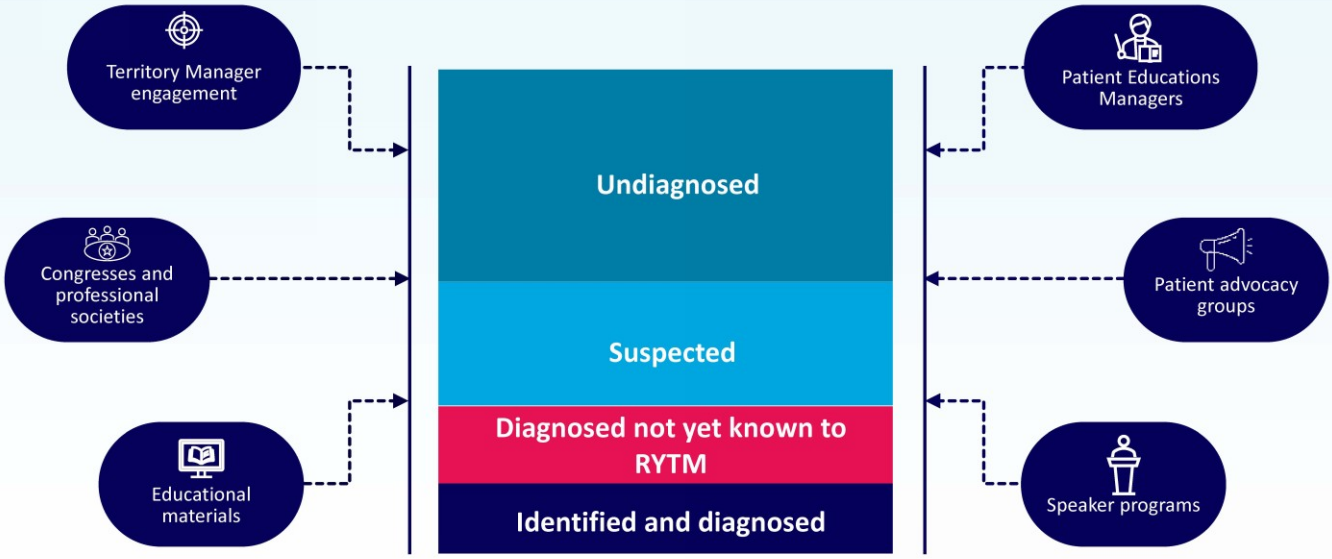
Rhythm InTune Support Services

Personalized program to achieve access, set treatment expectations and support patient adherence and continuity of therapy

Rhythm InTune
Support made personal

Rhythm® PHARMACEUTICALS

Multi-channel Engagement to Continue Identifying Patients with BBS



International Market Access

Significant Market Opportunity for BBS and POMC, PCSK1 and LEPR Deficiencies in Europe

POMC, PCSK1 and LEPR Deficiency Obesities

~100
individuals identified
in **EU4 + UK**

Estimated European prevalence
600 - 2,500

Bardet-Biedl Syndrome

>1,500
individuals identified in **EU4 + UK**
(~20 academic medical centers
with >40 BBS patients)

Estimated European prevalence
~2,500

Global Launch Underway for POMC, PCSK1 and LEPR Deficiency

- ✓ **United Kingdom**
  Commercial launch in October 2022 following UK NICE recommendation
- ✓ **Germany**
  Launched, first sales in 2Q22 following exemption from G-BA lifestyle drug exclusion list
- ✓ **France**
  Reimbursed since March 2022 via early access program
- ✓ **Italy**
  Commercial launch in 4Q 2022
- ✓ **Netherlands**
  Commercial launch in 4Q 2022
- ✓ **Austria**
  Named patient sales
- ✓ **Turkey**
  Named patient sales
- ✓ **Argentina**
  Early access

IMCIVREE for Treatment of Obesity and Control of Hunger in Patients with Bardet-Biedl Syndrome

EC Marketing Authorization Received Sept. 6, 2022

France
Reimbursed early-access program achieved in July 2022

Germany
G-BA exemption procedure ongoing
Launch expected 1H2023

United Kingdom
Submission through Reliance Procedure completed
NICE HST evaluation initiated

Italy
Dossier submitted

Spain
Dossier submitted

Netherlands
On track for dossier submission in 1Q23

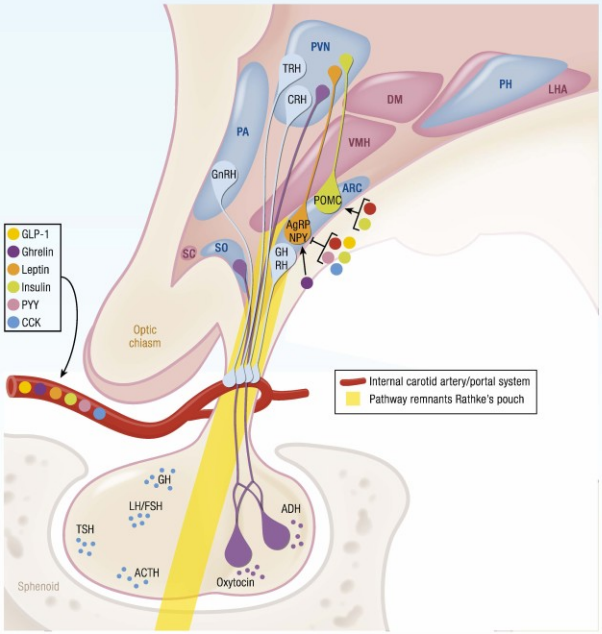
Hypothalamic Obesity

Hypothalamic Obesity: A Rare, Acquired Form of Obesity Following Injury to the Hypothalamic Region

Craniopharyngioma and **other suprasellar brain tumors** and treatment – tumor resection surgery and radiation – is most common cause

MC4R pathway deficiency following injury to hypothalamic region causes reduced energy, hyperphagia and rapid-onset, severe obesity

No approved treatments available



van Iersel et al. *Endo Rev.* 2020 (PMID: 30247642)

Rhythm® PHARMACEUTICALS

Setmelanotide and Hypothalamic Obesity: A Transformative Opportunity for Rhythm

5,000 – 10,000* patients
Estimated U.S. prevalence

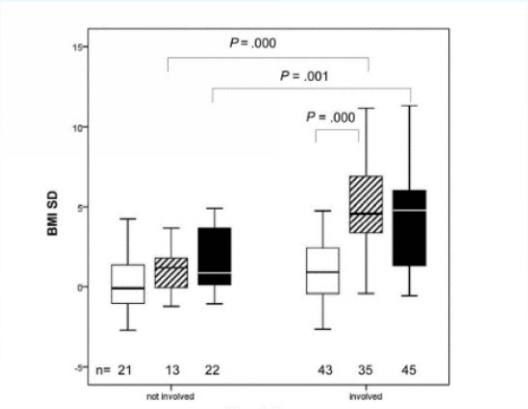
~500* additional cases diagnosed in U.S. each year

- ✓ Unmet medical need is high; no approved therapies
- ✓ MC4R pathway deficiency following injury to hypothalamic region
- ✓ Patients are identified; no genetic testing required
- ✓ Patients are engaged with the system receiving specialist care for pituitary complications

*To estimate the number of patients with incident and prevalent craniopharyngioma and astrocytoma with obesity, Rhythm analyzed the literature and used the number of new cases of each per year in the United States, overall survival rates after a diagnosis of each brain tumor type and obesity rates among those patients at diagnosis or post-diagnosis. See appendix for details.

Longitudinal Analysis of Patients with Childhood-onset Craniopharyngioma Illustrates Impact of Hypothalamic Involvement in BMI

Patients with CP with hypothalamic involvement develop significant increase in BMI standard deviation



+0.80
Median change in BMI SD

Patients with CP **without hypothalamic involvement** at diagnosis had a minimal median BMI SD increase during the first 8-12 years after diagnosis.

+4.29
Median change in BMI SD

Patients with CP and **with hypothalamic involvement** at diagnosis developed a significant increase in BMI standard deviation during the first 8–12 years after diagnosis

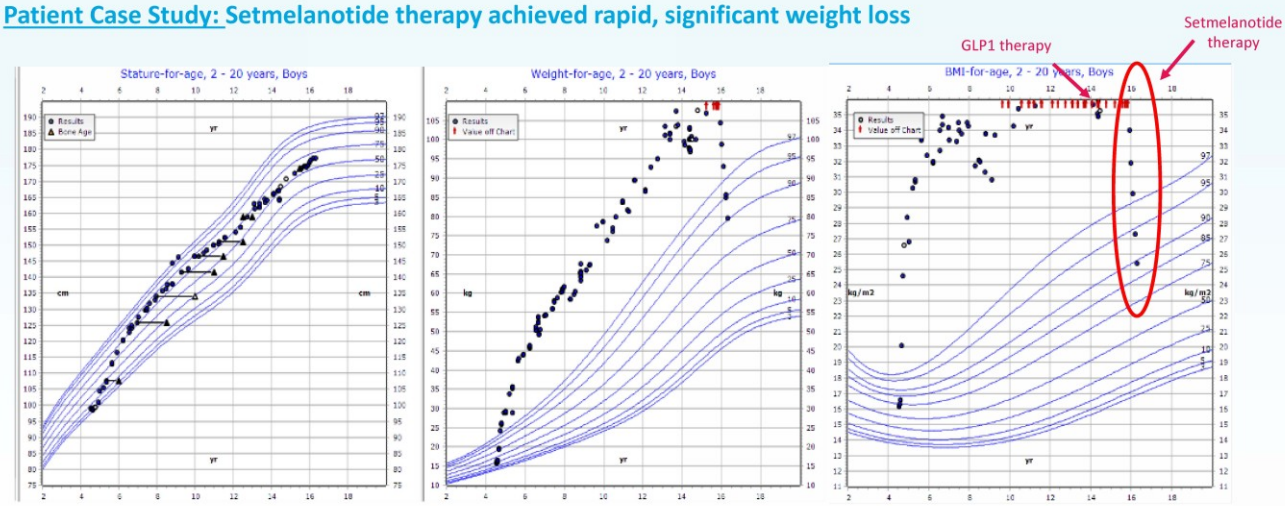
KEY: Body mass index (BMI) SDs is shown for patients at time of diagnosis of CP (white box), 8-12 years after diagnosis (hatched box) and 12+ years after diagnosis. The horizontal line in the middle of each box depicts the median; top and bottom edges of each box respectively mark the 25th and 75th percentiles.

Adapted from Sterkenburg, et. al., *Neuro Oncol*. 2015; doi: 10.1093/neuonc/nov044

Rhythm® PHARMACEUTICALS

HO: Aggressive, Rapid Weight Gain follows Therapy for CP

Patient Case Study: Setmelanotide therapy achieved rapid, significant weight loss



Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota

Setmelanotide Achieved Significant BMI Reduction at 16 Weeks in Patients with Hypothalamic Obesity in Phase 2 Trial

Full analysis set population (N=18)

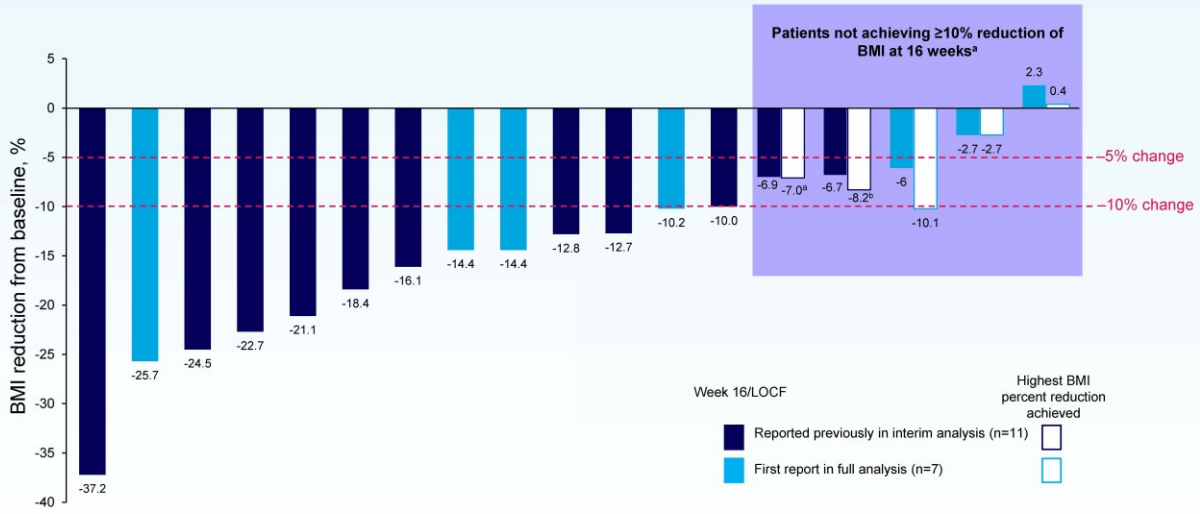
16 of 18
patients achieved
primary endpoint of ≥5% reduction in BMI
(P<0.0001)

14 of 18
patients achieved
≥10% reduction in BMI

−14.5%
mean change
in **BMI** at 16 weeks

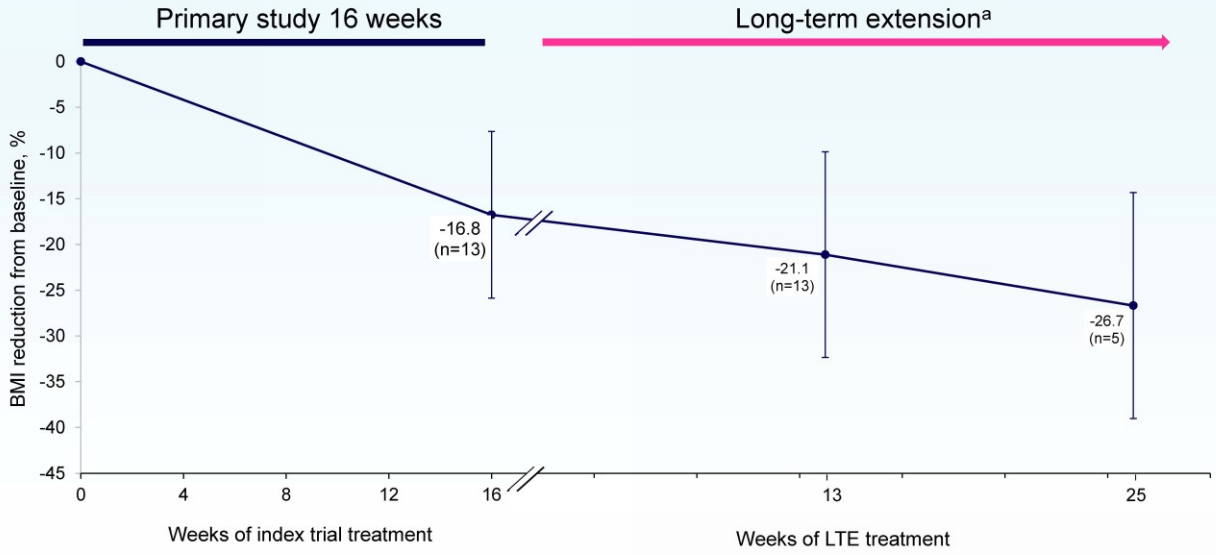
As presented during The Obesity Society's ObesityWeek® 2022, November 1-4, 2022 in San Diego, CA

Setmelanotide Achieved Consistent BMI Reduction at 16 Weeks



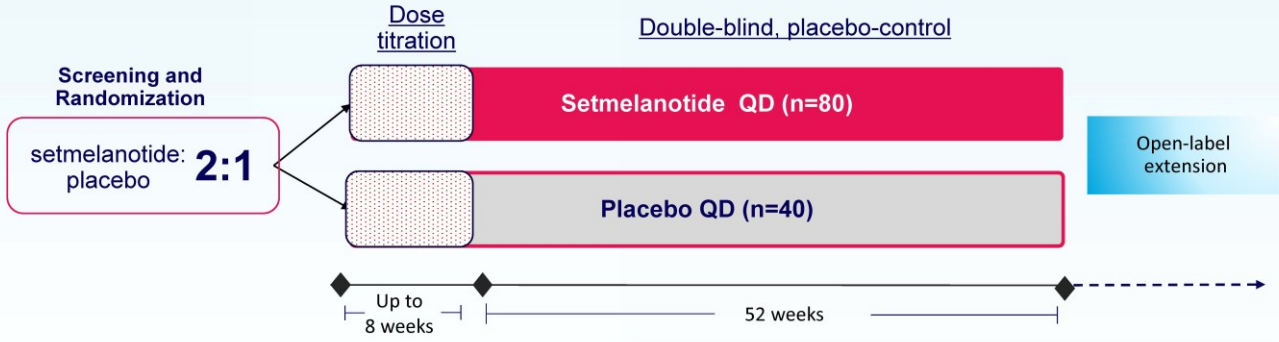
[a]–7.0% last on treatment Week 4. [b]–8.2% last on treatment Week 12. BMI, body mass index; LOCF, last observation carried forward.

Mean Percent Change in BMI in Patients With ≥3 Months of Follow-up in the Long-term Extension Trial



Errors bars are the standard deviation. [a]Fourteen patients have entered the long-term extension trial; one patient had not reached 3 months as of a cut-off date of September 23, 2022. BMI, body mass index.

Phase 3 Double-blind, Randomized Controlled Trial with 120 Patients Expected to Begin in Early 2023



Starting dose for all patients is 0.5mg QD; Maximum dose for patients<6yo is between 1.5mg QD and 3.0mg QD based on body weight; maximum dose for patients >6yo with a body weight of 30 kgs or more is 3.0mg QD.

Primary endpoint: Mean % change in BMI from baseline to after approximately 52 weeks on a therapeutic regimen of setmelanotide compared with placebo.

BMI, body mass index; QD, once daily.

Significant Unmet Need with an Active Patients Community Waiting for an Effective Therapy

Raymond A. Wood foundation

FDA Patient Listening Session on Hypothalamic Obesity

> "Hyperphagia is the biggest cause of low quality of life of all the conditions from the tumor (worse than low vision, diabetes insipidus, adrenal insufficiency, etc.)"
>
> *-- Patient*

> "He demonstrated excessive hunger upon returning home from the hospital. He foraged at night. We locked up food to avoid having to stay up all night to monitor his night eating."
>
> *-- Caregiver*

> "Within 6 months I gained 30 pounds and couldn't get a doctor to even hear my concerns or issues regarding the sudden weight gain and lack of muscle tone."
>
> *-- Patient*

Excerpted from FDA Listening Session, hosted in October 2021 by the Raymond A. Wood Foundation

Clinical Development

Meaningful Expansion of Addressable Patient Population

Multiple Ongoing and Planned Clinical Trials Evaluating Setmelanotide

Enrollment complete

Pediatrics Trial
Phase 3
Patients aged 2 to <6 years

Weekly Formulation
Phase 3
Switch Trial

Weekly Formulation
Phase 3 *de novo*
Trial planned for
1H2023

Emanate
Phase 3 Trial

Daybreak
Phase 2 Trial

Hypothalamic obesity
Phase 3 Trial planned
for 1Q2023

EMANATE and DAYBREAK Studies to Drive Significant Expansion of 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

Daybreak
Obesity and Hunger Clinical Trial

† 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 census) presents with severe early onset obesity (Hales et al 2018‡); ~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, respectively. € Planned EMANATE trial would include patients with variants classified as pathogenic, likely pathogenic or suspected pathogenic;

Setmelanotide Generally Well-tolerated Across Development Program

Setmelanotide has been evaluated in 639 patients with obesity, with some individual patient treatment durations 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	**545**
> 1 year	**94**
> 2 years	**40**
> 3 years	**17**
> 4 years	**3**
> 5 years	**2**

* Data as of March 8, 2021, inclusive of trial participants who received daily or weekly formulation of setmelanotide.

Rhythm's Strategic Priorities for 2023

Execute on U.S. commercial strategy with **BBS launch**

Achieve access and launch **IMCIVREE for <u>both</u> BBS and POMC, PCSK1 and LEPR** in select international markets

Initiate Phase 3 trial to evaluate setmelanotide in **hypothalamic obesity**

Expand IMCIVREE opportunity through additional studies:

- EMANATE Ph 3
- Pediatrics Ph 3
- Weekly Ph 3
- DAYBREAK Ph 2

Well Capitalized: Cash Sufficient to Fund Planned Operations into at least 2025

$347.8 Million*
Cash, cash equivalents and short-term investments as of 09/30/22

Guidance*
Cash on hand expected to be sufficient to fund operations into **2025**

55.8 Million
Common shares outstanding

Analyst coverage†
BofA Securities; Canaccord Genuity; Cowen; Goldman Sachs; Ladenburg Thalmann; Morgan Stanley; Needham; Stifel; Wells Fargo

* Partial exercise of the underwriters' option to purchase additional shares as part of public offering, which resulted in additional net proceeds of $14.2, not included in cash on-hand as of Sept. 30, 2022; † Analyst coverage includes all brokerage firms known by the company as of September 2022 to have analysts covering the company. This list may not be complete and is subject to change. Analyst opinions, estimates or forecasts are their own and may not represent the opinions, estimates or forecasts of the company.

Appendix

Additional Supporting Slides

Phase 3 EMANATE 3 Trial to Evaluate Setmelanotide Across Four Genetic Subtypes

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.

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

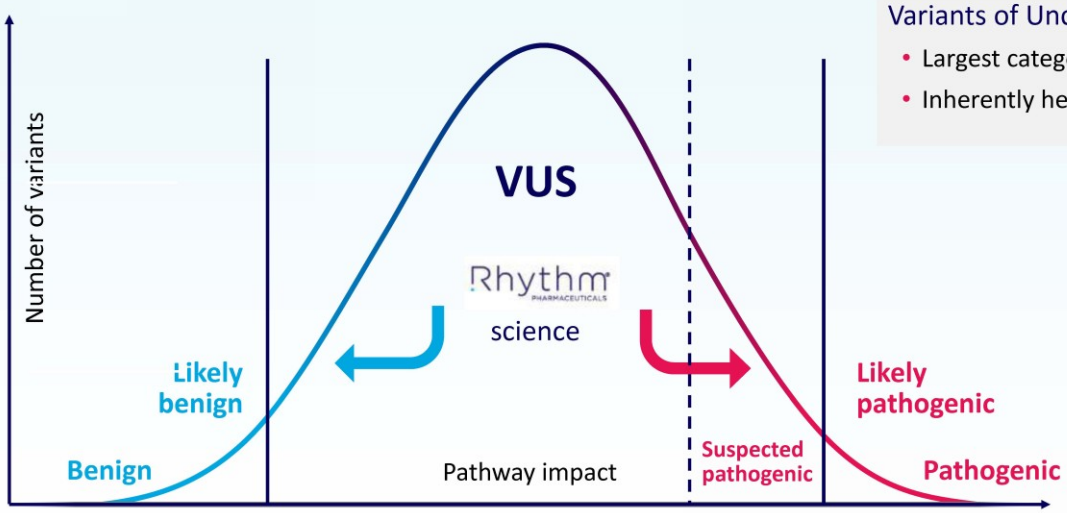
HETs Obesity *POMC/PCSK1/LEPR Heterozygous Insufficiency*	SRC1 Deficiency Obesity	SH2B1 Deficiency Obesity
34.3% of patients **(12/35)** achieved the primary endpoint of **≥5% weight loss** from baseline at Month 3	**30%** of patients **(9/30)** achieved the primary endpoint of **≥5% weight loss** or **≥0.15 reduction in BMI Z score** from baseline at Month 3	**42.9%** of patients **(15/35)** achieved the primary endpoint of **≥5% weight loss** or **≥0.15 reduction in BMI Z score** from baseline at Month 3
Responses to setmelanotide were maintained through 6 and 9 months		

Long-term BMI Reductions at 12 Months on Setmelanotide Therapy in HETs, SRC1 and SH2B1 Supportive of Success in Phase 3 EMANATE Trial

HETs Obesity *POMC/PCSK1/LEPR Heterozygous Deficiency*	**SRC1 Deficiency Obesity**	**SH2B1 Deficiency Obesity**
-8.7% **mean BMI reduction** **(n=17)** at **12 months** on therapy	**-10.1%** **mean BMI reduction** **(n=8)** at **12 months** on therapy	**-9.7%** **mean BMI reduction** **(n=14)** at **12 months** on therapy

* As presented at the **Endocrine Society** Annual Meeting & Expo (ENDO 2022) held **June 11-14, 2022** in **Atlanta.**

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



Variants of Uncertain Significance

- Largest category of rare variants
- Inherently heterogeneous

*ACMG Guidelines Richards et al, 2015

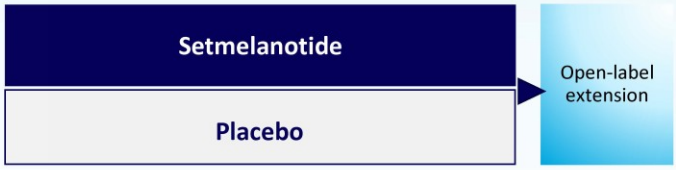
Phase 3 EMANATE Trial Comprised of Four Independent Sub-studies

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

a.	POMC/ PCSK1*	86 patients	• Pathogenic • Likely pathogenic • VUS*-Suspected pathogenic
b.	LEPR*	86 patients	• Pathogenic • Likely pathogenic • VUS-Suspected pathogenic
c.	SRC1	112 patients	• All VUS
d.	SH2B1	112 patients	• Pathogenic • Likely pathogenic • VUS

Enrollment 12-18 Months

Each sub-study: Patients randomized 1:1



52 weeks

Endpoints

- Primary: Difference in mean percent change in BMI from baseline to 52 weeks in setmelanotide arm compared to placebo arm
- Key secondary: Additional measurements of effects on weight-related and hunger/hyperphagia endpoints

* VUS – Variant of uncertain significance.

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

Heterozygous POMC/PCSK1 and LEPR sub-studies are 90% powered to show >8% treatment effect vs. 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 placebo
- Setmelanotide responders anticipated to demonstrate >10% treatment effect at 52 weeks
- Setmelanotide mean treatment effect (weighted responder and non-responder) anticipated to be >8% at 52 weeks

PLP: pathogenic, likely pathogenic or suspected pathogenic

EMANATE Secondary Endpoints to Illustrate Effect on Weight and Hunger

Secondary endpoints

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

Phase 2 Daybreak Trial to Evaluate Setmelanotide Across 10 New Genes

Daybreak

Obesity and Hunger Clinical Trial

Relevance to MC4R Pathway: Rhythm's ClinGen-based framework suggests all 10 genes have very strong relevance to MC4R Pathway

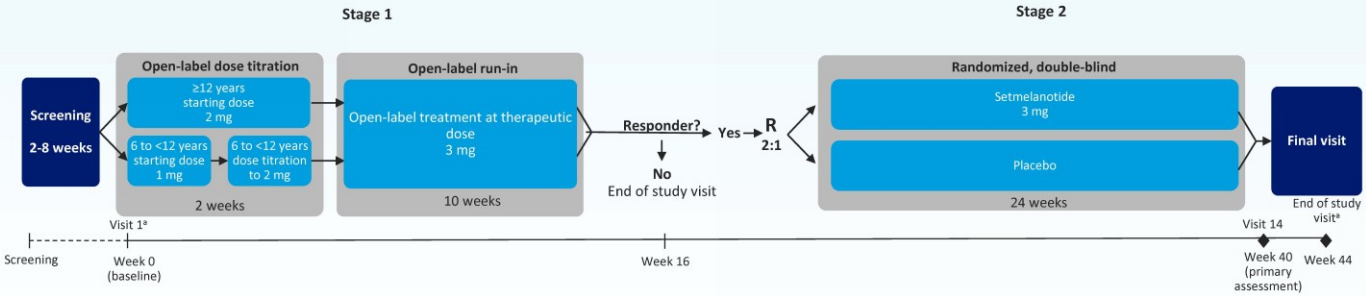
Efficient, two-stage trial design

- **16-week, open-label run-in** in allows for fast signal-seeking in individual gene cohorts
- **24-week, double-blind treatment** period enables robust proof of concept
- Each genetic cohort can read out independently

First patient: Enrolled in January 2022

Approximately 13.1% of patients with early-onset obesity test positive for DAYBREAK-eligible variants with Rhythm's URO

Phase 2 DAYBREAK Trial Designed to Evaluate Setmelanotide Therapy in 10 Genes with Strong or Very Strong Relevance to MC4R Pathway



[a]Virtual visit. R, randomization.

Enrollment Completed in Phase 3 Trial in Pediatric Patients Ages 2 to 6

International one-year, open-label study

Enrollment complete with 12 patients

- Half with biallelic POMC, PCSK1 or LEPR deficiency
- Half 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 been 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 open-label QW for all patients
- Primary endpoint: responder analysis, based on the proportion of patients with no weight gain of 5 percent or greater from baseline to week 13

Phase 3 randomized, double-blind, placebo-controlled "de novo" study of once-weekly (QW) formulation of setmelanotide to be initiated in 1H 2023

- 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 adherence

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

Primary endpoint is the proportion of patients by gene who enter Stage 2 and are responders 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 5%
- 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

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

Phase 3 trial achieved all predefined primary and key secondary endpoints

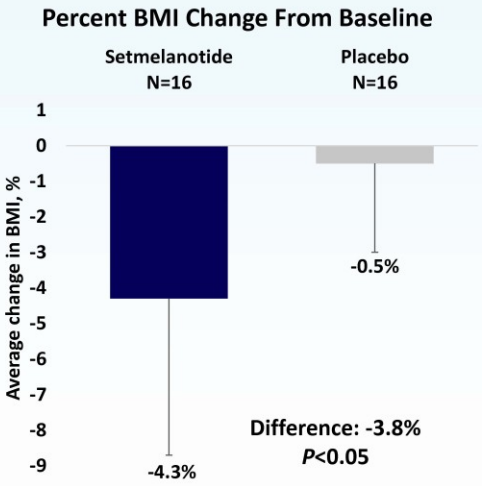
Adults ≥ 18 years old (n=15)		Patients younger than 18 (n=14)	
46.7% (7/15) had **≥10% weight reduction**	**60%** (9/15) had **≥5% weight reduction**	**85.7%** (12/14**) had a **reduction in BMI-Z ≥0.2**	**–0.75** points **mean change in BMI Z score**
–9.1% mean % **change in BMI**		**–9.5%** mean % **change in BMI**	

*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 than 12 at enrollment 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 Endocrine Society Annual Meeting in March 2021.

Phase 3 Trial: Setmelanotide Led to Significant BMI Reduction in 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 Improvements in 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 HRQOL		
	Adults (≥18 years old)	Children (8-17 years old)
Patients, n	11	9
	IWQOL-Lite total score*	PedsQL total score**
Baseline, mean (standard deviation)	74.9 (12.6)	67.2 (18.9)
Change at week 52, mean (SD)	**+12.0 (10.8)**	**+11.2 (14.4)**

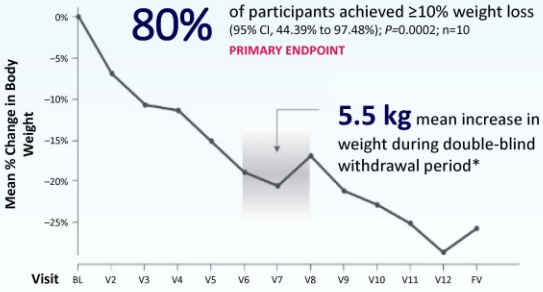
***Impact of weight on quality of life or IWQOL:** Is a zero to 100 range, with zero being the worst possible and 100 best possible score. A total score increase of 7.7 to 12 is considered clinically meaningful improvement; Pre-defined ranges are: Impairment: <71.8 = severe, 71.9-79.4 = moderate, 79.5-87.0 = mild, 87.1-94.6 = none.
****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 greater is considered clinically meaningful. Impairment is defined as a score < 68.2.

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

POMC/PCSK1

80% of participants achieved ≥10% weight loss (95% CI, 44.39% to 97.48%); *P*=0.0002; n=10

PRIMARY ENDPOINT



5.5 kg mean increase in weight during double-blind withdrawal period*

LEPR

45.5% of participants achieved ≥10% weight loss (95% CI, 16.75% to 76.62%); *P*<0.0002; n=11

PRIMARY ENDPOINT

5.0 kg mean increase in weight during double-blind withdrawal period*

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. 22, 2020 corporate conference call.