Rhythm Pharmaceuticals

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

November 2021

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.

Transforming Care of Patients with Rare Genetic Diseases of Obesity

IMCIVREE® (setmelanotide) injection

FDA-approved in November 2020

EC marketing authorization received July 2021

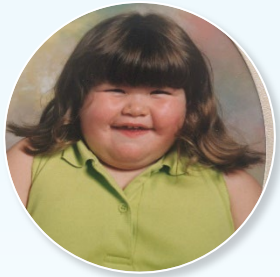
Commercial availability in U.S. meeting expectations and market access advancing in key **international markets**

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

Clinical development **meaningfully expands** addressable patient population

Early-onset, Severe Obesity and Hyperphagia Characterize Rare Genetic Diseases of Obesity

3 YEARS



11 YEARS, 231 POUNDS

23 YEARS, 450 POUNDS

INFANCY:

Has “normal” weight at birth

Begins to rapidly gain weight at 9 weeks

4 YEARS:

Diagnosed with POMC heterozygous deficiency obesity

CHILDHOOD:

Self-isolation and missed school days

Asthmatic

Increased pain and pressure on her knees make play and physical education difficult

ADOLESCENCE:

Prescribed anti-depressants

Numbness and agonizing back pain

Abnormal pubertal development

23 YEARS (CURRENT):

Sleep apnea

Some cardiac issues

Insulin resistance

Cracked and bleeding skin

Lost in the system

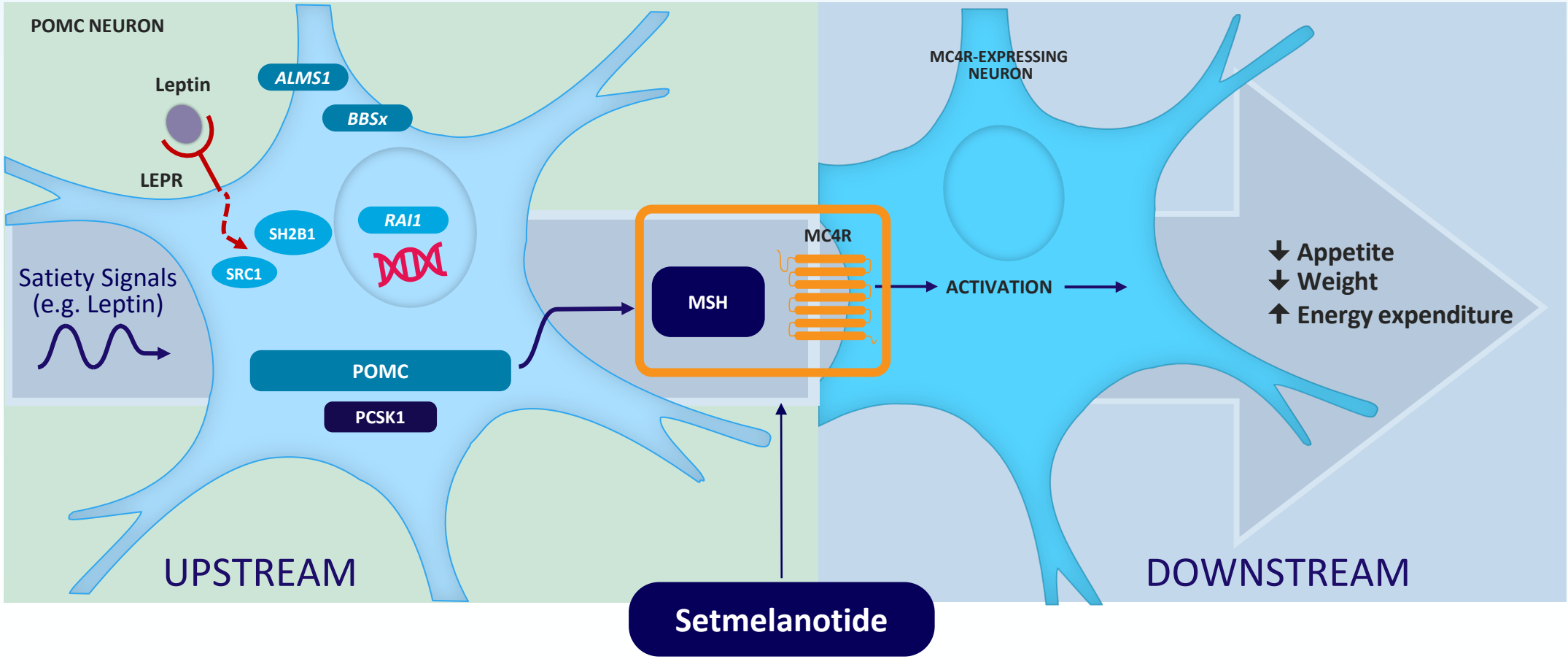
Little knowledge or awareness

No tools, testing or treatment

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

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

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



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

Genes Approved

POMC

PCSK1

LEPR

(biallelic)

U.S. and EU Regulatory Submissions Filed

BBS (*all*)

ALMS1

Genes in Clinical Development

EMANATE Phase 3	DAYBREAK Phase 2
POMC	**31** additional genes related to MC4R pathway
PCSK1	
LEPR	
SRC1	
SH2B1	

(heterozygous or single allele variants)

Setmelanotide lifecycle advancements

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

Clinical Development Programs Designed to Expand the Setmelanotide 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 expansion

Phase 3 EMANATE Trial€

Five independent sub-studies

45,000†	**Heterozygous POMC/PCSK1 deficiency**
25,000†	**Heterozygous LEPR deficiency**
20,000†	**SRC1 deficiency**
23,000†	**SH2B1 deficiency**
100,000†	**PCSK1 N221D deletion**

Phase 2 DAYBREAK Trial Exploring an additional **31 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 obesity who may benefit from setmelanotide based on sequencing results and current estimated responder rates; 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 2018ł); ~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 of uncertain significance, and patients with N221D variant;

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 Potential Options

IMCIVREE® (setmelanotide) injection

Six clinical trials in 2021

Future clinical trials

Rhythm® PHARMACEUTICALS

Rhythm Leadership – Strong Team with Broad Biopharma Experience

					
David Meeker, MD *Chair, President and Chief Executive Officer*	**Hunter Smith** *Chief Financial Officer*	**Linda Shapiro Manning, MD, PhD** *Chief Medical Officer*	**Jennifer Chien** *Executive Vice President, Head of North America*	**Yann Mazabraud** *Executive Vice President, Head of International*	**Pamela Cramer** *Chief Human Resources Officer*
SANOFI GENZYME	Celgene	novo nordisk; MERCK; Boehringer Ingelheim	SANOFI GENZYME; Krystal	SANOFI GENZYME; trevi THERAPEUTICS	FOUNDATION MEDICINE; PAREXEL
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 in obesity medicine as an HCP and industry leader*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years global experience in organizational effectiveness, talent development and human resources*

IMCIVREE® (setmelanotide)

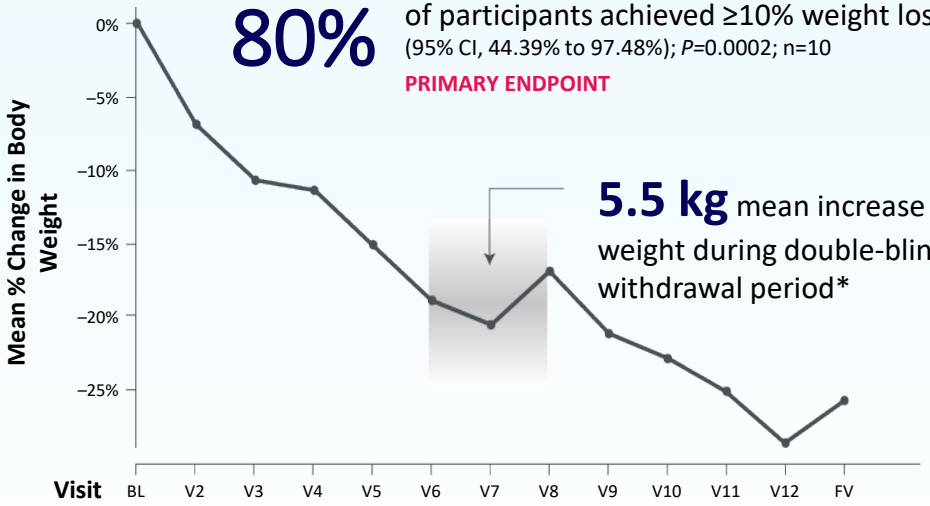
Commercial availability in U.S. meeting expectations and market access advancing in key international markets

U.S. and EU Approvals of IMCIVREE Based on Phase 3 Data 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

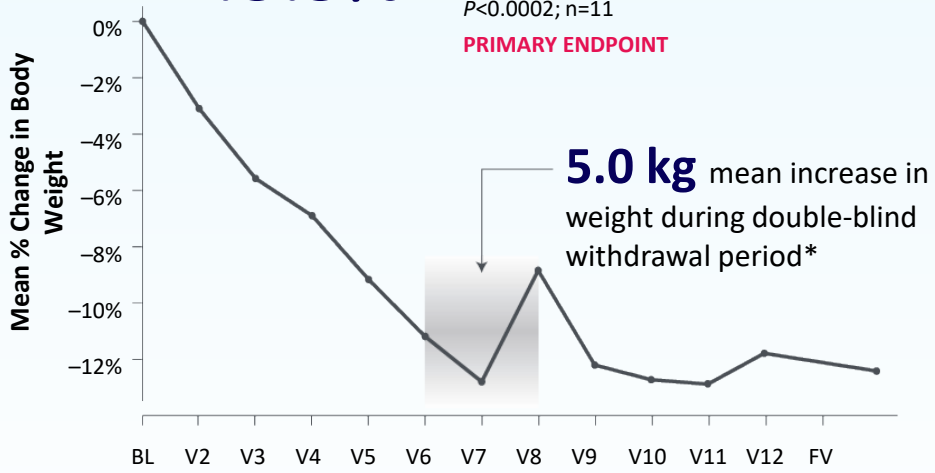


5.5 kg mean increase in weight during double-blind withdrawal period*

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.

Rhythm® PHARMACEUTICALS

IMCIVREE Launch

First two quarters of IMCIVREE commercial availability:

- >$1.3M in net sales
- 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.”

Market Access and Reimbursement in Key International Markets

Germany

- Procedure for **Annex II** (Lifestyle products) **exemption** initiated by GBA September 2021
  - If positive, reimbursement by all Statutory Health Insurances
  - Final decision at plenary session in Q1 2022
- **Commercial launch** expected Q2 2022

France

- **Fast-track** procedure obtained January 2021
- **Reimbursement dossier** submitted July 2021
- Ongoing process with HAS

United Kingdom

- Selected for **Highly Specialized Technology** evaluation
- **NICE** Committee meeting in December 2021

Italy

- **Reimbursement dossier** submitted July 2021
- Waiting for AIFA feedback

Spain

- **Reimbursement dossier** submission slightly delayed due to local regulatory requirements
- Submission expected in November 2021

The Netherlands

- **Reimbursement dossier** submitted

Israel

- **Reimbursement dossier** submitted
- Decision expected January 2022

Sweden

- Dossier development initiated

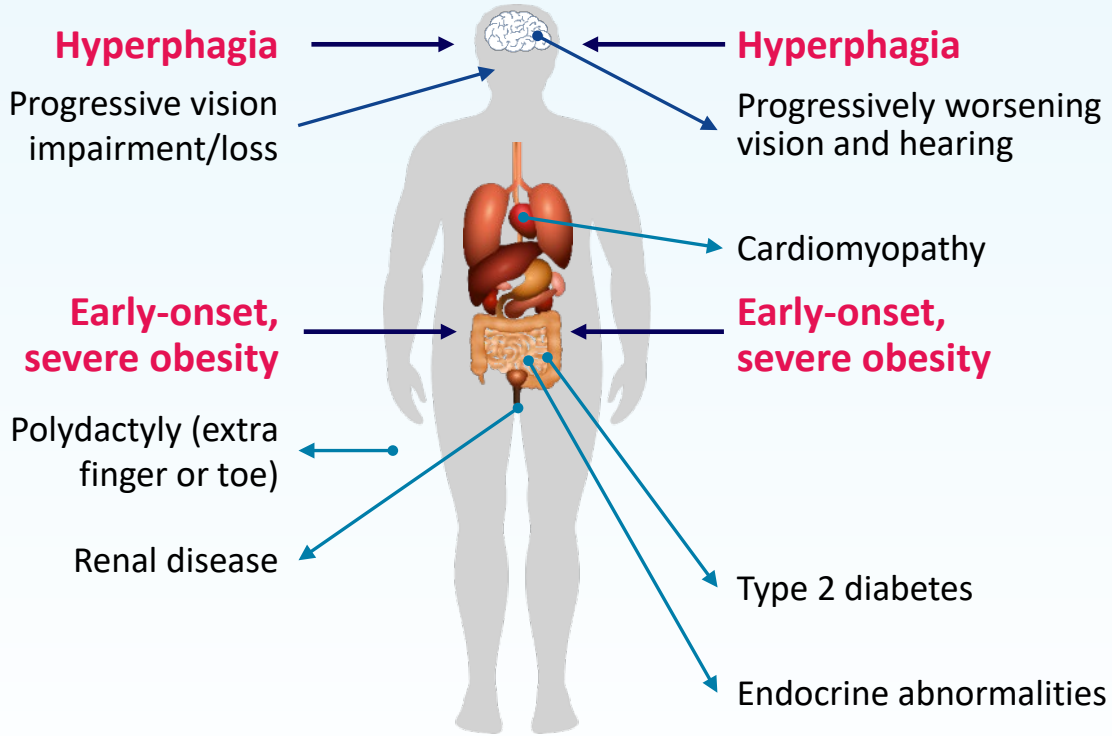
Bardet-Biedl and Alström Syndromes

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

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

Bardet-Biedl syndrome[1]

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



Alström syndrome[2,3]

Rare ciliopathy disorder associated with **ALMS1 mutation**

"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 school because she was thinking about what was in her lunchbox or what she was going to get at lunch …"*

Caregiver

> *…At one point, [~2 years old] he found where the white flour was…. and was able to pull the container out of the pantry and just sat down and was eating flour."*

Caregiver

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 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)

46.7%
(7/15) had
≥10% weight reduction

60%
(9/15) had
≥5% weight reduction

–9.1% mean % **change in BMI**

Patients younger than 18 (n=14)

85.7%
(12/14**) had a
reduction in BMI-Z ≥0.2

–0.75
points
mean change in BMI Z score

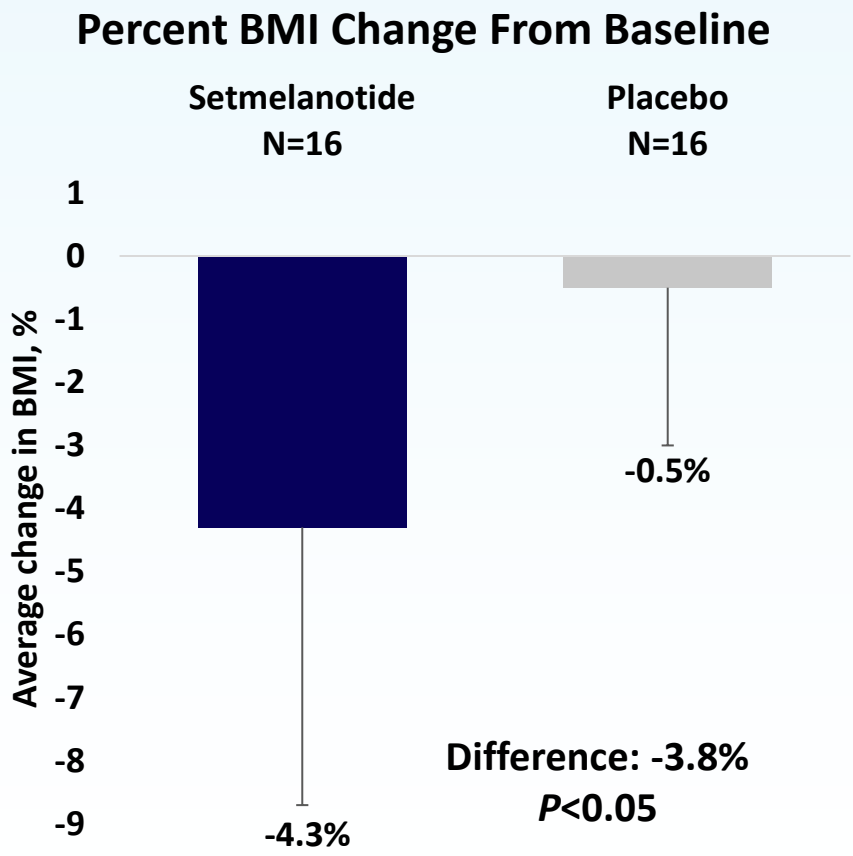
–9.5% mean % **change in BMI**

*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

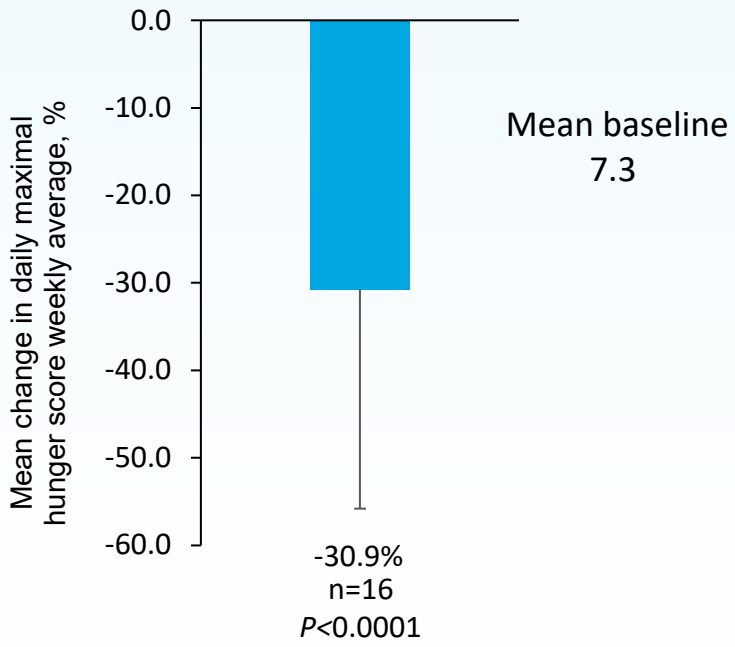
Patients with BBS treated with setmelanotide achieved an average BMI reduction of **–1.5 kg/m²** **(–3.8%)** at Week 14 compared with patients on placebo who saw ***negligible weight loss*** (*P*<0.05)



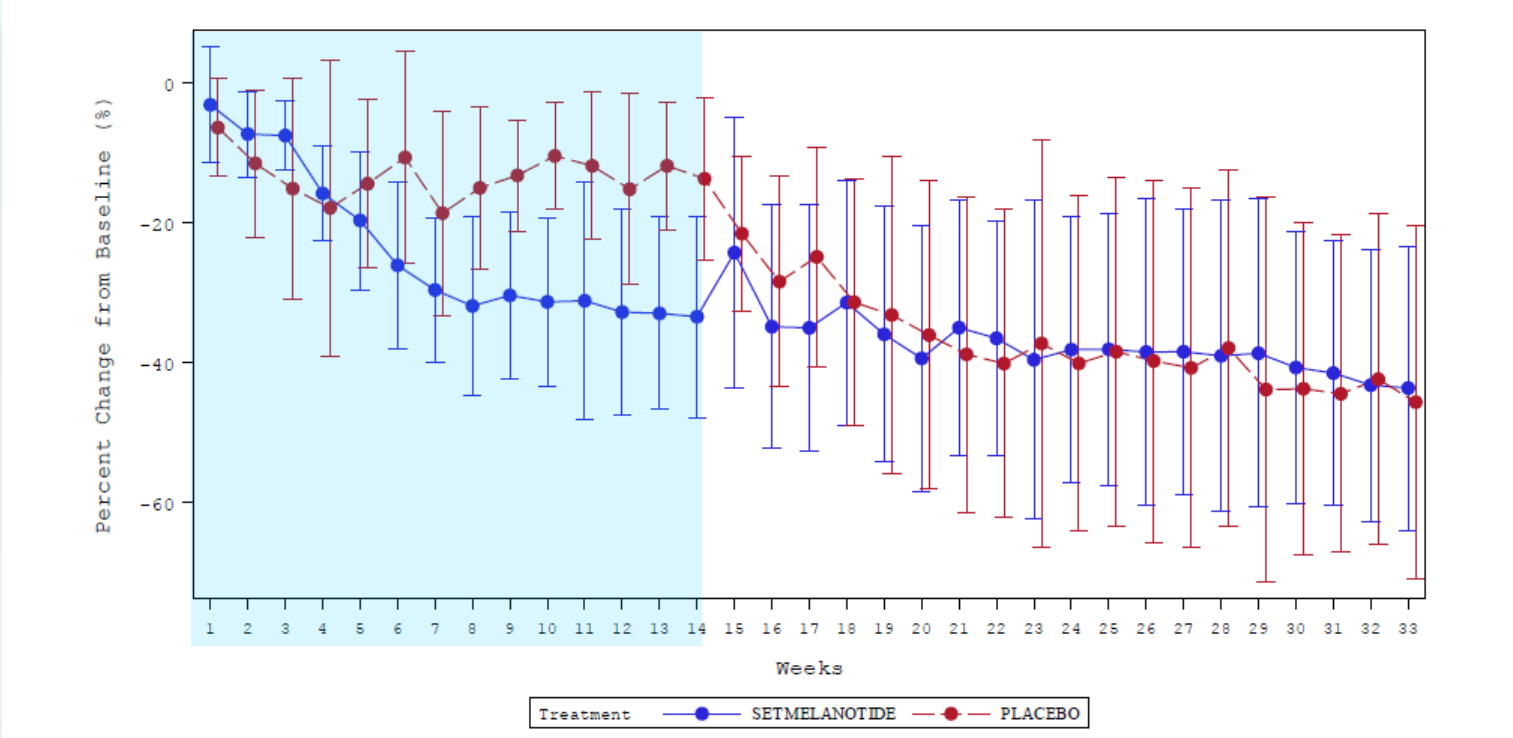
As presented at ESPE 2021 – 59th Annual European Society for Paediatric Endocrinology Meeting, September 2021.

Rhythm® PHARMACEUTICALS

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



Data show separation in hunger reduction during placebo period followed by placebo group reaching treatment levels rapidly after crossover; all patients on placebo 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. Data on file at Rhythm.

Rhythm® PHARMACEUTICALS

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

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

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

U.S projected commercial launch mid-2022

Type II Variation Application Submitted to EMA in October 2021

*All patients who met the primary endpoint defined as more than 10 percent weight loss had BBS and none had Alström syndrome.

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**

Estimated European prevalence estimated to be

~2,500

patients

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

New Market Research Highlights Positive Impressions of IMCIVREE Profile Among Physicians Treating BBS

HCPs:

- Obesity universally viewed as a serious concern
- Reasons to prescribe:
  - age range (6+); mechanism of action; effectiveness in weight loss
- Dosing and safety/tolerability acceptable
- Do not foresee barriers in initiating treatment

75%

of respondents would prescribe setmelanotide as first-line therapy for obesity in BBS

Double-blind, qualitative primary market research via in-depth, 1-hr telephone interviews with 30 US HCPs who manage obesity in BBS

BBS Territory Managers Now in the Field and Focused on Targeted Physician Engagement

BBS Territory Managers

20 Average years in pharma/biotech sale

6 Average years of rare disease experience

100% have launch experience

6 average number of launches

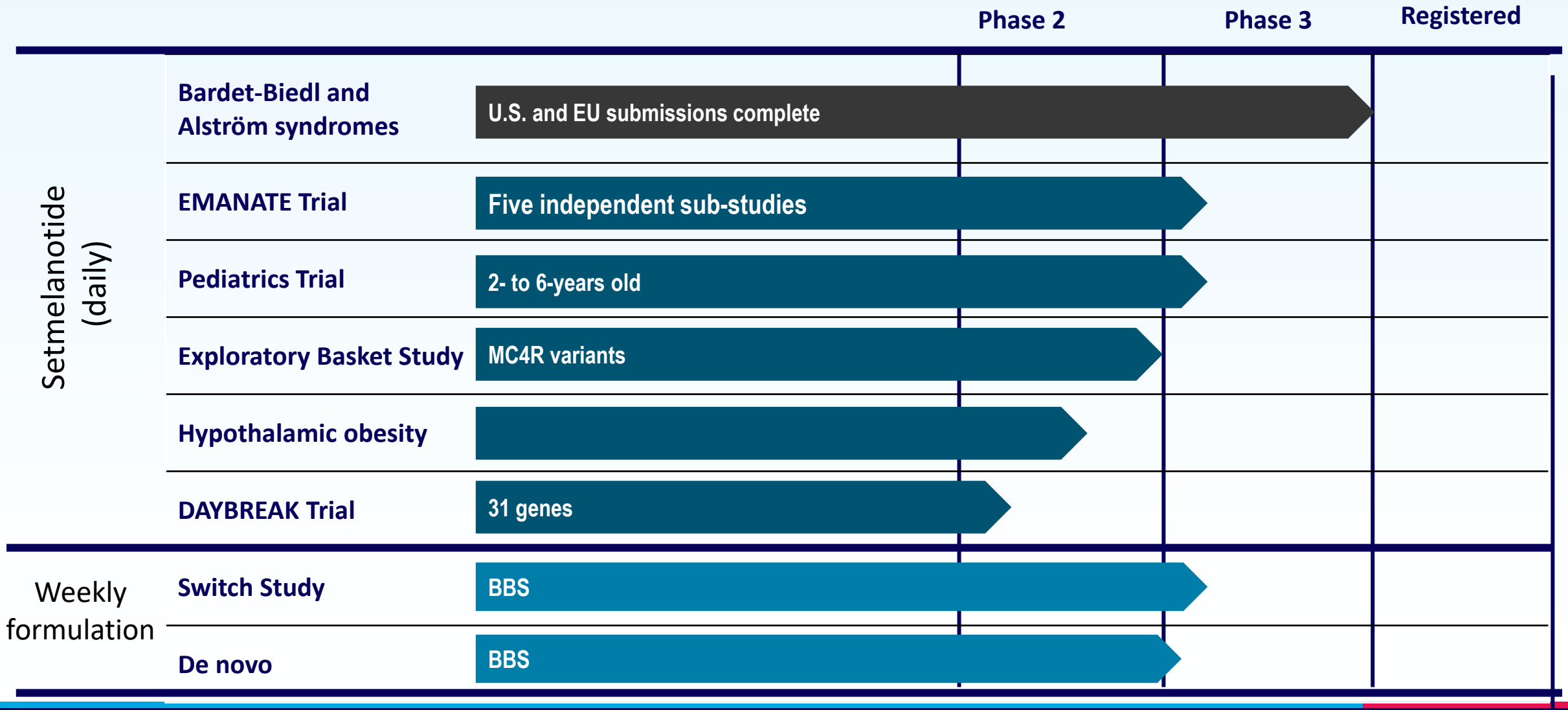
Targeted physician engagement

- Continued engagement with top-tier MD targets (~125)
- Additional MD targets likely to have BBS patients in their care identified by machine learning algorithm

Clinical Development

Meaningful Expansion of Addressable Patient Population

Clinical Programs Designed to Achieve Label Expansion on Track



Rhythm® PHARMACEUTICALS

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

Phase 3 EMANATE Trial€

Five independent sub-studies

45,000†	**Heterozygous POMC/PCSK1 deficiency**
25,000†	**Heterozygous LEPR deficiency**
20,000†	**SRC1 deficiency**
23,000†	**SH2B1 deficiency**
100,000†	**PCSK1 N221D deletion**

Phase 2 DAYBREAK Trial Exploring an additional **31 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 2018ł); ~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 of uncertain significance, and patients with N221D variant;

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 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 Deficiency Obesity

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

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

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

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: 4Q2021 or 1Q2022

Total Addressable Market: potential of 100-200,000 patients in the U.S.

Emanate

Obesity and Hunger Clinical Trial

Phase 2 Daybreak Trial to Evaluate Setmelanotide Across 31 New Genes

Daybreak

Obesity and Hunger Clinical Trial

Relevance to MC4R Pathway: All 31 genes have strong or very strong relevance to MC4R Pathway based on ClinGen framework

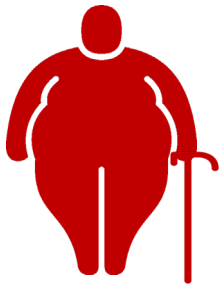
Efficient, two-stage trial design

- **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: 4Q2021

Almost 40% of patients with early-onset obesity had DAYBREAK-eligible variants in Rhythm's URO sequencing program

Improved URO with Expanded Gene Panel Launched in July 2021

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 Sept. 30, 2021

~1,800

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

~11,500

sequence samples completed

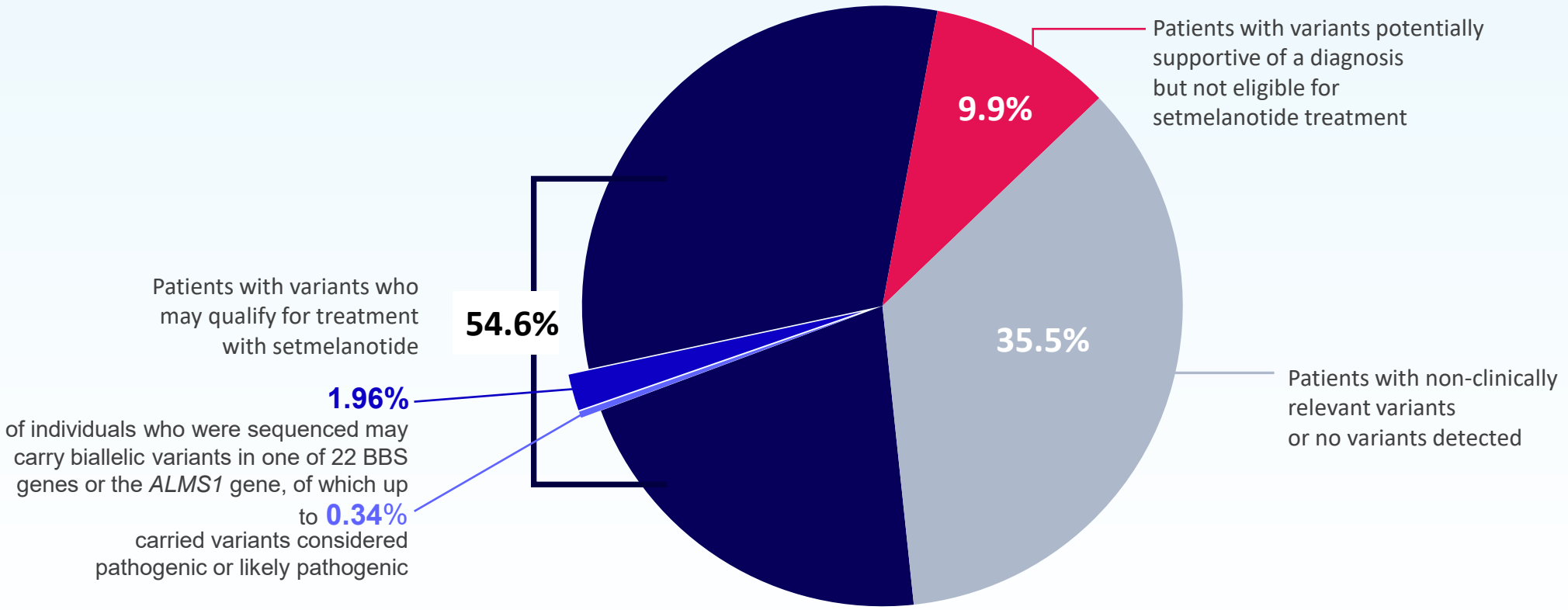
~20%
6 years old and younger

~80%
7 years old and older

* As identified by Rhythm based on proprietary criteria.

Rhythm® PHARMACEUTICALS

URO: 54% of Sequenced Individuals with Severe Obesity Carry Variants in Genes with Known Relevance to MC4R Pathway

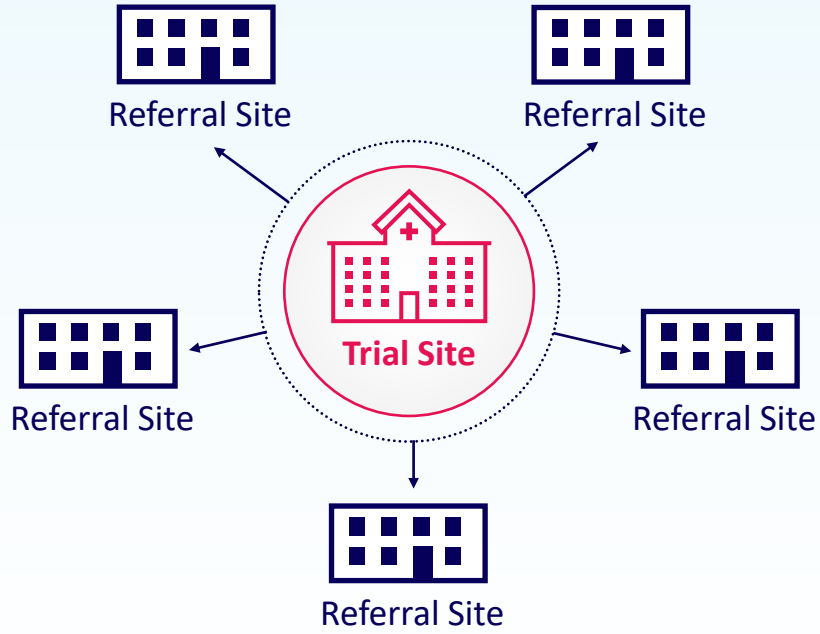


* Represents a weighted yield from 8,599 URO samples collected as of July 12, 2021. Prior to May 2021, Rhythm's URO panel tested for variants in 40 obesity-related genes, including 11 genes eligible for the DAYBREAK or EMANATE trials; data for those 11 genes is available in all 8,599 samples. Rhythm 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. Data 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

Parallel Operations to Support both EMANATE and DAYBREAK

Site initiations underway

- 75+ 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
- Investigator meetings planned in November and December



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.

Continued Transformational Progress Expected in 2021 and 2022

	2H 2021
✓	EU, Great Britain authorization for POMC, PCSK1 and LEPR
✓	Present full data analyses from pivotal Phase 3 trial in BBS at ESPE and TOS 2021
✓	U.S. FDA acceptance of BBS and AS sNDA
	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 *(4Q 2021 or 1Q 2022)*
	1H 2022
	Initiate Phase 3 “*de novo* study” of weekly formulation
	Initial data from Phase 2 Basket study in MC4R-rescuable patients
	Initial data from Phase 2 trial in hypothalamic obesity
	March 16: PDUFA target date for BBS and AS sNDA

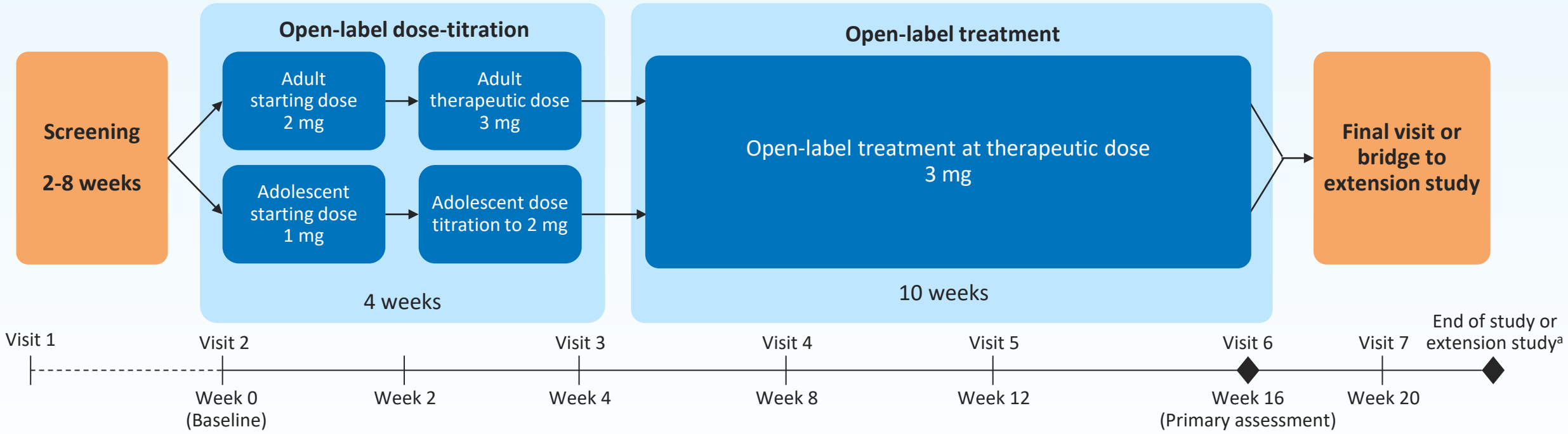
Cash Expected to be Sufficient to Fund Operations into 2H 2023

SHARES OUTSTANDING *as of 9/30/2021*	50,268,312 (basic and diluted share count)
CASH, CASH EQUIVALENTS AND SHORT-TERM INVESTMENTS *as of 9/30/2021*	$328.4 million

Appendix

Results from Exploratory Phase 2 Basket Trial

Phase 2 Basket Study Evaluated Response at Three Months of Therapy



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

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

Clinical Characteristics of Patients Enrolled in Exploratory Phase 2 Basket Study

	HETs deficiency obesity Heterozygous POMC, PCSK1 or LEPR	**SRC1 deficiency obesity**	**SH2B1 deficiency obesity**
	N=**35**	N=**30**[a]	N=**35**[a]
Mean age (range)	**39 years old** (15 - 68)	**31 years old** (9 - 66)	**31 years old** (8 - 67)
Mean weight	**316 lbs/ 143 kgs**	**270 lbs/ 123 kgs**	**280 lbs/ 127 kgs**
Mean BMI	**50 kg/m^2**	**45.4 kg/m^2**	**47.2 kg/m^2**

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

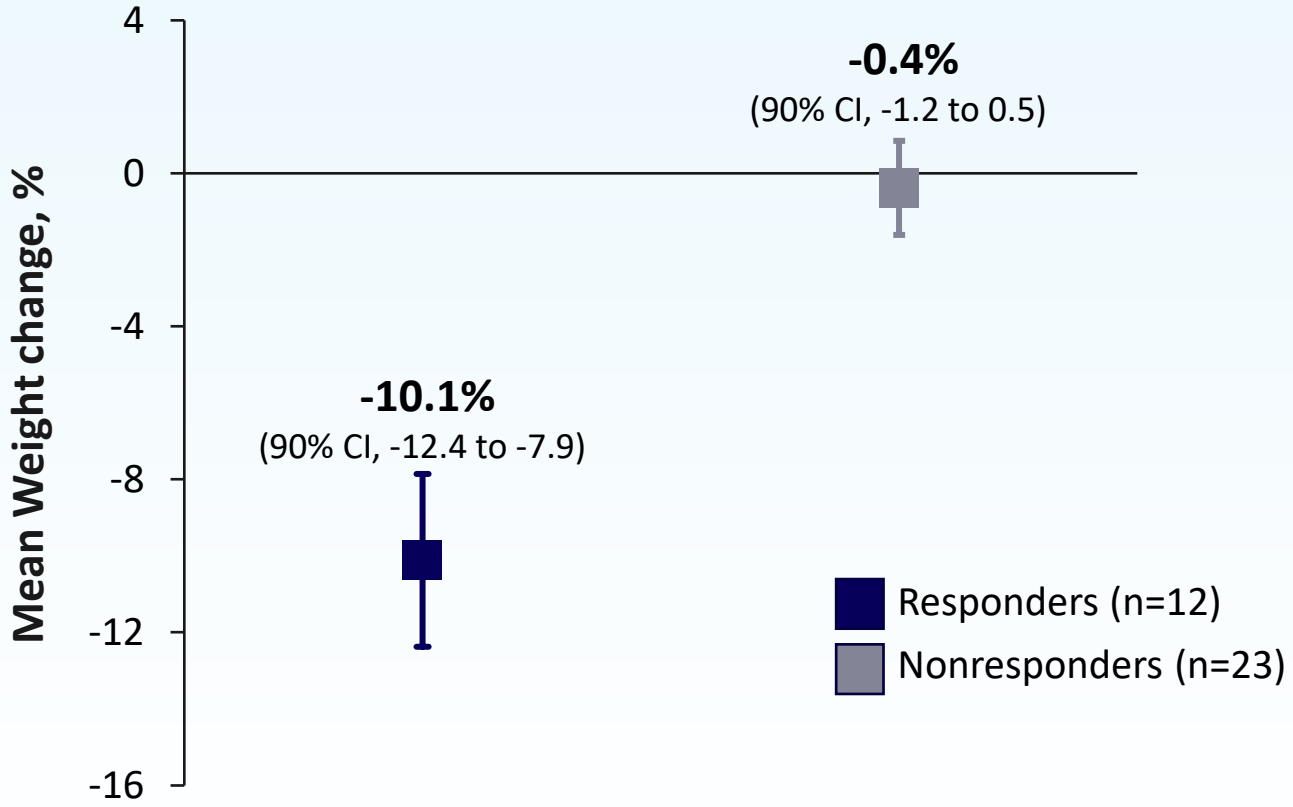
Phase 2 Basket Study: Response Rate and Weight Loss at Month 3
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

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: 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

Phase 2 Basket Study: Clear Separation of Responder vs. Non-responder Groups Supportive of Pathway Deficit in HETs

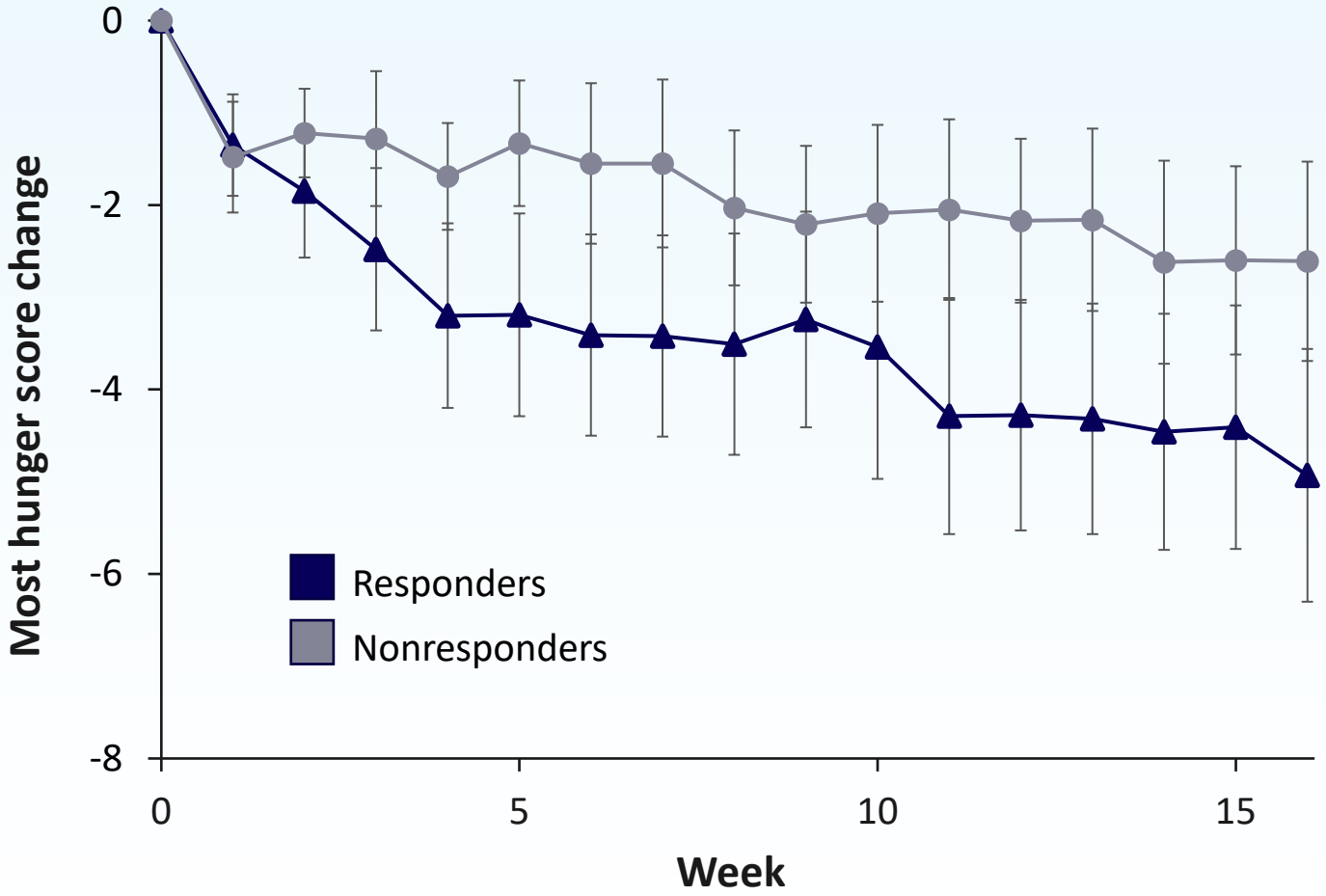


Data as of Dec. 17, 2020; Error bars represent the 90% confidence interval

Phase 2 Basket Study: Change in Most Hunger Score at Month 3 and Over Time

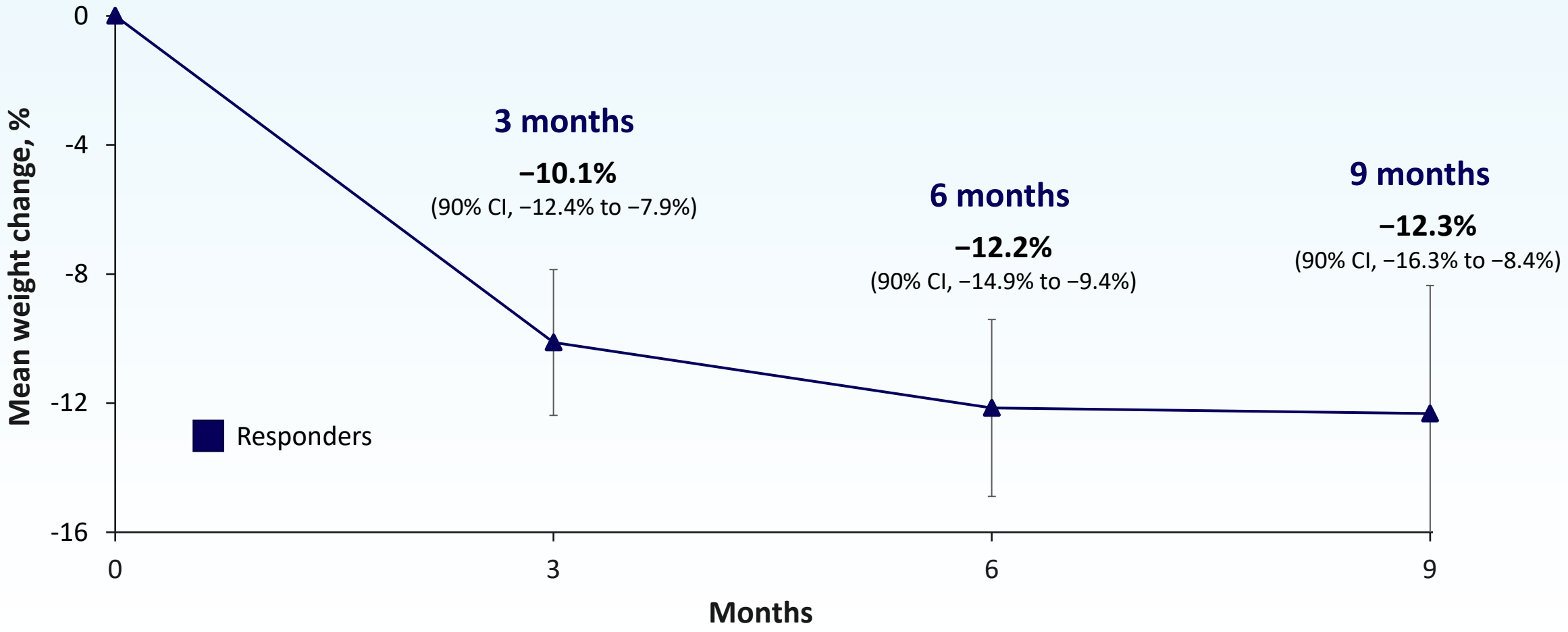
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

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

Long-term Extension Study: Responses to Setmelanotide Were Maintained Through 6 and 9 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, confidence interval

Phase 2 Basket Study: Approximately One-Third of Patients Respond to 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

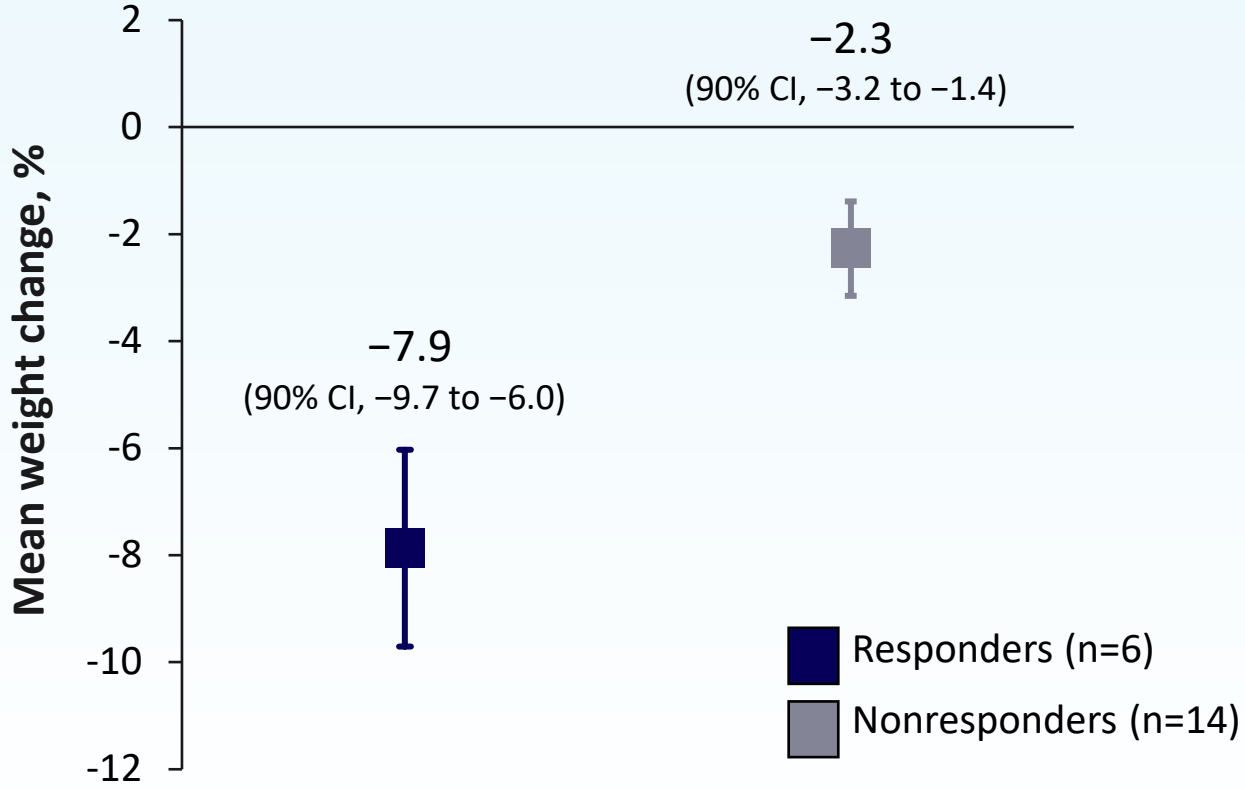
	Responders
≥5% weight loss in those ≥18 years old, n/N (%)	**6/20 (30)**
≥0.15 reduction in BMI Z score in those <18 years old, n/N (%)	**3/10 (30)**

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 was defined as ≥5% weight 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 efficacy, and family hardship due to the COVID-19 pandemic. BMI, body mass index.

Phase 2 Basket Study: Setmelanotide Decreases Body Weight in Adults with Clear Separation between Responders and Nonresponders

SRC1 Deficiency Obesity

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

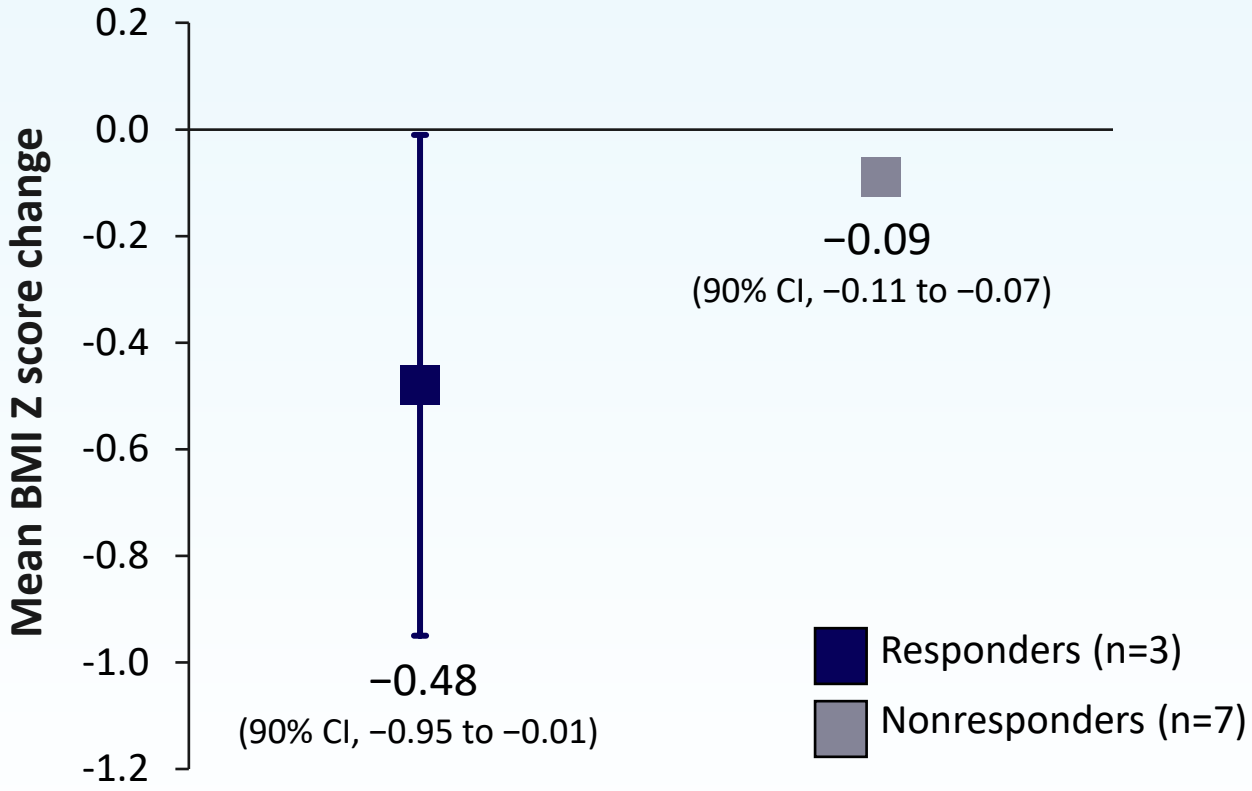


Full analysis set reported. In the Completers' set, mean percent weight change for responders was −8.7% (90% CI, −11.4% to −6.0%; n=4) and for nonresponders was −2.6% (90% CI, −3.8% to −1.3%; n=8). A responder was defined as ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% CI. CI, confidence interval; SD, standard deviation

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

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 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. BMI, body mass index; CI, confidence interval

Phase 2 Basket Study: More Than 40% of Patients Respond to 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

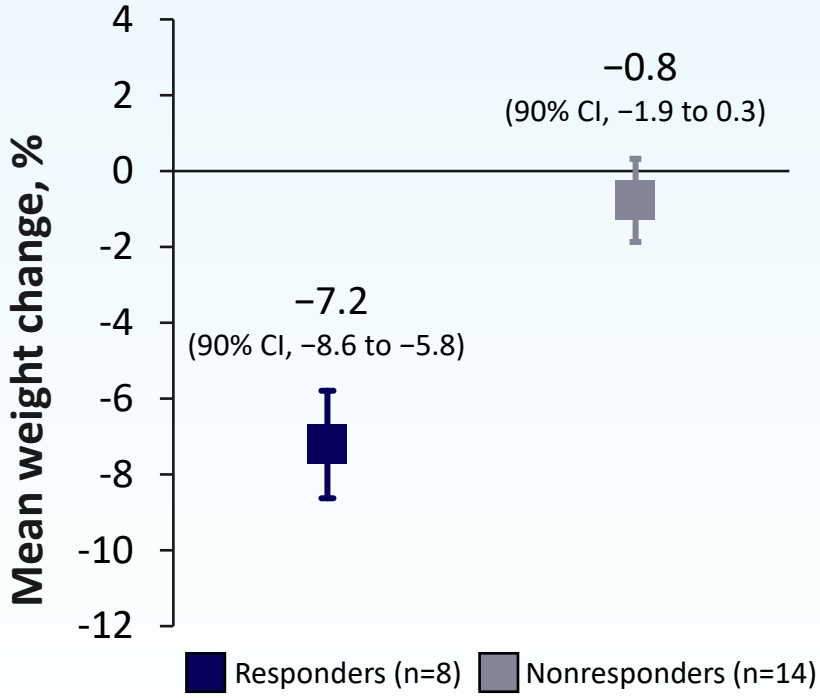
Proportion of patients	Responders
≥5% weight loss in those ≥18 years old, n/N (%)	**8/22 (36.4)**
≥0.15 reduction in BMI Z score in those <18 years old, n/N (%)	**7/13 (53.8)**

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 was defined as ≥5% weight 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 in Adults with Clear Separation between Responders and Nonresponders

SH2B1 Deficiency Obesity

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

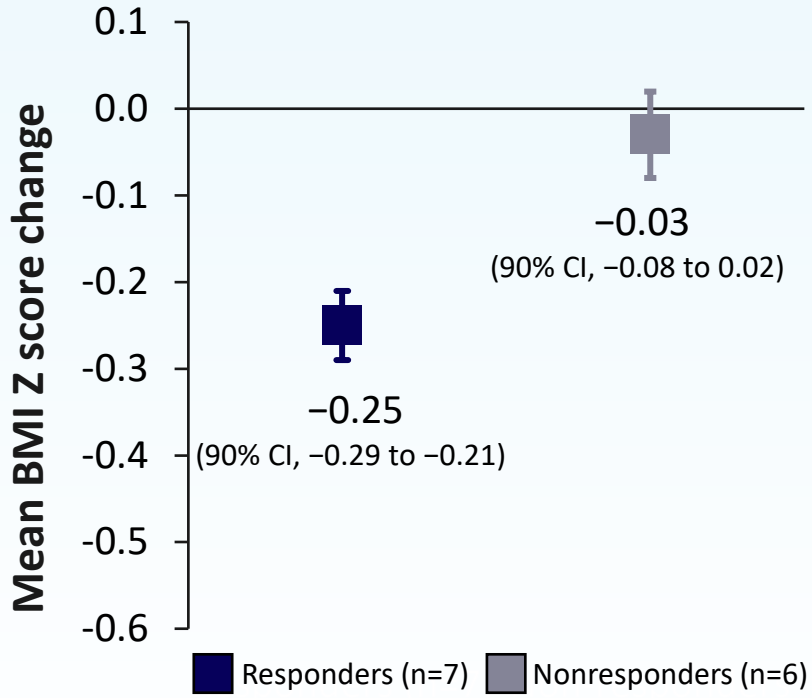


Full analysis set reported. In the Completers' set, in the combined population, mean percent weight change for responders was −7.3% (90% CI, −9.0% to −5.7%; n=7) and for nonresponders was −0.2% (90% CI, −2.8% to 2.4%; n=6). A responder was defined as ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% CI. CI, confidence interval; SD, standard deviation

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

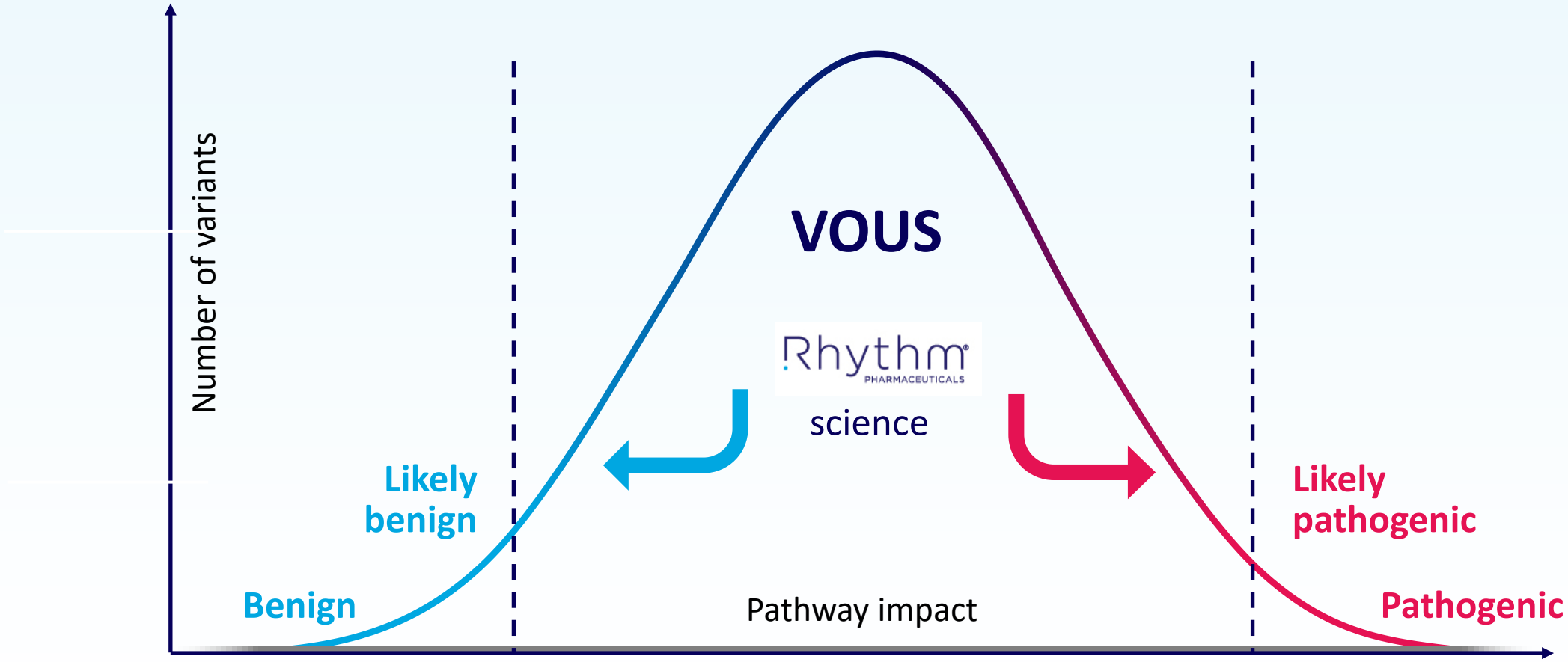
SH2B1 Deficiency Obesity

Mean (SD) overall BMI Z score change from baseline of **−0.15** (0.13; n=13)



Full analysis set reported. In the completers' set, in the combined population, mean BMI Z score change for responders was −0.25 (90% CI, −0.30 to −0.19; n=6) and for nonresponders was −0.05 (90% CI, −0.16 to 0.07; n=3). A 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. BMI, body mass index; CI, confidence interval; NA, not available; SD, standard deviation

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



*ACMG Guidelines Richards et al, 2015

Phase 2 Basket Study: Weight Loss at Month 3 by ACMG Subgroup in HETs

Pathogenic

Likely Pathogenic

VOUS

Likely Benign

Benign

	Responders, n (%)[a]	Non-responders, n (%)
Pathogenic/likely pathogenic (n=8)	4 (50)	4 (50)
Variant of uncertain significance (n=19)	4 (21)	15 (79)
N221D (n=8)	4 (50)	4 (50)

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

Additional Supporting Slides

Phase 3 Trial in Pediatric Patients Ages 2 to 6 years old to Initiate 2H 2021

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 to Initiate 2H 2021

Phase 3 randomized, double-blind "switch study"

- 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

- 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

Phase 3 EMANATE 3 Trial Comprised of Five Independent Sub-studies

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

First patient: 4Q2021 or 1Q2022

Each sub-study:

- Placebo-controlled: 110 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***
2. **LEPR***

Stratification:
Likely pathogenic, pathogenic or VUS**
Age: 6-11, 12-17, 18-65.

3. **SRC1**
4. **SH2B1**
5. **PCSK1 N221D**

Stratification:
Age: 6-11, 12-17, 18-65.

* Heterozygous; ** VUS= variant of uncertain significance

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

Protocol caps enrollment of VUS variant at 50% for POMC/LEPR/PCSK1 heterozygous cohorts

Overall study has 90% power to show >7% treatment effect vs. placebo

- 90% power to show >10% treatment effect in 50% sample size (ie, PLP or “responder” sub-population

Assumption to achieve mean treatment effect v placebo of >7%

- 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

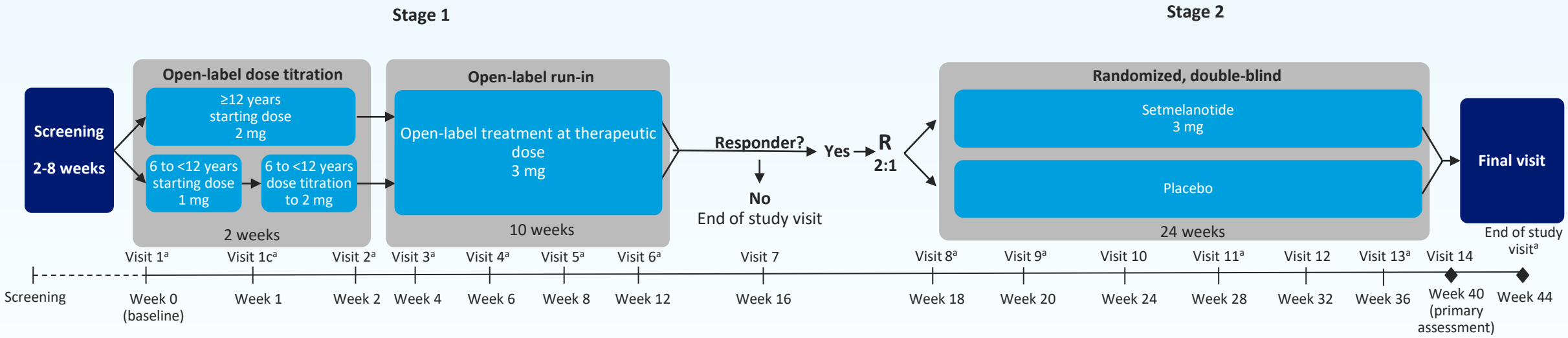
VUS: variant of unknown significance; PLP: pathogenic or likely pathogenic

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 Designed to Evaluate Setmelanotide Therapy in 31 Genes with Strong or Very Strong Relevance to MC4R Pathway



[a]Virtual visit. R, randomization.

MC4R Pathway Genes Eligible For Enrollment[a]

CPE	*LEP*	*NRP1*	*PLXNA4*	*SEMA3E*
CREBBP	*MAGEL2*	*NRP2*	*RPGRIP1L*	*SEMA3F*
DNMT3A	*MC3R*	*PHIP*	*SEMA3A*	*SEMA3G*
HTR2C	*MC4R*	*PLXNA1*	*SEMA3B*	*SIM1*
ISL1	*MECP2*	*PLXNA2*	*SEMA3C*	*TBX3*
KSR2	*MRAP2*	*PLXNA3*	*SEMA3D*	*TRPC5*
				TUB

[a]Patients with variants categorized as pathogenic, likely pathogenic, or a variant of uncertain significance based on American College of Medical Genetics criteria. MC4R, melanocortin-4 receptor

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

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.