Rhythm Pharmaceuticals

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

September 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

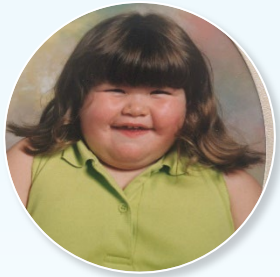
Commercial availability in U.S. meeting expectations and market access advancing in key **international markets**

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

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.*

Rare Genetic Diseases of Obesity are Distinct from General Obesity

Genetic variants impair MC4R pathway, disrupting satiety signaling, caloric intake and energy expenditure

- Early-onset, severe obesity
- **Hyperphagia**: a pathological hunger associated with persistent and potentially extreme food-seeking behavior
- Genetically defined patient population
- Resistant or refractory to therapies and interventions, including bariatric surgery
- Multiple complications and co-morbidities associated with obesity

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

Estimated patients who may benefit from setmelanotide based on sequencing results and current estimated responder rates

~5M*

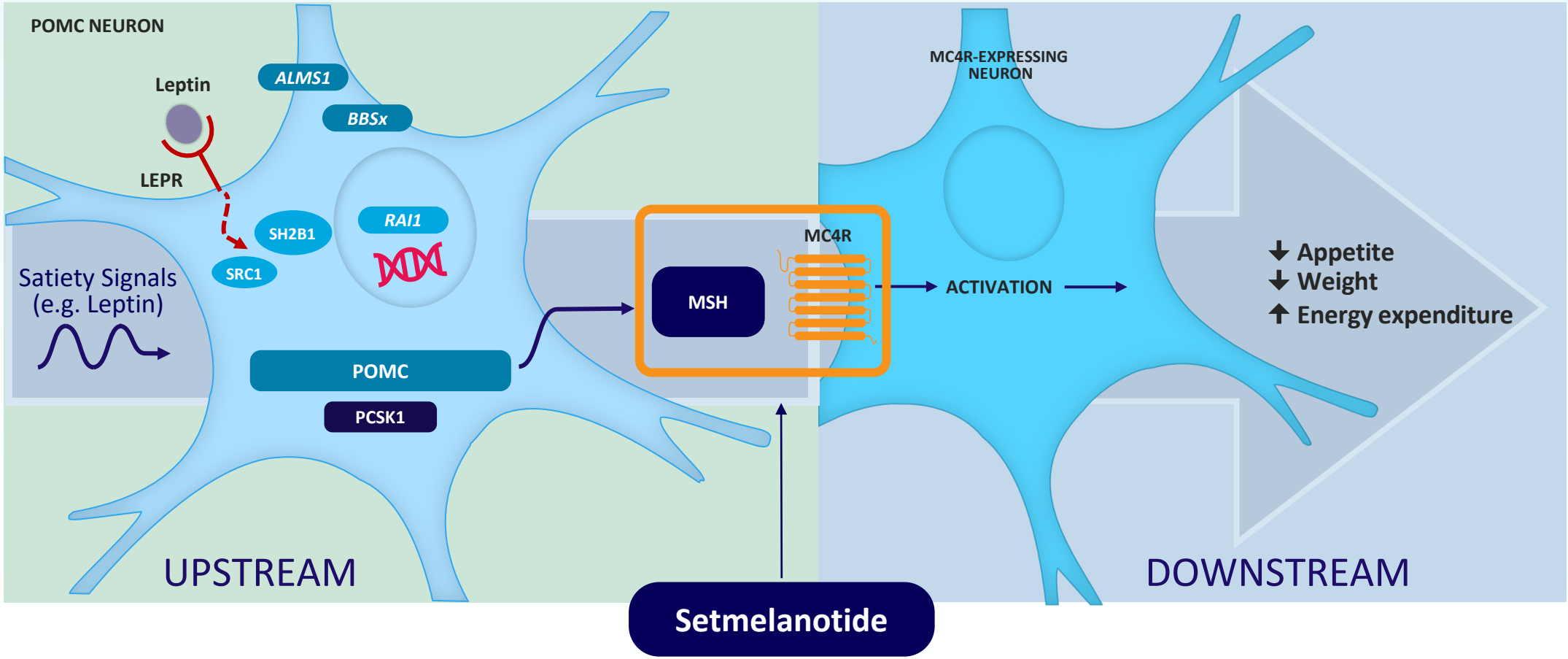
People in the U.S. have early-onset severe obesity

IMCIVREE® (setmelanotide) injection	**Obesity due to POMC, PCSK1 or LEPR deficiency**	**600 – 2,500****
sNDA and MAA planned for 2H21£	**Bardet-Biedl and Alström syndromes**	**2,000 – 3,000****
Phase 3 EMANATE Trial	**HET obesity and obesity due to SRC1 or SH2B1 deficiencies€**	**100,000 – 200,000****
Phase 2 DAYBREAK Trial	**31 genes with strong or very strong ties to MC4R pathway**	**TBD**

* 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); ** Estimated prevalence of U.S. patients based on company estimates; £ Regulatory submission for BBS remain on track, but path forward for Alström syndrome is pending final analysis of full data from phase 3 trial; € Planned trial would include patients with variants classified as pathogenic, likely pathogenic or of uncertain significance, and patients with N221D variant; †Estimated prevalence of U.S. patients with addressable variants of the MC4R.

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

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



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

Genes Approved
POMC
PCSK1
LEPR
(biallelic)

Genes for Regulatory Submission
BBS (*all*)
ALMS1

Genes in Clinical Development

Phase 2	Phase 3
31 additional genes related to MC4R pathway	POMC
	PCSK1
	LEPR
	SRC1
	SH2B1
(heterozygous or single allele variants)	

Setmelanotide lifecycle advancements

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

Synergistic Strategy Drives Patient Finding 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

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Rhythm Leadership – Strong Team with Broad Biopharma Experience

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

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

Linda Shapiro Manning, MD, PhD
*Chief Medical Officer**

novo nordisk® MERCK Boehringer Ingelheim

20-plus yeas in obesity medicine as HCP and industry leader

Jennifer Chien
Executive Vice President, Head of North America

SANOFI GENZYME Krystal

More than 20 years leading global commercial strategy in rare diseases

Yann Mazabraud
Executive Vice President, Head of International

SANOFI GENZYME trevi THERAPEUTICS

20 years leading global commercial strategy in rare diseases

Pamela Cramer
Chief Human Resources Officer

FOUNDATION MEDICINE PAREXEL

20-plus years global experience in organizational effectiveness, talent development and human resources

*Effective Sept. 10, 2021

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IMCIVREE® (setmelanotide)

Commercially available in the United States;

Received EC authorization in July 2021

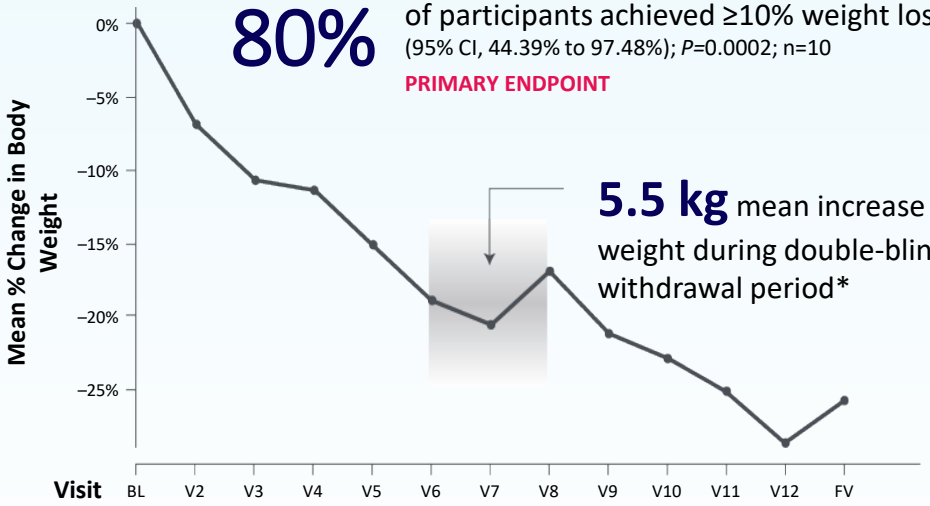
U.S. and EU Approvals of IMCIVREE Based on Phase 3 Data from Largest Studies Conducted in Obesity due to POMC, PCSK1 or LEPR Deficiency

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*

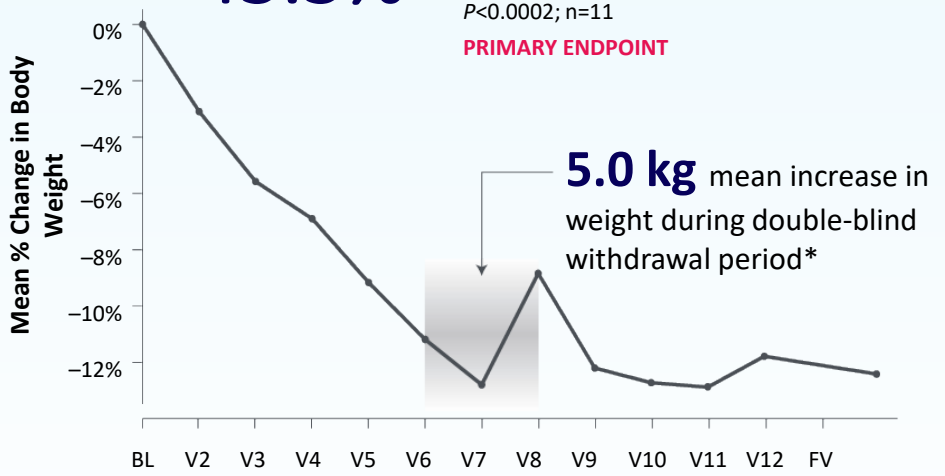


LEPR

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 (4) and LEPR (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 *

BL, baseline; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; FV, final visit; V, visit. †N=9 POMC participants and N=7 LEPR participants who achieved weight loss threshold (5 kg or 5% if <100 kg) after the first open-label active treatment phase. **Reference:** IMCIVREE Prescribing Information; * Data as of Nov. 16, 2020 cutoff as presented Dec. 22, 2020, corporate conference call.

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IMCIVREE U.S. Commercial Availability Strategy Meeting Expectations

Focus on infrastructure for patient education and services, physician engagement and market access

Positive payor decisions made on IMCIVREE

- Prior authorizations consistent with Prescribing Information
- Genetic confirmation, BMI with touch point at 12-16 weeks on therapy

Market Access and Reimbursement in Key International Markets on Track with First Commercial Sales expected in 1H 2022

Germany

- Very **positive interactions with G-BA** (German Federal Joint Committee) and Statutory Health Insurances
- Commercial launch with reimbursement expected early next year

France

- **Fast-track** procedure obtained
- Reimbursement dossier submitted to ANSM in July

United Kingdom

- Selected for **Highly Specialized Technology** evaluation
- HTA calendar validated with **NICE**:
  - HEOR model under review
  - NICE Committee meeting in December 2021

Italy

- Reimbursement dossier submitted to AIFA in July

Spain

- Reimbursement dossier on track for August submission

The Netherlands

- Reimbursement dossier submission ongoing

Israel

- Reimbursement dossier submission ongoing

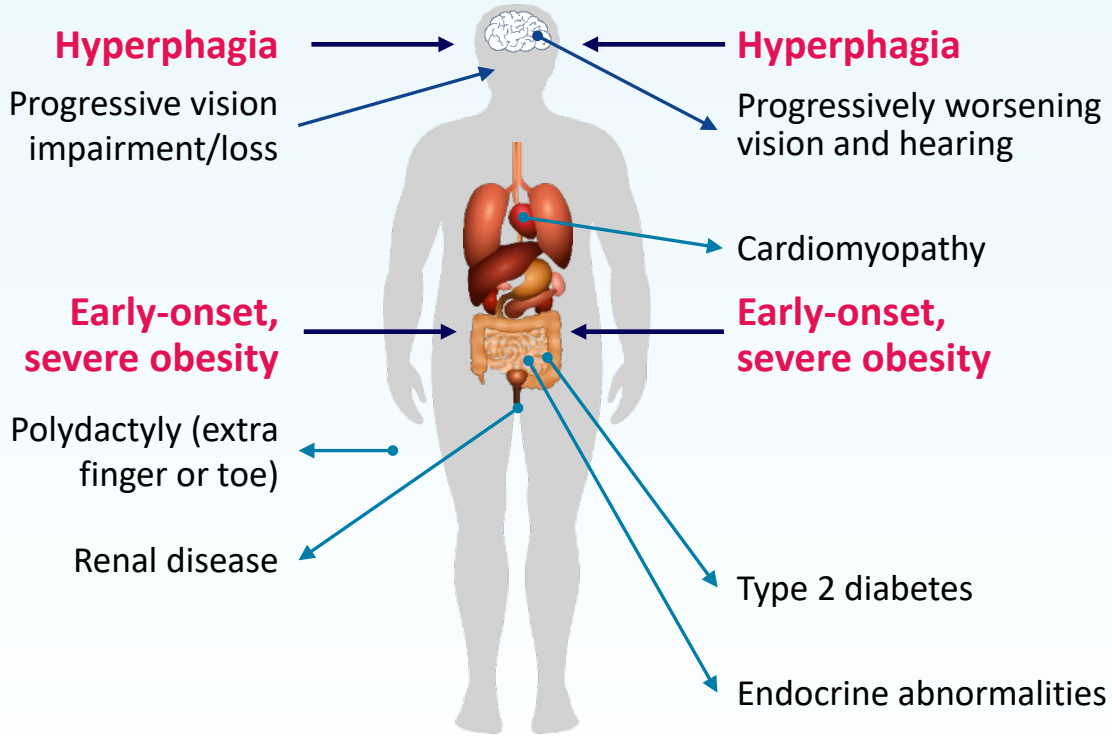
Bardet-Biedl and Alström Syndrome

U.S. and EU regulatory filings planned for 3Q/4Q 2021

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.

Pivotal Phase 3 Data Supportive of Registration

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

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

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

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

Vast Majority of BBS Patients* had Clinically Meaningful Response to Setmelanotide

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

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

93%
patients younger than 18
(13/14**) with 52-week data had a **reduction in BMI-Z ≥0.2**

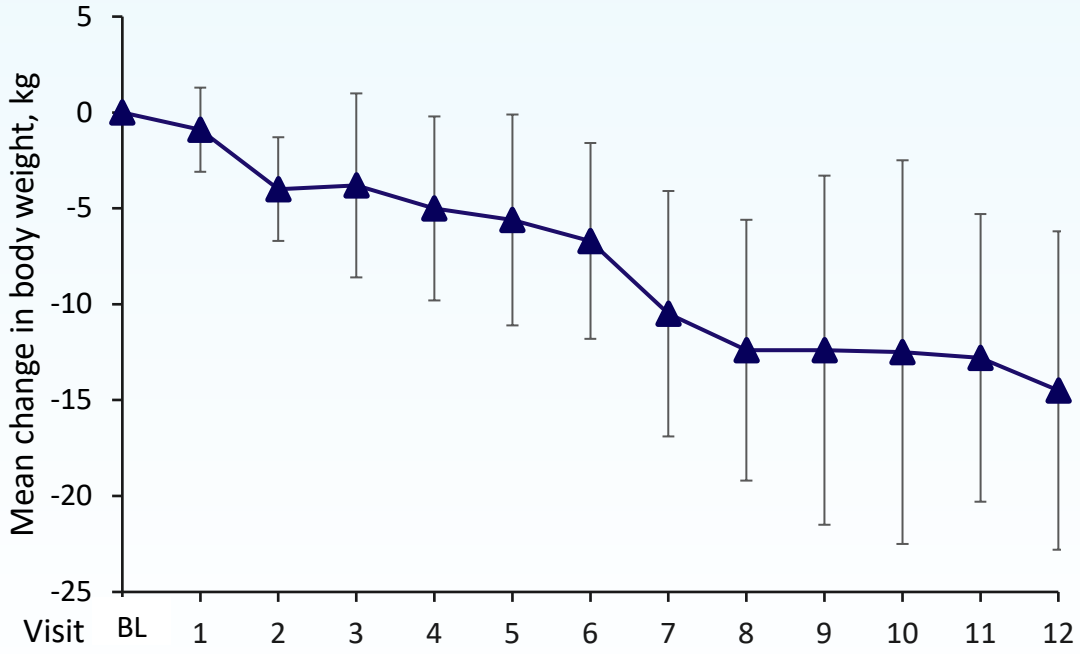
9.3% BMI reduction at 52 weeks in **all BBS patients**£

*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; £ Company data on file.

Statistically Significant Body Weight Reduction Achieved in Adolescent and Adults Patients with BBS at Week 52

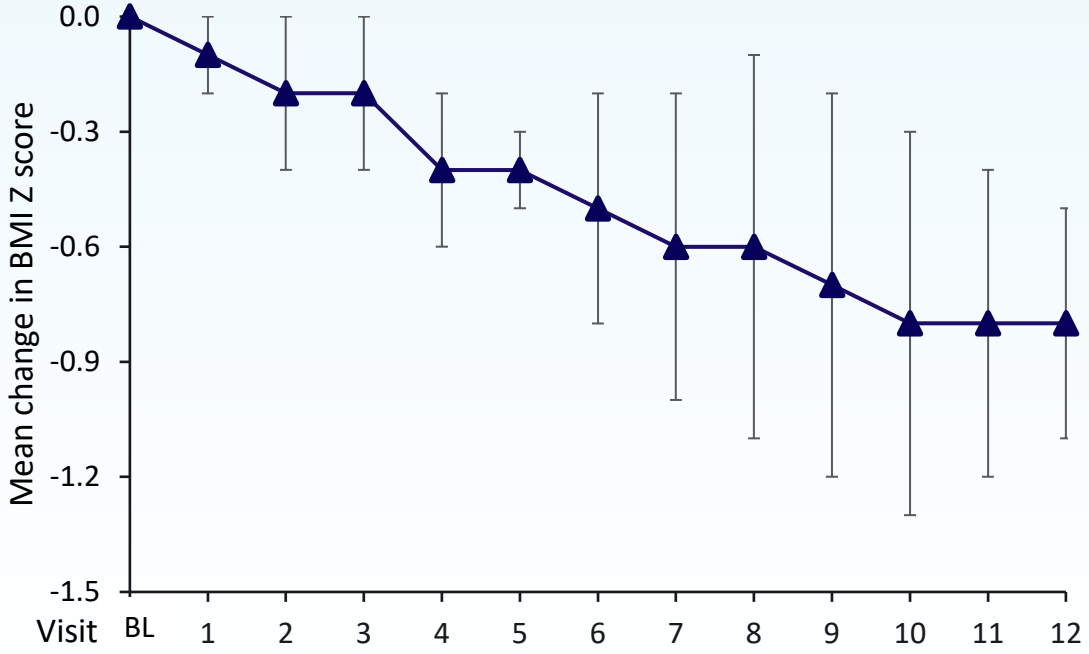
Body weight for participants aged ≥18 years (n=15):

Mean ± SD change in weight was -11.8 ± 10.3 kg, or -9.4% ± 8.2% (p<0.0001)



BMI-Z for participants aged <18 years (n=16[a]):

Mean ± SD change in BMI-Z score was -0.8 ± 0.4, or -24.5% ± 22.3 (p=0.0006)



[a]Baseline, n=16 and Week 52, n=14. [b]Data shown by study visit do not include data imputed for participants who received <52 weeks of setmelanotide at the time of the primary analysis.
BBS, Bardet-Biedl syndrome; BL, baseline; BMI, body mass index; SD, standard deviation. As presented at the annual meeting of the Pediatric Endocrine Society on April 30, 2021.

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Field Force Now Engaging Established BBS Patient Community

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

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

European prevalence estimated to be **>2,500** patients

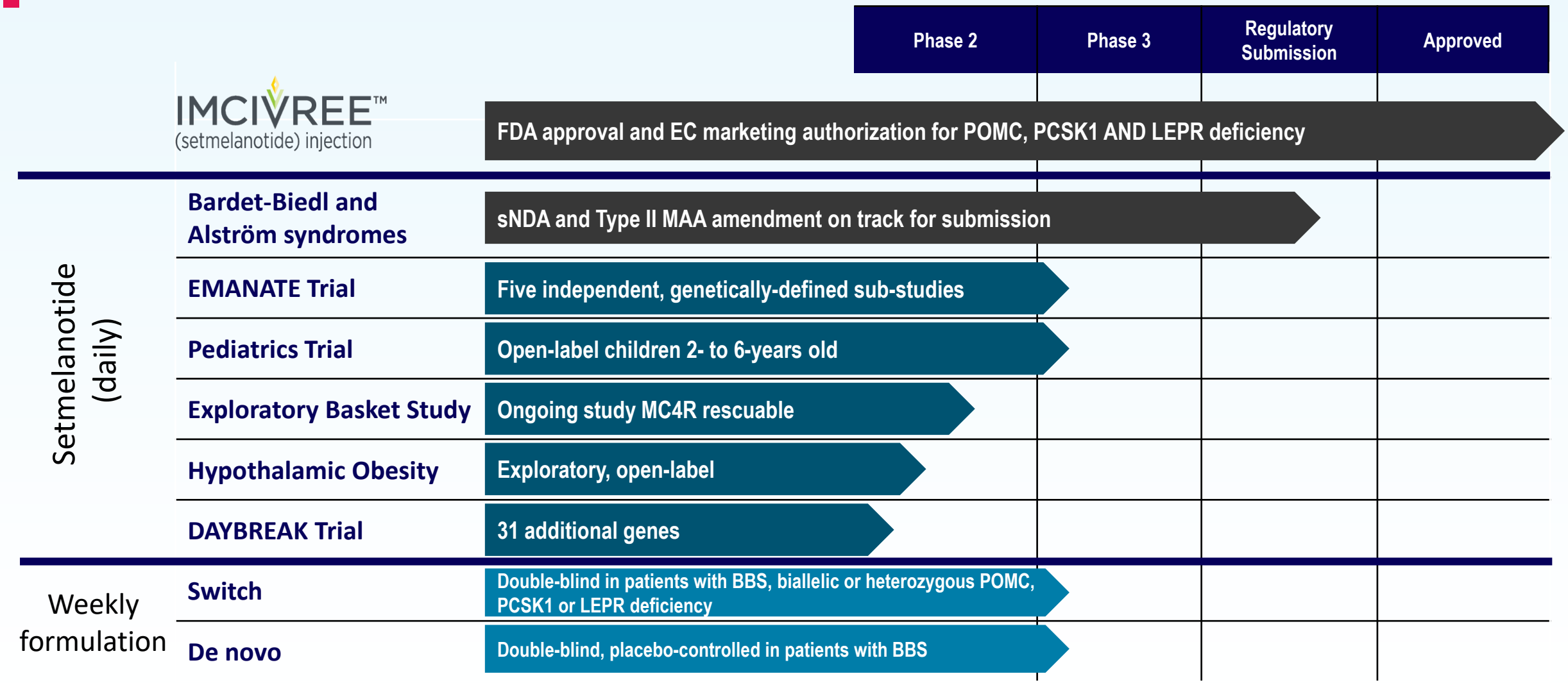
More than **1,500** individuals identified in **EU4 + UK** at ~20 academic medical centers with >40 BBS patients

BBS Territory Managers

- Engagement of current BBS treaters and diagnosers
- Disease education of HCPs to support appropriate evaluation and testing

Clinical Development: Meaningful Expansion of Addressable Patient Population

Rhythm Pipeline Designed to Achieve Label Expansion



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Parallel Operations to Support both EMANATE and DAYBREAK

IQVIA engaged as contract research organization

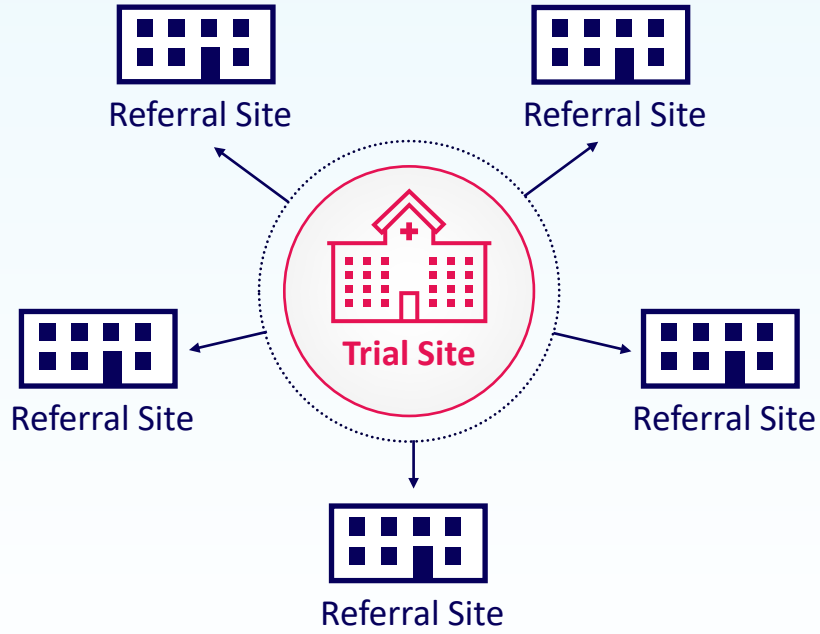
Site initiations set to begin in 3Q 2021

- All sites to service both trials
- 75+ sites in 14 countries in North America, Europe and the Middle East

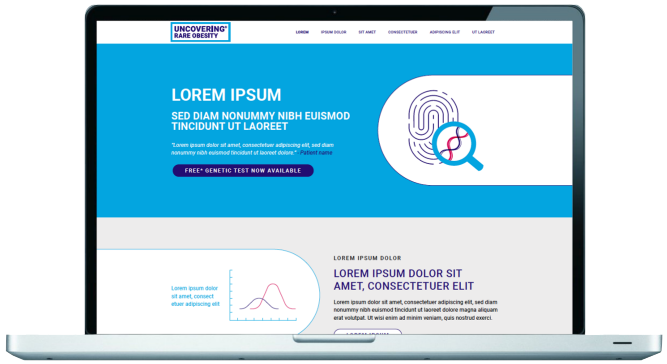
Enrollment over 12 to 18 months

- First patient in for both trials expected in Q4 2021
- **EMANATE** 52 weeks to execute treatment period
  - Individual sub-studies may readout and potentially be registered independently
- **DAYBREAK** 40 weeks to execute treatment periods
  - Individual genes may readout independently

Uncovering Rare Obesity sponsored genetic test drives enrollment for clinical trials



Improved URO with Expanded Gene Panel Launched in July 2021



New HCP ***website*** to consolidate all information and operations

Data generated from URO as of June 2021

~1,600
U.S. health care providers
with pediatric endocrinologists and pediatricians accounting for
>50%

~10,000
sequence samples completed

~20%
6 years old and younger

~80%
7 years old and older

47.2 kg/m²
Average BMI from adults

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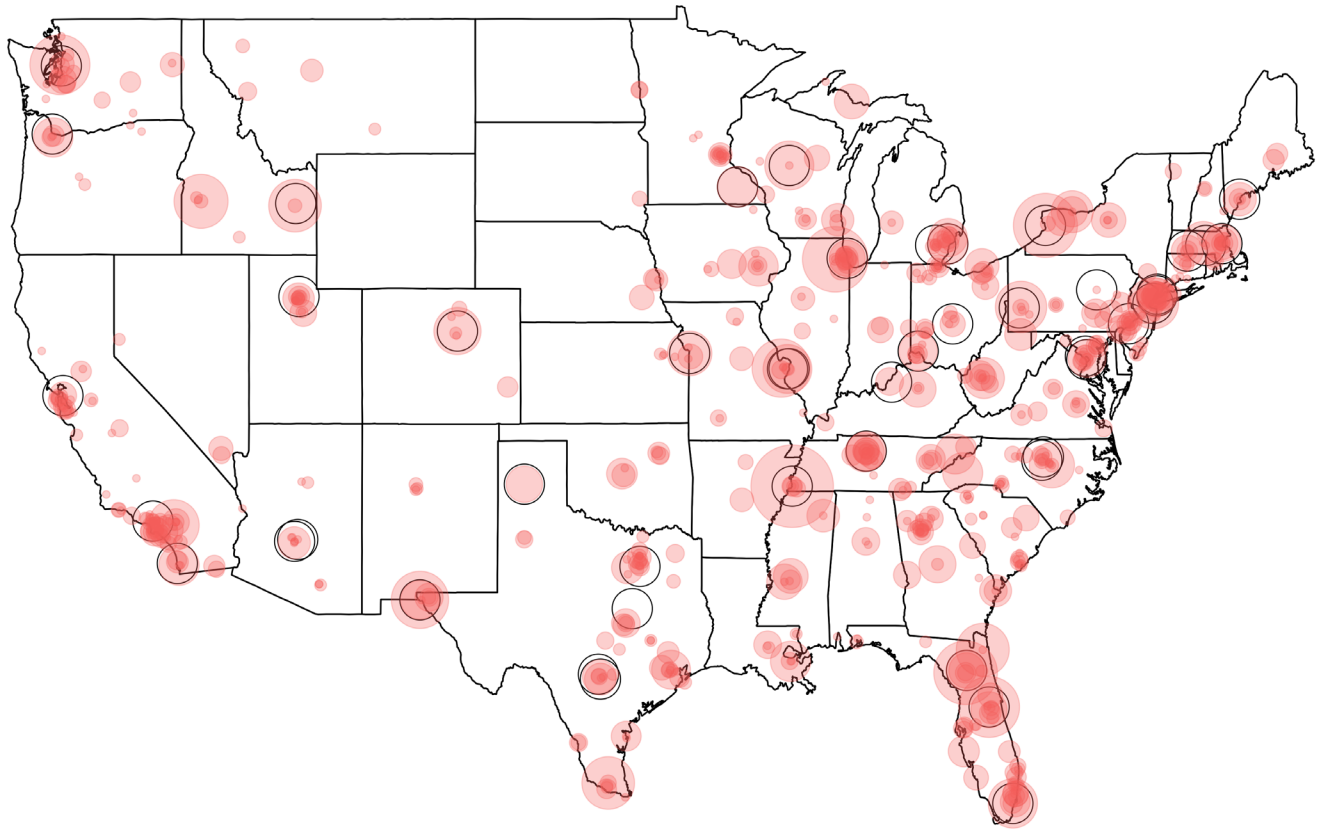
URO Geo-targeting and Referral Network Strategy to Drive Clinical Trial Enrollment



50 miles radius around target DAYBREAK and EMANATE trial sites

HCP URO tester (circle size reflects number of tests)

~650 patients

identified through who are eligible for enrollment in EMANATE or DAYBREAK trials and live within 50 miles of a clinical trial site

EMANATE Phase 3 Master Protocol Includes 5 Independent Sub-studies

110 patients per sub-study, 55 per arm (therapy and placebo)

1. **POMC/PCSK1***
2. **LEPR***

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

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

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

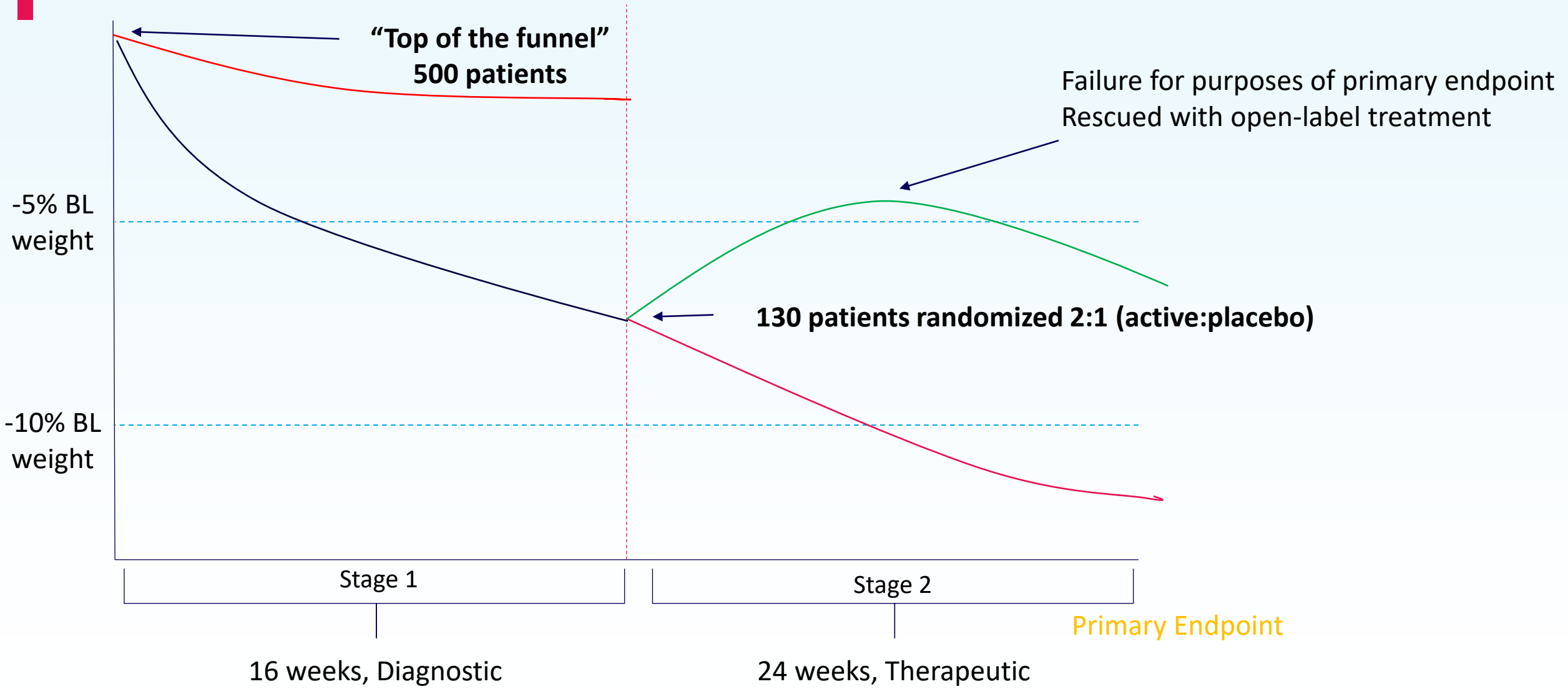
Primary endpoint:
Difference in mean percent change BMI at 52 weeks compared to placebo

Secondary endpoints:
Additional measurements of effect on weight and hunger

Design allows for independent success in each sub-study

* Heterozygous; ** VUS= variant of uncertain significance

DAYBREAK Trial: Phase 2, Two-stage, Double-blind, Placebo-controlled Study to Evaluate Setmelanotide in 31 MC4R Pathway Genes



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 randomization QD vs QW, crossover to 13 weeks open-label QW
- 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 de novo randomized, double-blind, placebo-controlled trial of once weekly formulation of setmelanotide

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

Weekly formulation of setmelanotide designed to improve compliance and adherence

Setmelanotide Generally Well-tolerated Across Development Program

Setmelanotide has been evaluated in 639 patients with obesity, with some individual patient treatment duration now exceeding five years

Setmelanotide has been generally well-tolerated

Most AEs are mild:

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

Discontinuations are rare; no increase in CV parameters:

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

Patient experience with setmelanotide*

Duration on therapy	# of patients
< 1 year	**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.

Transformational Progress Expected in 2021

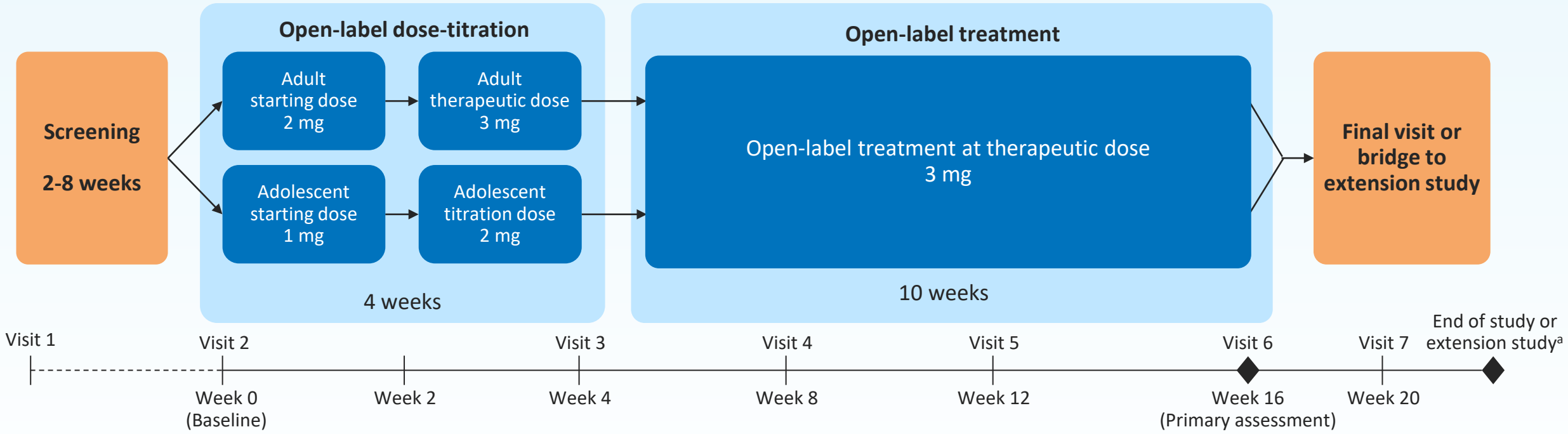
	1H 2021
✓	Proof-of-concept data in HET patients, SRC1 and SH2B1 deficiency obesities
✓	Update on genetic sequencing and epidemiology data
✓	IMCIVREE commercially available in U.S. for POMC, PCSK1 and LEPR deficiency obesities
✓	Initiate Phase 2 trial in hypothalamic obesity
	2H 2021
✓	EU decision on POMC, PCSK1 and LEPR MAA
	Present full data analyses from pivotal Phase 3 trial in BBS at ESPE 2021
	U.S. and EU regulatory submissions for BBS and AS
	Initiate Phase 3 trial in pediatric patients aged 2-6 years old
	Initiate Phase 3 EMANATE trial
	Initiate Phase 2 DAYBREAK trial
	Initiate two Phase 3 trials for weekly formulation
	1H 2022
	Initial data from Phase 2 Basket study in MC4R-rescuable patients
	Initial data from Phase 2 trial in hypothalamic obesity

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

SHARES OUTSTANDING *as of 6/30/2021*	50,209,484 (basic and diluted share count)
AUDITED ESTIMATED CASH, CASH EQUIVALENTS AND SHORT-TERM INVESTMENTS *as of 6/30/2021*	$368.2 million

Appendix

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 Heterozygous POMC, PCSK1 or LEPR	**SRC1 deficiency obesity**	**SH2B1 deficiency obesity**
Mean age (range)	N=**35** **39 years old** (15 - 68)	N=**13*** **32 years old** (12 - 66)	N=**17*** **30 years old** (12 - 60)
Mean weight	**316 lbs/ 143 kgs**	**258 lbs/ 117 kgs**	**272 lbs/ 123 kgs**
Mean BMI	**50 kg/m²**	**44 kg/m²**	**44 kg/m²**
	5 patients had **failed bariatric surgery**	**3** patients had **failed bariatric surgery**	**4** patients had **failed bariatric surgery**

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

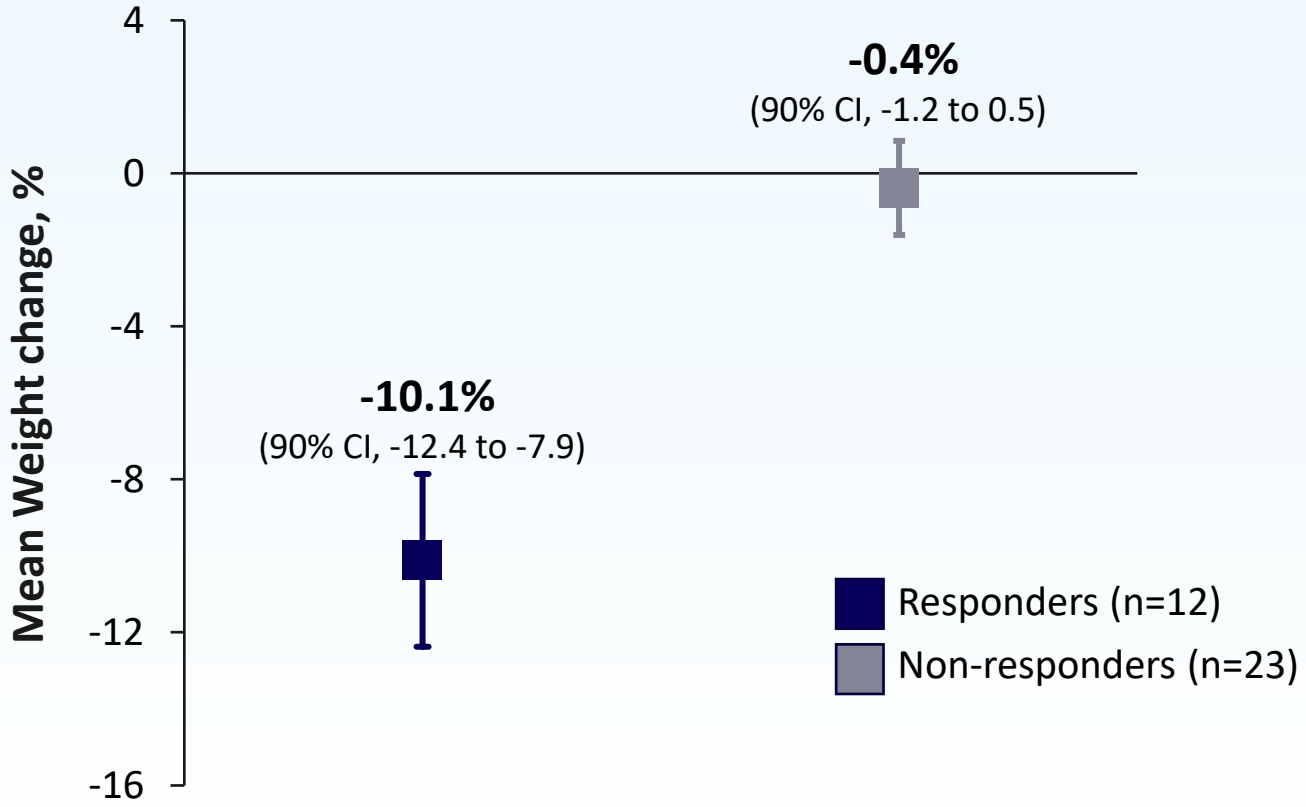
Response Rate and Weight Loss at Month 3 (Overall)
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

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

	Baseline	Month 3	Percent change from baseline
Mean (SD) body weight: 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.

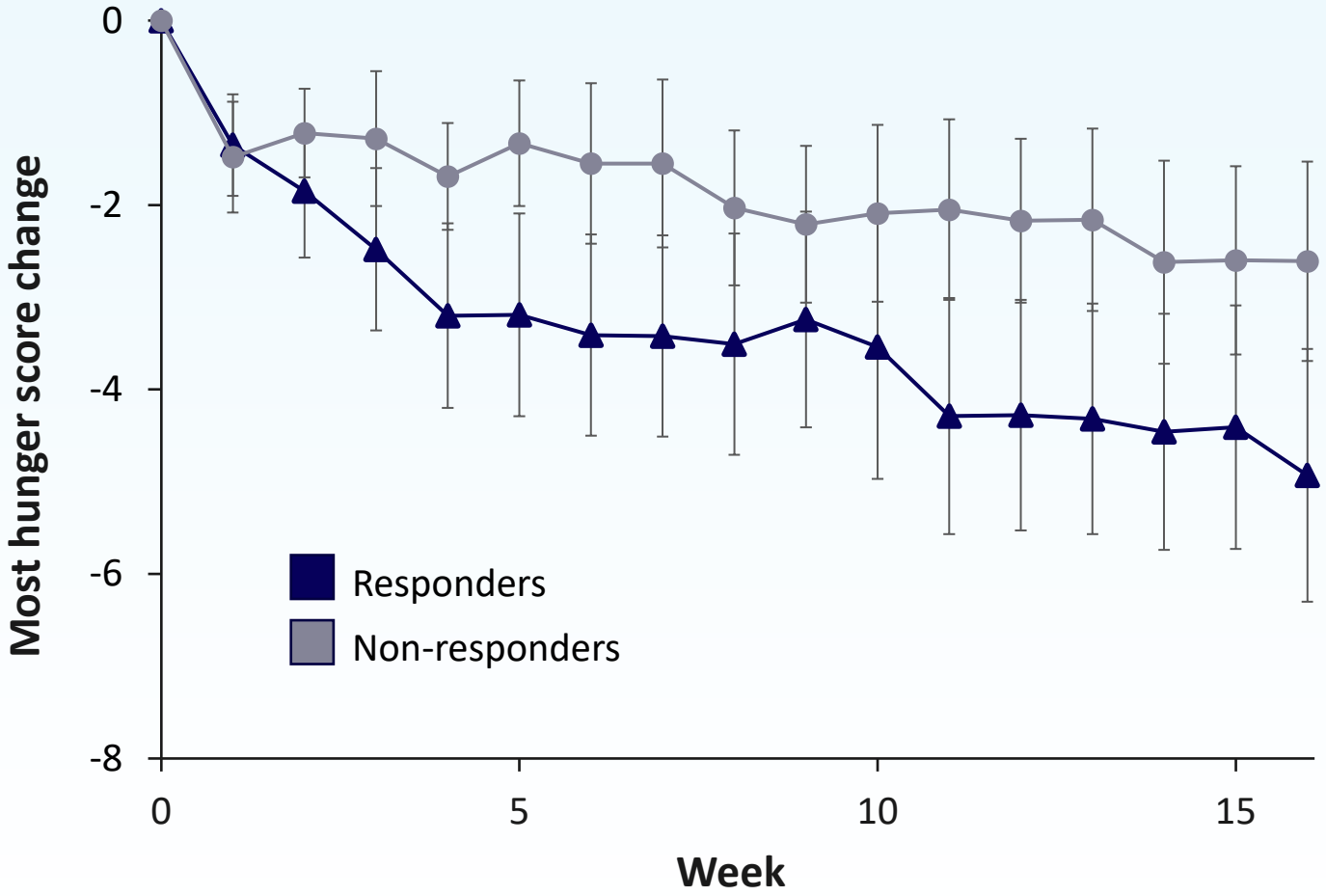
Clear Separation of Responder, Non-responder Groups Supportive of Pathway Deficit in HETs



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

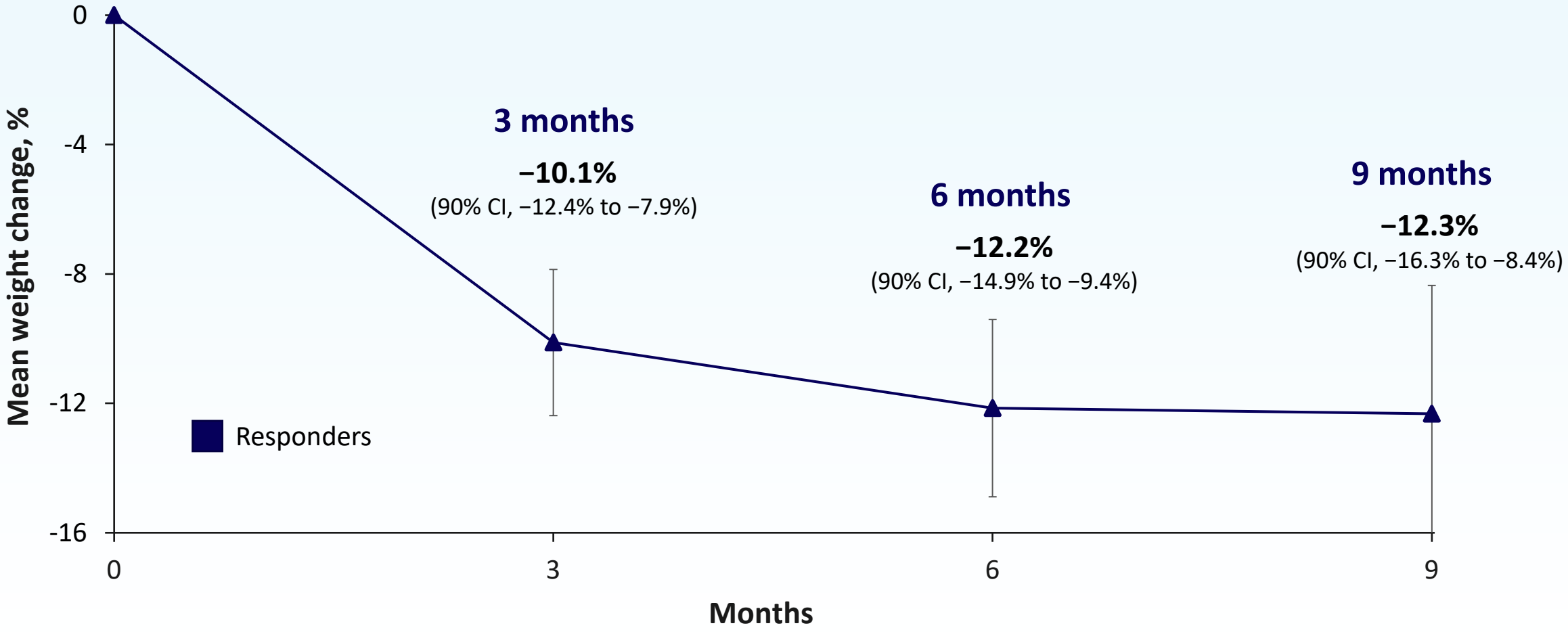
Change in Most Hunger Score at Month 3 and Over Time
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

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



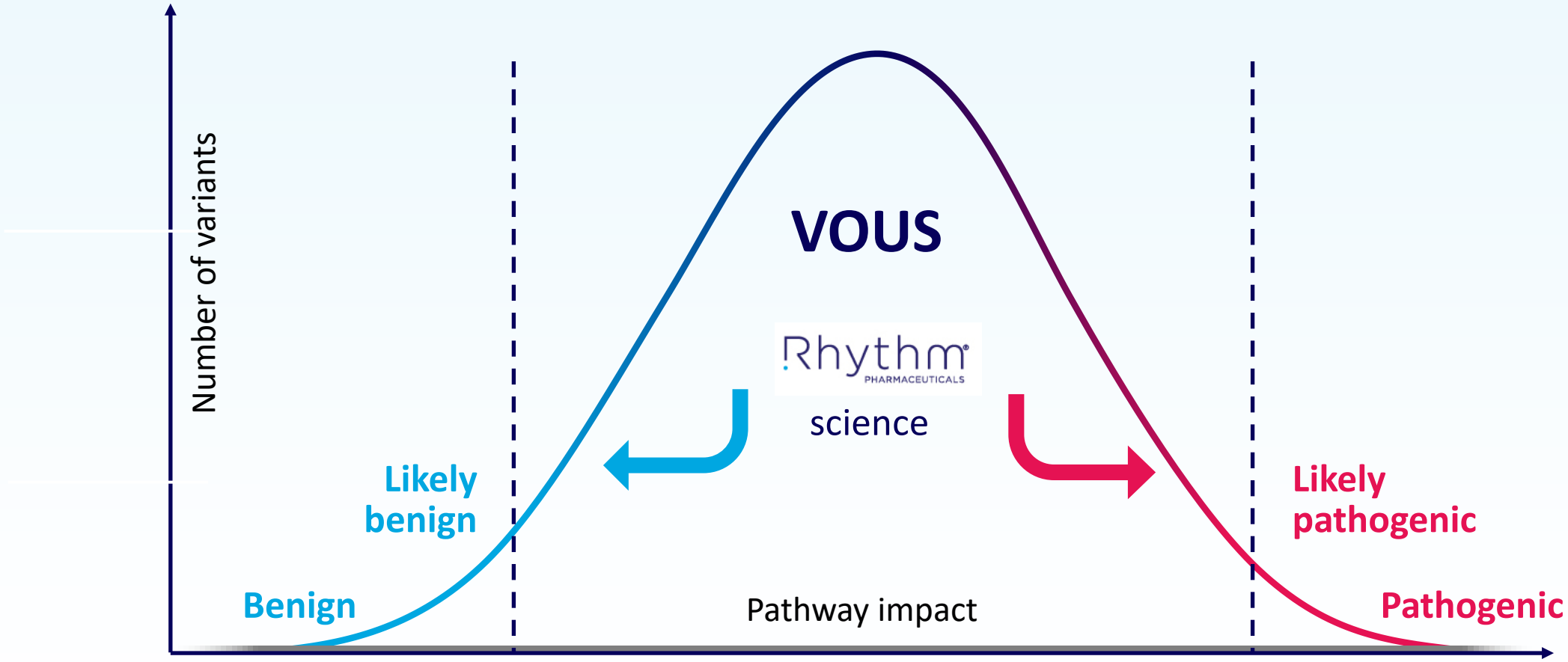
Data as of Dec. 17, 2020; Responder is defined by Month 3 weight loss; CI, confidence interval; Error bars represent the 90% CI.

Responses to Setmelanotide Were Maintained Through 6 and 9 Months



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.

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



*ACMG Guidelines Richards et al, 2015

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 (50.0)	4 (50.0)
Variant of uncertain significance (n=19)	4 (21.1)	15 (78.9)
N221D (n=8)	4 (50.0)	4 (50.0)

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

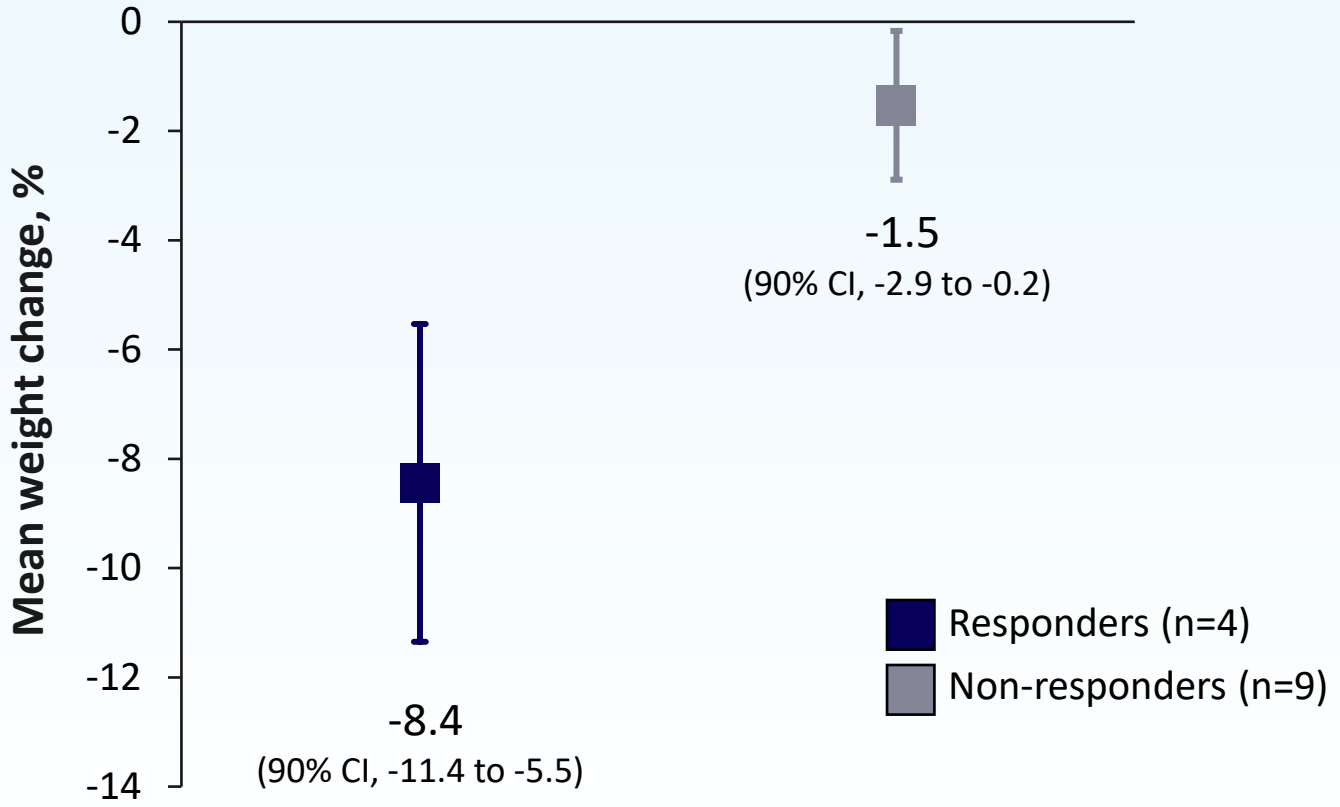
Response Rate and Weight Loss at Month 3 (Overall)
SRC1 Deficiency Obesity – Completers Set

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

	Baseline	Month 3	Percent change from baseline
Mean (SD) body weight: Responders (n=4)	**116.6 kg** (29.1)	**106.4 kg** (24.6)	**-8.4%** (2.5)

Interim data as of Dec. 17, 2020.

Clear Separation of Responder, Non-responder Groups Supportive of Pathway Deficit in SRC1 – *Completers Set*



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

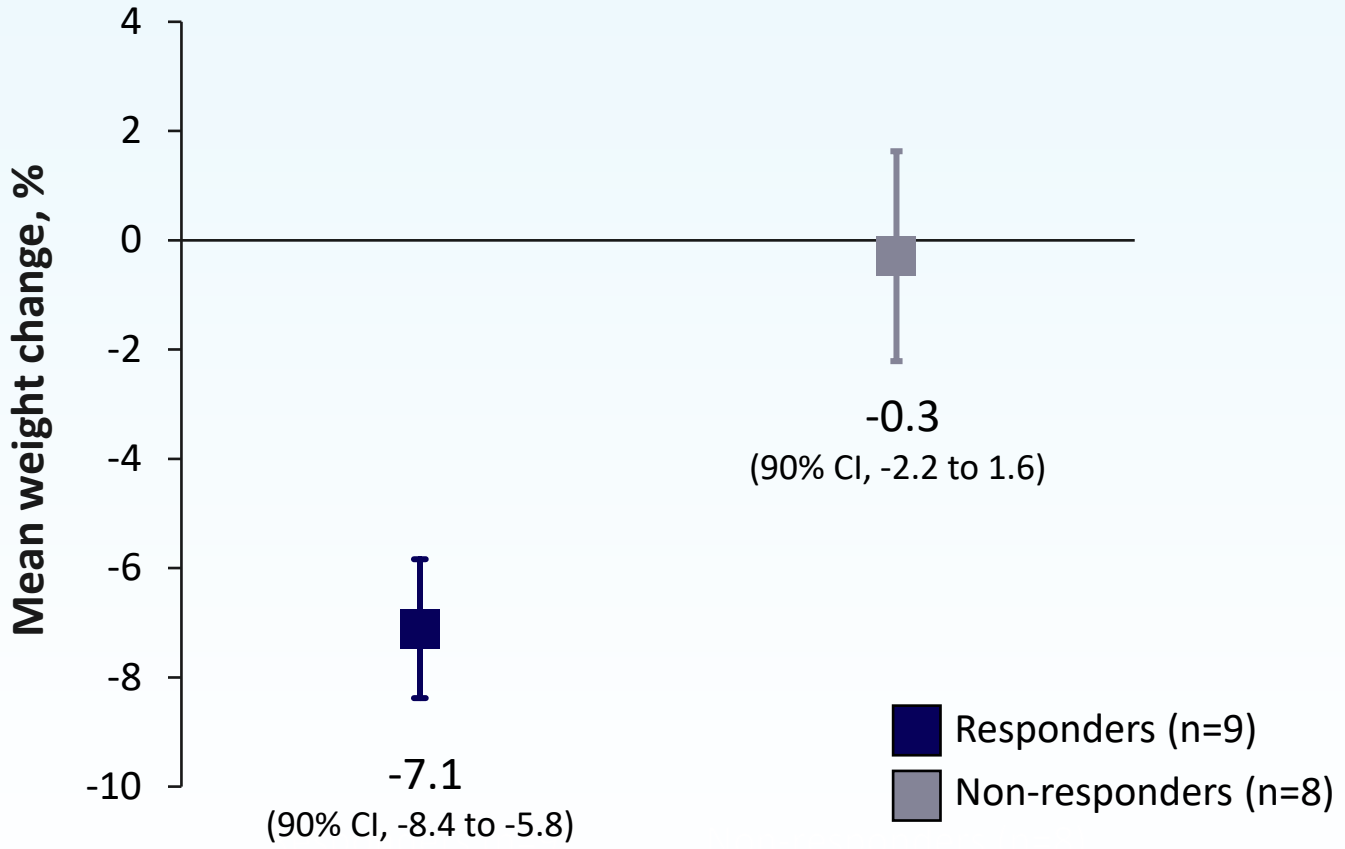
Response Rate and Weight Loss at Month 3 (Overall)
SH2B1 Deficiency Obesity – Completers Set

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

	Baseline	Month 3	Percent change from baseline
Mean (SD) body weight: Responders (n=9)	**123.6 kg** (28.1)	**114.8 kg** (26.4)	**- 7.1%** (2.1)

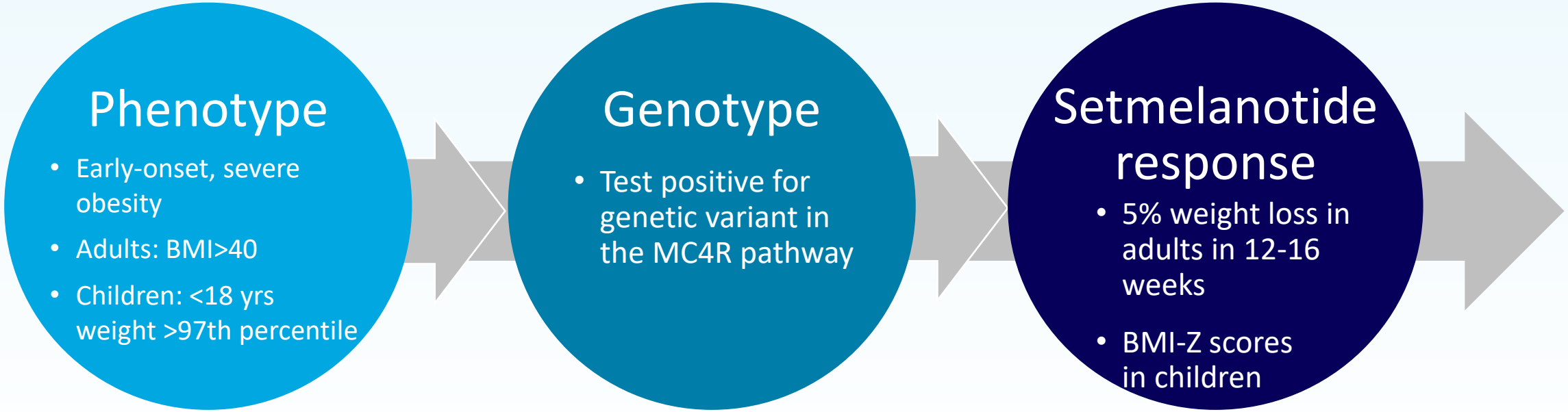
Interim data as of Dec. 17, 2020.

Clear Separation of Responder, Non-responder Groups Supportive of Pathway Deficit in SH2B1 – *Completers Set*



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

New Paradigm: Targeted, Three-step Approach to Identifying and Treating Patients with Rare Genetic Diseases of Obesity



EMANATE Primary Endpoint: Difference in mean percent change BMI at 52 weeks compared to placebo

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

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

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

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 are anticipated to demonstrate >10% treatment effect at 52 weeks
- Setmelanotide mean treatment effect (weighted responder and non-responder) is anticipated to be >8% at 52 weeks

EMANATE 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 percent change body weight
- Mean percent change in the weekly average most hunger score at 52 weeks compared to placebo
- Mean body weight loss, and % body weight loss in responders with ≥5% body weight loss (if >18 years of age), and a decrease in % BMI by 3% (if <18 years of age) after 12 weeks compared to placebo responders
- Mean change in symptoms of hyperphagia and mean change in impacts of hyperphagia at 52 weeks compared to placebo

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 who are responders compared to placebo

- Responders >18 achieve 10% or greater body weight reduction from baseline
- Responders <18 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 compared to placebo
- Mean BMI-Z change in patients <18 compared to placebo
- Mean change in waist circumference in patients >12 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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