Rhythm Pharmaceuticals

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

March 2021

Forward Looking Statements

This presentation contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including without limitations statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipated timing for initiation of clinical trials and release of clinical trial data and our expectations surrounding potential regulatory submissions, approvals and the timing thereof, 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", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including but not limited to, our ability to enroll patients in clinical trials, the outcome of clinical trials, the impact of competition, the impact of management departures and transitions, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our expenses, the impact of the COVID-19 pandemic on our business operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and other reports we file with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this presentation or to update them to reflect events or circumstances occurring after the date of this presentation, whether as a result of new information, future developments or otherwise.

Global Company Focused on Transforming the Care of Patients with Rare Genetic Diseases of Obesity

Founded in 2008 in Boston

- In-licensed setmelanotide from Ipsen in 2010
- IPO in 2017

90+ employees in United States and Europe

IMCIVREE™
(setmelanotide) injection

Approved in November 2020

- Breakthrough Therapy, PRIME and orphan drug designations in US and EU
- Phase 2 data published in *NEJM* and *Nature Medicine*

Approved drug w/ strong efficacy data and consistent safety profile

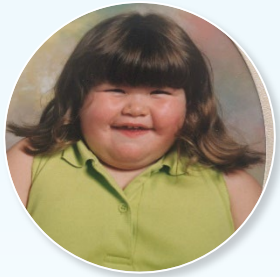
Planned market expansion through robust clinical development program

Integrated, global approach to patient finding

Strong management team with proven track record in rare disease

Living with Early-onset, Severe Obesity and Hyperphagia of 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

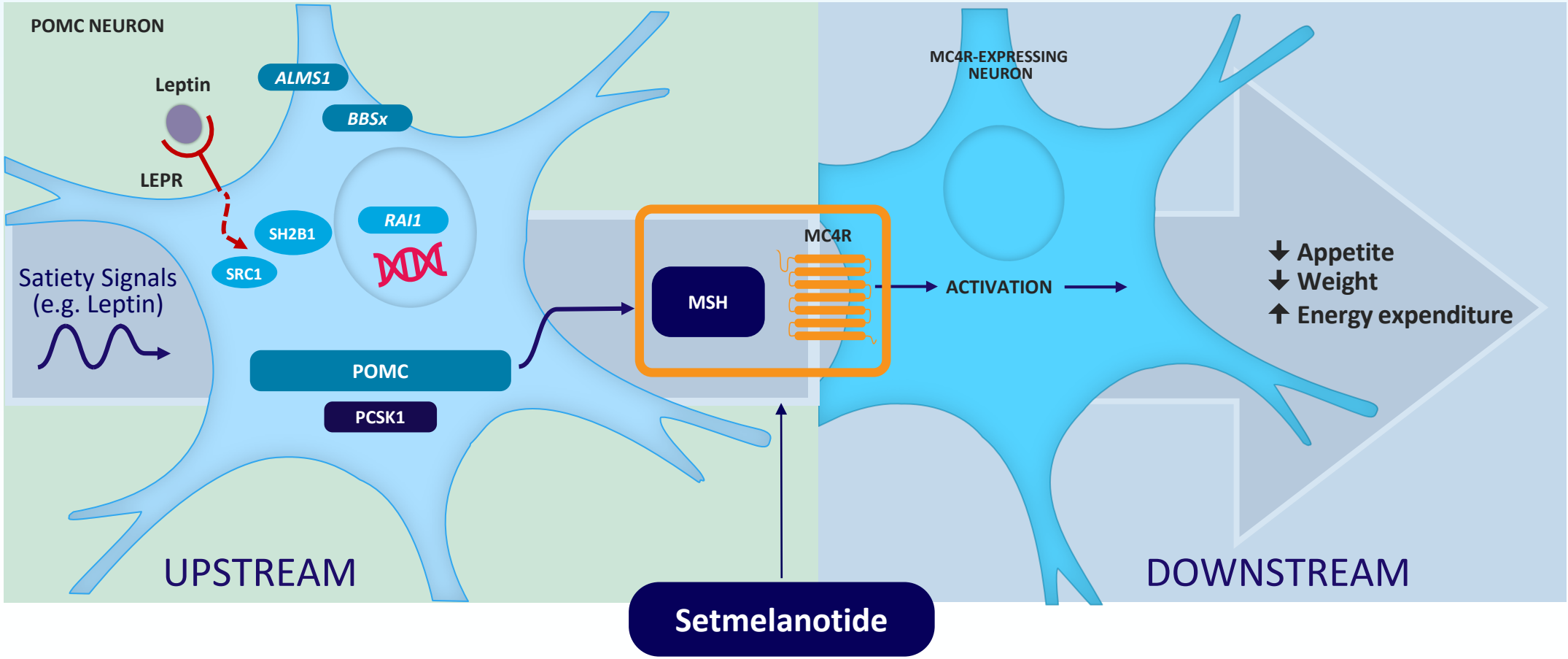
Little knowledge or awareness

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, and Energy Expenditure, and, Consequently, Body Weight

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



Severe Obesity due to MC4R Pathway Deficiencies Stands Out

BMI > 40 Kg/M^2

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 for general obese

Multiple complications and co-morbidities associated with obesity

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

~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 planned for 2H21	Pathogenic, likely pathogenic and VOUS yield for HETs, SRC1 and SH2B1; and N221D	100,000 – 200,000**
Phase 2	MC4R-rescuable deficiency obesity	~10,000†

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

* 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018ǂ); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017); ** 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; †Estimated prevalence of U.S. patients with addressable variants of the MC4R.

Synergistic Community Building and Sequencing Drive Patient ID for Clinical Trials and Commercialization

Community Building

- Disease state education and awareness
- Patient advocacy relations
- Medical field team
- Education programs (i.e. GOLD)
- 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

Yann Mazabraud
Executive Vice President, Head of International

SANOFI GENZYME
trevi THERAPEUTICS

20 years leading global commercial strategy in rare diseases

Jennifer Chien
Executive Vice President, Head of North America

SANOFI GENZYME
Krystal

More than 20 years leading global commercial strategy in rare diseases

Murray Stewart, MD
Chief Medical Officer

novelion THERAPEUTICS
gsk

20-plus marketed products and NDAs 10-plus INDs

Simon Kelner
Chief Human Resources Officer

MERCK
teva

25-plus years global HR leadership experience in biopharma

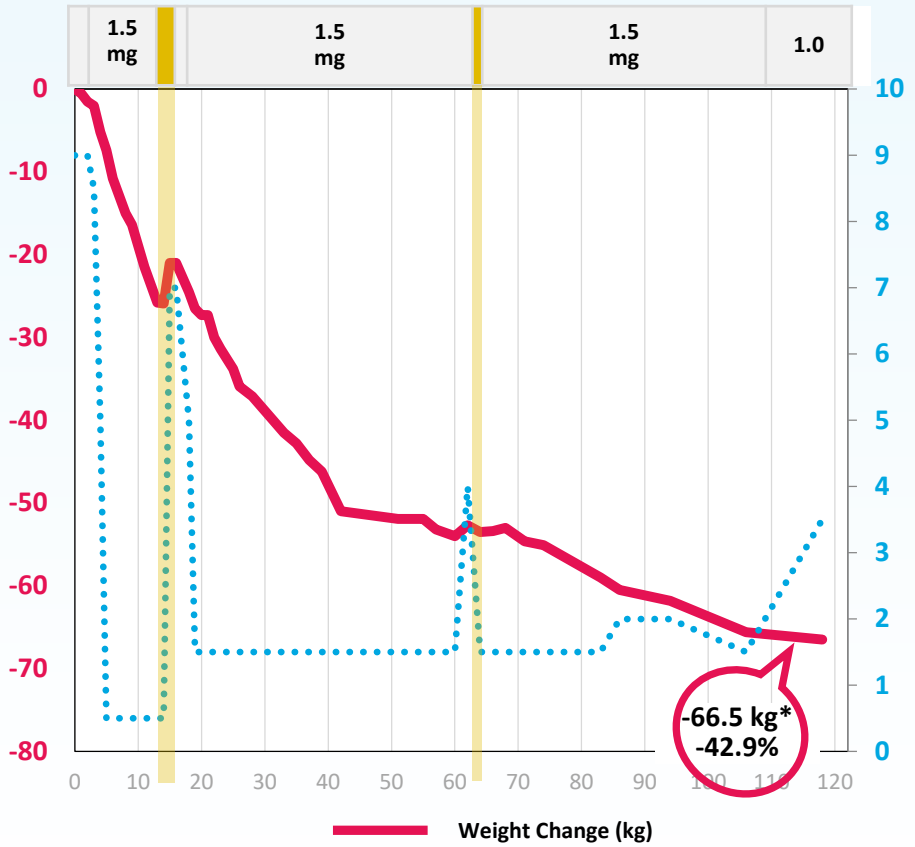
IMCIVREE™ (setmelanotide)

Commercially available in the United States with EU regulatory submission under review

Setmelanotide Journey began with Phase 2 Data Published in *New England Journal of Medicine*[1] and *Nature Medicine*[2]

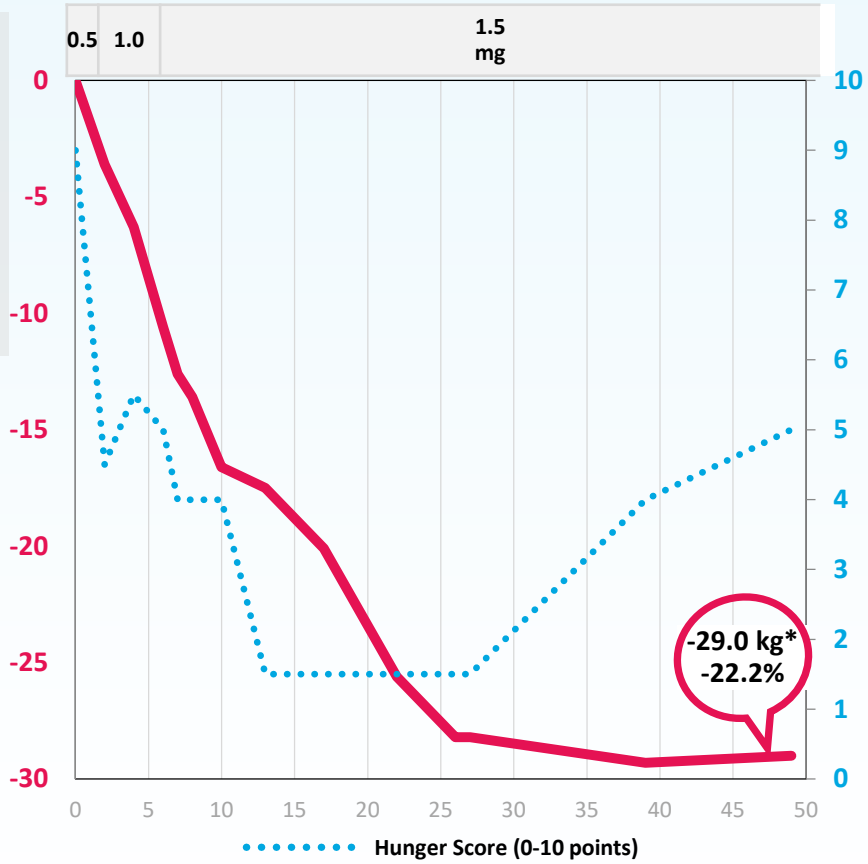
POMC Patient #1*

20 yr old female
Starting Weight = 155.0 kg
Starting BMI = 49.8 kg/m²



LEPR Patient #1*

23 yr old male
Starting Weight = 130.6 kg
Starting BMI = 39.9 kg/m²



(1) Kühnen, et. al, Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. *N Engl J Med*. July 2016. (2)Biebermann, et al. MC4R Agonism Promotes Durable Weight Loss in Patients with Leptin Receptor Deficiency. *Nat Med.* 2018 May 7; * Figures represent longer-term data as presented in January 2019 with cumulative weight lost in kgs | Not all patients had similar responses; *Yellow vertical bars represent intervals with dose withdrawal or modifications;*

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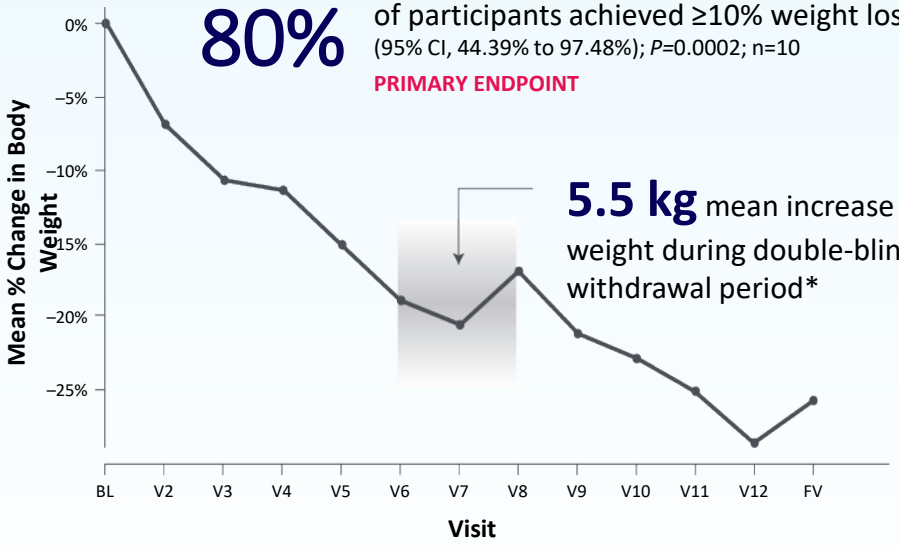
Approval of IMCIVREE Based on Phase 3 Data from Largest Studies Conducted in Obesity due to POMC, PCSK1 or LEPR Deficiency

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*

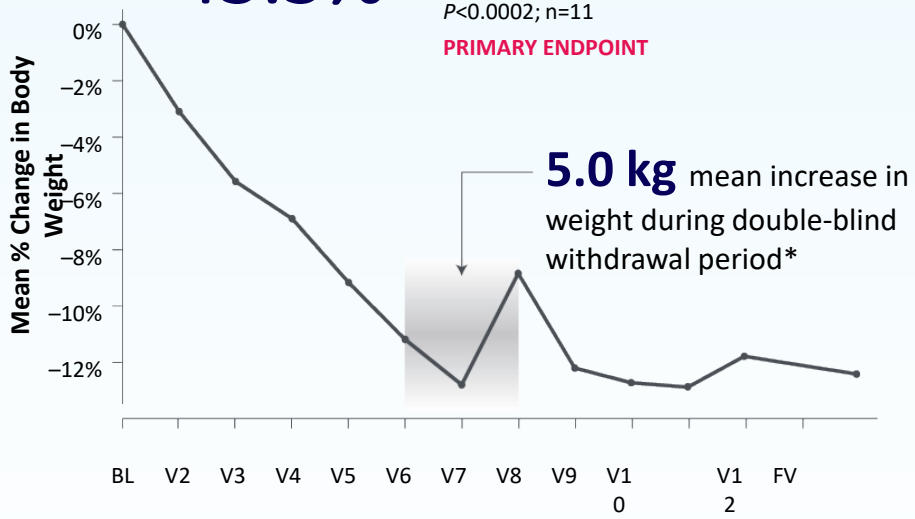


LEPR

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*



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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Approved by U.S. FDA in November 2020; Commercialization in 1Q21

IMCIVREE™
(setmelanotide) injection

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

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

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

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

Bardet-Biedl Syndrome

Phase 3 Update

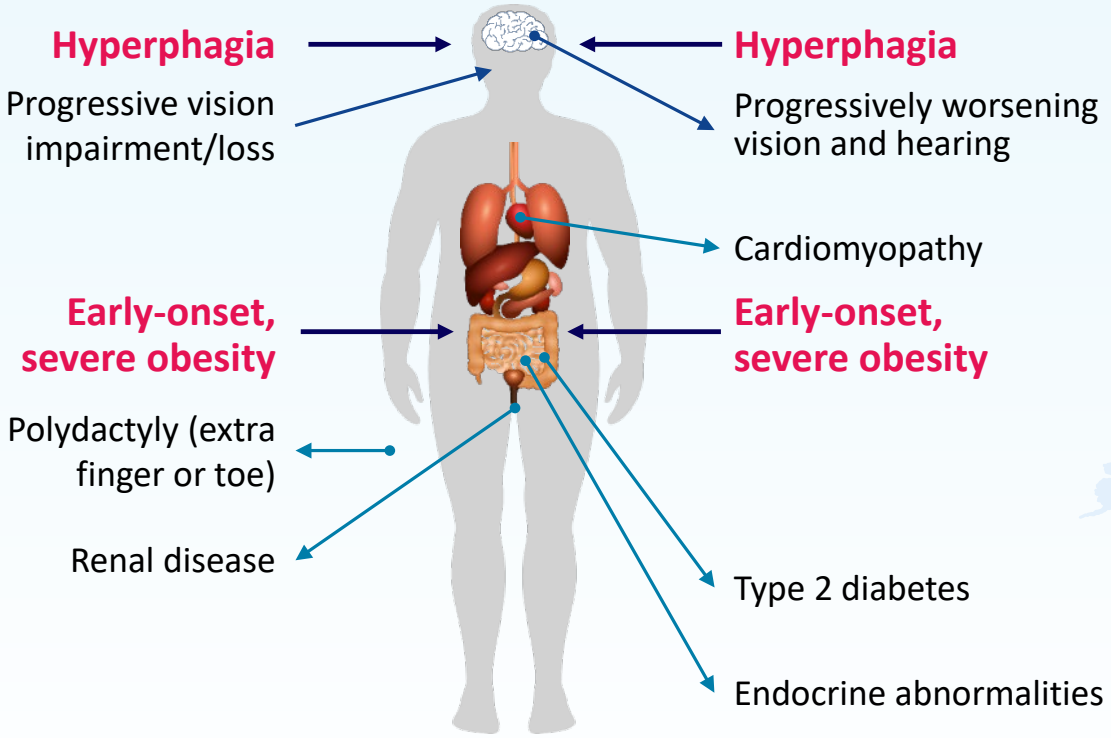
Bardet-Biedl and Alström Syndromes Associated with Severe Obesity and Hunger

Bardet-Biedl syndrome[1]

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

U.S. prevalence estimated to be

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



Alström syndrome[2,3]

Rare ciliopathy disorder associated with **ALMS1 mutation**

Worldwide prevalence estimated to be

500 to **1,000** patients

"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.

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

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

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

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

All primary endpoint responders were BBS patients.

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

A Closer Look at Patients with Bardet-Biedl Syndrome

28 BBS
Patients included in primary analysis set

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

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

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

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

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

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

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

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

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

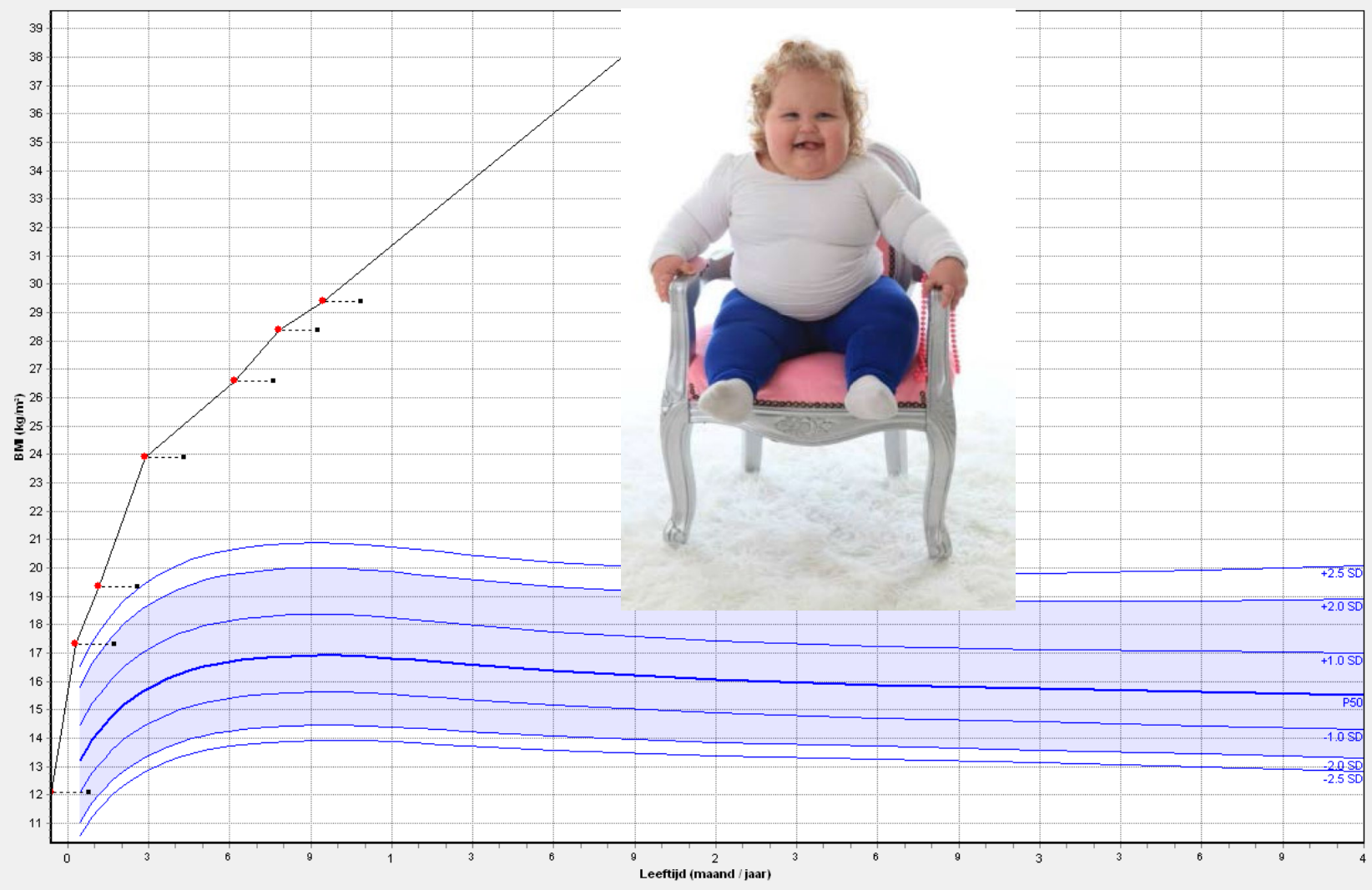
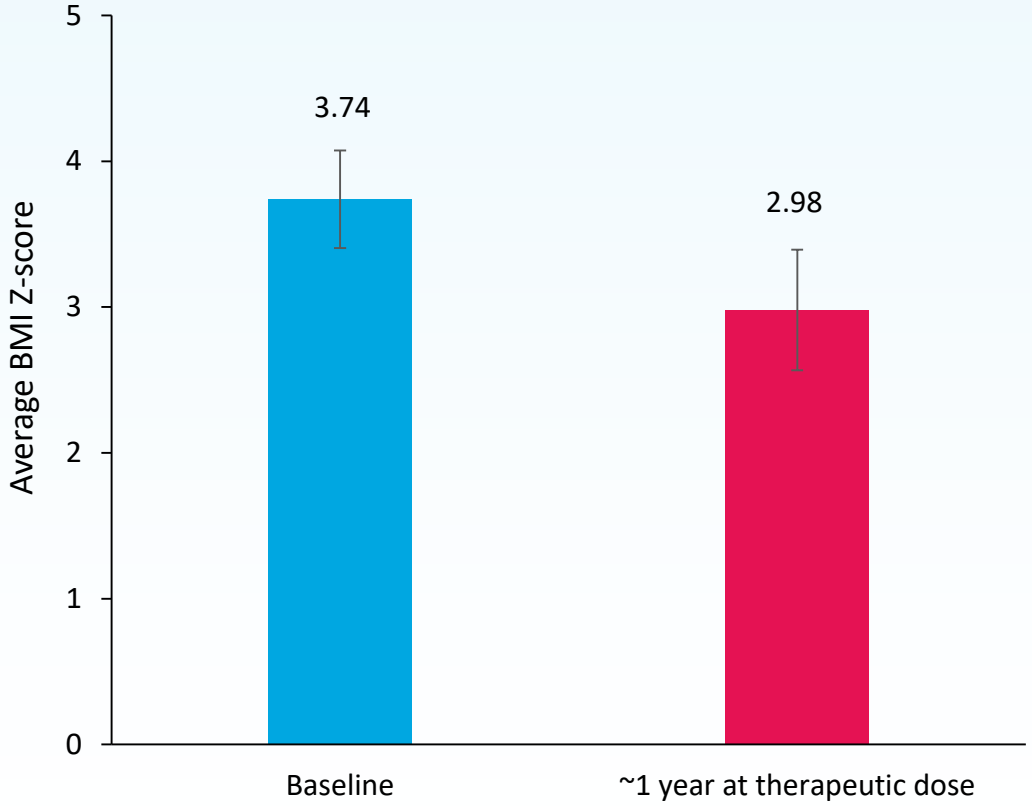


Chart adapted from Kleinendorst et al 2017
Data on file. Image used with permission.

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

Participants aged <18 years (n=16)

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



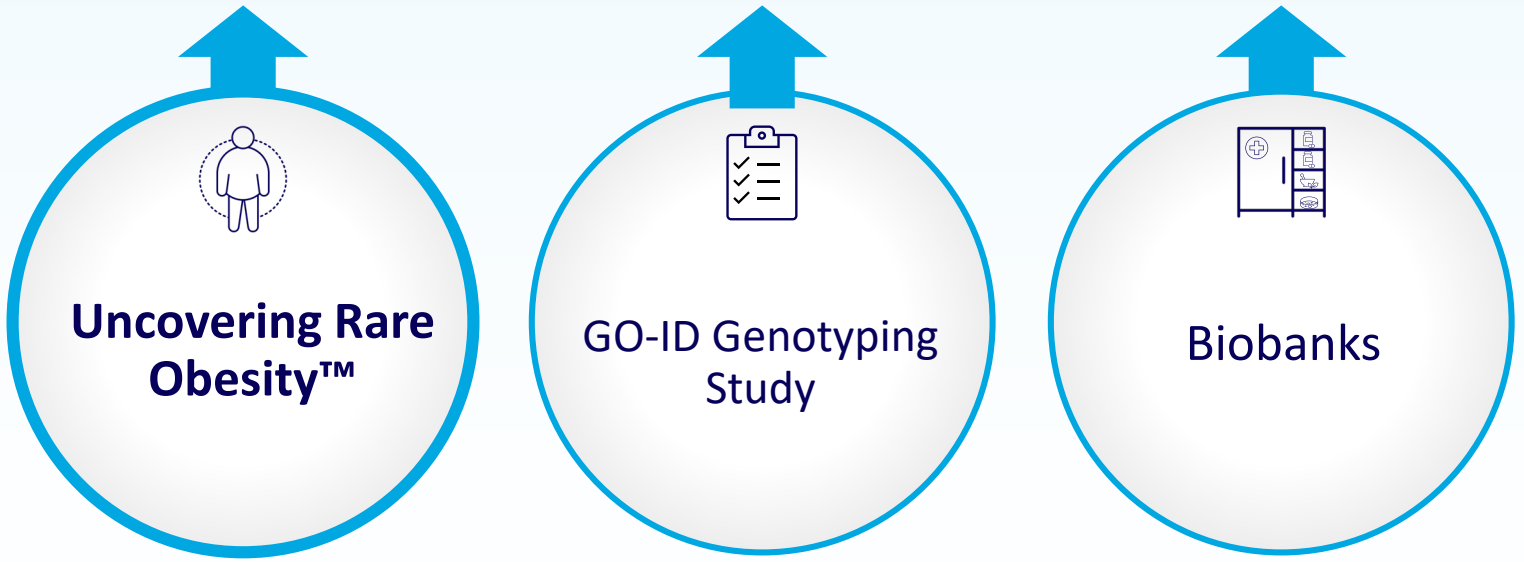
BMI, body mass index. Error bars are the standard error of the mean, which was calculated by dividing the standard deviation by the square root of n.

Growth Fueled by Genetics and Clinical Development

DNA Sequencing Efforts Fuel Integrated Approach to Patient Finding

~37,500*

Sequencing samples in Rhythm's DNA database



Largest-known DNA Database for Obesity

- MC4R Pathway research
- Build community
- Increase awareness
- Identify patients

* Total number of samples in sequencing database as of Sept. 30, 2020.

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Key Learning: Not All Genetic Variants are Created Equal

ACMG variant classification guidelines* can inform impact on MC4R pathway and patient cohort stratification in trials

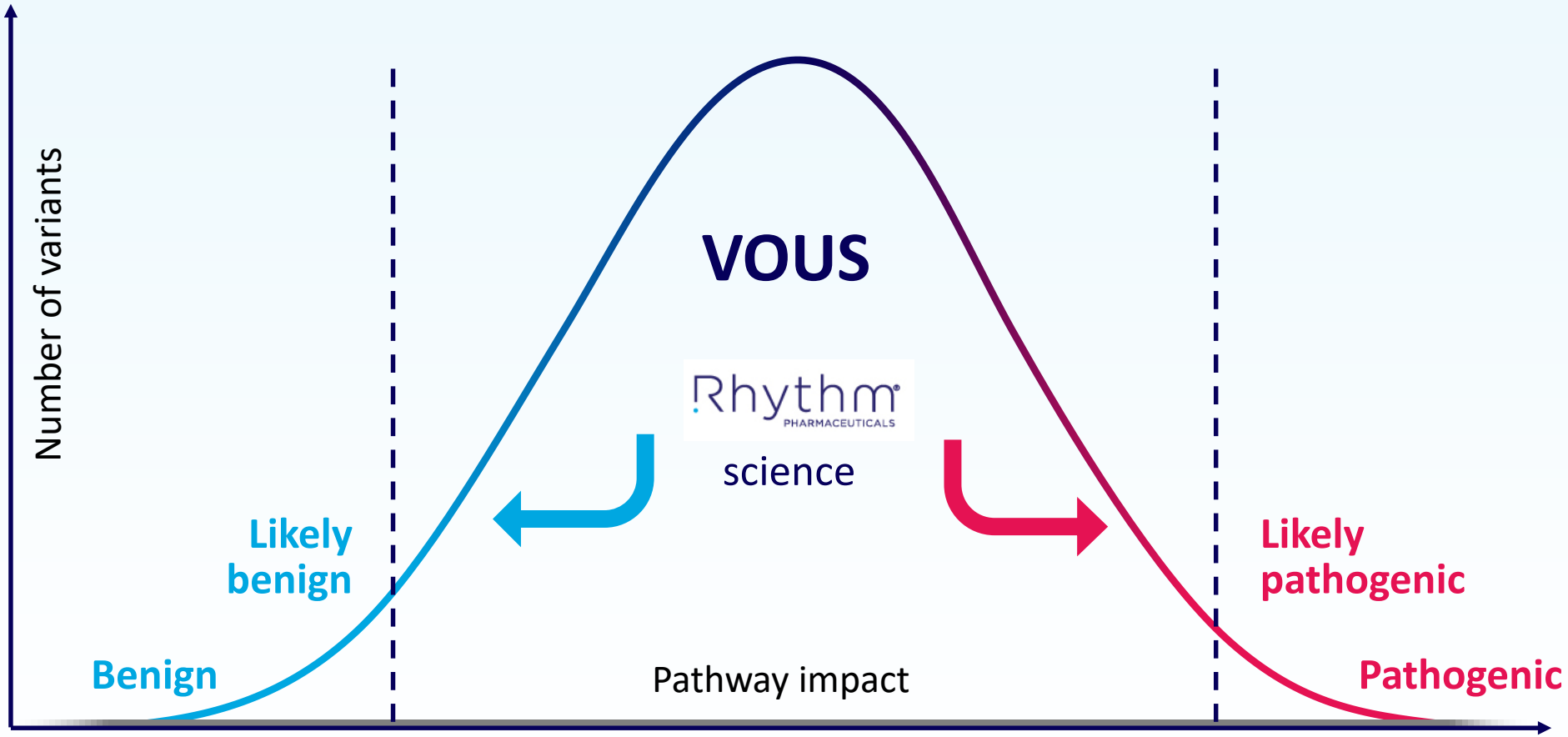
Pathogenic

Likely Pathogenic

Variant of uncertain significance

Likely Benign

Benign



*ACMG Guidelines Richards et al, 2015

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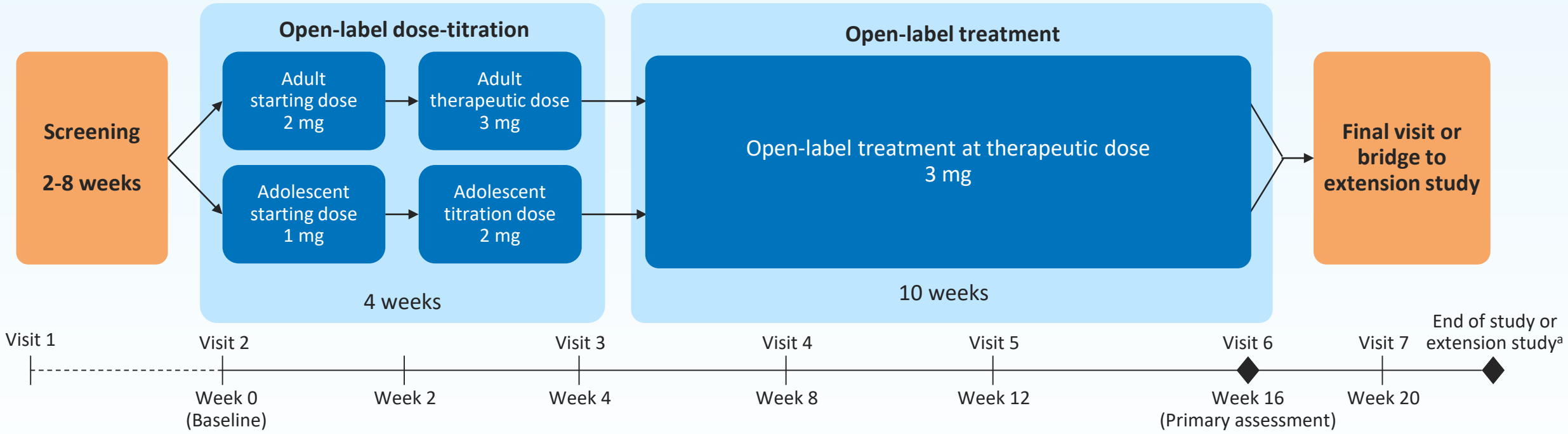
Phase 2 Basket Study Evaluated Response at Three Months of Therapy



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**
	N=**35**	N=**13***	N=**17***
Mean age (range)	**39 years old** (15 - 68)	**32 years old** (12 - 66)	**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 yet reached 12 we

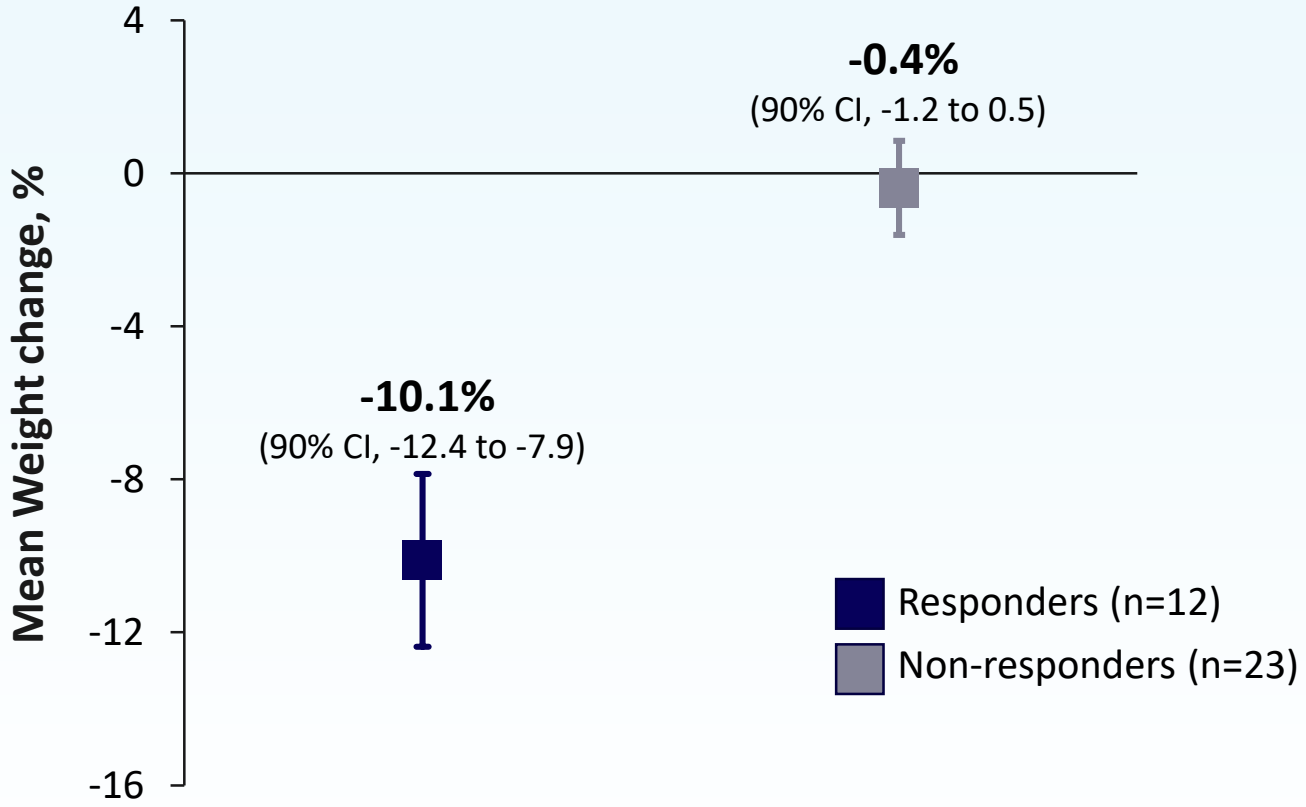
Response Rate and Weight Loss at Month 3 (Overall)
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

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.

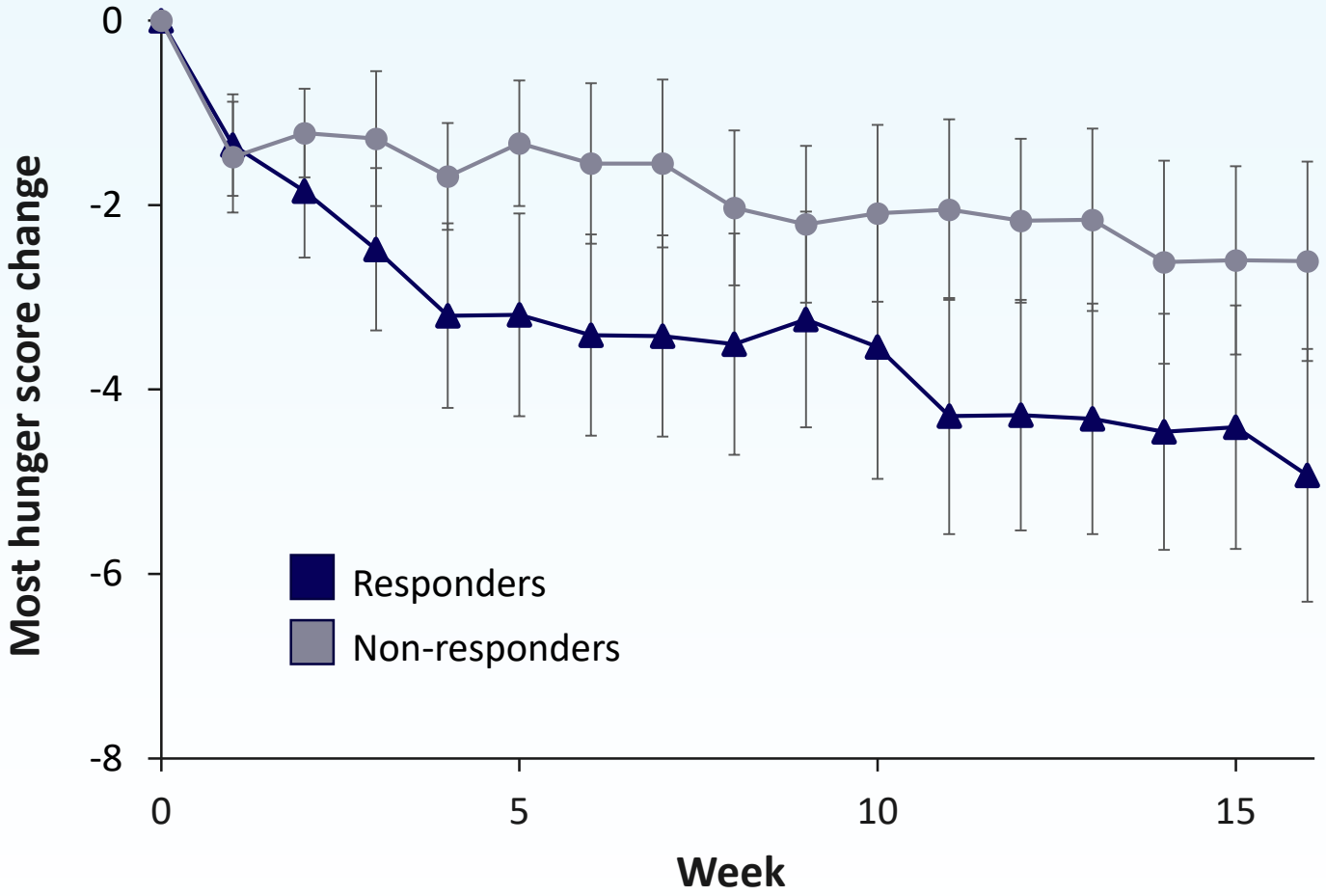
Response Rate and Weight Loss at Month 3 (Responder/Non-responder)
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity



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

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

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

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

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.

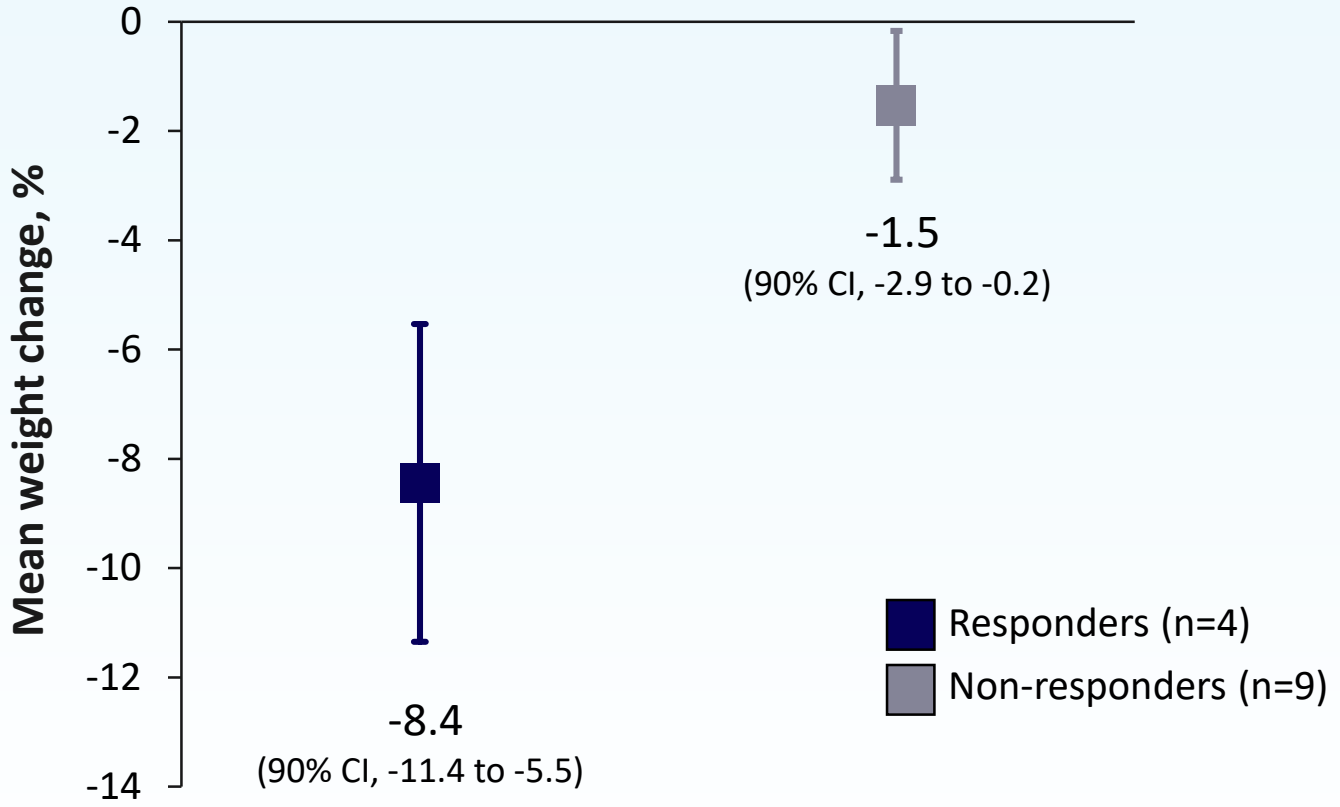
Response Rate and Weight Loss at Month 3 (Overall)
SRC1 Deficiency Obesity – Completers Set

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.

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



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

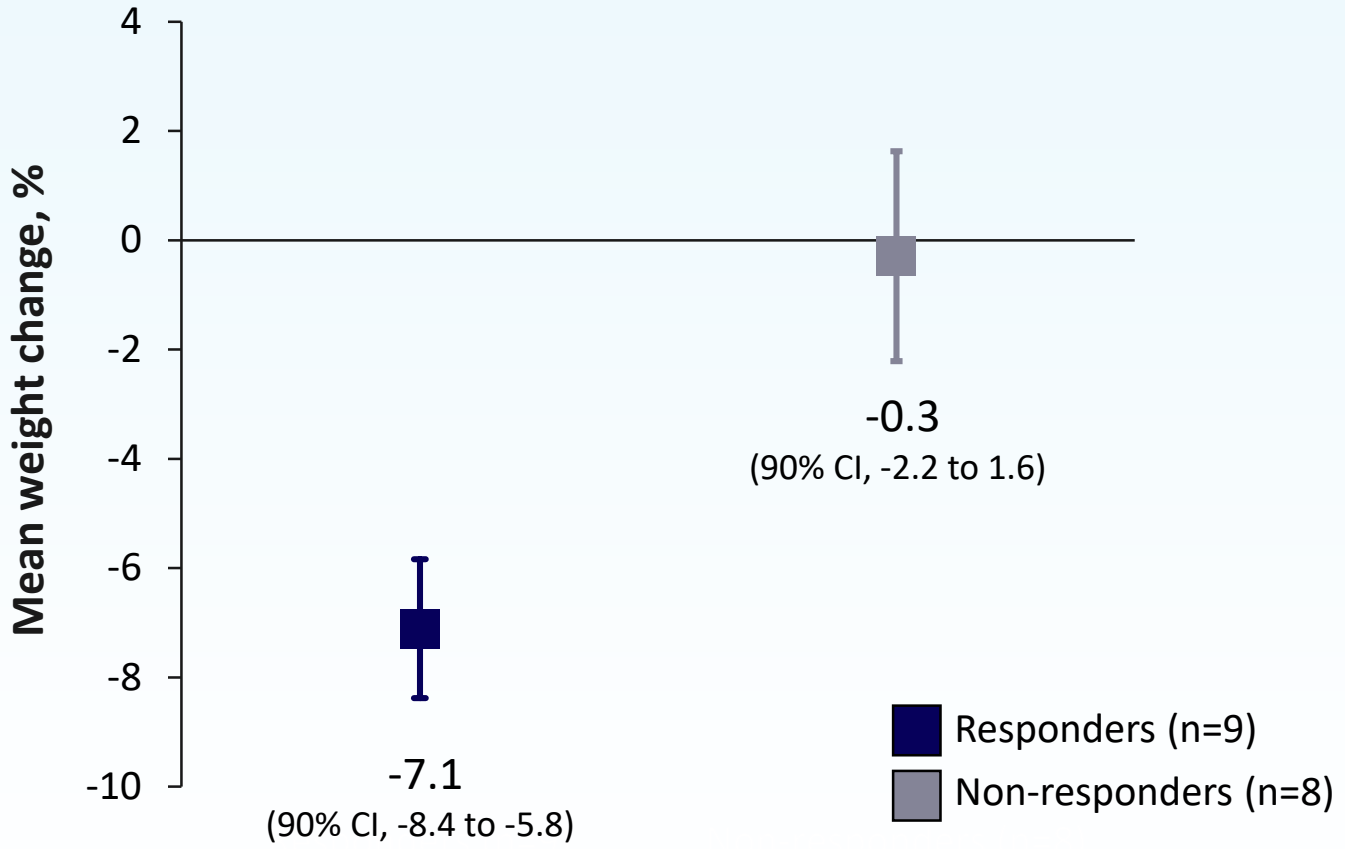
Response Rate and Weight Loss at Month 3 (Overall)
SH2B1 Deficiency Obesity – Completers Set

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

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

Interim data as of Dec. 17, 2020.

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



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

Setmelanotide Generally Well-tolerated Across Development Program

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

Setmelanotide has been generally well-tolerated

Most AEs are mild:

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

Discontinuations are rare; no increase in CV parameters:

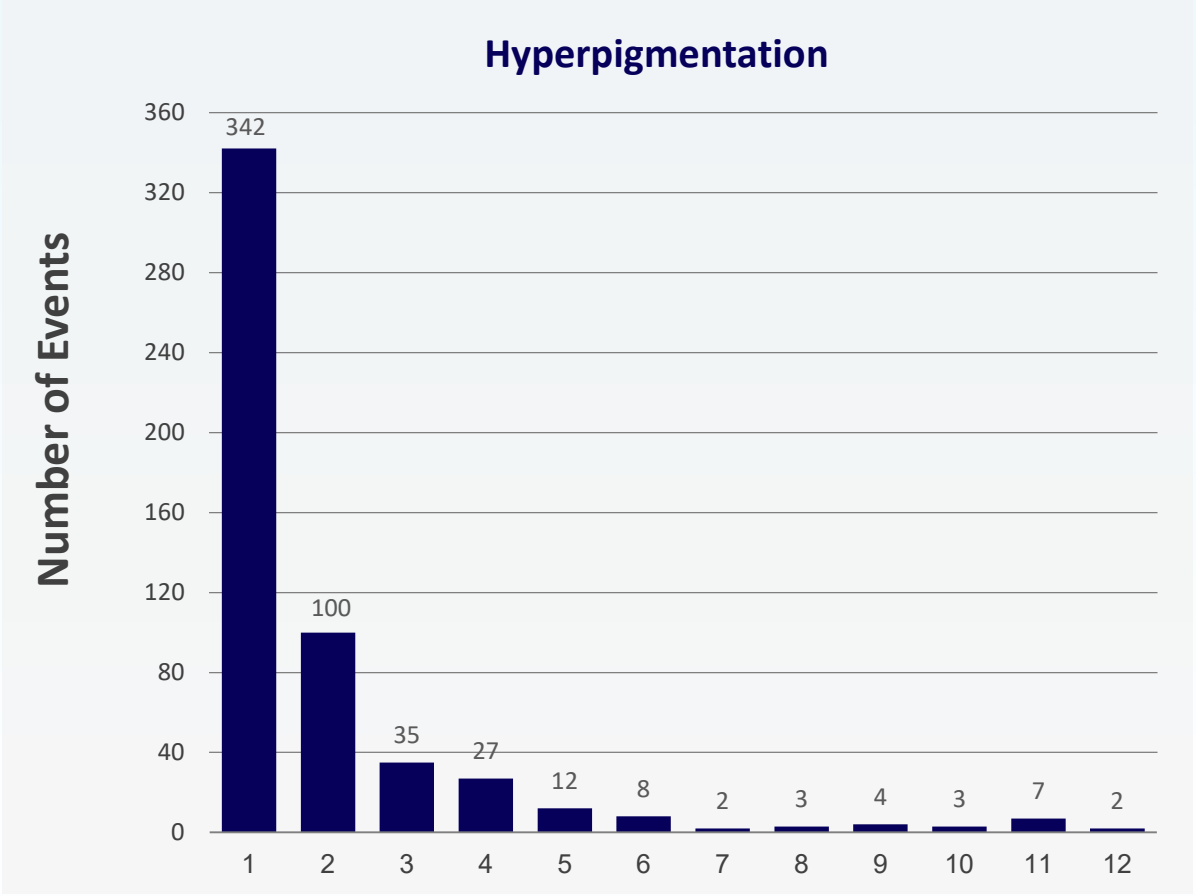
- In POMC and LEPR pivotal trials, setmelanotide was not associated with significant changes to blood pressure or heart rate

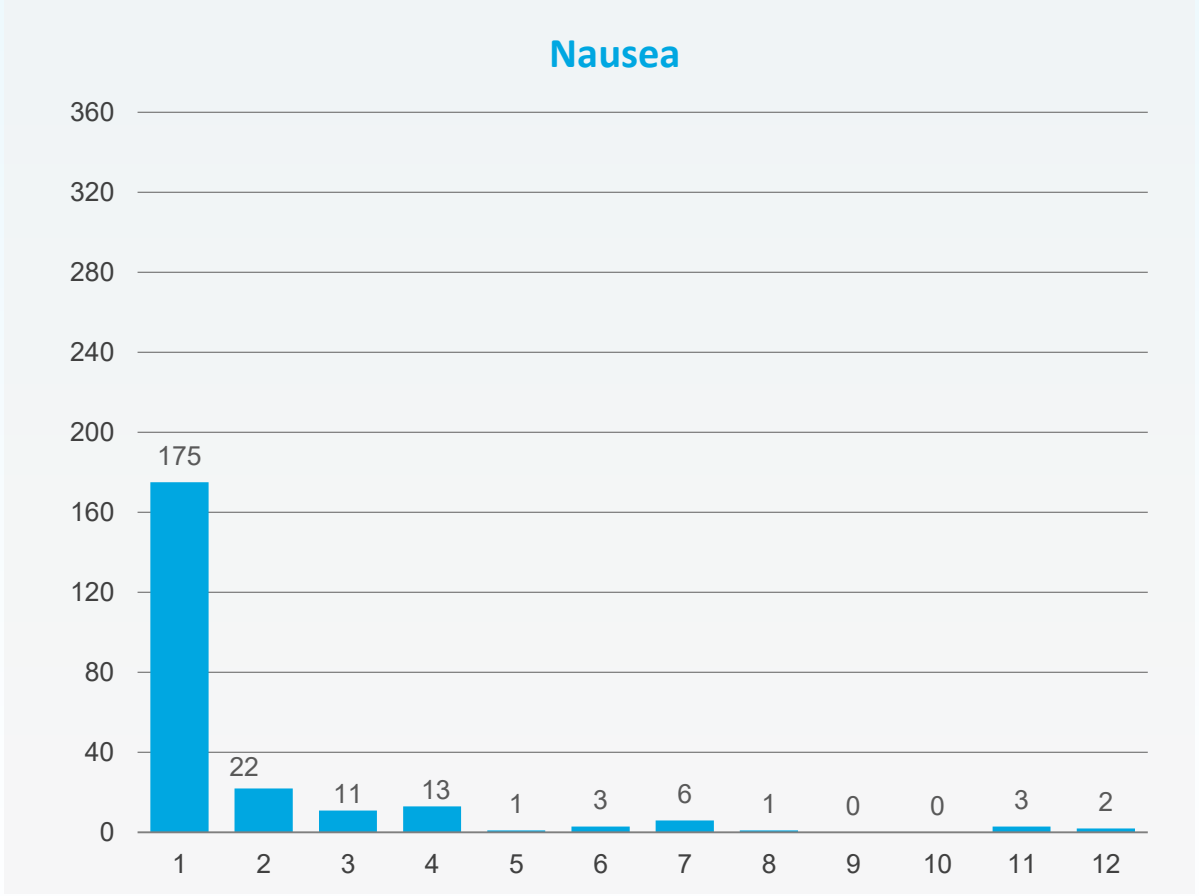
Patient experience with setmelanotide*

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

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

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

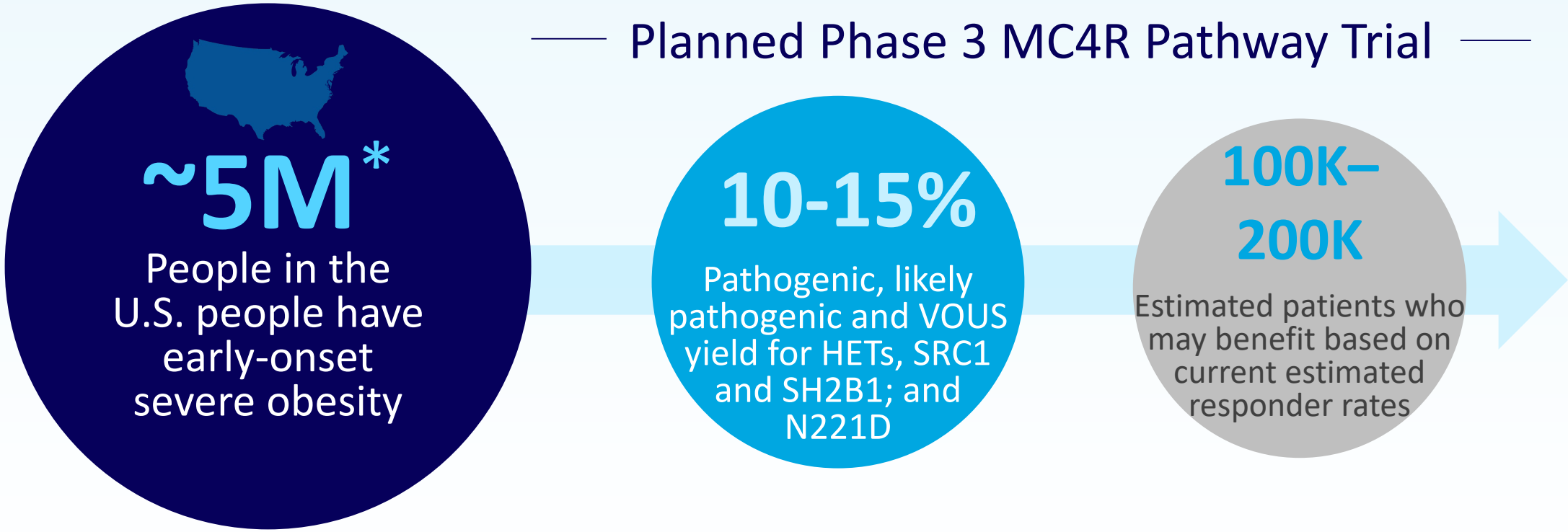




Months

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

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



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

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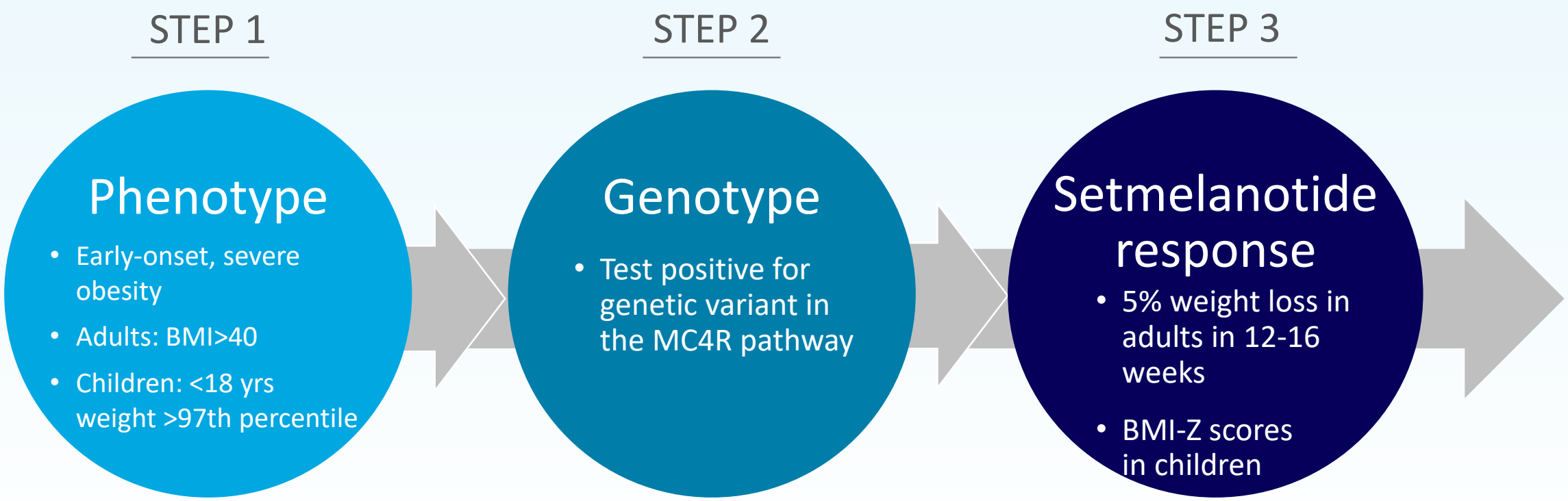
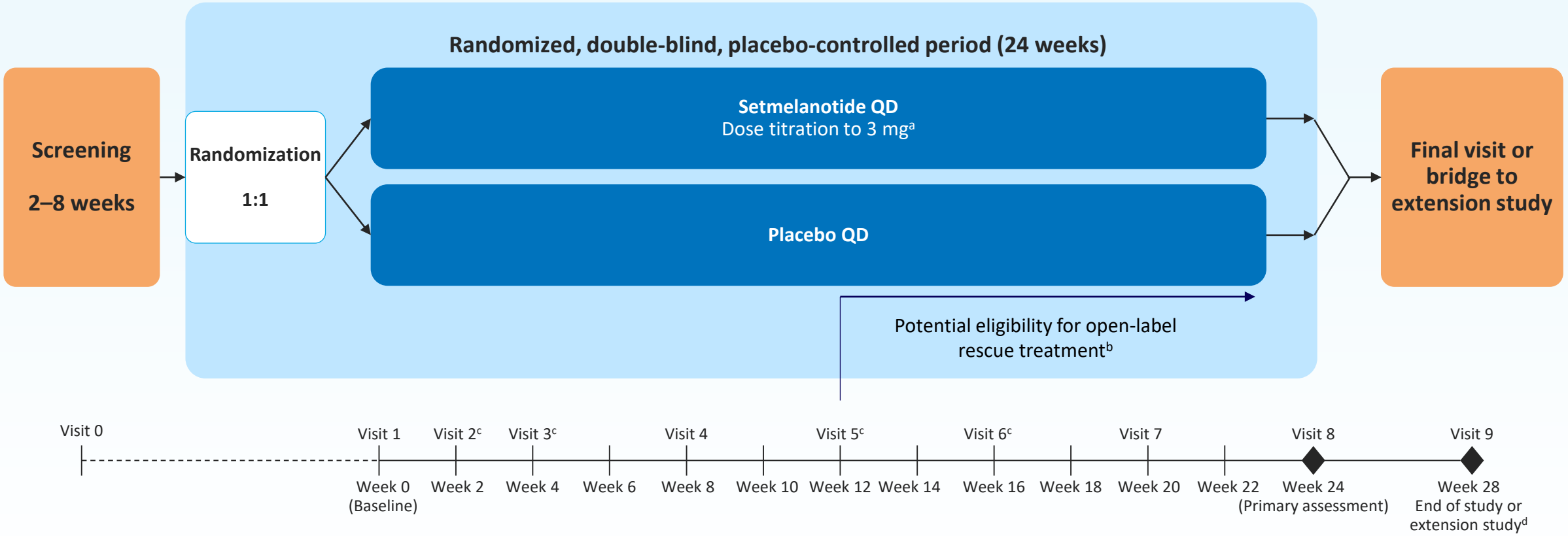
Targeted but Simple, Three-step Approach to Treating Obesity



Based on data from more than 100 patients in Phase 2 and Phase 3 clinical studies, patients who achieved 5 percent weight loss at approximately 12 to 16 weeks on setmelanotide therapy tended to achieve 10 percent weight loss within a year. Weight loss of this magnitude, particularly in patients with severe, early-onset obesity, is considered clinically meaningful.

Path Forward: Phase 3 MC4R Pathway Study Designed to Evaluate Response After 24 Weeks of Treatment*



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

Gene Selection Methodology Validated with Initial Genes

Approach is based on the existing ClinGen framework* incorporating MC4R pathway specific nuances

Gene expression

Cellular and molecular function

Physiological function

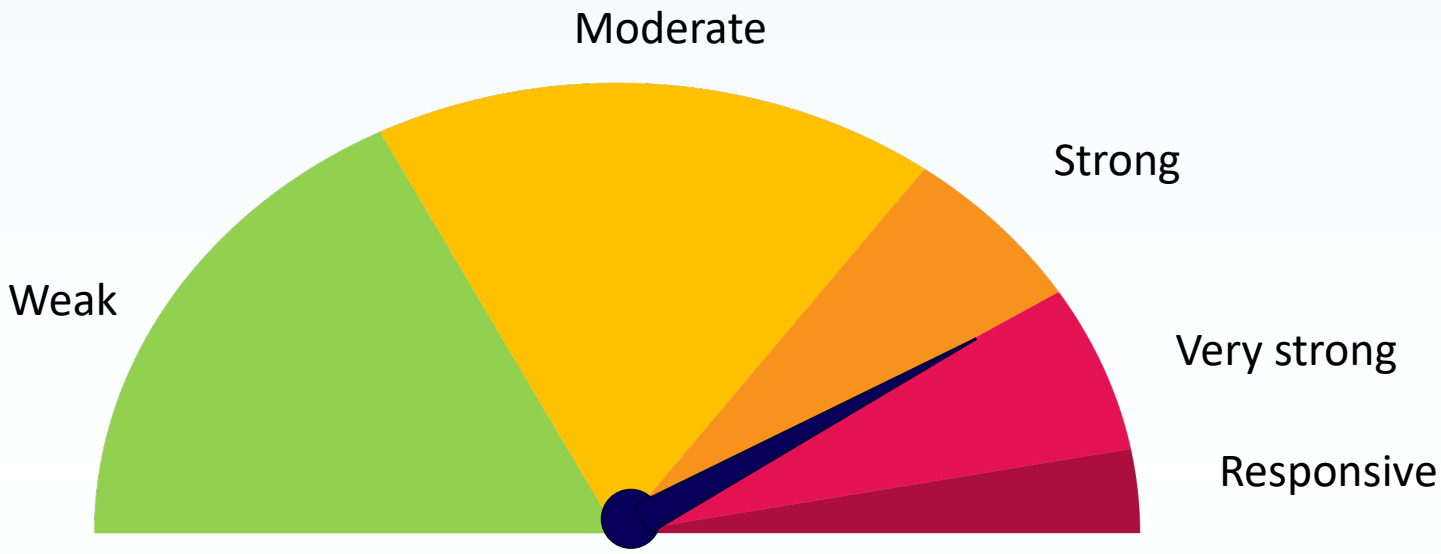
Functional rescue

Weight

Obesity-related epidemiology

Weight

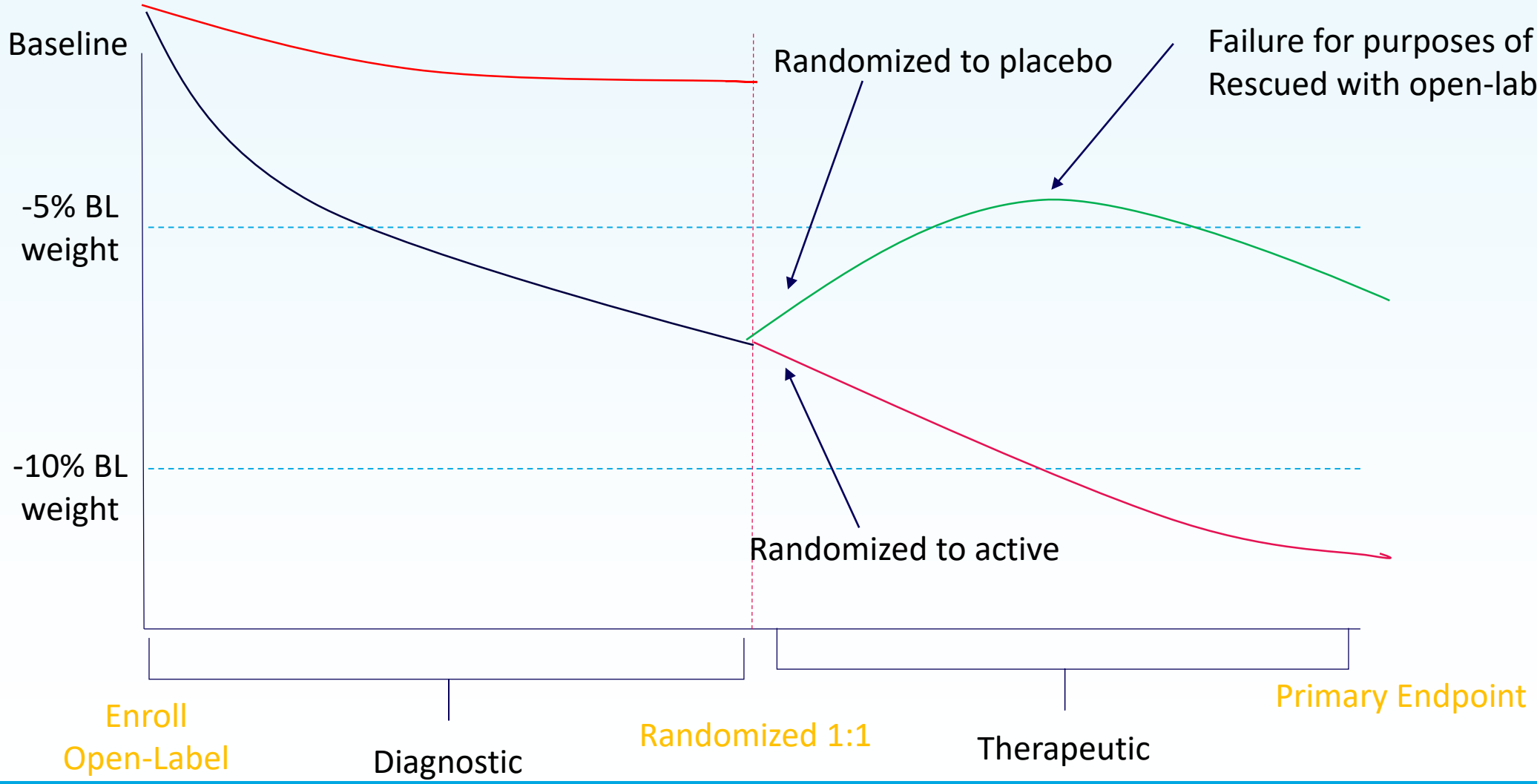
Clinical response



*Strande et al., 2017

Rhythm® PHARMACEUTICALS

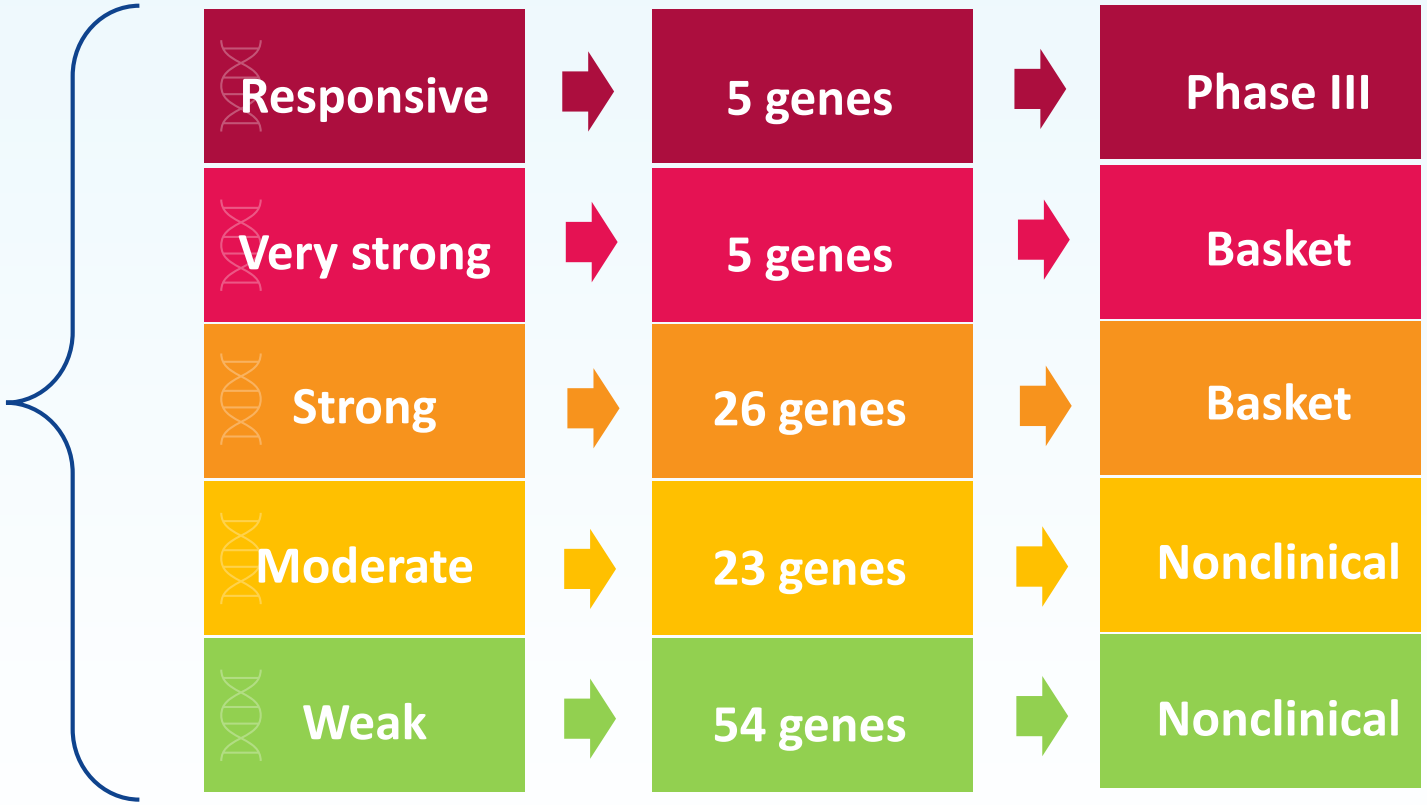
Expanded Phase 2 MC4R Pathway Basket Study to Evaluate Setmelanotide in 31 Additional Pathway-relevant Genes



Further Expansion of the MC4R Pathway

113

Genes with potential ties to MC4R pathway



Rhythm® PHARMACEUTICALS

Transformational Progress Expected in 2021

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


Rhythm®
PHARMACEUTICALS

Rhythm Pipeline Focused on MC4R Pathway Diseases

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

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

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

SHARES OUTSTANDING *as of 12/31/2020*	44,235,903 (basic share count)
AUDITED ESTIMATED CASH, CASH EQUIVALENTS AND SHORT-TERM INVESTMENTS *as of 12/31/2020*	$ 172.8 million

Net proceeds from sale of PRV: **$98.5M**

Net proceeds from follow-on offering of 5,750,000 shares: **$161.6**

Pro rata: $432.9M