Advancing Setmelanotide to Treat Obesity due to Genetic Variants within the MC4R Pathway

Research & Development Event

January 26, 2021

Rhythm PHARMACEUTICALS

Today's Agenda

Introductions

Hunter Smith, Chief Financial Officer

Welcome and Overview

David Meeker, M.D., Chair, Chief Executive Officer and President

Clinical Data Update on Setmelanotide

Murray Stewart, M.D., Chief Medical Officer

Translational Research and the MC4R Pathway

Alastair Garfield, Ph.D., Head of Translational Research and Development

Closing Remarks and Q&A

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 our expectations regarding prevalence for our target indications, which are based on our internal calculations and estimates, the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, anticipated timing for enrollment and release of our clinical trial results, the timing for filing of NDA, MAA or other similar filings, our goal of changing the paradigm for the treatment of rare genetic disorders of obesity, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, 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.

Welcome

David Meeker, M.D.
Chair, Chief Executive Officer and President

Key Takeaways for Today

- Multiple genetic defects lead to MC4R pathway deficiencies
- Obesity is complex and not all patients with a pathway defect will respond to setmelanotide
- Growing confidence in our ability to identify genes that will respond
- Evolving paradigm to identify potential setmelanotide responders
- Individually each genetically defined population is rare – in the aggregate, these diseases are not so rare (*Rare Disease Paradox*)
- Strategy: Expanded sequencing efforts coupled with expansion of basket trial approach

Living with Early-onset, Severe Obesity and Hyperphagia

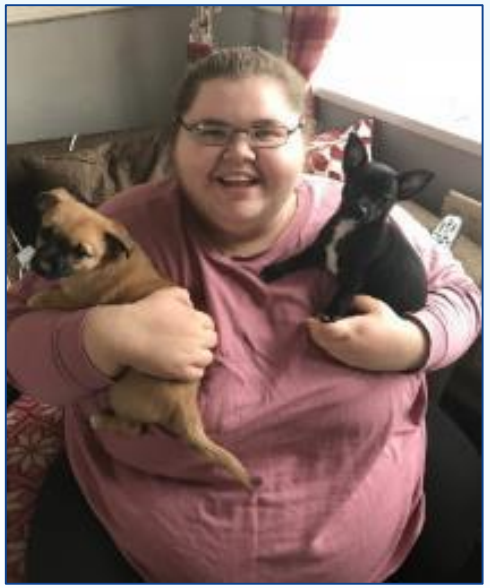
Hallmark Symptoms of Rare Genetic Diseases of Obesity

Adalissa and Solomon with their siblings (unaffected)

"They are constantly, all day long saying they are hungry and asking what's for the next meal and what are we eating the next day. We keep a menu planned and if we deviate from that menu it's a disaster."

"We have had to put locks on our cupboards and fridge and freezer to protect them from themselves!"

*– Olivia, Mother of Adalissa and Solomon, siblings diagnosed with **BBS***



Katy, at 23 years old, 450 pounds

"It causes extreme unrelenting hunger and excessive eating. As a child…the fridge and food was controlled massively…but nobody could understand that I was desperately hungry and just wanted to stop that feeling."

*- Katy, diagnosed with **POMC heterozygous deficiency obesity***

Our mission:

Change the Paradigm for the Treatment of Rare Genetic Diseases of Obesity

Classic Rare Disease Challenges Apply to Genetic Obesities

Lost in the system

Little knowledge

Little awareness

No tools or testing

No treatment

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

The Rare Genetic Disease of Obesity Paradox

<200,000 Definition population of *a* rare disease

~7,000 Rare diseases

>30M Total patients affected with rare diseases in the U.S.

~5,000*

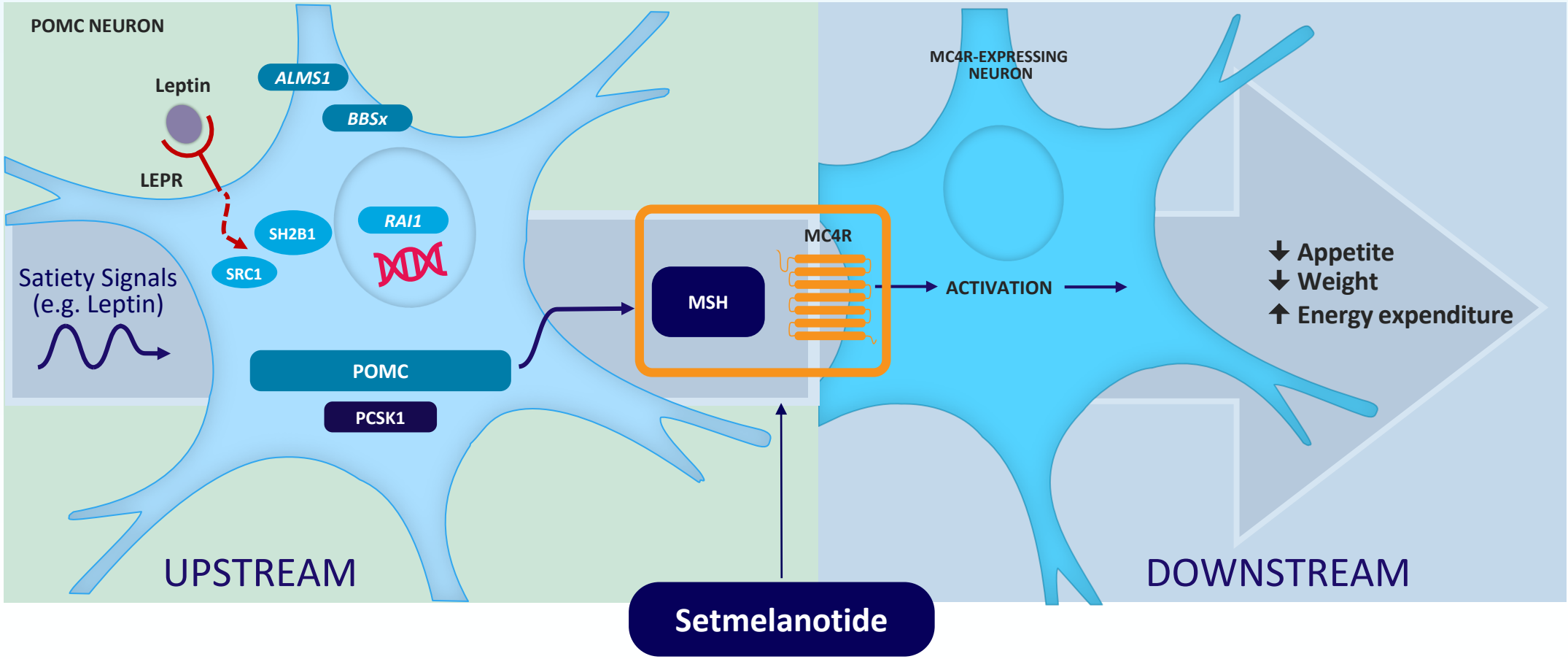
- Obesity due to POMC, PCSK1 or LEPR Deficiency (*FDA approved*)
- Bardet-Biedl syndrome (*Ph3*)
- Alström syndrome (*Ph3*)

Initial indications are ultra-rare. But with additional genes, in the aggregate, not so rare.

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

MC4R Pathway Biology is Clear and Strong

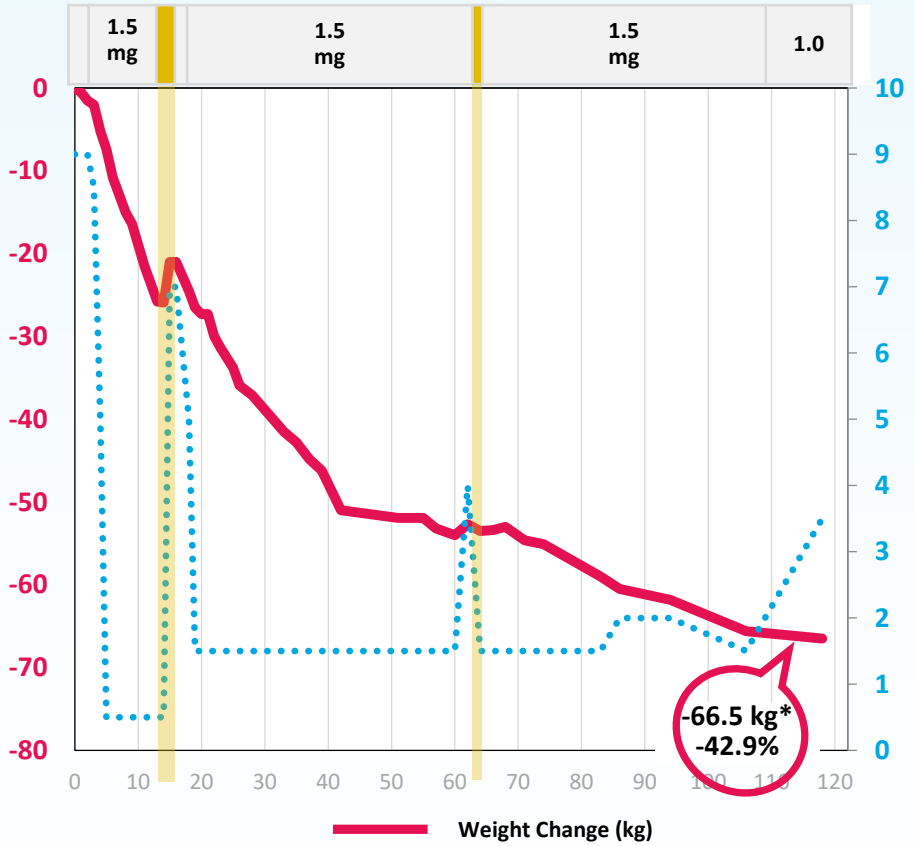
Setmelanotide can redress MC4R pathway impairment contributing to early onset, severe obesity



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

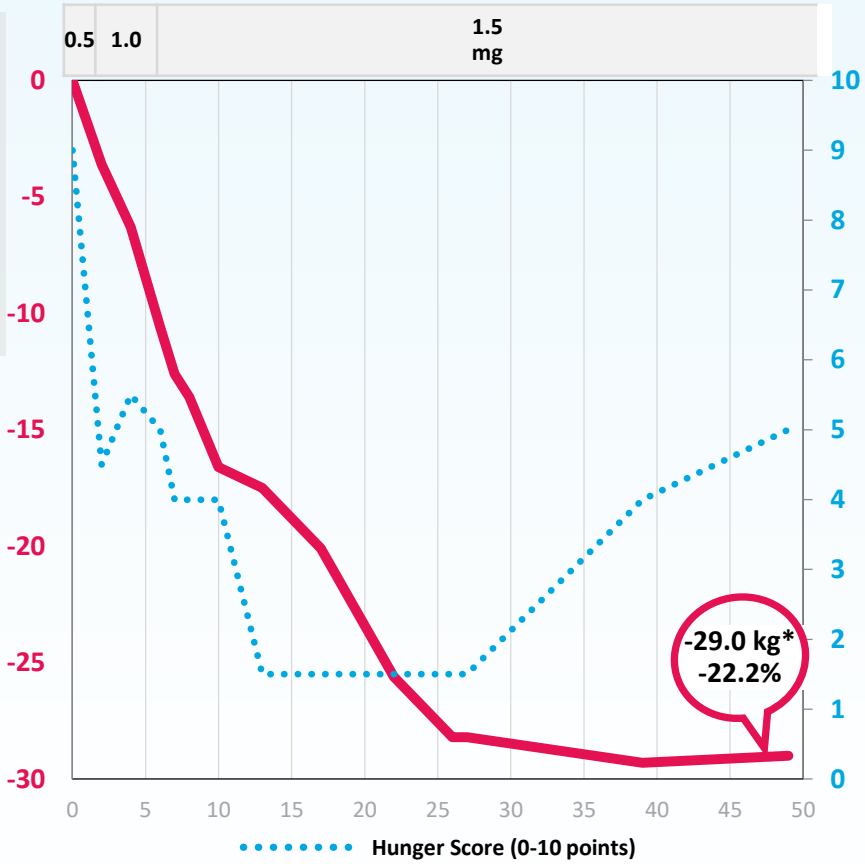
POMC Patient #1*

20 yr old female
Starting Weight = 155.0 kg
Starting BMI = 49.8 kg/m^2



LEPR Patient #1*

23 yr old male
Starting Weight = 130.6 kg
Starting BMI = 39.9 kg/m^2



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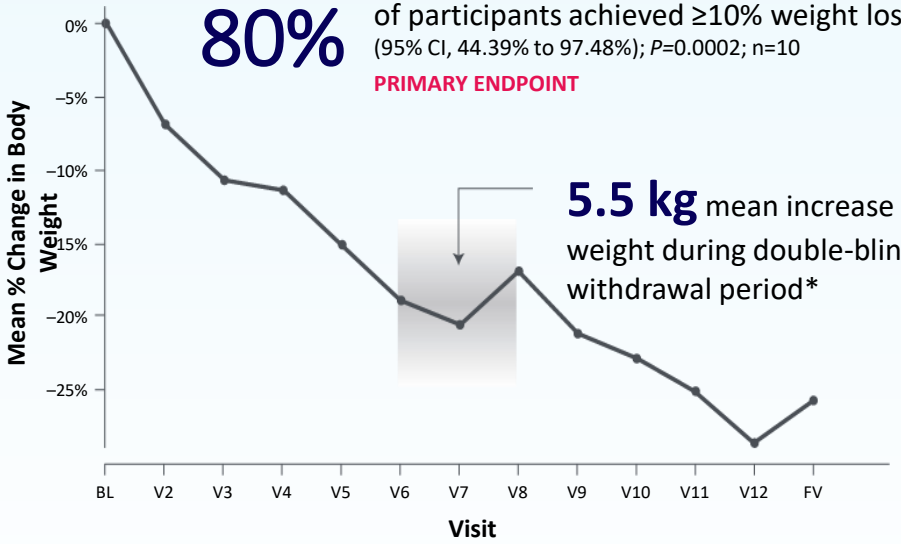
Approval of IMCIVREE Based on Phase 3 Data from Largest Studies Conducted in Obesity due to POMC, PCSK1 or LEPR Deficiency

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*

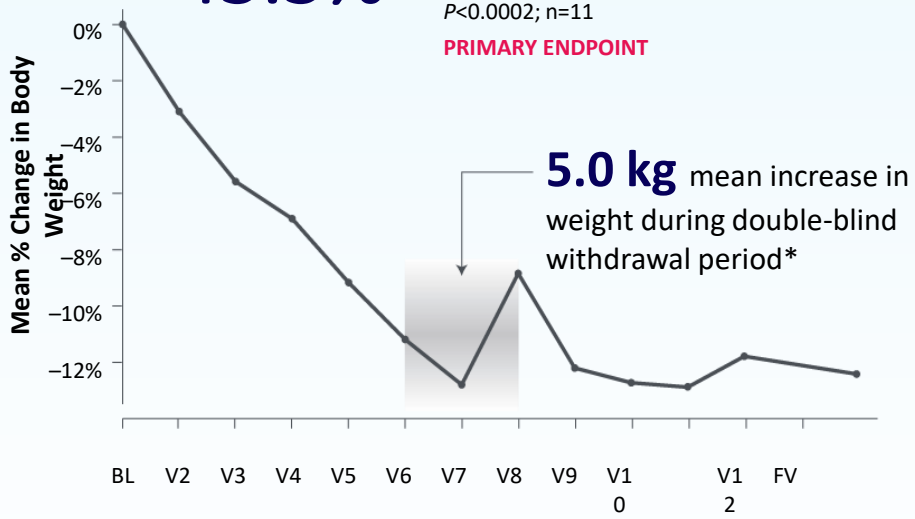


LEPR

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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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

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.

Consistent Safety Profile Across All Programs in 590 Patients

Setmelanotide has been generally well-tolerated

Most treatment-related AEs were mild:

- Mild injection site reactions
- Skin hyperpigmentation
- Nausea/vomiting: mild and early in treatment

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.

Working Toward Changing the Paradigm for the Treatment of Rare Genetic Diseases of Obesity

Validation

FDA approved

for chronic weight management for obesity due to **POMC, PCSK1** or **LEPR** deficiency

Meaningful Opportunity

Positive topline results in **Bardet-Biedl syndrome**

Growth Potential

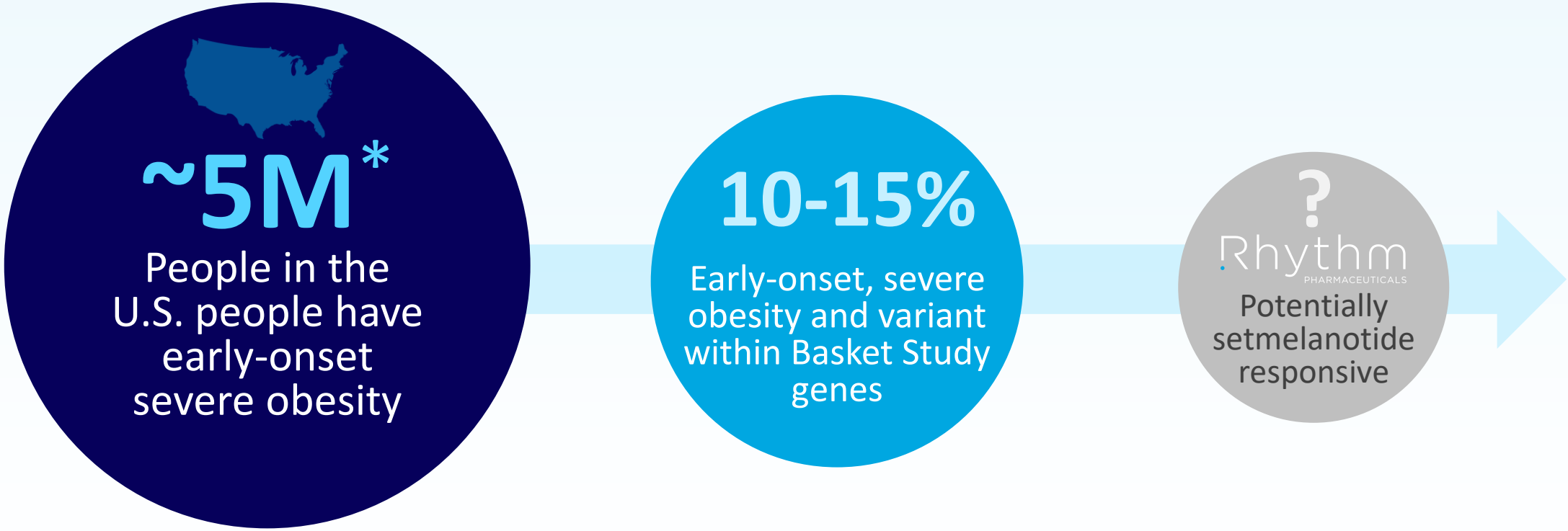
Established proof-of-concept in **new indications in Phase 2 Basket Study**

Drive COMMUNITY BUILDING and GENETIC SEQUENCING

*IMCIVREE (setmelanotide) is 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.

What is the Growth Opportunity?

While obesity affects tens of millions in the United States, Rhythm is focused on rare genetic diseases of obesity arising due to MC4R pathway dysfunction

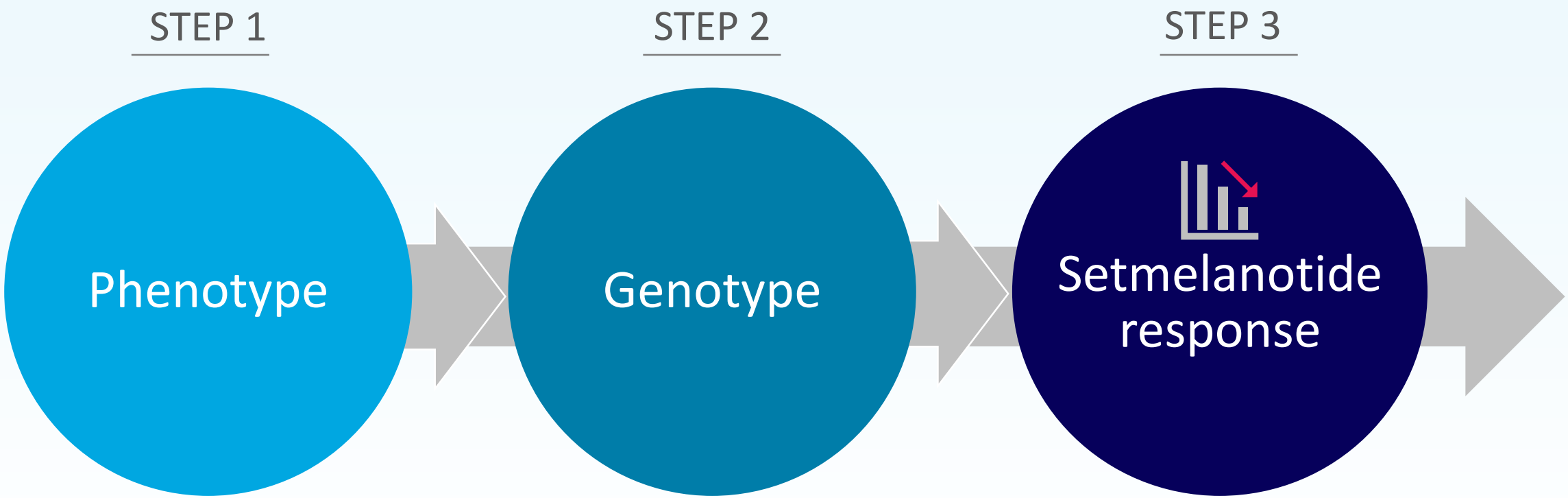


* 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018[1]); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017)

Obesity is a Complex Disease

- Monogenic disease?
- Monogenic contributor?
- Background genetics?
- External influences?

Rhythm is Taking a Simple Approach to a Complex Problem



What Have You Heard?

Unmet medical need is significant

MC4R pathway biology is strong

Setmelanotide development program is building confidence in the expanded opportunity

Today's Focus: Proof of Concept Achieved in Basket Indications with Significant Potential Market Opportunity

- Rhythm's largest data readout from five genetic cohorts with 65 patients
- Proof of concept achieved in five MC4R pathway genes
- Estimated U.S. target patient population across these five genes expanded to 100K-200K
- Largest known genetic obesity database of approximately 37,500 individuals
- Support our approach for gene selection and variant classification
- Two new trials planned for MC4R pathway diseases in a total of 36 genes

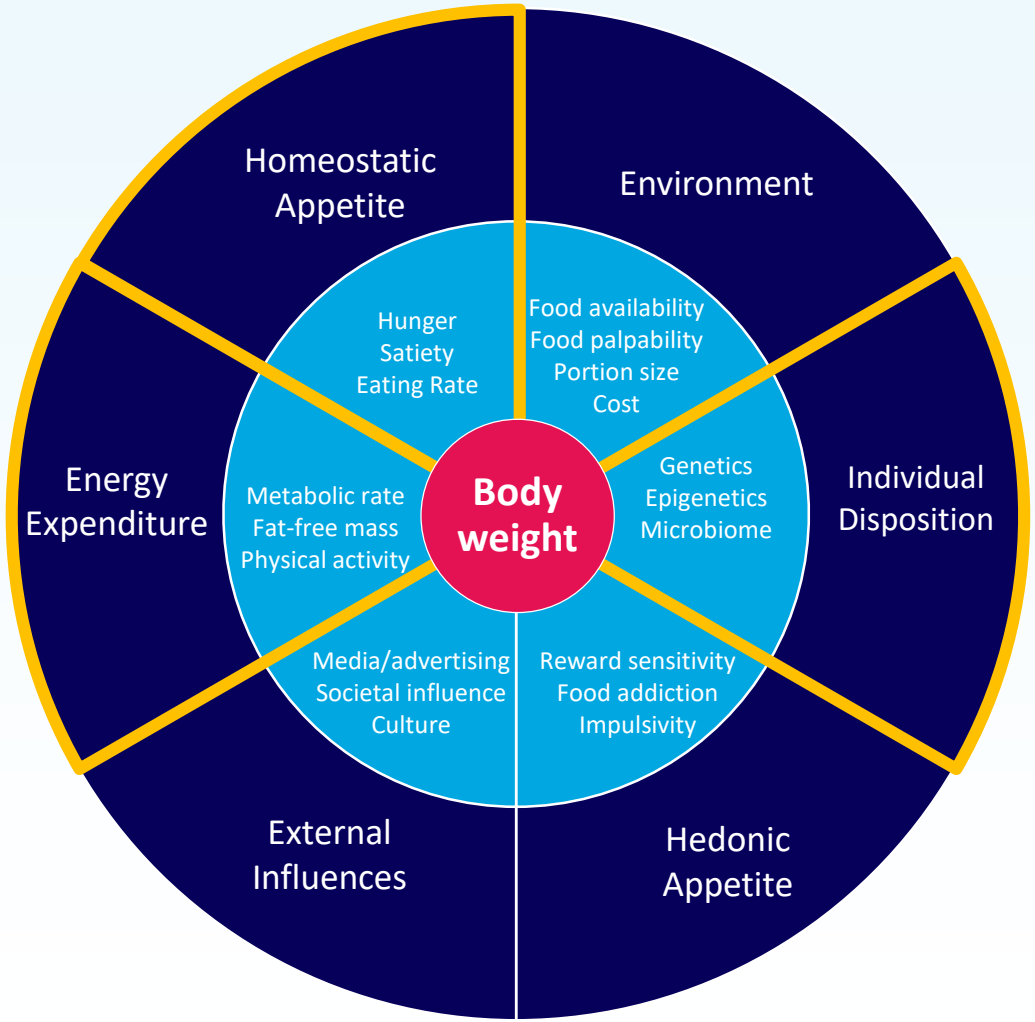
Clinical Data Update on Setmelanotide

Murray Stewart, M.D.
Chief Medical Officer

Update on Setmelanotide Clinical Development

- Rhythm's precision approach to obesity
- Proof-of-concept data for HETs (POMC, PCSK1 and LEPR) and SRC1 and SH2B1
- Statistically significant and clinically meaningful BMI-Z score reductions in children with BBS
- New pivotal trial planned in HETs, SRC1 and SH2B1 and new exploratory MC4R Pathway Basket Study planned in 31 new genes

Challenges in Treating Obesity



Adapted from Ziauddeen et al 2012

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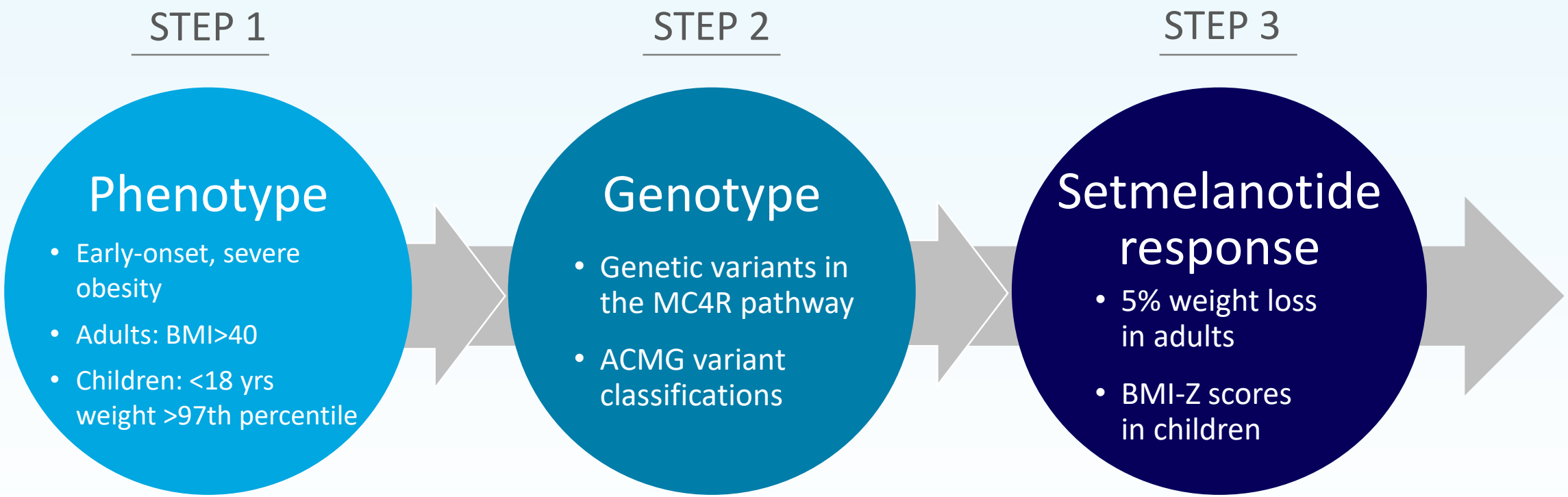
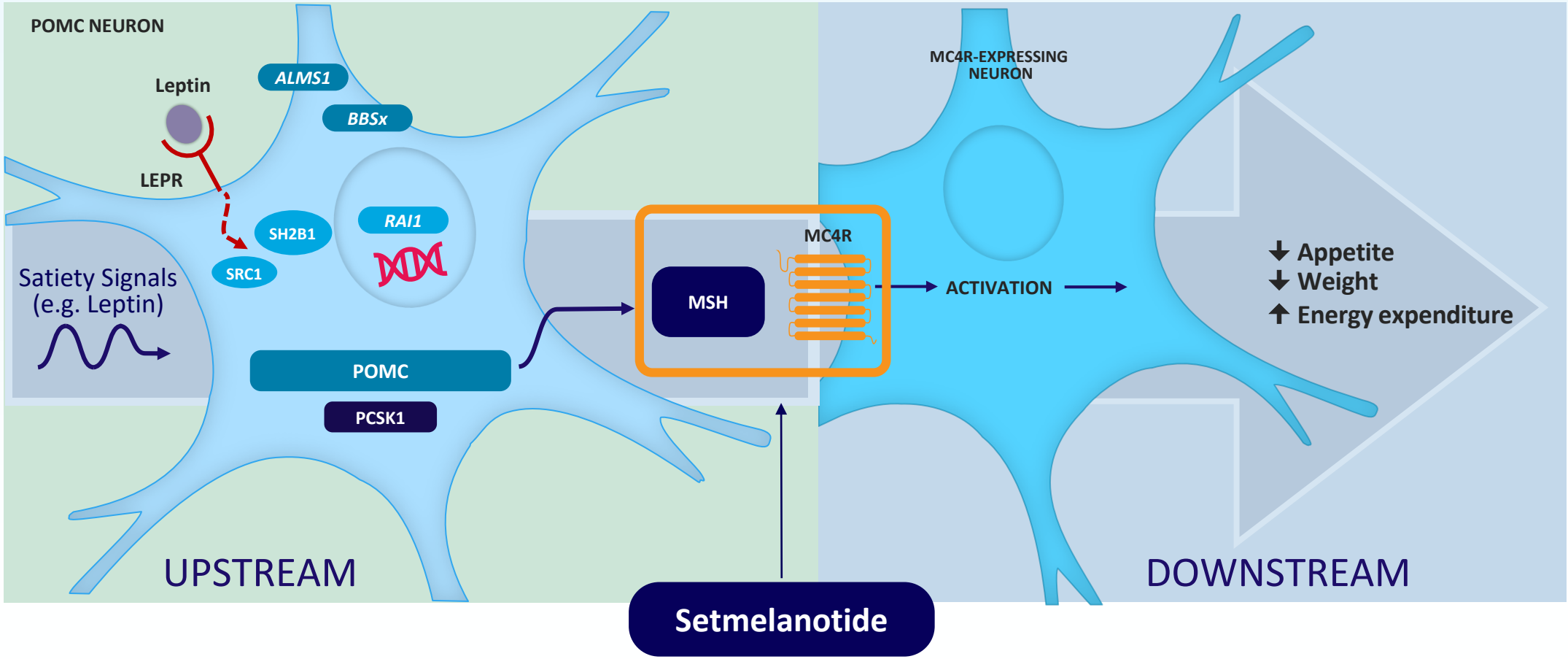
Targeted but Simple Approach to Treating Obesity

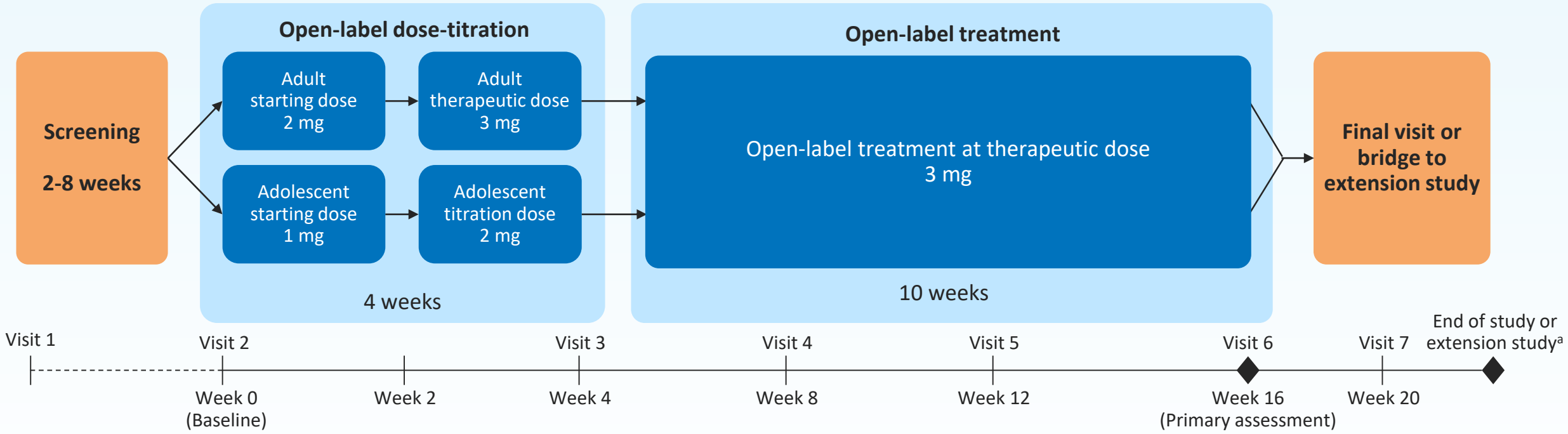


MC4R Pathway Biology is Clear and Strong: Regulates Hunger, Caloric Intake, and Energy Expenditure, and, Consequently, Body Weight

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



Phase 2 Basket Study Design to Evaluate Response at Three Months on Therapy



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

POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

Efficacy Results

HETs Patient Demographics – Full Analysis Set

Baseline Characteristics	HETs patients (N=35)
Mean age (years) at enrollment (SD)	39 (18)
Range	15, 68
Female	68.6%
Male	31.4%
Mean weight lbs (SD)	315.9 (65.7)
Range lbs	210, 459
Mean weight kg (SD)	143.3 (29.8)
Range kg	95, 208
BMI Mean kg/m^2 (SD)	50, (9)
Range	35, 79

Hets, POMC/PCSK1/LEPR heterozygous deficiency obesity; SD, standard deviation.

Patient Cohorts Pre-specified by ACMG Variant Classification

Pathogenic

Likely Pathogenic

VOUS

Likely Benign

Benign

Baseline Characteristics	HETs Patients (N=35)
Pathogenic/Likely pathogenic	8
Variant of uncertain significance	19
N221D	8

ACMG, American College of Medical Genetics; Hets, POMC/PCSK1/LEPR heterozygous deficiency obesity.

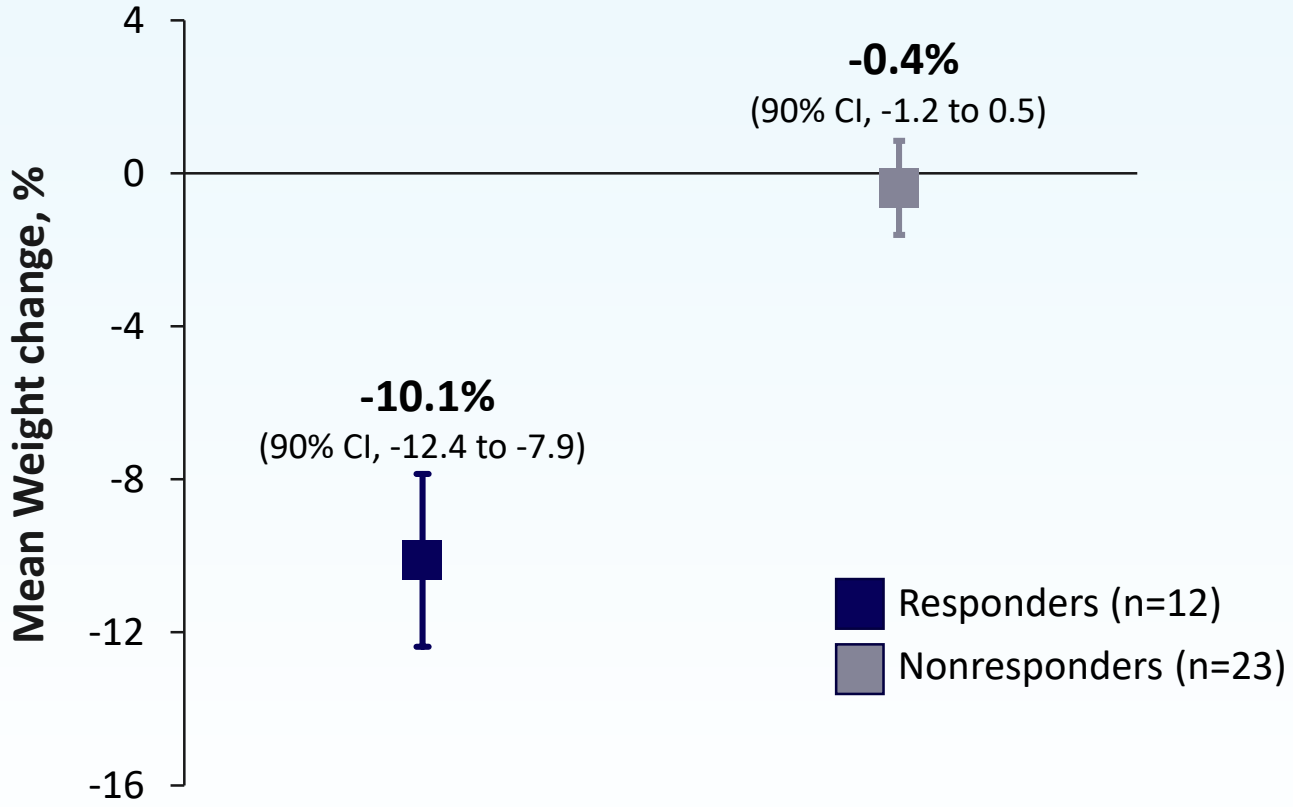
Response Rate and Weight Loss at Month 3 (Overall)
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity

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: Overall (n=35)	**143.3 kg** (29.8)	**138.1 kg** (30.7)	**-3.7%** (5.6)
Mean (SD) body weight: Responders (n=12)	**144.7 kg** (32.6)	**130.7 kg** (33.5)	**-10.1%** (4.4)

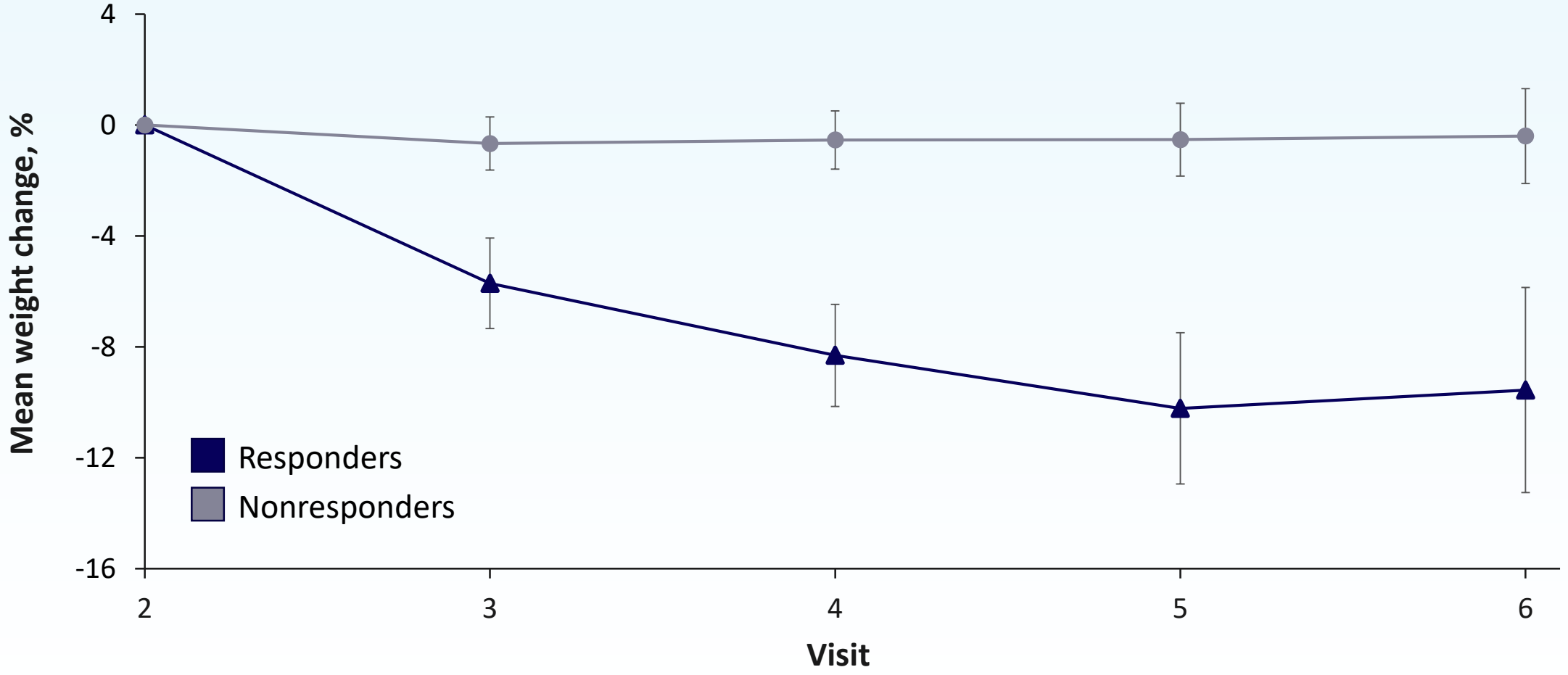
* Data include six patients who withdrew early, last observed value carried forward, as of Dec. 17, 2020.

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



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

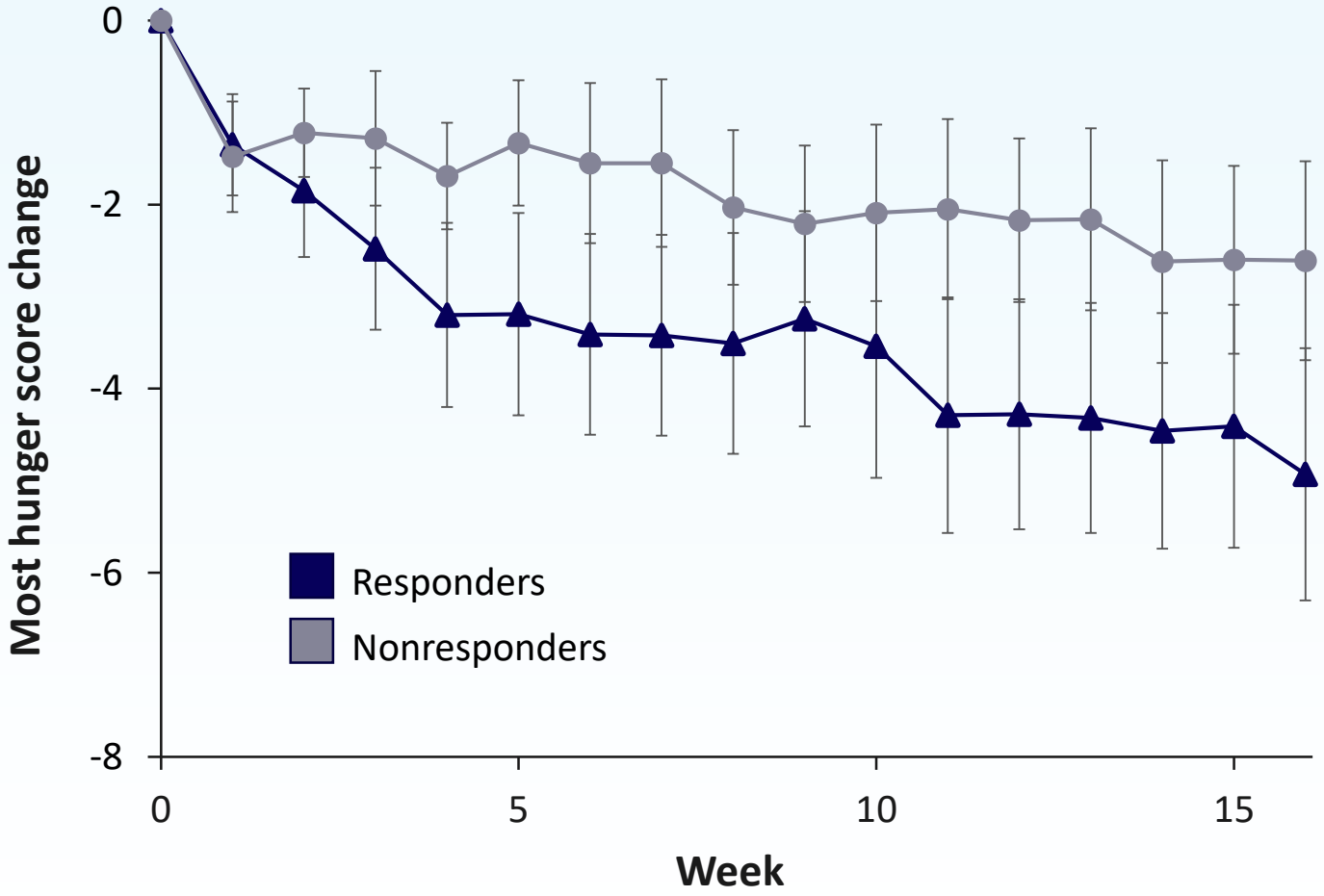
Percent Weight Loss Over Time
POMC/PCSK1/LEPR Heterozygous Deficiency Obesity



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)**
Nonresponders (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

	Responders, n (%)[a]	Nonresponders, 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.

Setmelanotide Achieved Proof of Concept in HETs

- Overall: Approximately 35% of patients responded with ≥5% weight loss at 12 weeks
- Strong separation between responders and non-responders supports three-step approach
- Enhanced responder rate seen within cohorts stratified by ACMG variant classification
- N221D represents potential expansion opportunity

SRC1 and SH2B1 Deficiency Obesity

Interim Efficacy Results

SRC1 and SH2B1 Patient Demographics – Completers Set

Baseline Characteristics	SRC1 (N=13)	SH2B1 (N=17)
Mean age (years) at enrollment (SD)	32 (18)	30 (15)
Range	12, 66	12, 60
Female	77%	58%
Male	23%	41%
Mean weight lbs (SD)	258 (44)	272 (60)
Range lbs	168, 313	161, 357
Mean weight kg (SD)	117 (20)	123 (27)
Range kg	76, 142	73, 162
BMI Mean kg/m^2 (SD)	44 (6)	44 (9)
Range	34, 55	32, 68

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.

Data cutoff date of Dec. 17, 2020.

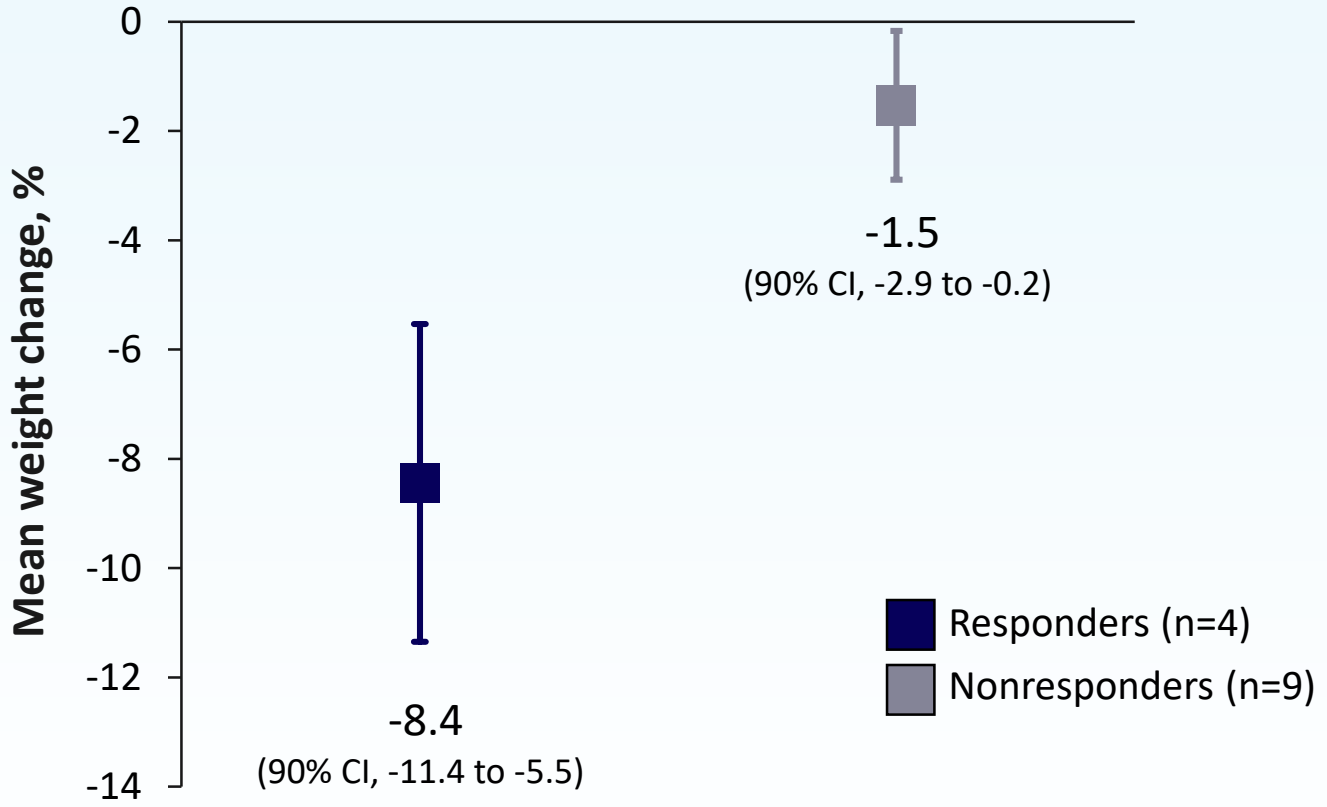
Response Rate and Weight Loss at Month 3 (Overall)
SRC1 Deficiency Obesity – Completers Set

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: Overall (n= 13)	**117.1 kg** (20.3)	**112.6 kg** (18.5)	**-3.7%** (4.0)
Mean (SD) body weight: Responders (n=4)	**116.6 kg** (29.1)	**106.4 kg** (24.6)	**-8.4%** (2.5)

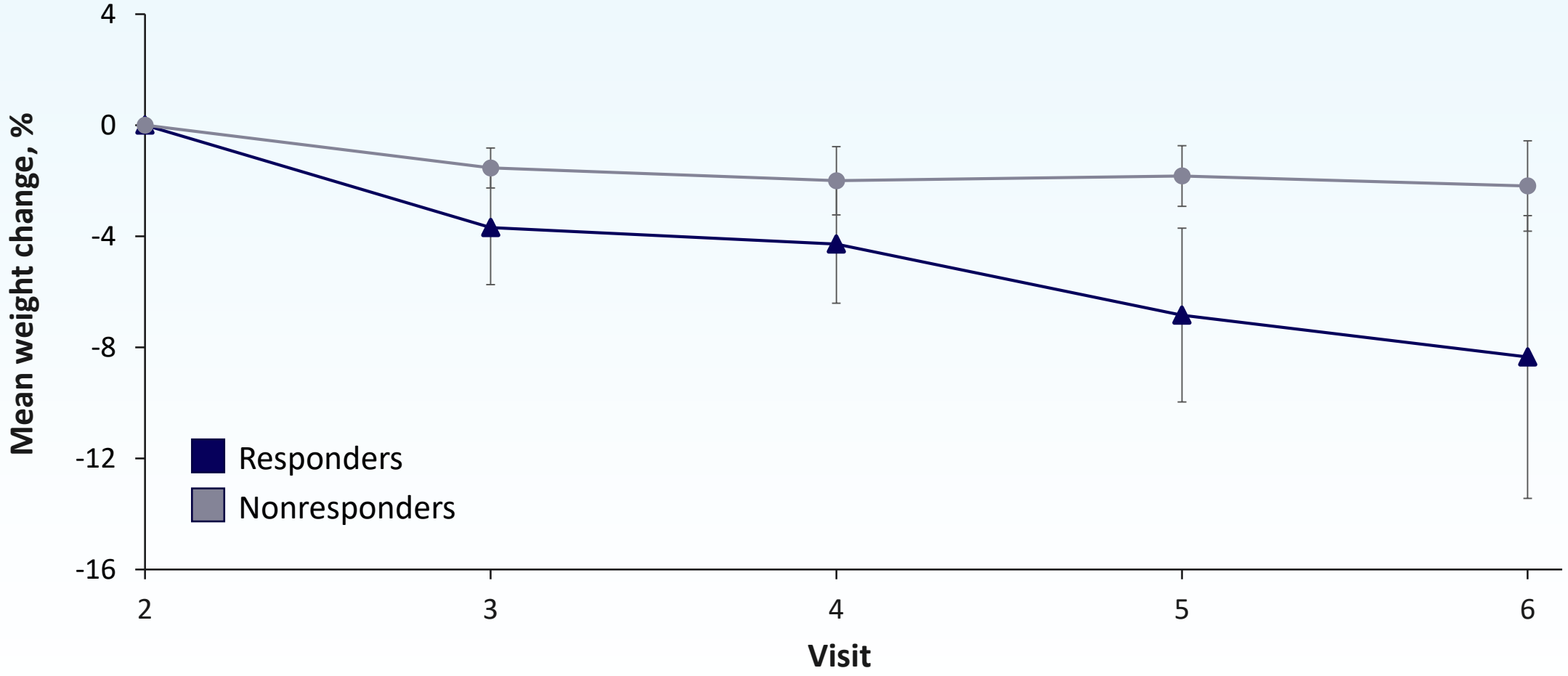
Interim data as of Dec. 17, 2020.

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



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

Percent Weight Loss Over Time
SRC1 Deficiency Obesity – Completers Set



Error bars represent the 90% confidence interval.

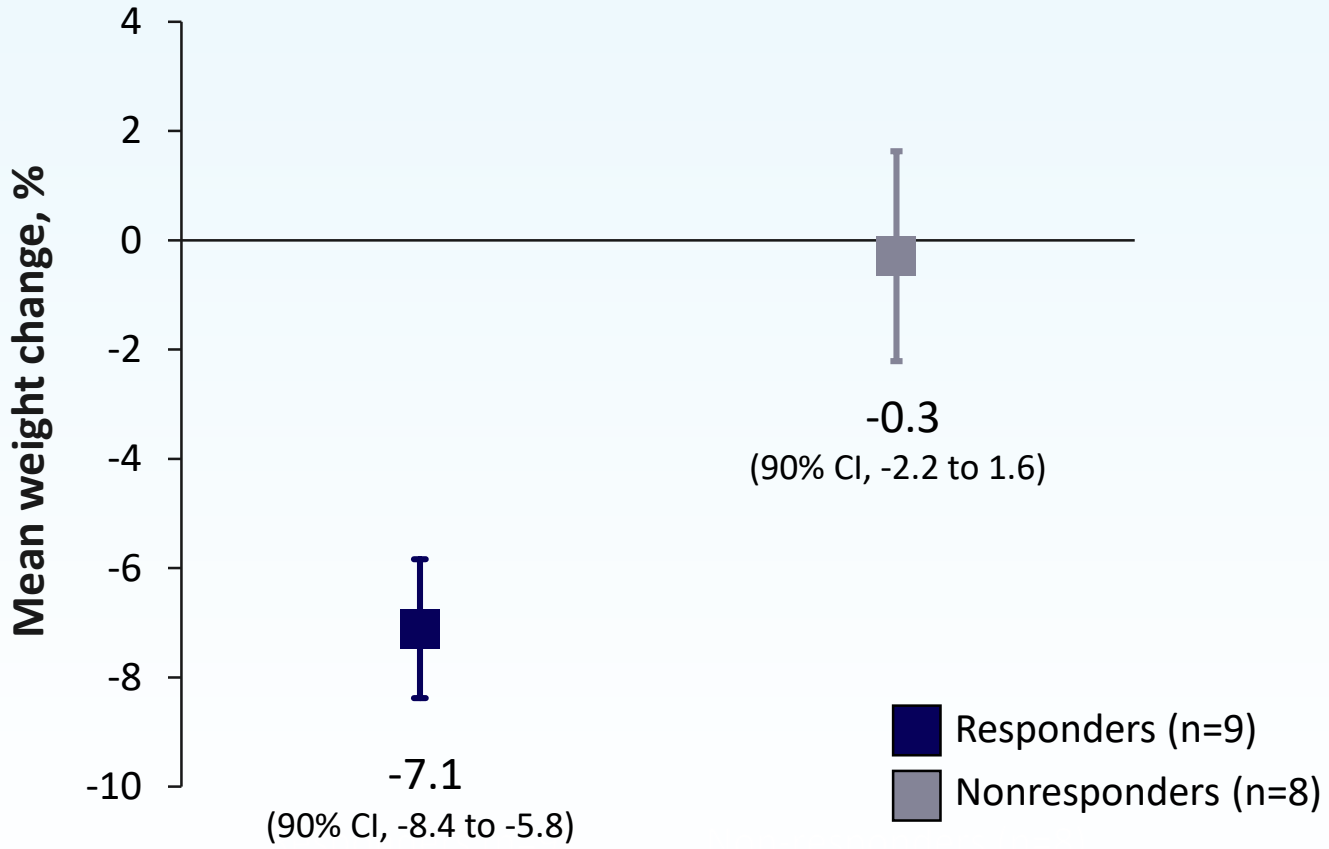
Response Rate and Weight Loss at Month 3 (Overall)
SH2B1 Deficiency Obesity – Completers Set

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: Overall (n=17)	**123.4 kg** (27.4)	**118.6 kg** (27.3)	**-3.9%** (4.2)
Mean (SD) body weight: Responders (n=9)	**123.6 kg** (28.1)	**114.8 kg** (26.4)	**- 7.1%** (2.1)

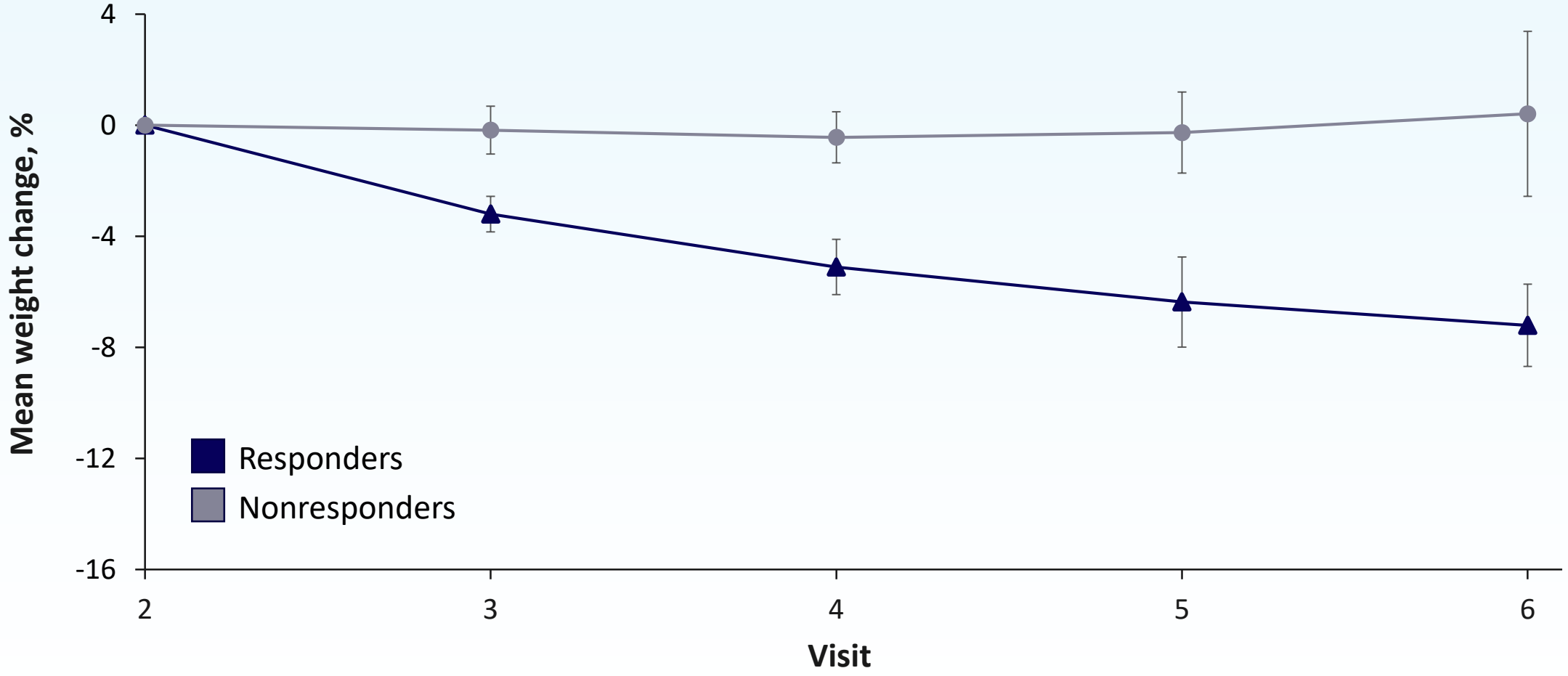
Interim data as of Dec. 17, 2020.

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



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

Percent Weight Loss Over Time
SH2B1 Deficiency Obesity – Completers Set



Error bars represent the 90% confidence interval.

Results of Setmelanotide Administration on Adults and Pediatric Patients

Setmelanotide and BMI-Z Scores for Pediatric BBS Patients in Phase 3 Trial

- BMI-Z score, or BMI standard deviation score, represents the number of standard deviations from median BMI by child age and sex.
- Setmelanotide achieved statistically significant and clinically meaningful improvements in BMI-Z scores in pediatric patients with obesity due to POMC, PCSK1 or LEPR deficiency.
- Setmelanotide achieved statistically significant and clinically meaningful improvements in BMI-Z scores in pediatric patients with BBS (predefined exploratory endpoint).

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

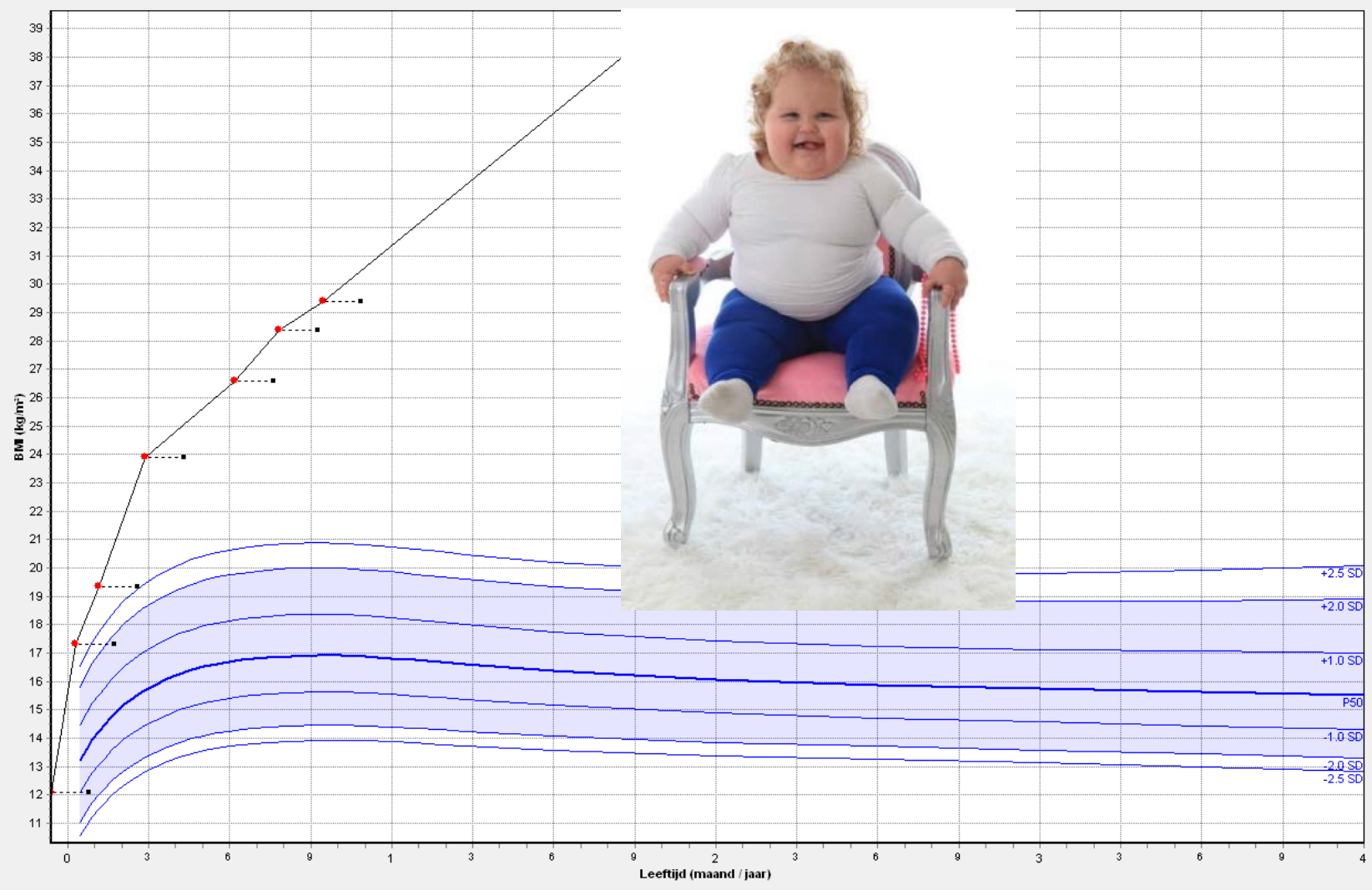
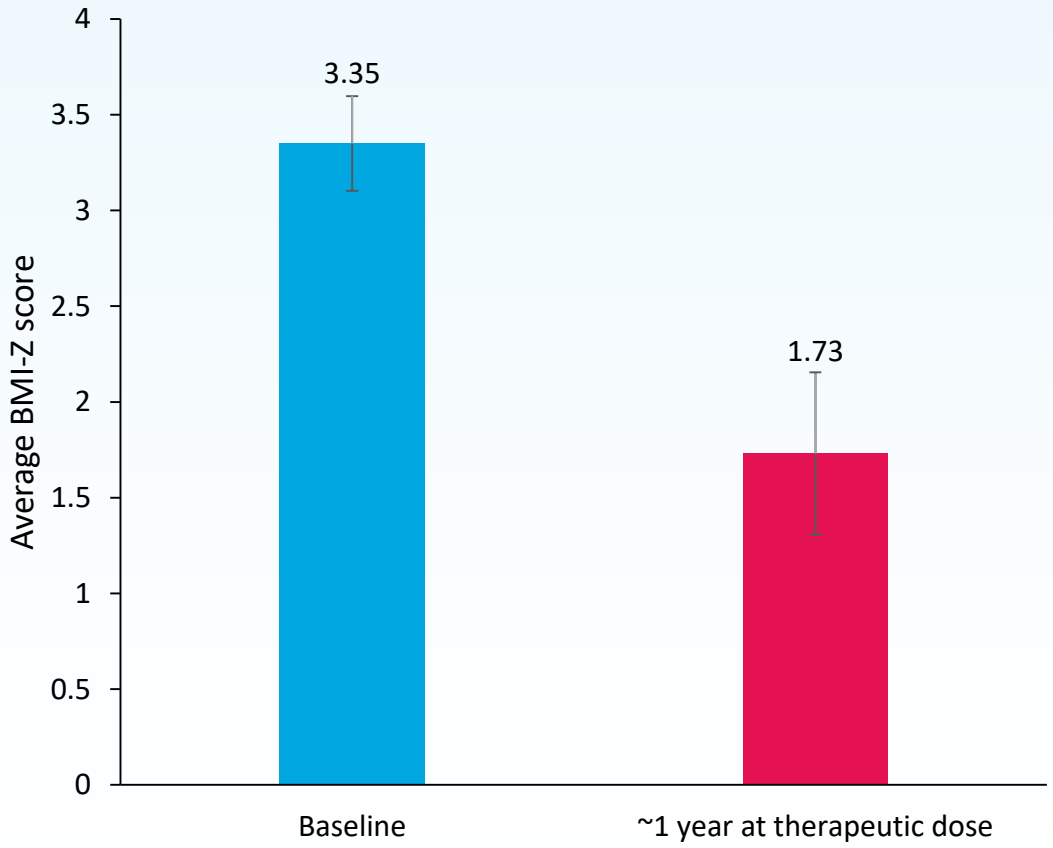


Chart adapted from Kleinendorst et al 2017
Data on file. Image used with permission.

Setmelanotide was Associated with Reductions in BMI and BMI-Z Score Over ~1 Year at Therapeutic Dose in POMC Patients

Participants aged <19 years (n=6)

Mean change from baseline: -1.6
Mean % change from baseline:-49.2%
(P=0.007)

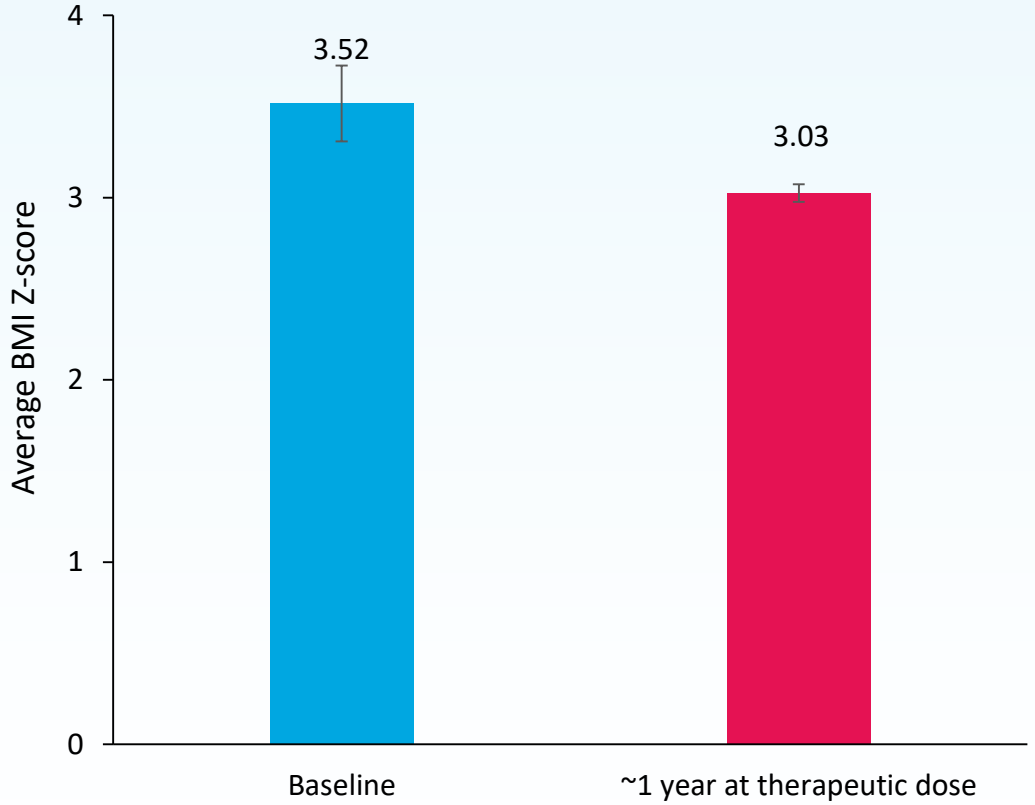


BMI, body mass index. Error bars are the standard error of the mean, which was calculated by dividing the standard deviation by the square root of N.

Setmelanotide was Associated with Reductions in BMI and BMI-Z Score Over ~1 Year at Therapeutic Dose in LEPR

Participants aged <19 years (n=3)

Mean change from baseline: -0.49
Mean % change from baseline: -13.35% (P=0.12)

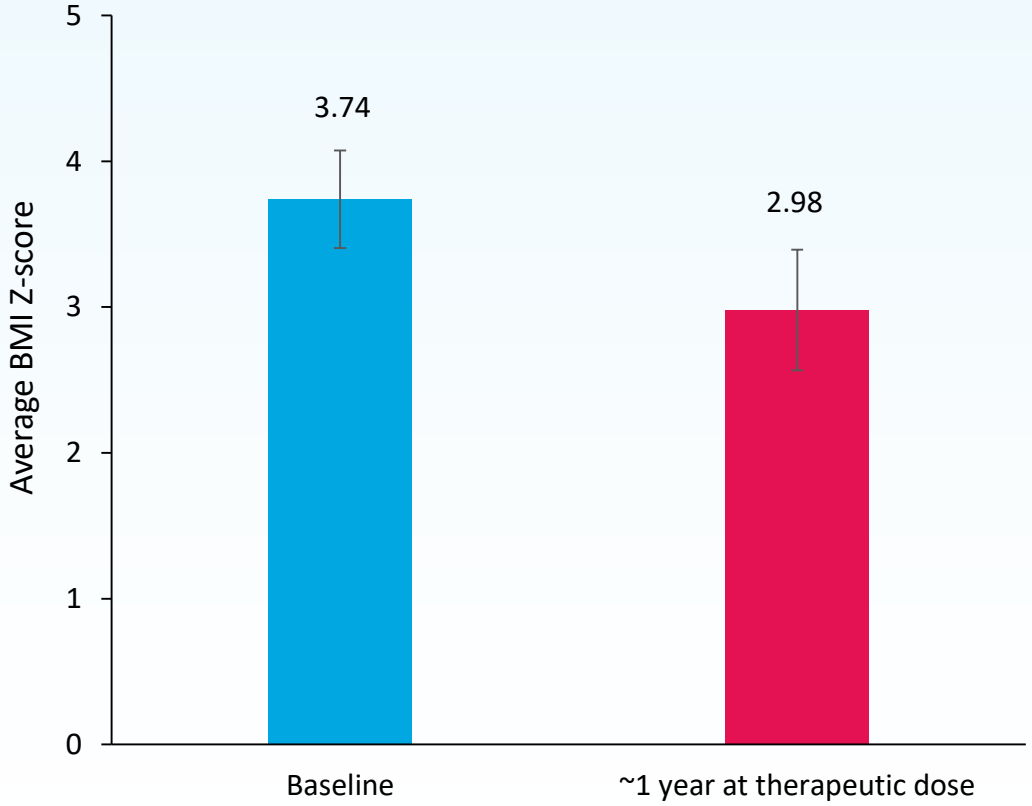


BMI, body mass index. One participant was not included in the ~1 year measurement due to discontinuation due to treatment-related adverse event.
Population includes imputed data based on linear mixed effect model from n=1 participant who died from a car accident after 26 weeks at therapeutic dose. BMI baseline analysis includes n=1 participant who withdrew from the study.
Error bars are the standard error of the mean, which was calculated by dividing the standard deviation by the square root of n.

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.

Safety Results Update

Setmelanotide Generally Well-tolerated Across Development Programs

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 have been mild:

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

Discontinuations have been rare; no meaningful increase in CV parameters

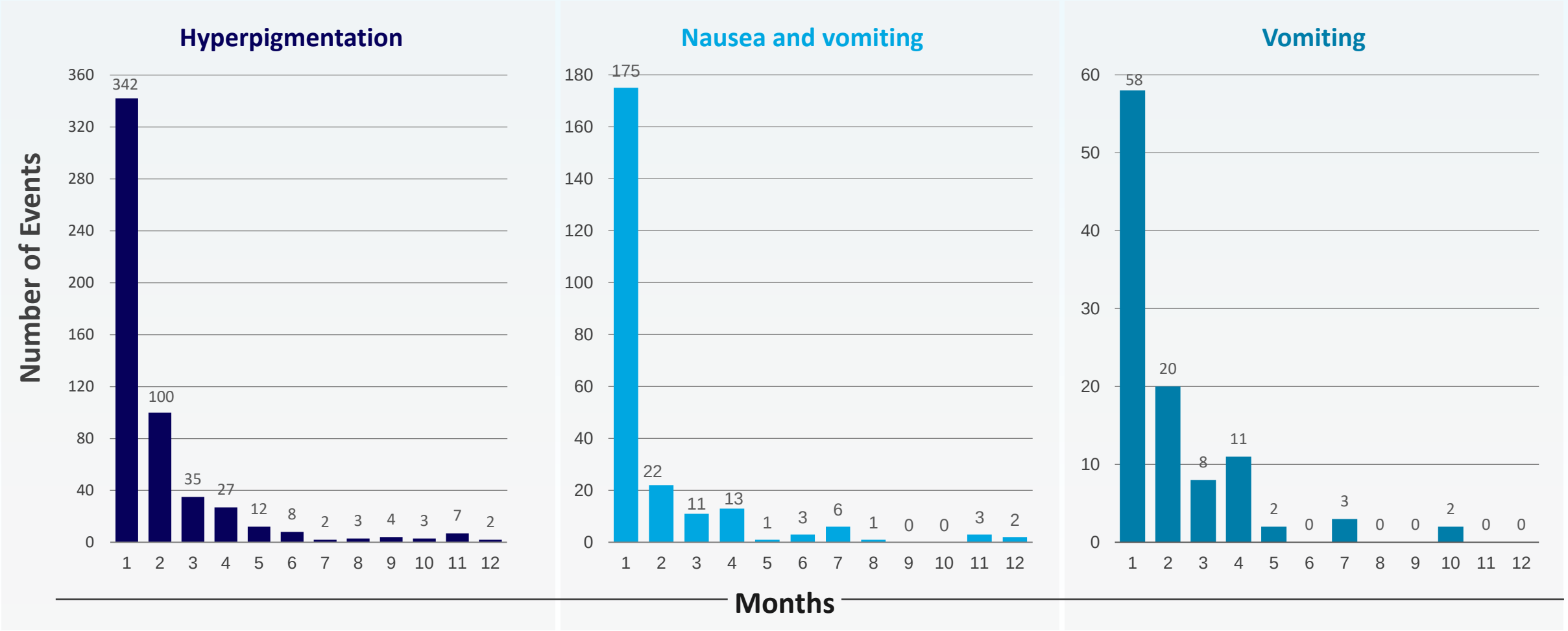
- In POMC and LEPR pivotal trials, setmelanotide was not associated with significant changes to blood pressure or heart rate

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



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

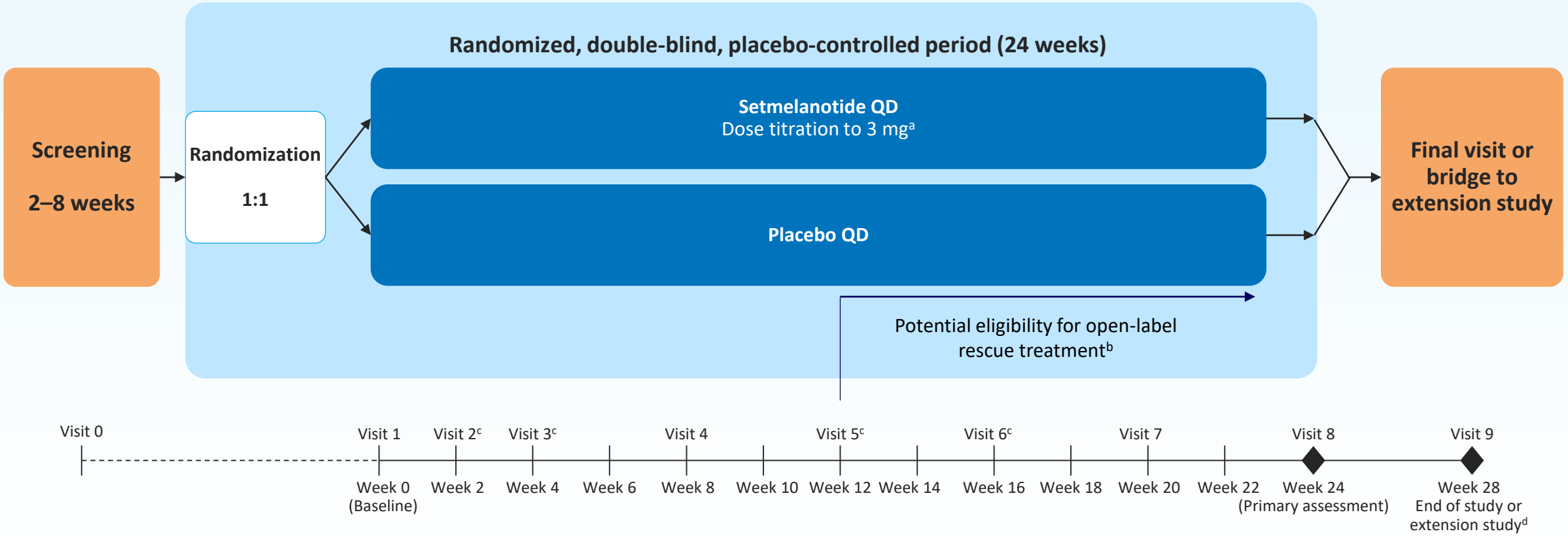
Rhythm PHARMACEUTICALS

Data Highlights from Exploratory Phase 2 Basket Study

- POC achieved in HETs (POMC, PCSK1 and LEPR), SRC1 and SH2B1 cohorts
- 30-50% of patients achieved >5% weight loss in 3 months
- Responders mean weight loss of 10% for HETs, 8% for SRC1 and 7% SH2B1
- Setmelanotide was generally well tolerated in these populations

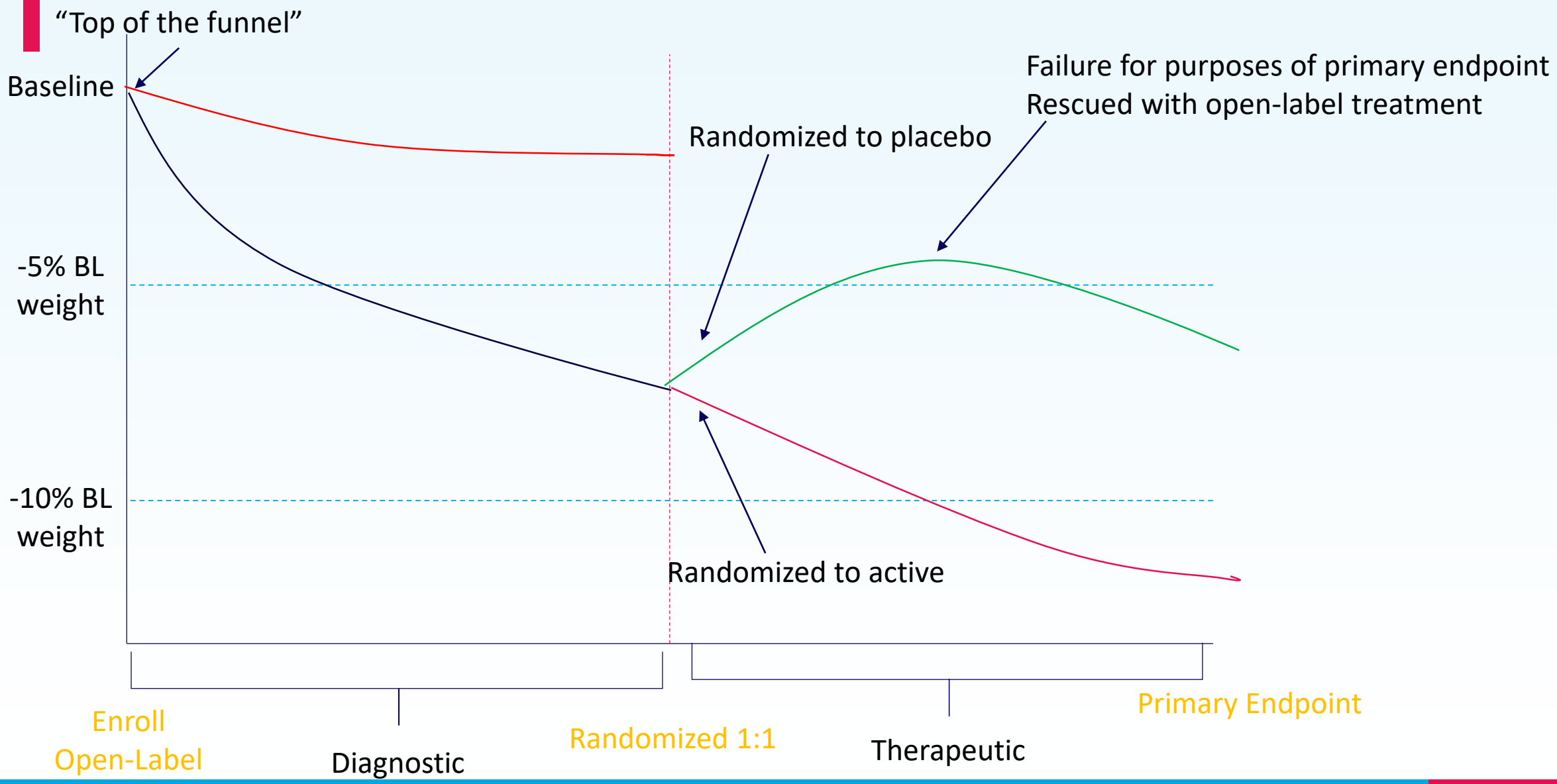
Future Clinical Plans

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.

Phase 2 MC4R Pathway Exploratory Study



Multiple Ongoing and Planned Clinical Trials to Advance Setmelanotide

1H2021

- Phase 2 Basket data - MC4R rescuable cohort
- Initiate Phase 2 study - hypothalamic obesity

2H2021

- Initiate Phase 3 MC4R Pathway Study - HETs, SRC1 and SH2B1
- Initiate exploratory MC4R Pathway Basket Study in 31 new genes
- Initiate pediatric study - children 2-6 years old
- Initiate registrational study - weekly formulation of setmelanotide

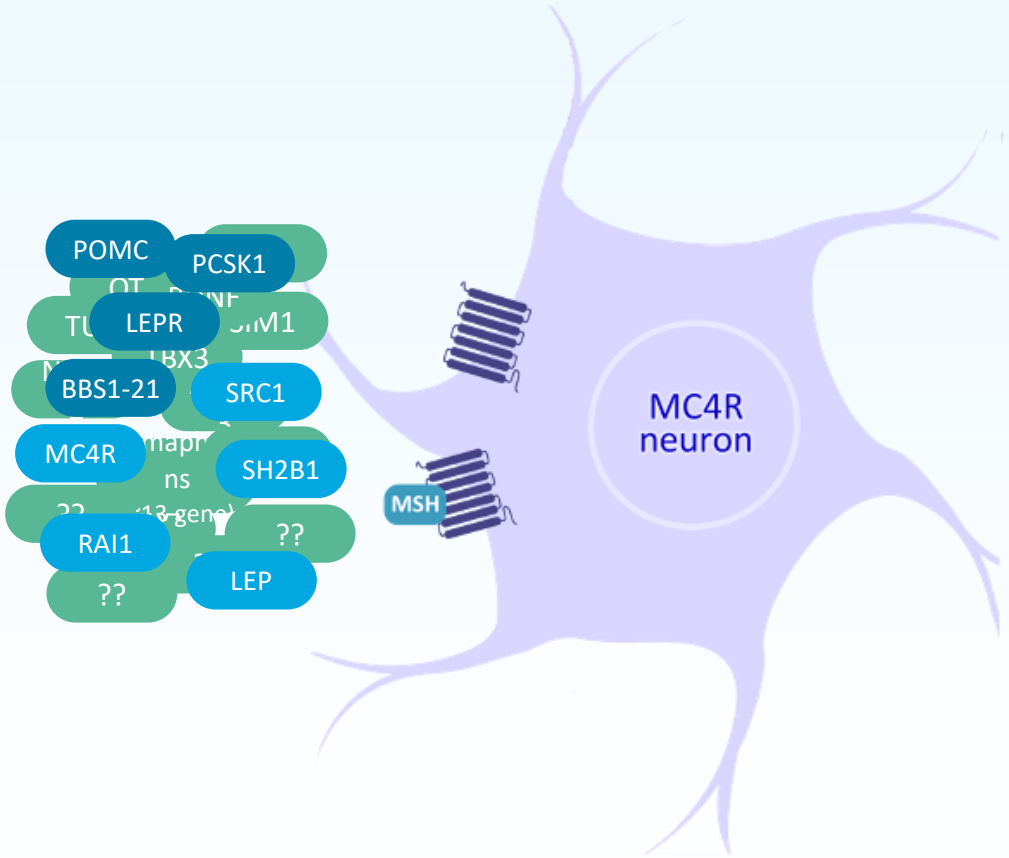
Translational Research and the MC4R Pathway

Al Garfield, Ph.D.

Head of Translational Research

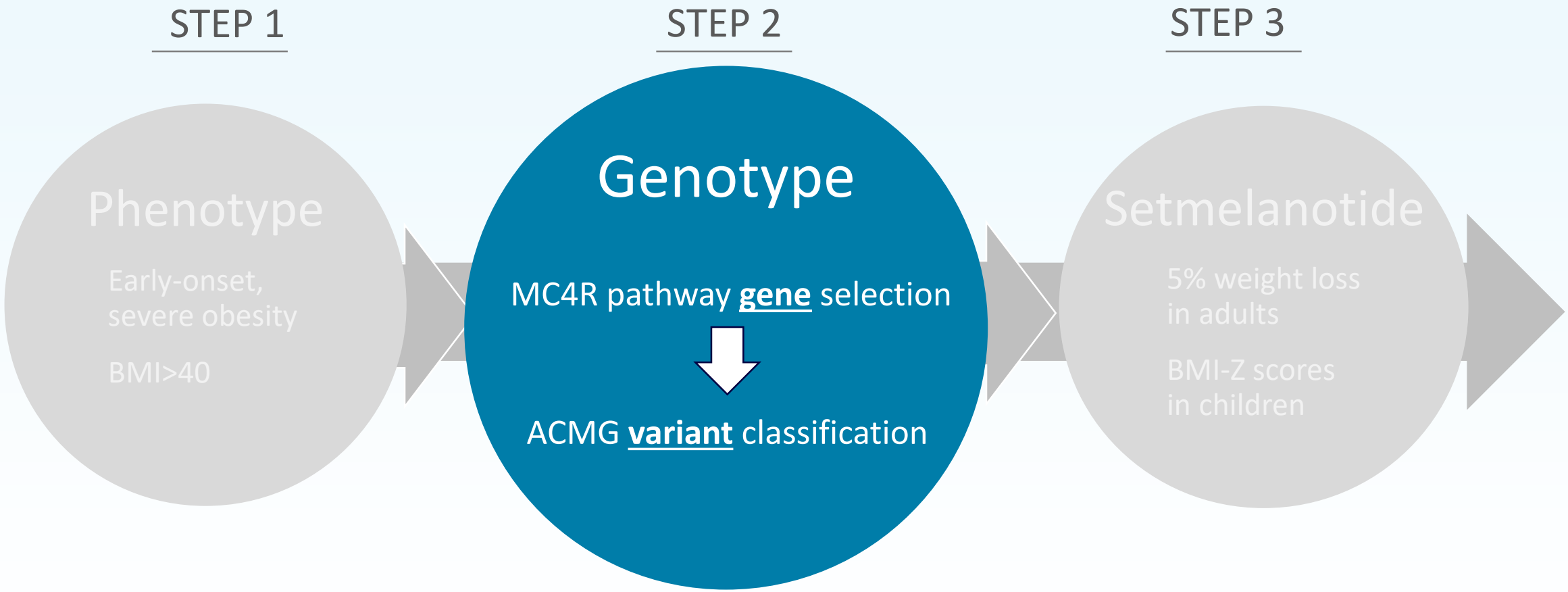
Basket Study Data Support Approach to Gene Selection

Preliminary data show responses in...



Gene	Indication	Mechanism	Setmelanotide Response
POMC	POMC deficiency obesity	Source of endogenous MC4R ligands	✓
PCSK1	POMC deficiency obesity	Enzyme required for production of MC4R ligands	✓
LEPR	LEPR deficiency obesity	Required for activation of POMC neurons	✓
BBSx	Bardet-Biedl Syndrome	Cilia genes required for POMC neuron activation	✓
ALMS1	Alstrom Syndrome	Cilia genes required for POMC neuron activation	?
PPL	HET obesity	Single variant of POMC, PCSK1 or LEPR	✓
SRC1	SRC1 deficiency obesity	Transcriptional activator of POMC	✓
SH2B1	SH2B1 deficiency obesity	Positive regulator of LEPR	✓
RAI1	Smith-Magenis Syndrome	Transcription factor of MC4R-pathway genes	?
MC4R	MC4R deficiency obesity	Receptor for POMC ligands	?

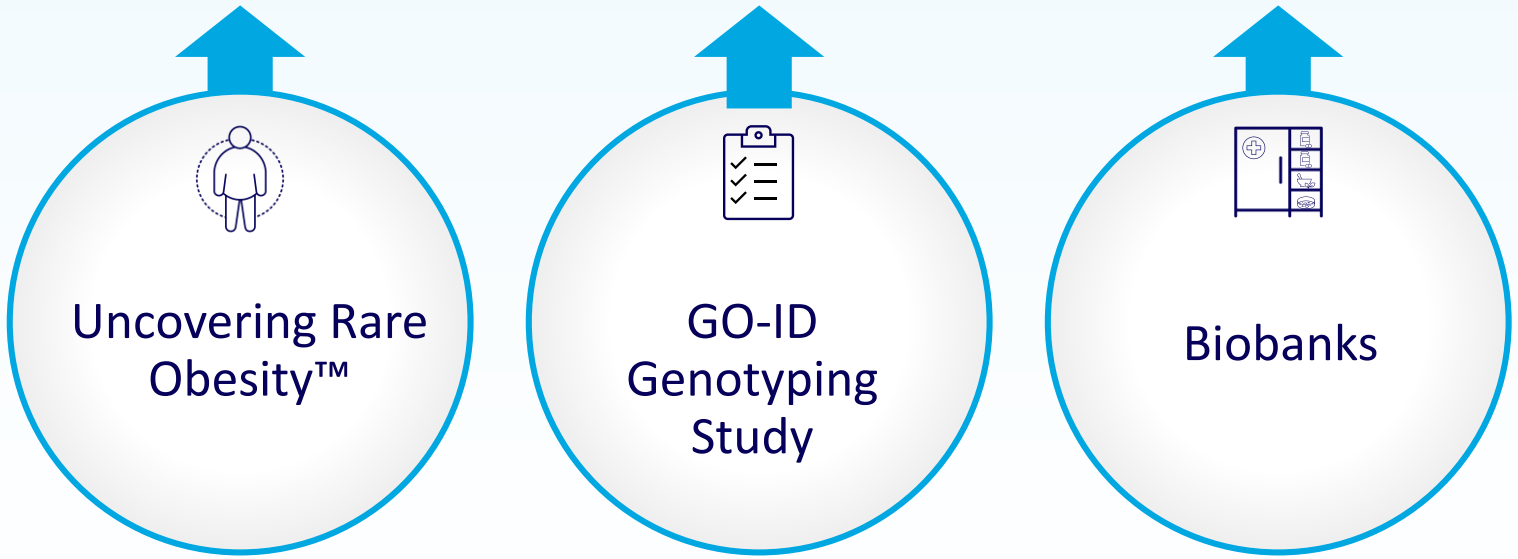
Expanded Opportunity Defined by Clinical Phenotype and MC4R Pathway Genotype



Sequencing Infrastructure Critical to Changing the Paradigm for Rare Genetic Disorders of Obesity

~37,500*

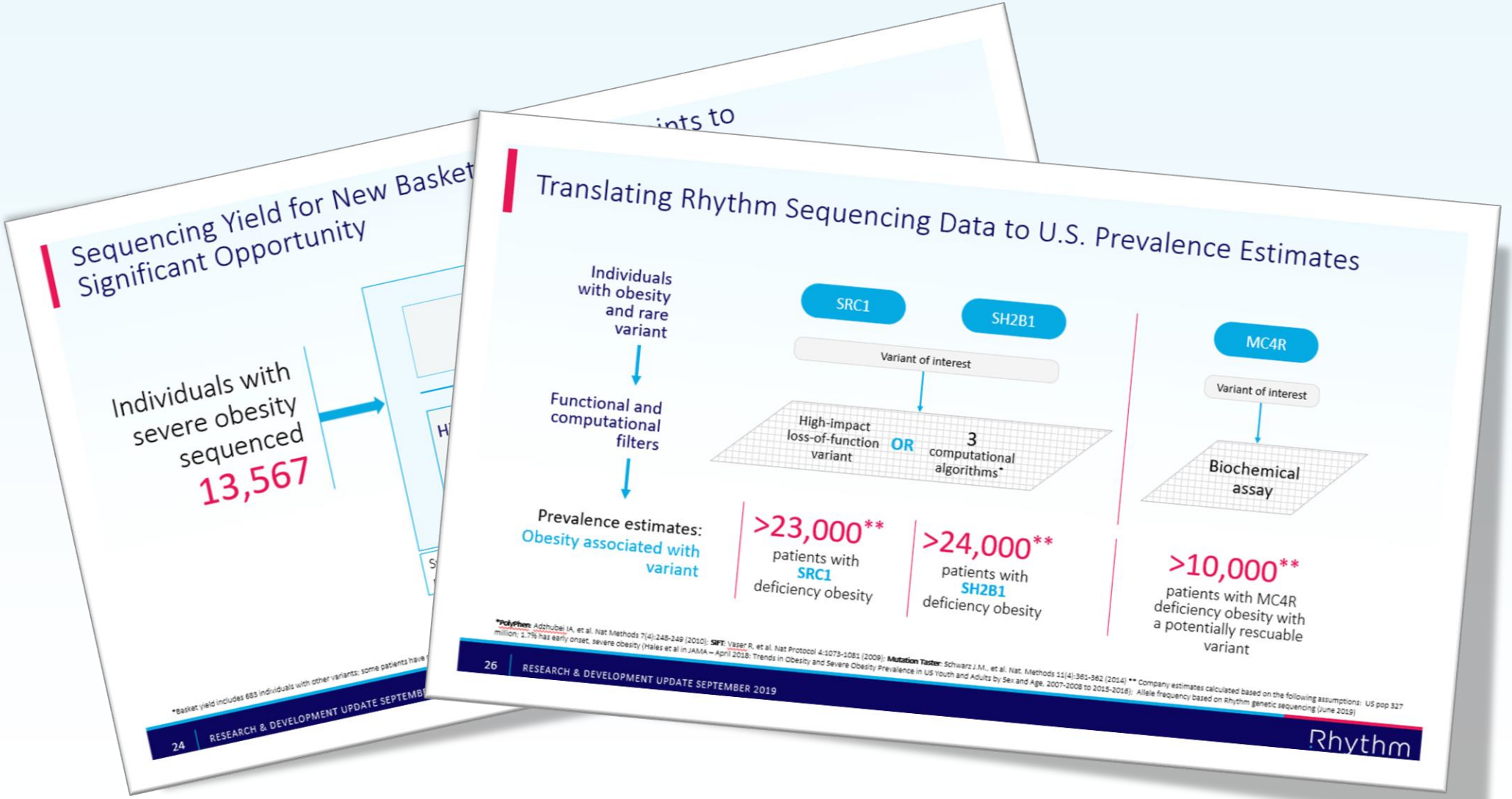
Sequencing samples in Rhythm's DNA database



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

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

First Steps in 2019 Leveraged Scientifically Rationalized Filters



Rhythm PHARMACEUTICALS

Not All Variants are Created Equal: Understanding the ACMG Variant Classification Guidelines*

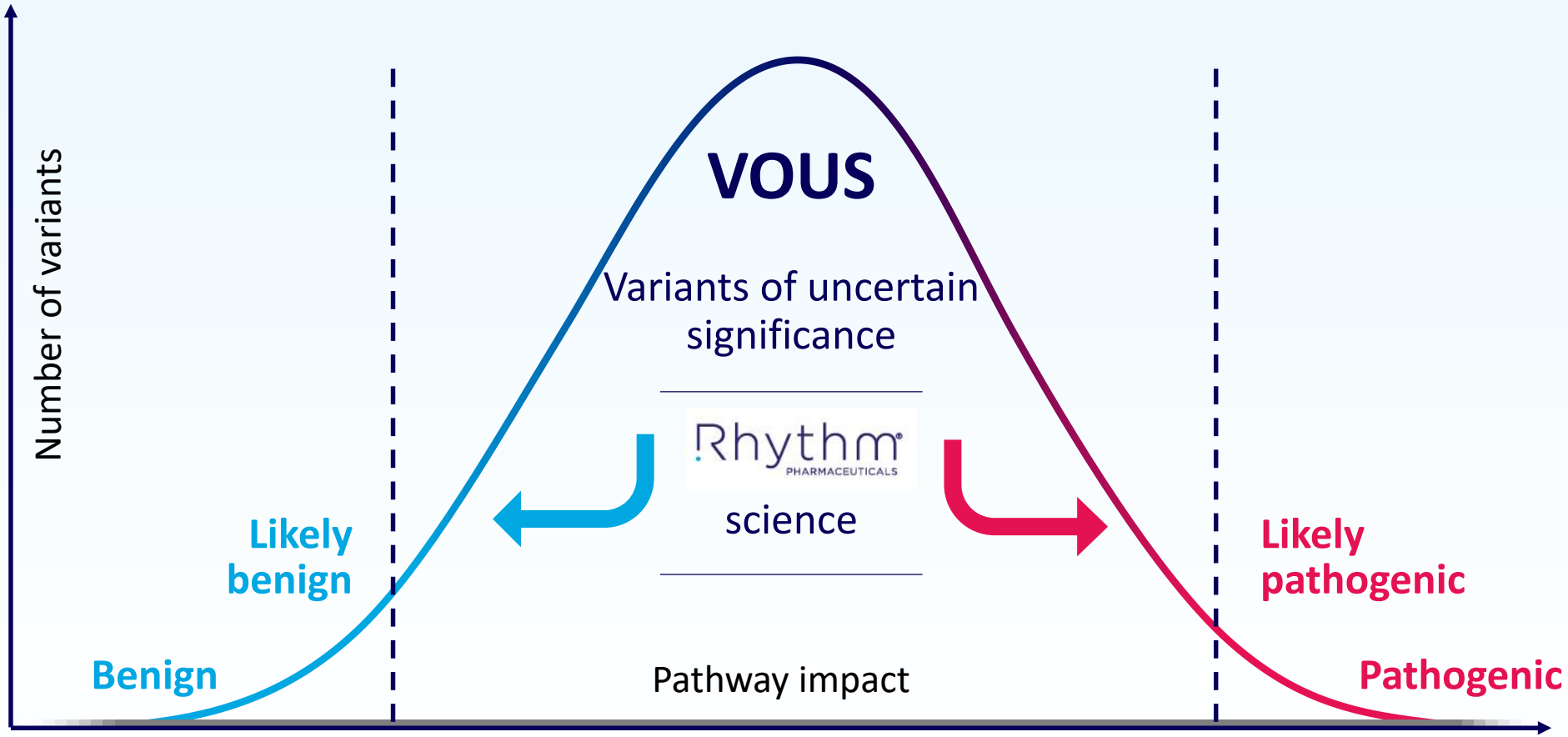
Pathogenic

Likely Pathogenic

VOUS

Likely Benign

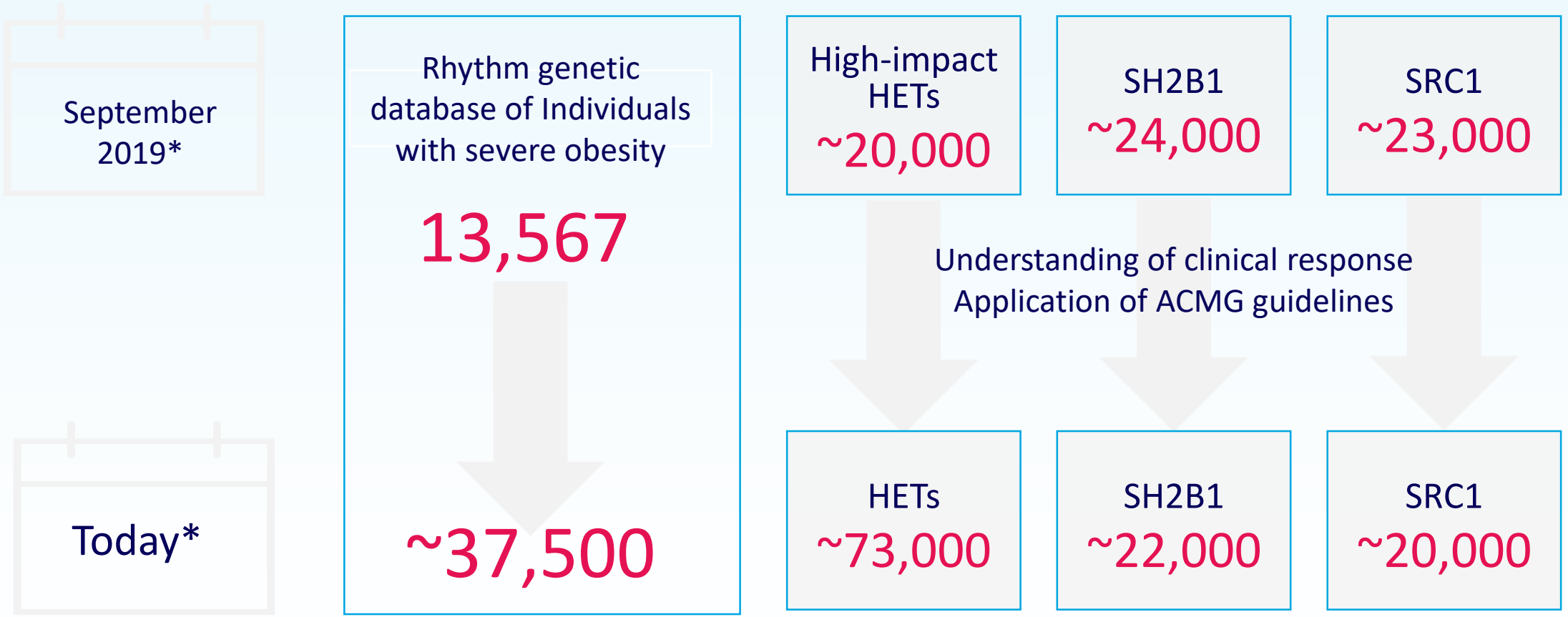
Benign



*ACMG Guidelines Richards et al, 2015

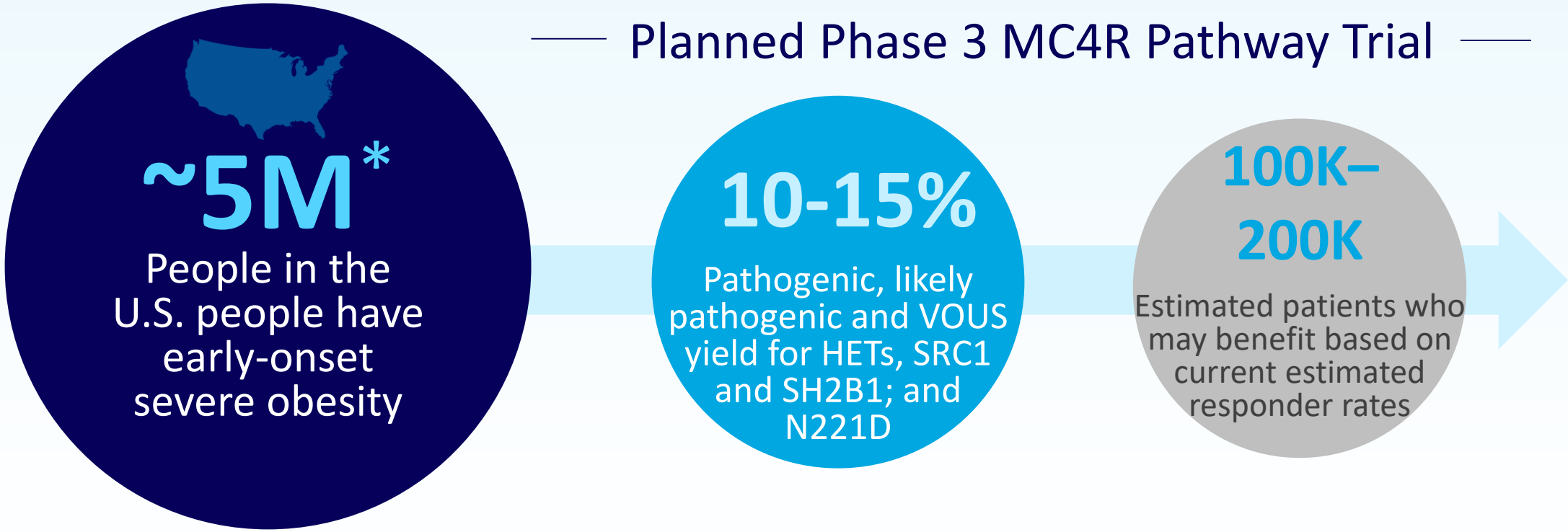
Rhythm PHARMACEUTICALS

Clinical Response Data Helps Refine Estimated Addressable U.S. Patients



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

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)

Rhythm PHARMACEUTICALS

Validated Gene Selection Process Offers Expanded Opportunity

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

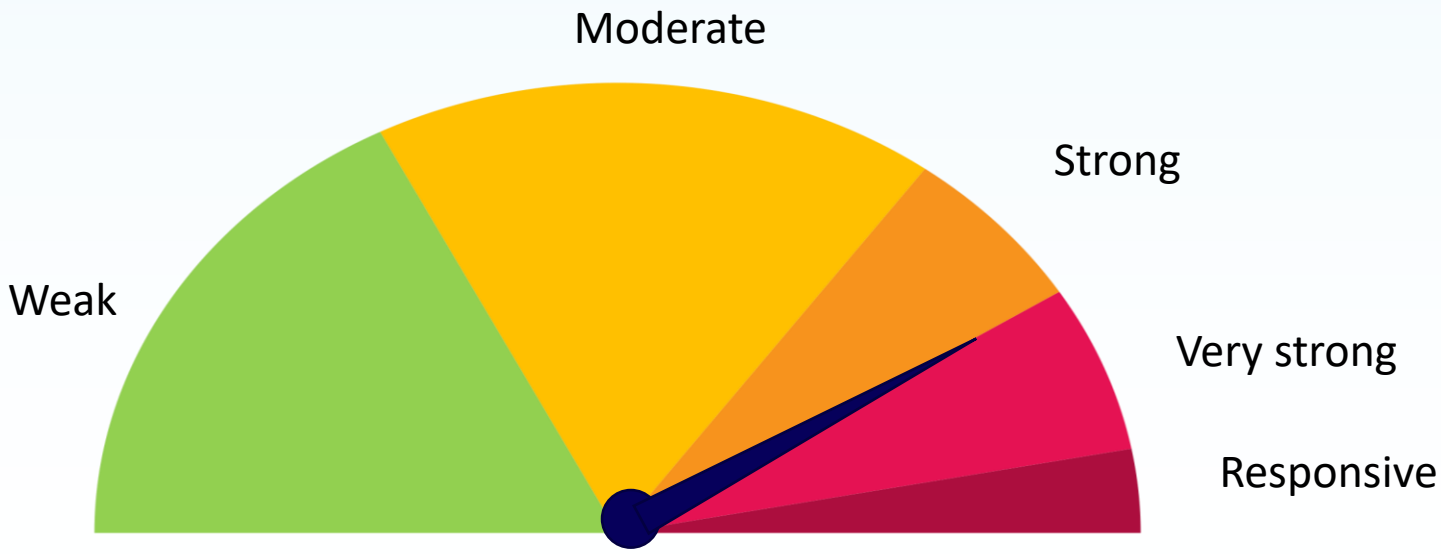
Functional rescue

Weight

Obesity-related epidemiology

Weight

Clinical response



*Strande et al., 2017

Genes that Graduated to Phase 3 Categorized as Strong or Very Strong

Validation of Approach

Rhythm gene	Gene expression	Gene molecular/cellular function	Gene physiological function	Functional rescue	Genetic epidemiology	Strength of pathway relevance	SET preliminary response in clinical study
POMC	✓	✓	✓	✓	✓	Very strong	✓
PCSK1	✓	✓	✓	?	✓	Strong	✓
LEPR	✓	✓	✓	✓	✓	Very strong	✓
SRC1	✓	✓	✓	?	✓	Strong	✓
SH2B1	✓	✓	✓	?	✓	Strong	✓
MC4R	✓	✓	✓	✓	✓	Very strong	?
RAI1	✓	✓	✓	?	✓	Strong	?
BBSx	✓	✓	✓	✓	✓	Very strong	✓
ALMS1	✓	?	✓	?	✓	Moderate	?

Translational Research Feeds Clinical Development

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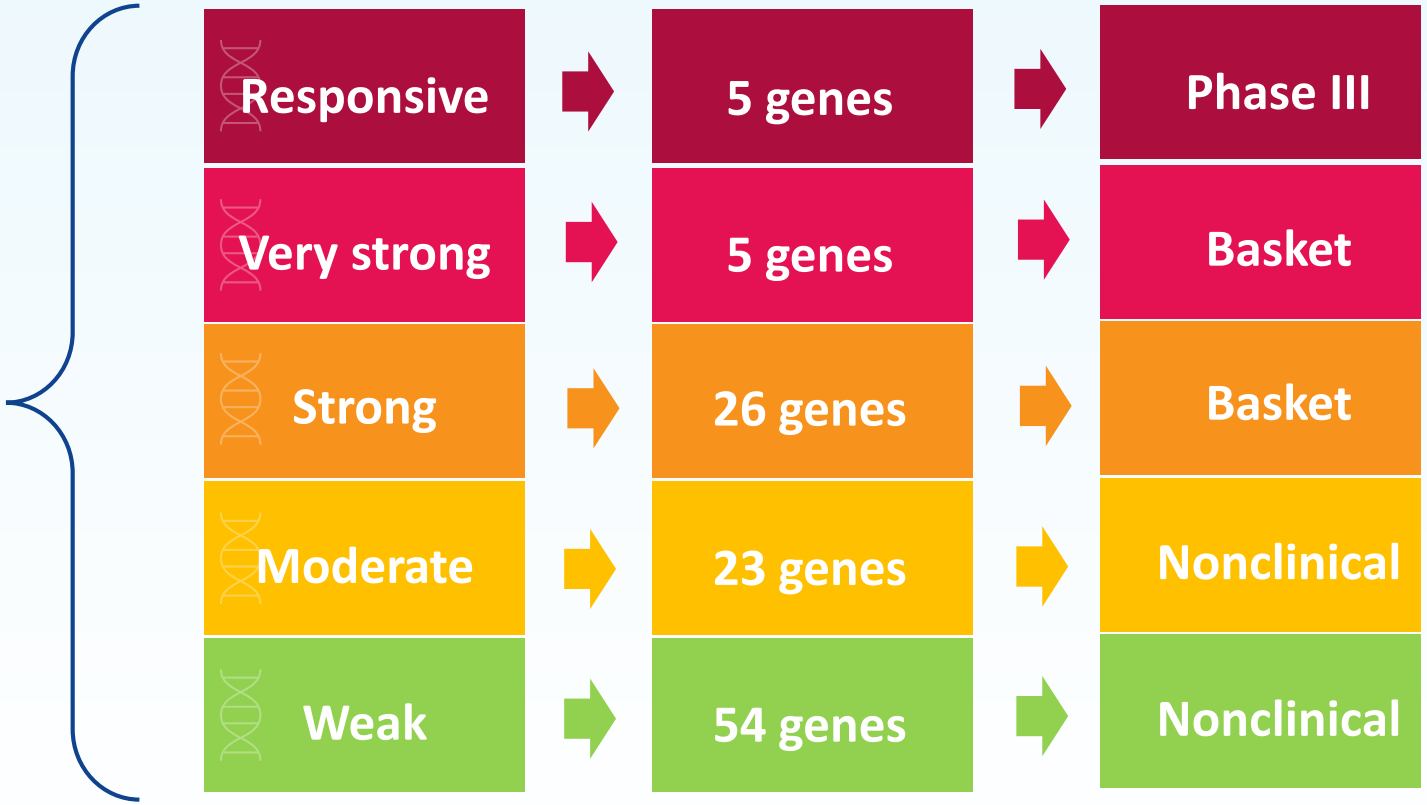
Genes with potential ties to MC4R pathway



Rhythm PHARMACEUTICALS

On Leading Edge of Genetic Obesity and Learning along the Way

- Phase 2 Basket Trial proof-of-concept data supports our gene selection approach
- Largest known genetic obesity database of approximately 37,500 individuals
- Clinical response rates and ACMG classification clarify addressable population estimates
- Data support gene selection and build confidence in our plans to initiate a new expanded Basket Trial with 31 new genes

Conclusion

David Meeker, M.D.
Chair, Chief Executive Officer and President

Now Approved in the United States

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.

Transformational Progress Anticipated 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

Today's Focus: Proof of Concept Achieved in Basket Indications with Significant Potential Market Opportunity

- Rhythm's largest data readout from five genetic cohorts with 65 patients
- Proof of concept achieved in five MC4R pathway genes
- Estimated U.S. target patient population across these five genes expanded to 100K-200K
- Largest known genetic obesity database of approximately 37,500 individuals
- Support of our approach for gene selection and variant classification
- Two new trials planned for MC4R pathway diseases in a total of 36 genes


Rhythm
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