Rhythm Pharmaceuticals

September 2024

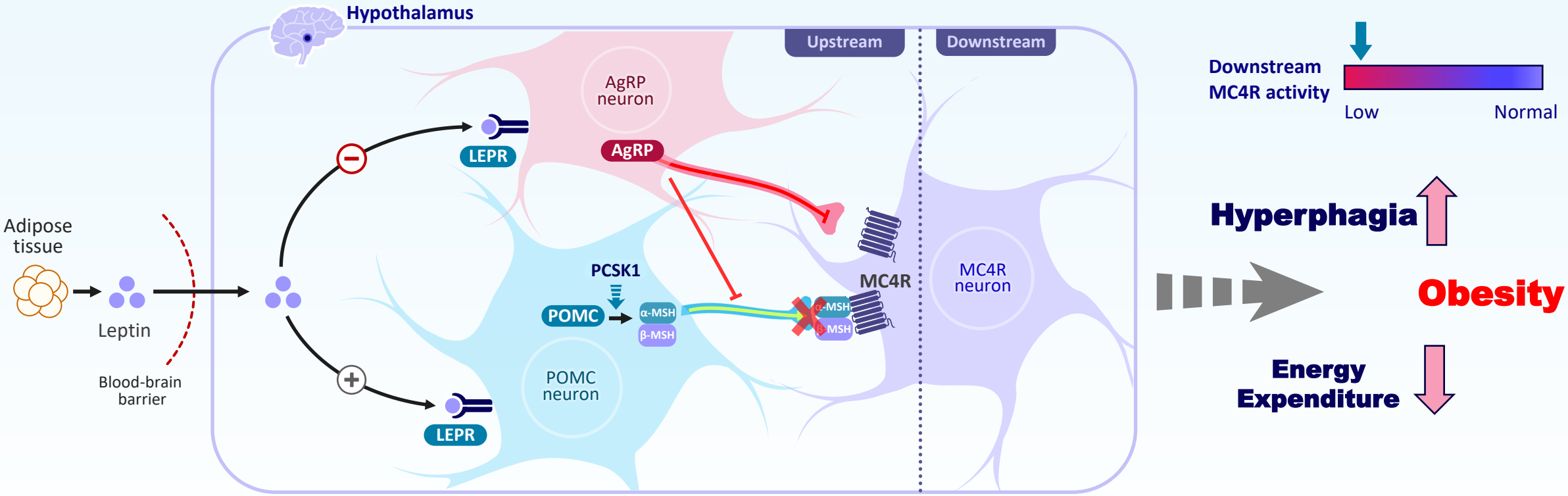
Forward Looking Statements

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, RM718 and LB54640, 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 and LB54640, the potential timing, payments due, and benefits of the global licensing agreement for LB54640 including with respect to the consummation of the transaction, expectations regarding the design, enrollment, or outcome of clinical trials of LB54640, the ability to reach any net sales or revenue milestones, obtaining regulatory approvals in connection with the global licensing agreement, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, anticipated milestones, our future financial performance and 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.

Rhythm's Value Drivers

1. BBS global commercial execution
2. Hypothalamic obesity offers a significant expansion opportunity
3. Advancing clinical development pipeline with new MC4R agonists, disease states

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



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

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

Rhythm® PHARMACEUTICALS

Hyperphagia and Early-onset Obesity Have a Significant Impact on Patients and their Families

IMCIVREE Patient Ambassador program launched with 8 patient/caregiver speakers

"I was hungry all day long. I even started sneaking food in the middle of the night because my mind was constantly on my hunger."

"Prior to IMCIVREE, I didn't realize how much of my mental energy was consumed by my hunger. I'm able to free up my mind and do more enjoyable things with my life."

Kathryn, Diagnosed with BBS at 6 years old

BORN WITH:

Autosomal recessive polycystic kidney disease (diagnosed in utero), polydactyly

2 YEARS OLD:

Visual impairment and developmental delays emerge

6 YEARS OLD:

Pronounced hyperphagia; clinical presentation prompted BBS diagnosis via genetic testing

TEEN YEARS:

Hyperphagia, obesity, and visual deficits worsen

28 YEARS OLD:

IMCIVREE prescribed by PCP

Clinical Development Programs Designed to Expand Opportunity in Hyperphagia and Severe Obesity

Approved in U.S., EU,+

4,000 - 5,000*
Bardet-Biedl syndrome

600 – 2,500*
POMC, PCSK1 and LEPR deficiencies

In ongoing Phase 3 trials

5,000 - 10,000*
Hypothalamic obesity

~53,000*
EMANATE genetic indications

Phase 2 DAYBREAK trial

Positive signals observed in **six new genes and gene families**

*Estimated prevalence of U.S. patients based on company estimates; does not include ex-U.S. prevalence estimates. Estimated U.S. patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results that factor in variant classifcations, as applicable, current estimated responder rates and that 1.7% of the U.S. population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018ł); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017).

Multiple Ongoing Programs in Rare Neuroendocrine Diseases

	Patient Population	Pre-clinical	Phase 1/2	Phase 3	Commercially Approved
IMCIVREE™ (setmelanotide) injection	POMC, PCSK1 or LEPR (PPL) deficiency				
	Bardet-Biedl syndrome (BBS)				
Setmelanotide *daily formulation*	Hypothalamic obesity		Enrollment complete		
	Emanate				
	Pediatrics (age 2 to <6 years, POMC or LEPR deficiency obesity or BBS)				
	Daybreak				
LB54640	Hypothalamic obesity				
RM-718	Rare pathway diseases				
Pre-clinical	Congenital Hyperinsulinism (CHI)				

Complete Denotes study underway Denotes planned study

Rhythm® PHARMACEUTICALS

Rhythm Leadership – Strong Team with Broad Biopharma Experience

David Meeker, MD
Chair, President and Chief Executive Officer

25-plus years; focus on rare genetic disease treatments, including Aldurazyme®, Fabrazyme® and Myozyme®

Hunter Smith
Chief Financial Officer

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

Jennifer Lee
Executive Vice President, Head of North America

20-plus years leading global commercial strategy in rare diseases

Yann Mazabraud
Executive Vice President, Head of International

20-plus years leading global commercial strategy in rare diseases

Joe Shulman
Chief Technology Officer

20-plus years experience leading CMC, supply chain planning and quality assurance and control

Alastair Garfield, PhD
Chief Scientific Officer

20 years experience in neurobiology of appetite /body weight regulation; rare disease drug discovery

Well Capitalized: Cash Sufficient to Fund Planned Operations into 2026

$319.1 Million

cash equivalents and short-term investments as of June 30, 2024

Guidance

Cash on hand expected to be sufficient to fund operations into **2026**[1]

61.1 Million

Common shares outstanding as of June 30, 2024

Analyst coverage[2]

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

[2]Analyst coverage includes all brokerage firms known by the company as of March 2024 to have analysts covering the company. This list may not be complete and is subject to change. Analyst opinions, estimates or forecasts are their own and may not represent the opinions, estimates or forecasts of the company.

What's New? Continued Strong Execution in 2024

Commercial progress

- Steady QoQ revenue growth
- Positive decision for BBS from NICE

Hypothalamic obesity

- Ph3 topline data on track for 1H2025
- First patient in Japanese cohort in Ph3 trial dosed

Next-generation MC4R agonists

- First patient dosed in Ph2 trial of oral LB54640 in hypothalamic obesity
- RM718 Ph1 SAD, MAD cohorts advancing

Advancing IMCIVREE Label Expansion to Treat 2-6yo Patients in Europe and United States

- ✓European Commission expanded IMCIVREE marketing authorization to include children as young as 2 years old
- ✓Completed sNDA submission to FDA in 2Q 2024; anticipated PDUFA date by the end of 2024

Ph3: Clinically Meaningful Reductions in BMI, BMI-Z in 2-<6yo Patients with POMC/LEPR Deficiency or BBS

83.3% (10 of 12)

of all patients achieved ≥0.2 reduction in BMI-Z score from baseline to Week 52

-18.380%

Mean percent change from baseline in BMI at Week 52

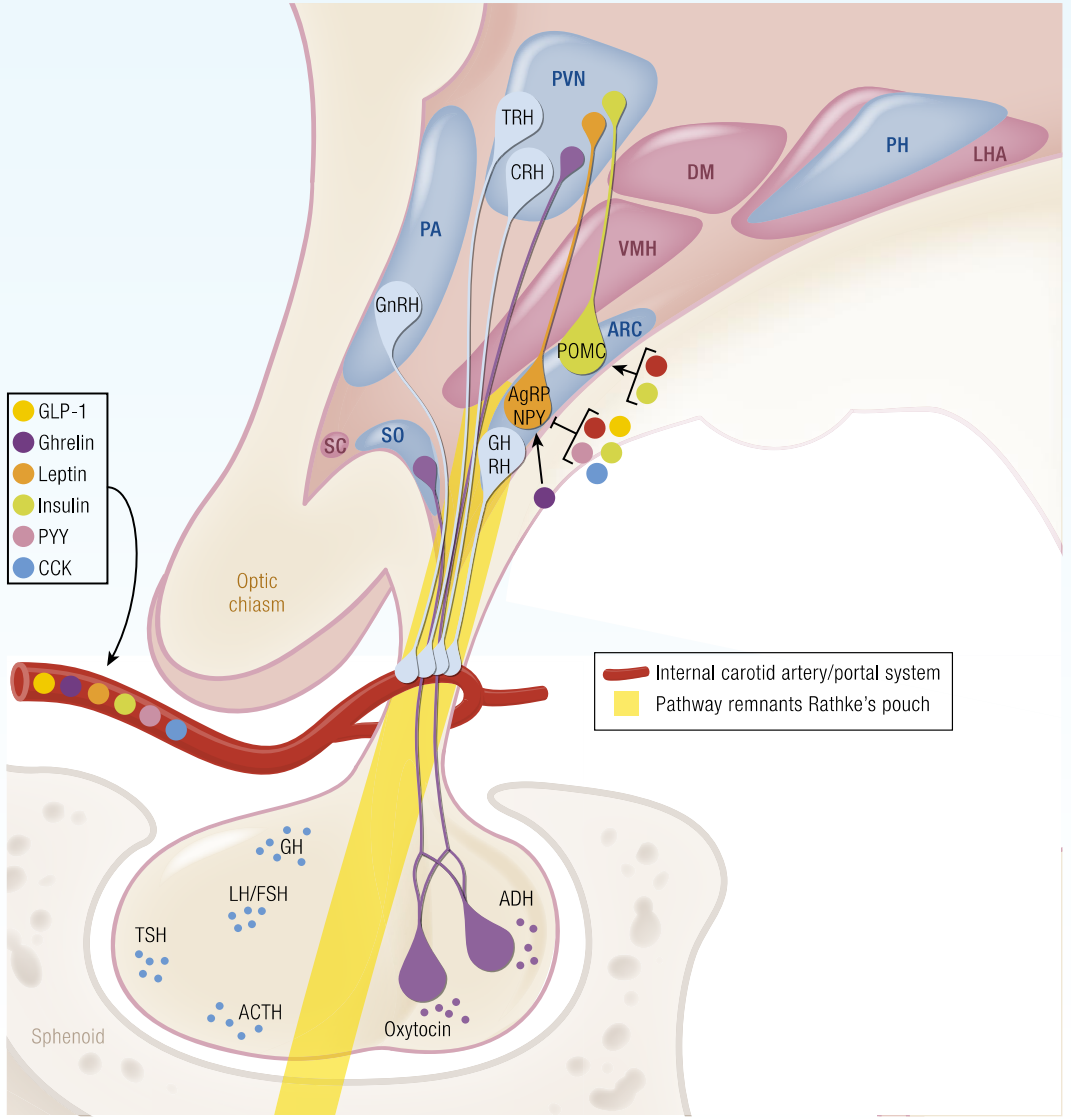
Hypothalamic Obesity

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

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

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

No approved treatments available



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

Rhythm® PHARMACEUTICALS

Setmelanotide and Hypothalamic Obesity: A Transformative Opportunity for Rhythm

5,000 – 10,000*

patients

Estimated U.S. prevalence

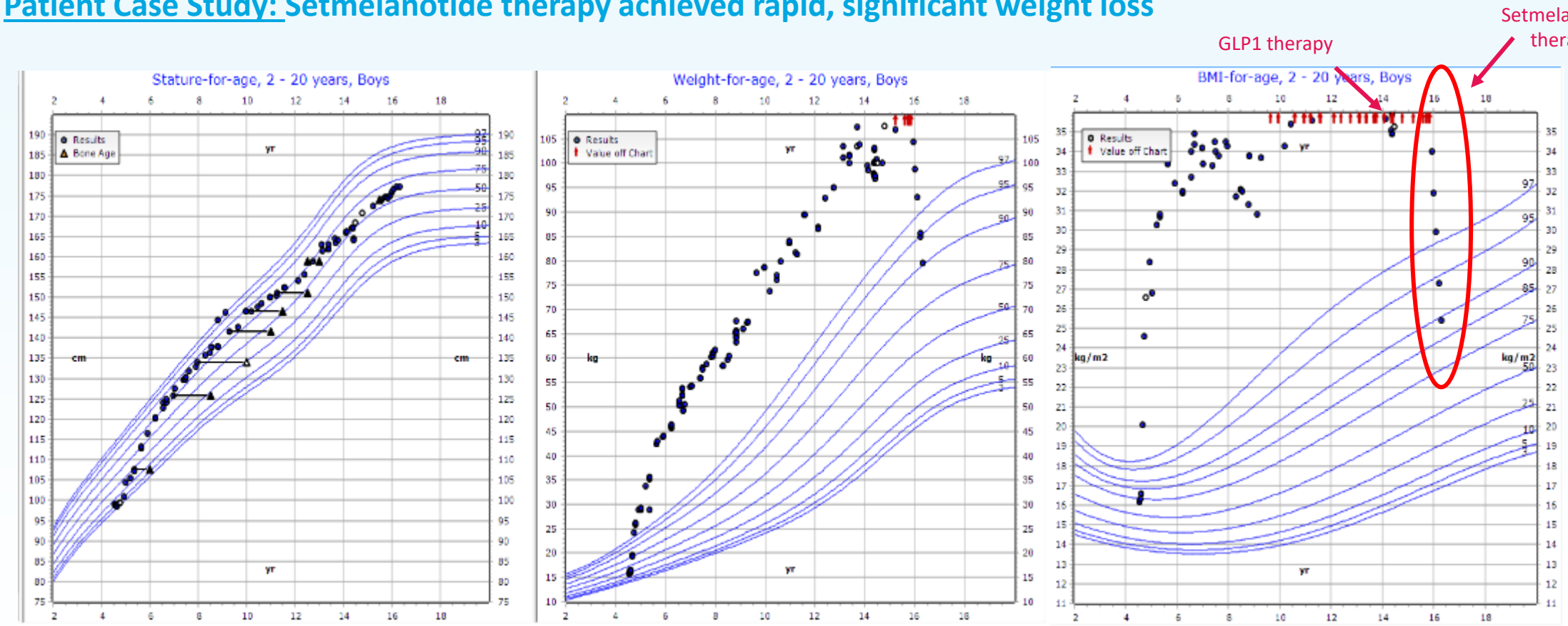
~500* additional cases diagnosed in U.S. each year

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

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

HO: Aggressive, Rapid Weight Gain follows Therapy for CP

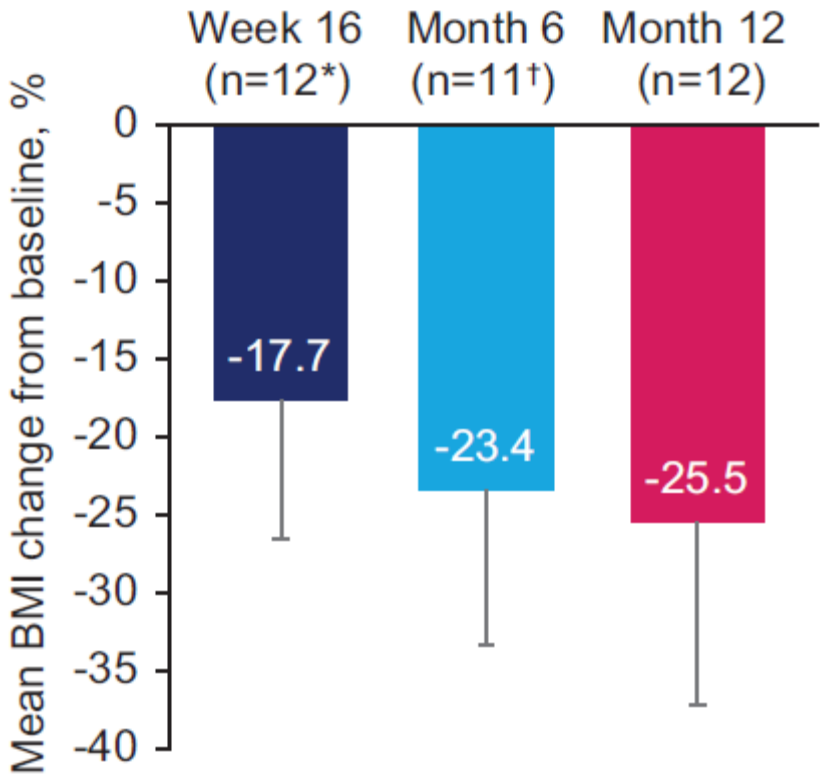
Patient Case Study: Setmelanotide therapy achieved rapid, significant weight loss

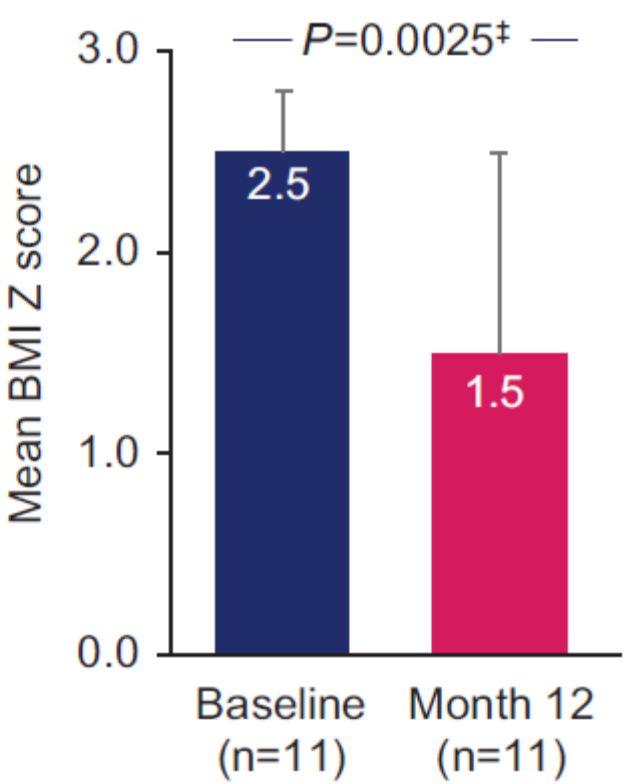


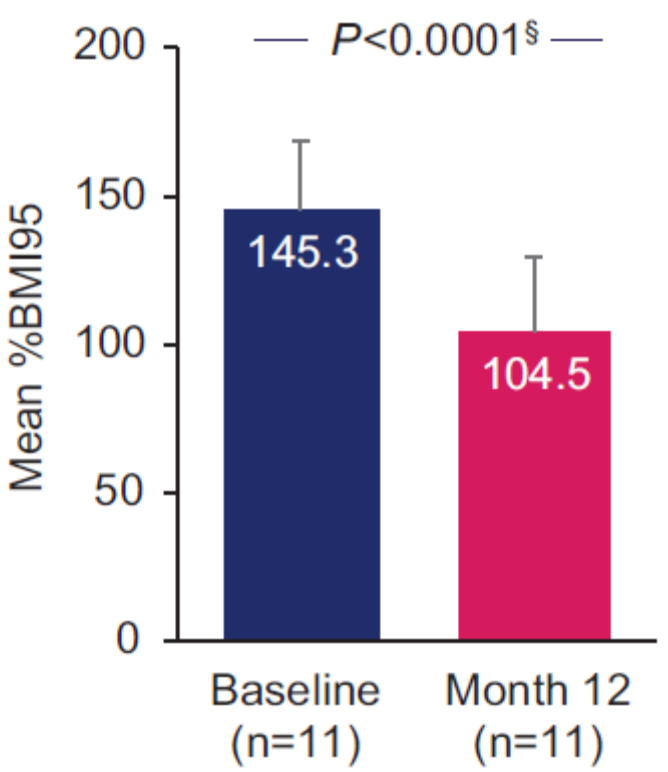
Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota

Rhythm® PHARMACEUTICALS

Setmelanotide Achieved Progressive, Deepening BMI Reduction at 16 Weeks, 6 and 12 Months in Patients with Hypothalamic Obesity

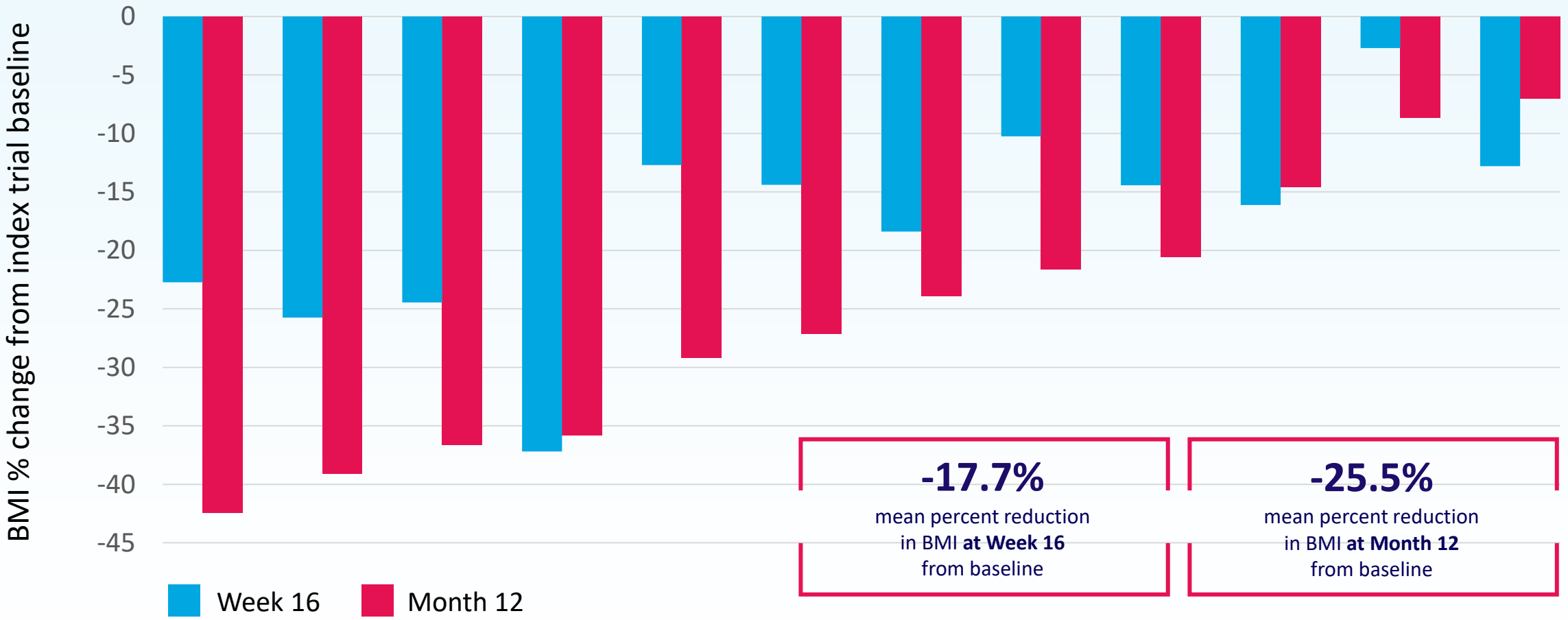






Error bars are the standard deviation. *Includes all patients who received 16 weeks of setmelanotide in the index trial and ≥12 months of treatment in the long-term extension. †One patient did not complete a Month-6 visit. ‡One sample *t*-test with 2-tailed *P*-values. §Paired *t*-test with 2-tailed *P*-values. BMI, body mass index; %BMI95, percent of the 95th percentile for BMI.

Setmelanotide Achieved Sustained and Deepened BMI Reduction in Patients with Hypothalamic Obesity at One Year

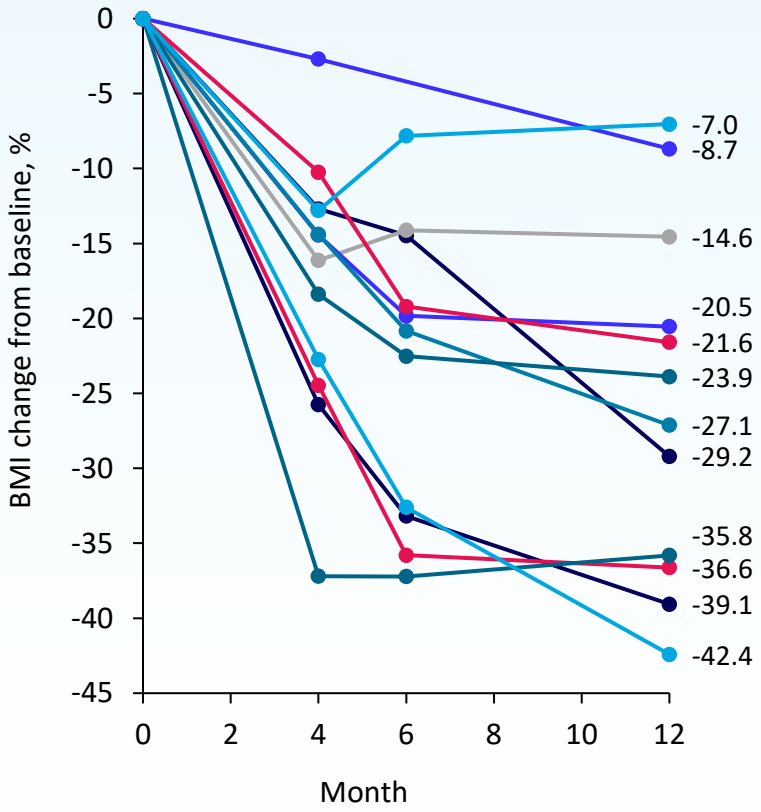


Adapted from data presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.

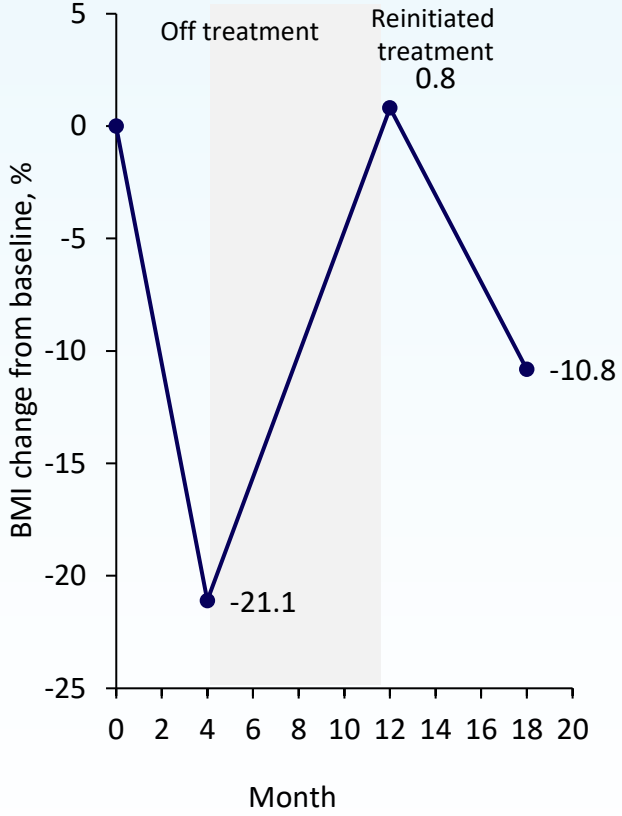
Rhythm® PHARMACEUTICALS

Hypothalamic Obesity: Patients Achieved 25.5% Mean BMI Reduction at One Year of Setmelanotide Therapy in Long-term Ext. Trial

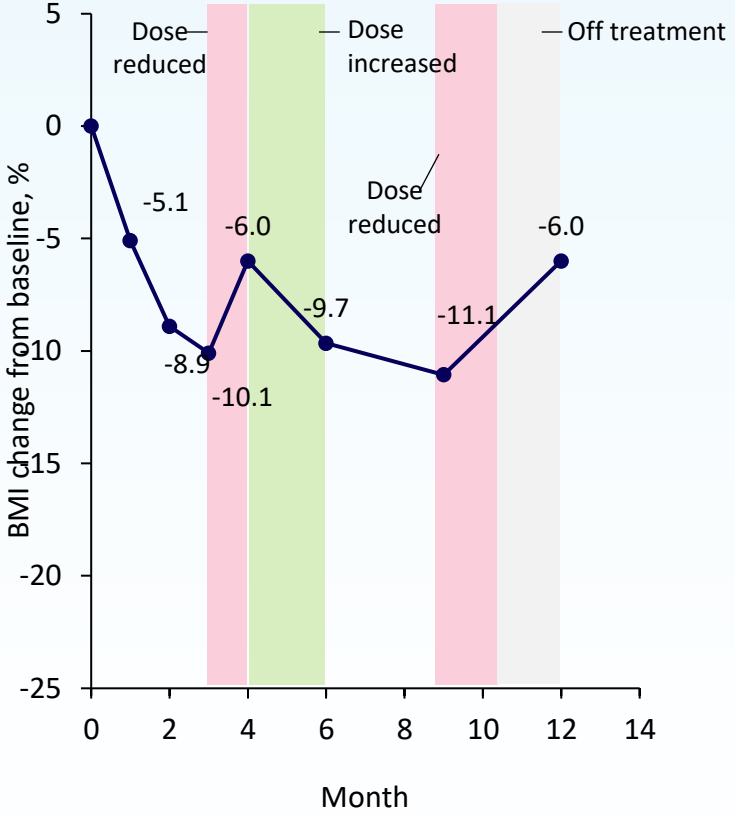
Patients on treatment at Month 12 (n=12)



Patient lost to follow-up (n=1)



Patient who discontinued treatment because of an AE (n=1)

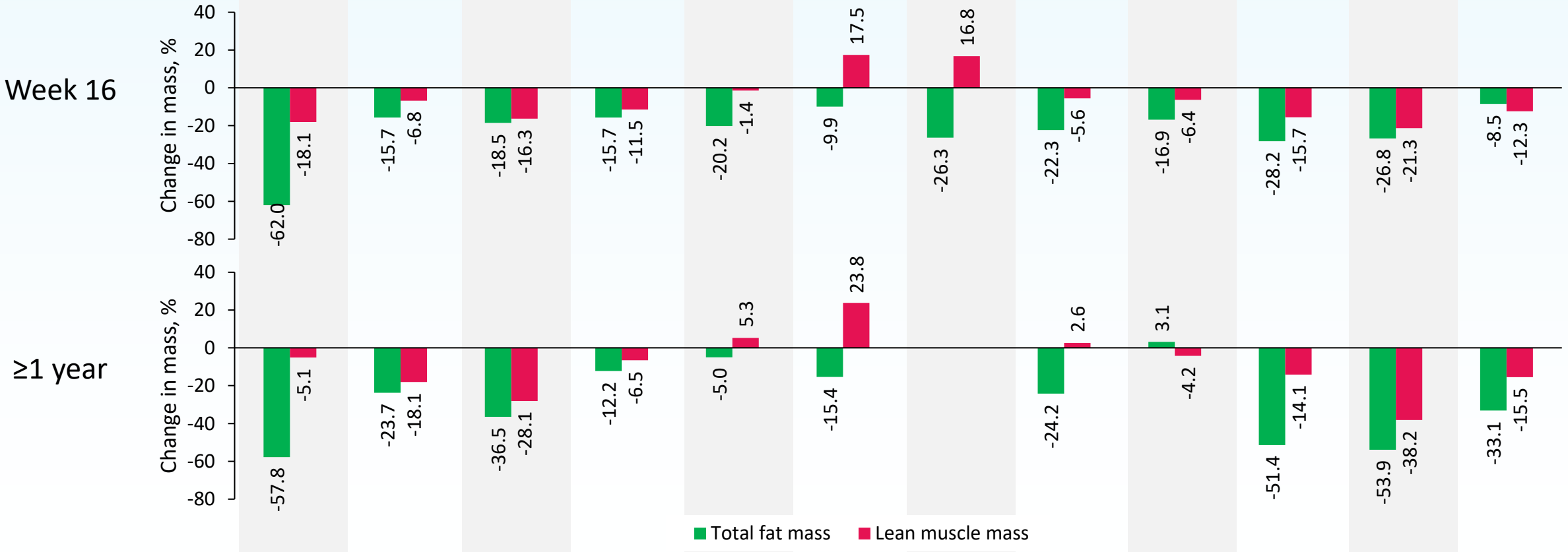


As presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.

Rhythm® PHARMACEUTICALS

Body Composition Data Show Greater Decreases in Total Fat Mass vs. Lean Muscle Mass

Patient number	1	2	3	4	5	6	7	8	9	10	11	12
Age at baseline	6	9	9	10	11	12	13	14	15	15	16	24
Percent change in BMI from baseline to Month 12	-35.8	-20.5	-39.1	-23.9	-7	-8.7	-21.6	-29.2	-14.6	-36.6	-42.4	-27.1



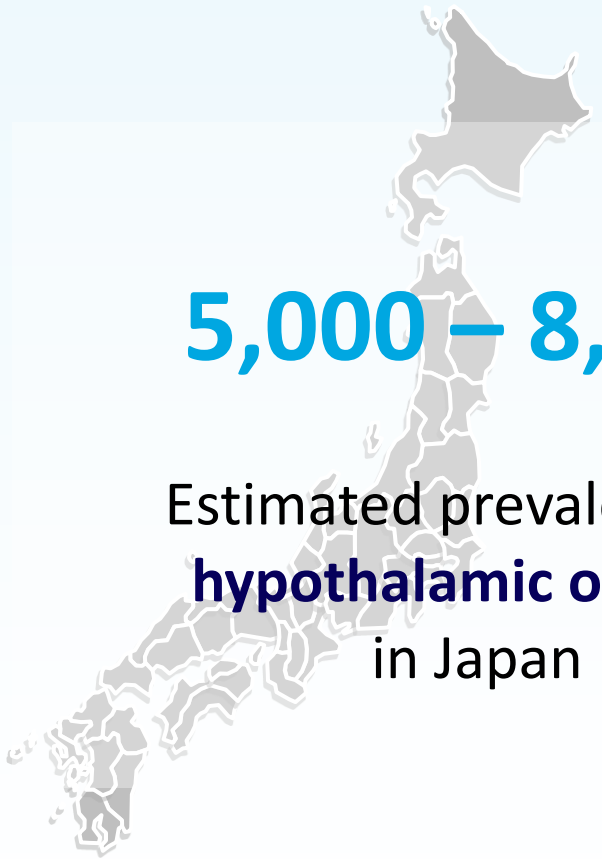
All Patients Achieved a Decrease in Obesity Severity at One Year

Three of 11 pediatric patients achieved normal weight at one year based on NIH, WHO weight classifications

BMI, kg/m^2	Adults (n=1)	WHO Classification (NIH[5])	Pediatric patients (n=11)*											BMI percentile[6]	
≥50	50	Obesity class III (extreme)			157	166					190	158		≥140%†	≥95th percentile
≥45 to <50								149							
≥40 to <45									144			140	141		
≥35 to <40	37	Obesity class II (severe)[5]	139	124	131	126				120	138			≥120% to <140%‡	
≥30 to <35		Obesity class I	96	109			109							≥95% to <120%§	
≥25 to <30		Overweight						86	89					≥85th to <95th percentile	
<25		Normal weight					83			73			79	≥5th to <85th percentile	

*Pediatric patients reported as %BMI95. †Or BMI ≥40 kg/m2 (whichever is lower). ‡Or BMI ≥35 to <40 kg/m2 (whichever is lower). §Or BMI ≥30 to <35 kg/m2 (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; NIH, National Institutes of Health; WHO, World Health Organization.

Significant Opportunity in Japan with Higher Per-capita Incidence and Prevalence of Hypothalamic Obesity



5,000 – 8,000

Estimated prevalence of **hypothalamic obesity** in Japan

- Prevalence is 2-3 times higher than in the USA & Europe due to a higher frequency of craniopharyngioma been reported
- **> 100** health care centers treating patients with hypothalamic obesity
- Single-payer system with established history of recognizing rare diseases

As announced in February 2024

Potential Path to Registration Set based on Feedback from Japan's PMDA

Japanese clinical development

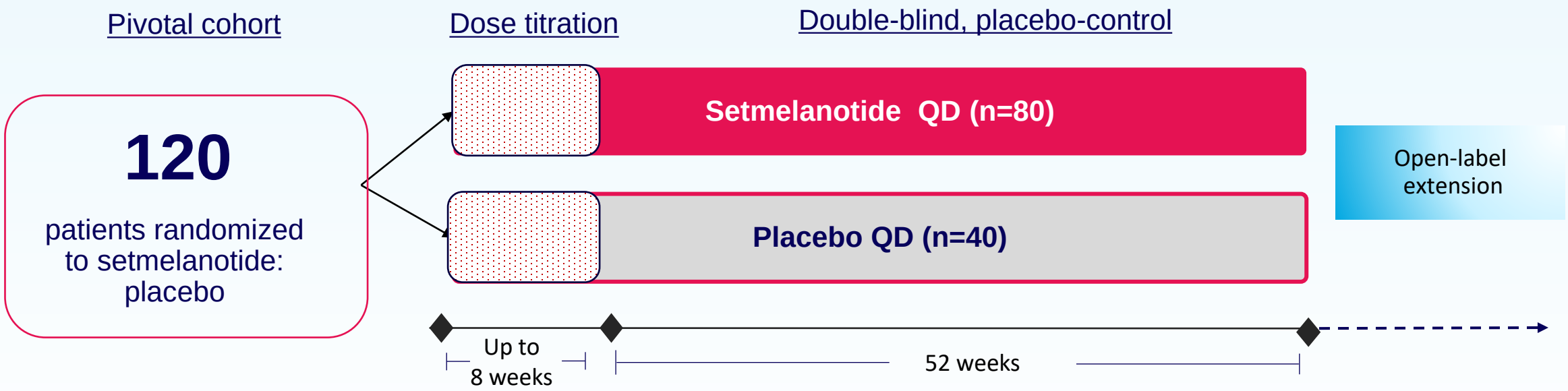
- Supplemental cohort of Ph3 trial to enroll 12 or more Japanese patients
- First patients dosed in 3Q 2024
- Pharmacokinetic data to be collected
- Bypasses earlier-stage trials in Japanese subjects

Regulatory submissions

- No anticipated impact on timing of anticipated FDA and EMA regulatory submissions
- Supplemental cohort in addition to pivotal dataset

PMDA: Pharmaceuticals and Medical Devices Agency

Phase 3 Hypothalamic Obesity Trial: Enrollment Complete, Top-line Data Expected in 1H2025



NOTE: Trial completion for patients enrolled in supplemental cohort, including 12 Japanese patients, does not affect regulatory submissions in the United States or European Union.

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

Rhythm Acquires Global Rights to Oral MC4R Agonist LB54640

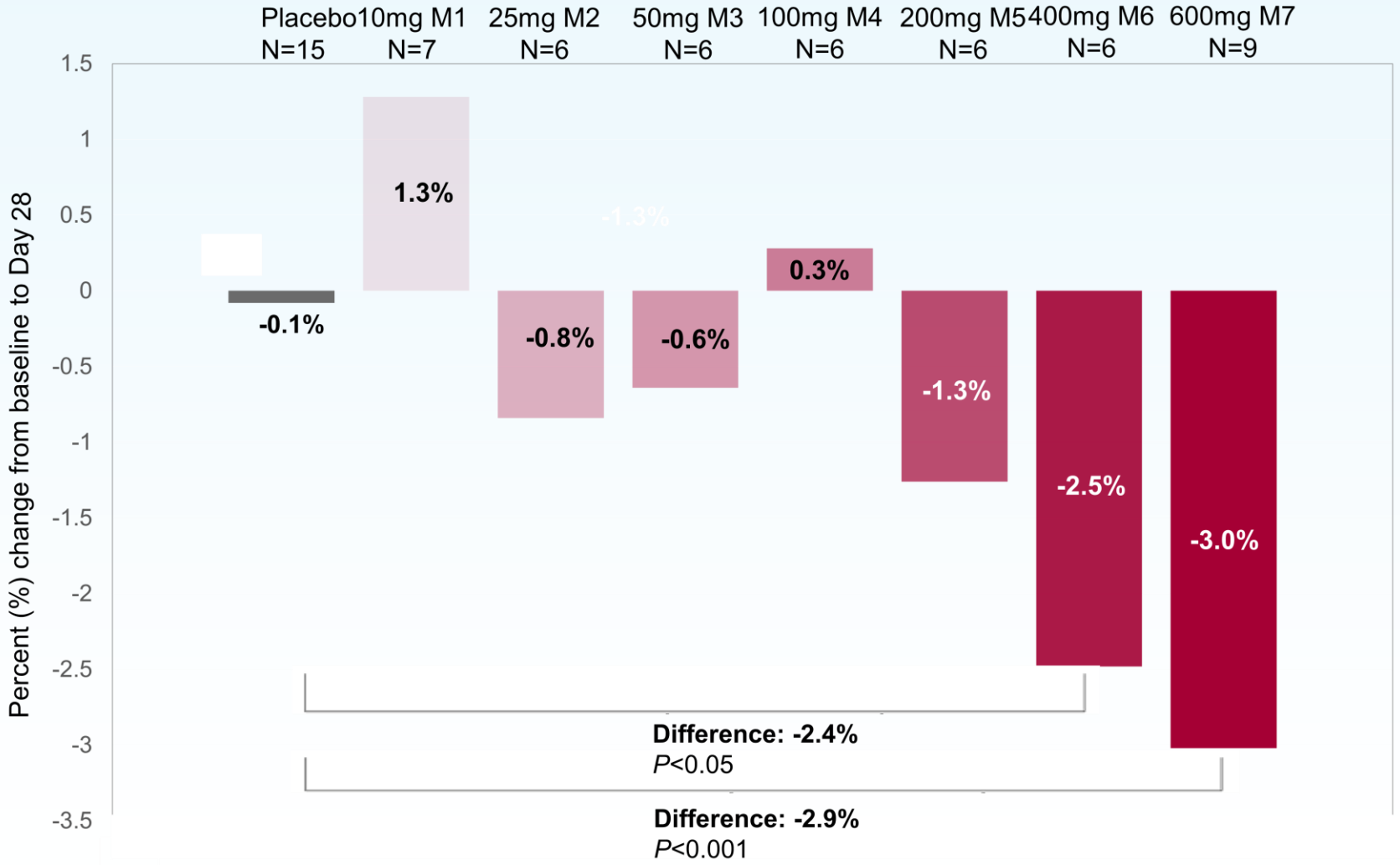
Rhythm, LG Chem Agreement Designed to Accelerate Development and Delivery of Additional Therapy Options for Patients

LG Chem
Life Sciences Company

Highly regarded global biopharma company with strong chemistry and translational science capabilities

LB54640: Oral, highly selective MC4R agonist with compelling Phase 1 data; no hyperpigmentation observed

LB54640 Showed Dose-response Body Weight Loss in Healthy Obese Volunteers



Favorable safety profile

- No serious adverse events
- No skin pigmentation, adrenal, or genitourinary adverse events observed
- Mild to moderate nausea, diarrhea, vomiting most common

As presented by LG Chem at The Obesity Society's ObesityWeek® 2022.

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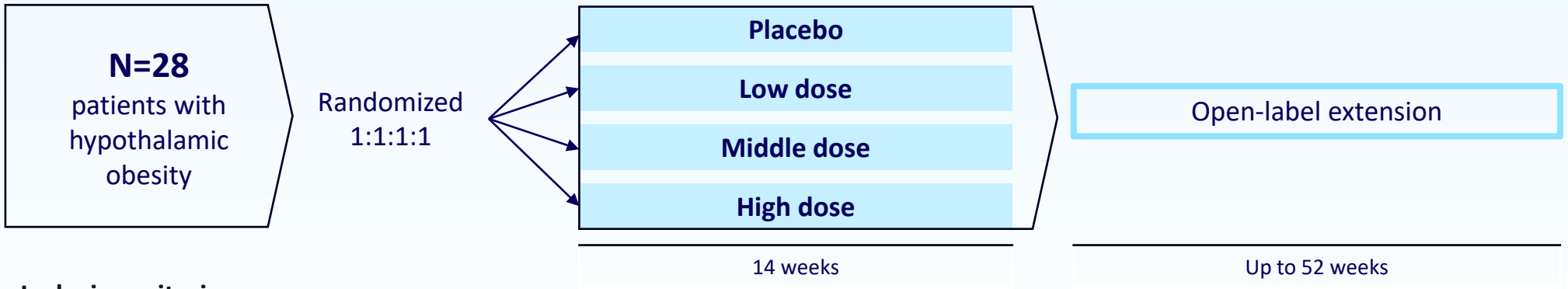
SIGNAL Trial: 14-week, Phase 2 Open-label Trial Evaluating LB54640 in Patients with Hypothalamic Obesity

First patients dosed in July 2024



Inclusion criteria

- ≥18yo BMI ≥30 kg/m2 for adults
- 12-<18 yo ≥95th percentile for patients
- Setmelanotide-naive

Efficacy endpoint

- Mean % change in BMI from baseline at 14 weeks

IMCIVREE Global Commercial Execution

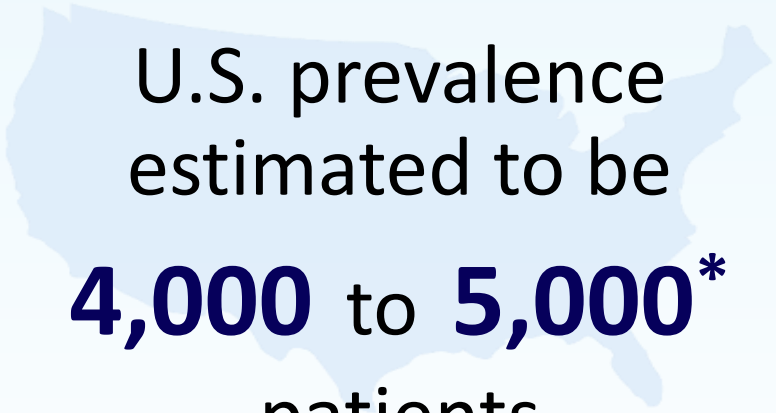
First and Only FDA- and EMA-approved Therapy that Targets Early-onset, Severe Obesity and Hyperphagia Associated with BBS

IMCIVREE™
(setmelanotide) injection

IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated for chronic weight management in patients with **monogenic or syndromic obesity** due to:

- Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).
- **Bardet-Biedl syndrome** (BBS).

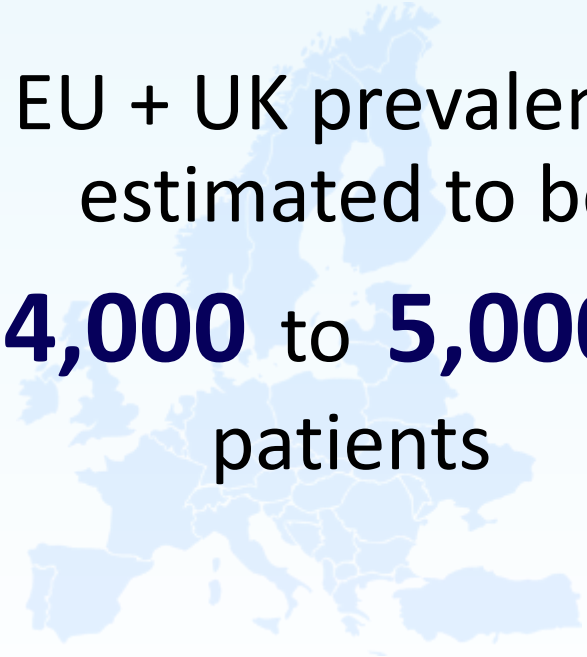
Bardet-Biedl Syndrome Opportunity in U.S. and Europe



U.S. prevalence estimated to be

4,000 to **5,000***

patients



EU + UK prevalence estimated to be

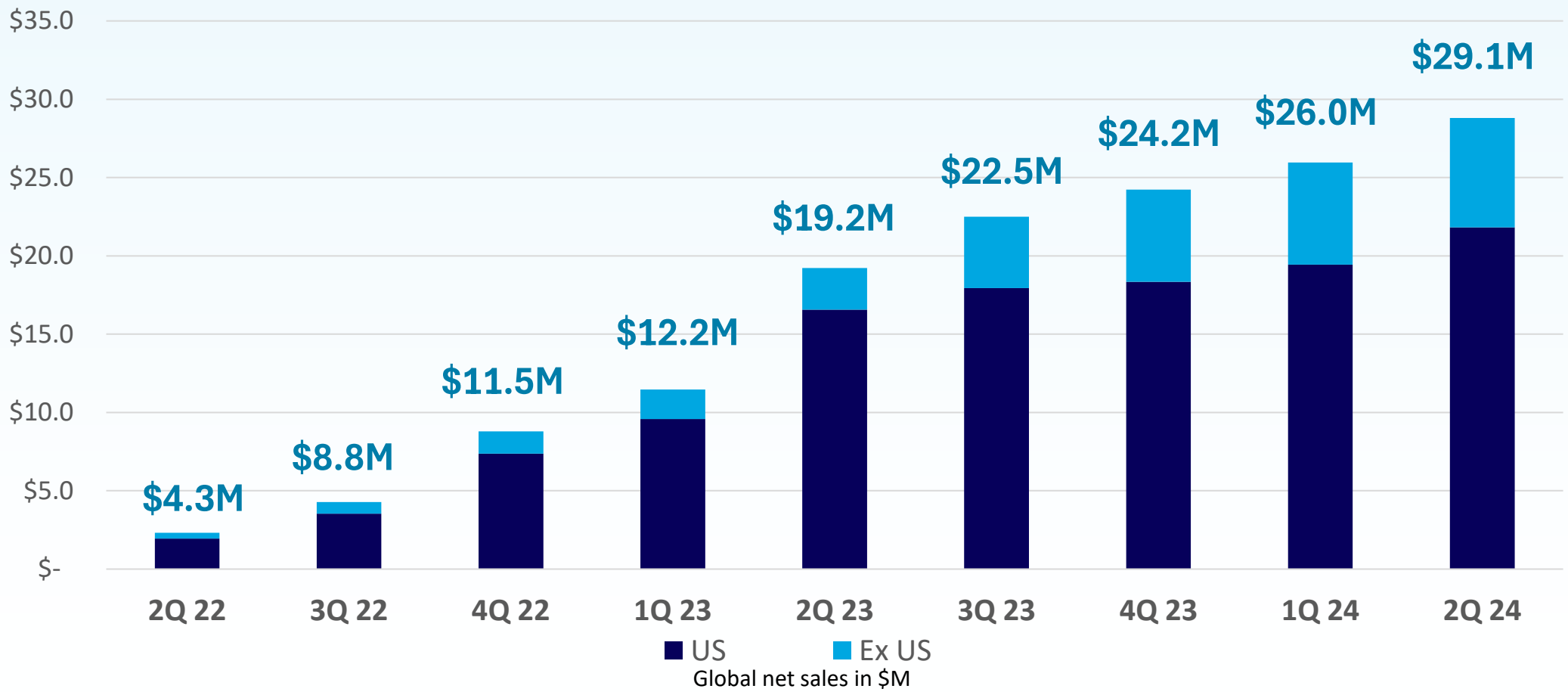
4,000 to **5,000** *

patients

*BBS prevalence estimates vary between populations, from 1 in 100,000 in northern European populations with higher prevalence rates in some additional regions throughout the world. Rhythm estimates the number of patients with BBS in the United States is between 4,000 and 5,000, with a similar number in continental Europe and the United Kingdom (UK) based on patient identification efforts and proprietary genetic sequencing data, as well as our belief that BBS, like most rare diseases, is underdiagnosed.

Steady Growth in Net Product Revenues since BBS Launch

FDA approved IMCIVREE for BBS in June 2022



Global net sales in $M

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Continued Progress in Securing Market Access for IMCIVREE

United Kingdom
Launched in POMC/LEPR; BBS launch expected in 2H2024 with NICE reimbursement

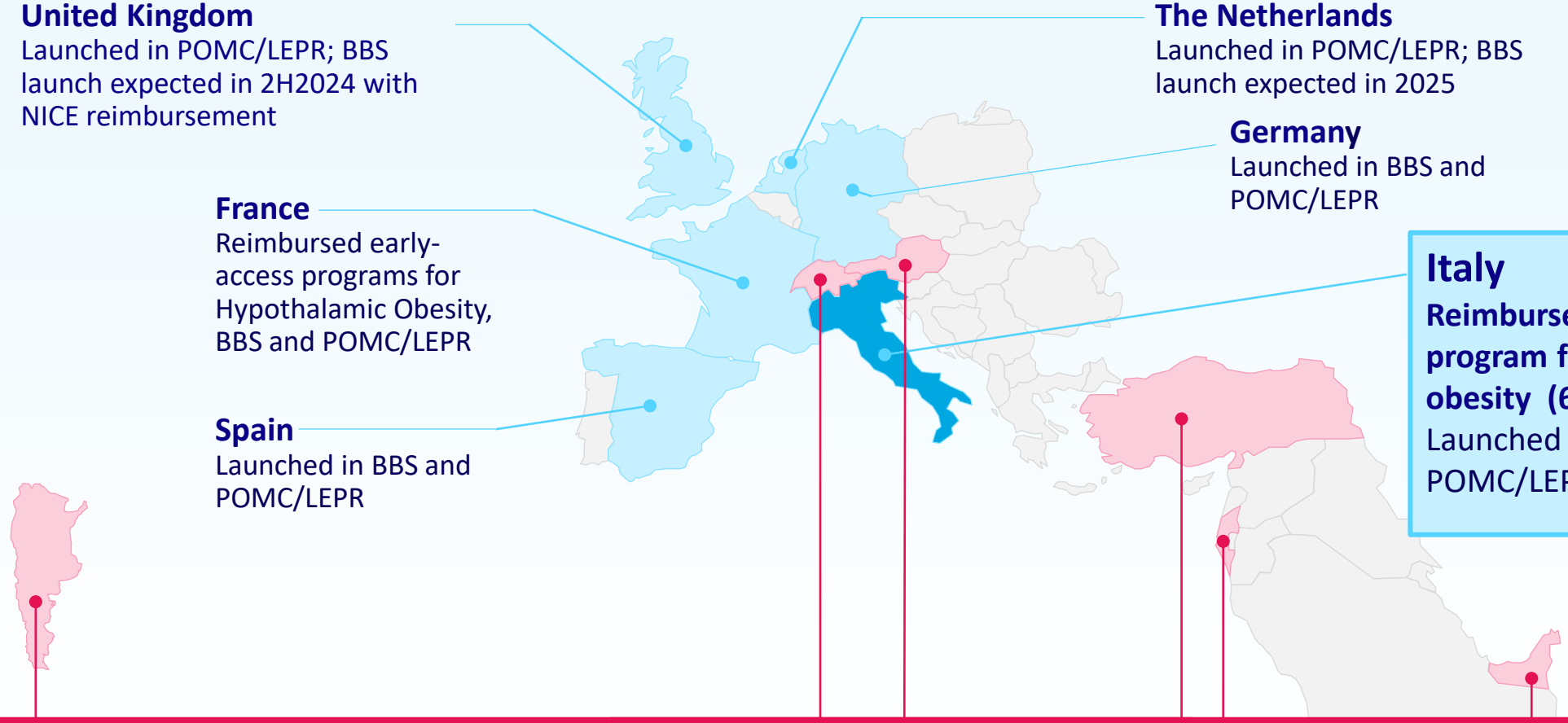
The Netherlands
Launched in POMC/LEPR; BBS launch expected in 2025

Germany
Launched in BBS and POMC/LEPR

France
Reimbursed early-access programs for Hypothalamic Obesity, BBS and POMC/LEPR

Spain
Launched in BBS and POMC/LEPR

Italy
Reimbursed early access program for hypothalamic obesity (6-24 years old)
Launched in BBS and POMC/LEPR.



EARLY ACCESS OR NAMED PATIENT SALES

Argentina · Switzerland · Austria · Turkey · Israel · United Arab Emirates

Rhythm InTune Support Services

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

Rhythm InTune
Support made personal

95% of BBS prescriptions are written for patients who are consented to InTune

Introduce IMCIVREE

Set expectations

Injection tips

Goal setting

Treatment support

Adherence

Discuss therapy with physician

Rhythm® PHARMACEUTICALS

Clinical Development

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

Phase 3 EMANATE Trial€

Four independent sub-studies

6,000†	**Heterozygous POMC/PCSK1 deficiency**
4,000†	**Heterozygous LEPR deficiency**
20,000†	**SRC1 deficiency**
23,000†	**SH2B1 deficiency**

Phase 2 DAYBREAK Trial

Stage 1, open-label data anticipated in 2H 2023 in ~5 genes

Emanate

Obesity and Hunger Clinical Trial

Daybreak

Obesity and Hunger Clinical Trial

† Estimated U.S. patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results, current estimated responder rates and that 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018ł); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017); £ U.S. and EU regulatory submissions for BBS and Alström syndrome filed in September and October 2021, respectively. € Planned EMANATE trial would include patients with variants classified as pathogenic, likely pathogenic or suspected pathogenic;

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

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

Targeted patient populations: Patients with pathogenic, likely pathogenic or suspected pathogenic variants

- **~5.1% patients** with early-onset obesity test positive for eligible variants with Rhythm's URO

Phase 2 data: supportive of probability of success in each study

Primary endpoint: BMI better suited to patient population including adults and children

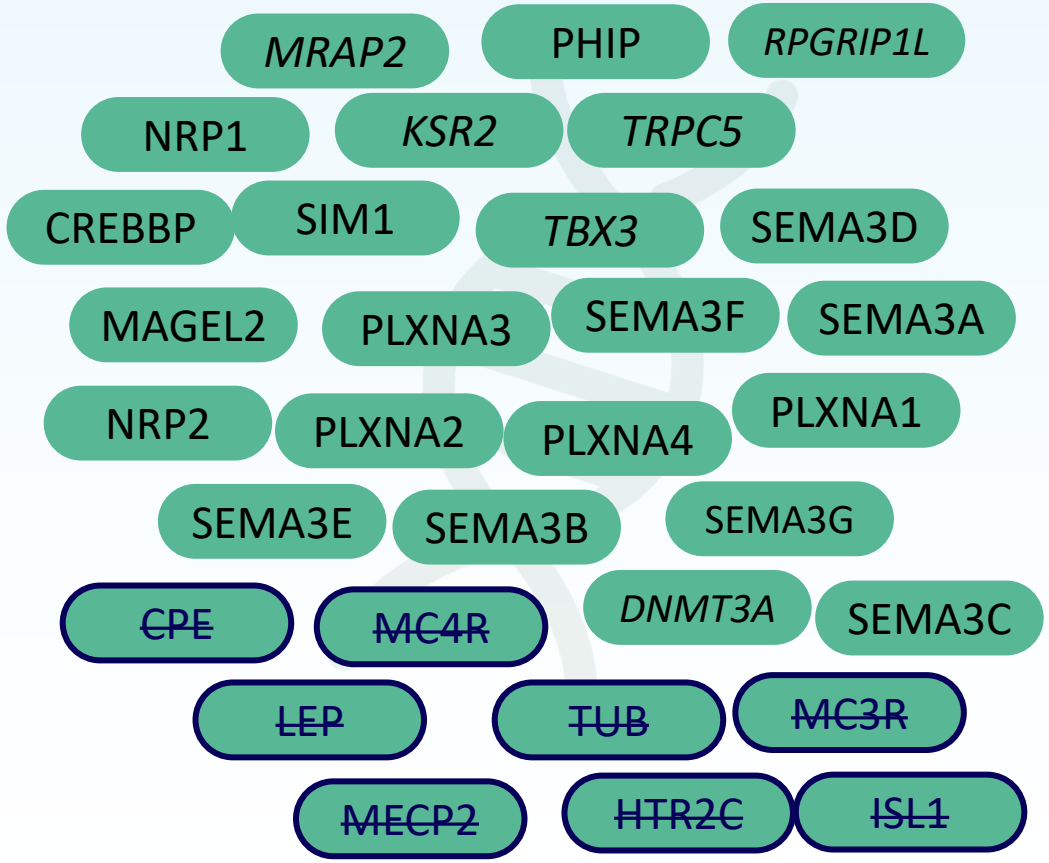
First patient: Enrolled in April 2022

Total addressable market: potential of 53,000 patients in the U.S.

Phase 2 DAYBREAK Trial Designed to Evaluate Setmelanotide Across Multiple Genes

Daybreak

Obesity and Hunger Clinical Trial



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Potential Efficacy Observed Across Multiple Gene or Gene Group Cohorts in Full Analysis Set

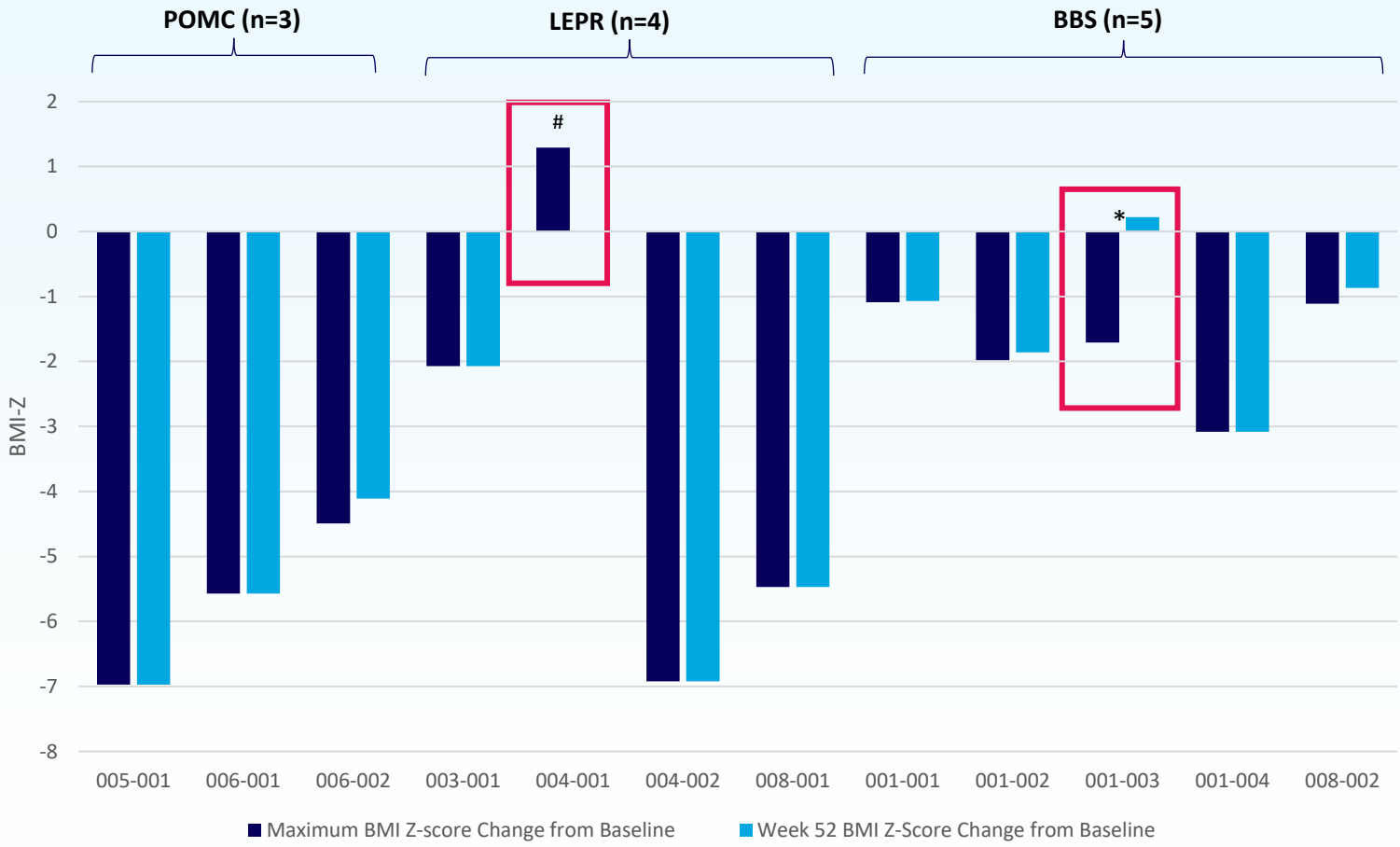
Strongest Potential Efficacy in Most Patients Observed in *PHIP* and *SEMA3*

SEMA3	***PLXNA***	***PHIP***	***TBX3***	***MAGEL2***	***SIM1***
30% **(12 of 40)**	**35.6%** **(16 of 45)**	**56.3%** **(9 of 16)**	**40%** **(2 of 5)**	***30%*** ***(3 of 10)***	**25%** **(5 of 20)**

patients responded with ≥ **5% reduction in BMI** at 16 weeks

Positive Data from Phase 3 Pediatrics Trial

Setmelanotide Achieved Consistent Reductions in BMI-Z Score



-3.04

Mean change from baseline in BMI-Z at Week 52 (N=12)

-4.3	**-1.3**
POMC/LEPR (n=7)	BBS (n=5)

*****Patient was not compliant with dosing (next slide); **#**Patient discontinued the study at Week 7 and was subsequently lost to follow-up
For patients who did not achieve their greatest reduction from baseline n BMI-Z score at Week 52 (52-week population), the maximum reduction in Z-score at any time is presented.

RM-718

First in Human, Three-part Phase 1 Study to Evaluate Safety, Tolerability, and PK of RM-718 QW Ongoing

Part A: SAD
RM-718 QW

Screening: 28 days
6 cohorts X 6 subjects ≥18y
n=36
Randomized 2:1 (RM-718: Placebo)
Single doses ascending 3mg - 50mg*
Safety follow up 10-14 days

Part B: MAD
RM-718 QW 4 doses

Screening: 28 days
6 cohorts X 6 subjects ≥18y
n=36
Randomized 2:1 (RM-718: Placebo)
Multiple doses ascending
3mg - 40mg*
Safety follow up 28 days

Part C: MAD Hypothalamic Obesity RM-718 QW 4 doses

Screening: 28 days
8 cohorts X 3 patients ≥12y
n=24
Open-label, multiple doses
ascending 10mg - 40mg*
Safety follow up 28 days
Transition to open-label extension

*Doses may be adjusted upward or downward based on emerging data; 2 additional cohorts may be permitted in Parts A and Part B based on emerging data. Part C dosing will be based on safety, tolerability, and available PK data from Parts A and B. Patients ≥18 years of age will complete Part C cohorts prior to initiating dosing in patients ≥12 to <17 years. Planned starting dose in Part C is 10mg. Part C doses will not exceed the highest Part A or Part B dose for which safety and tolerability data are supportive. Patients in Part C may be eligible to participate in an open-label extension study.

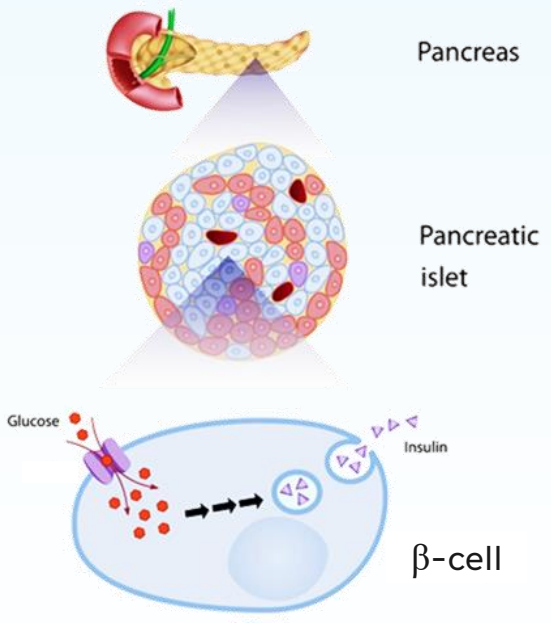
RM-718 has Demonstrated Similar or Improved Safety, Tolerability and Potential Efficacy Compared to Setmelanotide Weekly Formulation

- **In vivo safety results supportive of no off-target cardiovascular effects, like setmelanotide**
- **No hyperpigmentation observed in vivo**
- **In vivo results suggest potential efficacy for body weight reduction, hyperphagia reduction**
- **Potential for efficient development path with hypothalamic obesity**

Congenital Hyperinsulinism Pre-clinical Program

Xinvento Acquisition Expands Pipeline into Congenital Hyperinsulism (CHI)

Patients with CHI experience chronic dysregulation of insulin from pancreatic β-cells, resulting in hypoglycemias



- Most frequent cause of severe, persistent hypoglycemias in newborns and children
- Can cause brain damage in ~50% of patients
- Without proper and immediate treatment, can result in seizures, coma, permanent brain damage or death

1:29,000 - 31,000*

incidence in EU, U.S., UK and Japan

*Incidence based on recent studies (Yau et al 2020, Yamada et al 2020, and Chen et al, 2021.

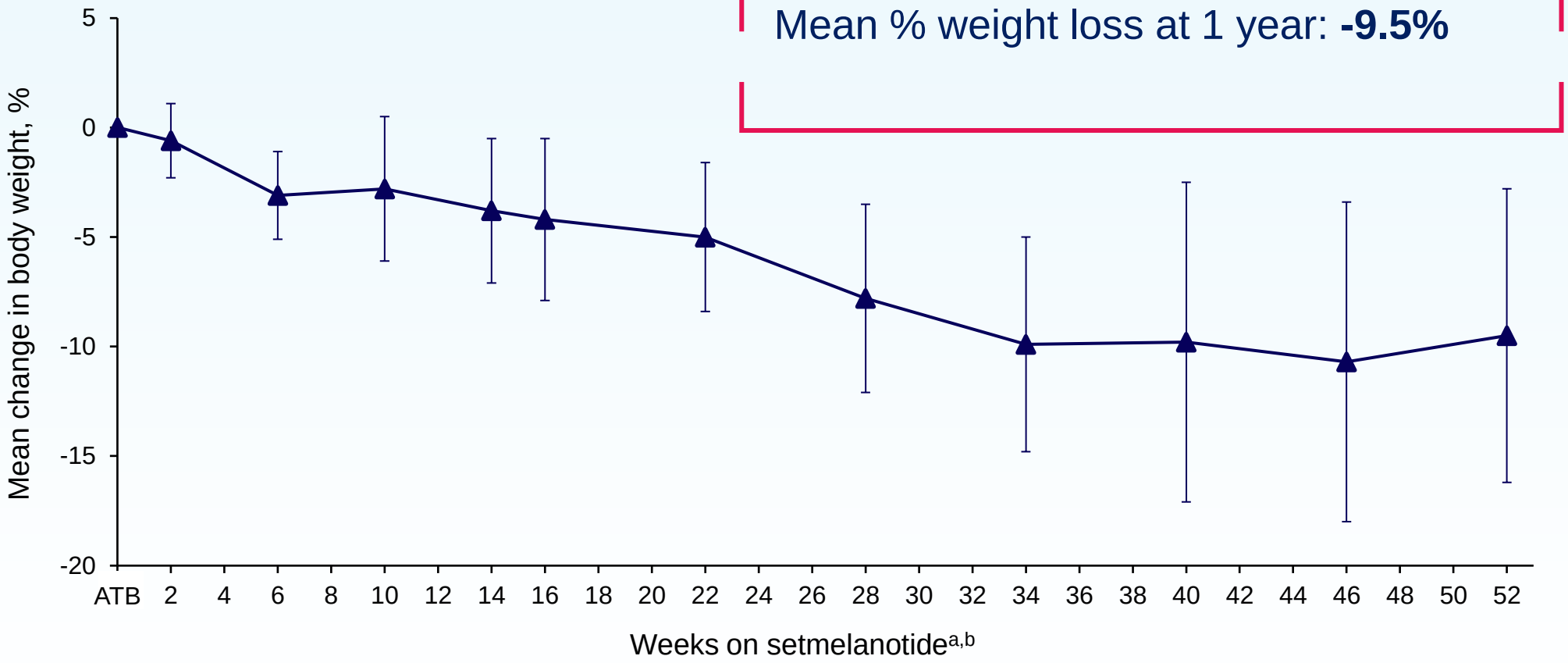
Appendix

Additional Supporting Slides

Bardet Biedl Syndrome Patients ≥18 Years Old

Completer Population

Mean % weight loss at 1 year: **-9.5%**



[a]Data shown do not include data imputed for patients who received <52 weeks of setmelanotide at the time of the analysis. [b]Populations sizes range from 7 to 15, with n=12 at 52 weeks on active treatment. Error bars are the standard deviation (SD). ATB, active treatment baseline (defined as last measurement before the first dose of setmelanotide; ie, Week 0 for setmelanotide group and Week 14 for placebo group); BBS, Bardet-Biedl syndrome.

Haws et al. Poster presented at ObesityWeek Annual Meeting; November 5, 2021.

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

Phase 3 trial achieved all predefined primary and key secondary endpoints

Adults ≥ 18 years old (n=15)

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

60%
(9/15) had
≥5% weight reduction

–9.1% mean % **change in BMI**

Patients younger than 18 (n=14)

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

–0.75
points
mean change in BMI Z score

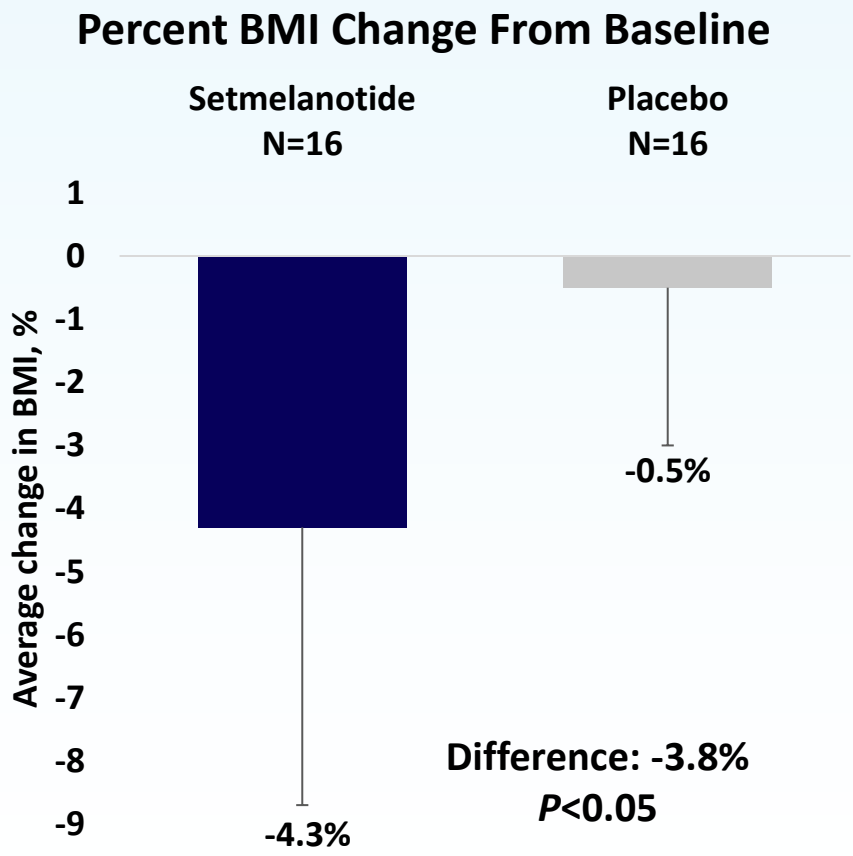
–9.5% mean % **change in BMI**

*A total of 28 patients were older than 12 years old and included in the primary analysts set, 15 adults and 13 patients between the ages of 12 and 18; ** One patient was younger than 12 at enrollment and therefore not evaluable in for the primary endpoint; As presented on Dec. 22, 2020, corporate conference call, reflecting data cut-off of Dec 2. 2020, and as presented at The Endocrine Society Annual Meeting in March 2021.

Phase 3 Trial: Setmelanotide Led to Significant BMI Reduction in Patients with BBS Versus Placebo at Week 14

14-week placebo-controlled data

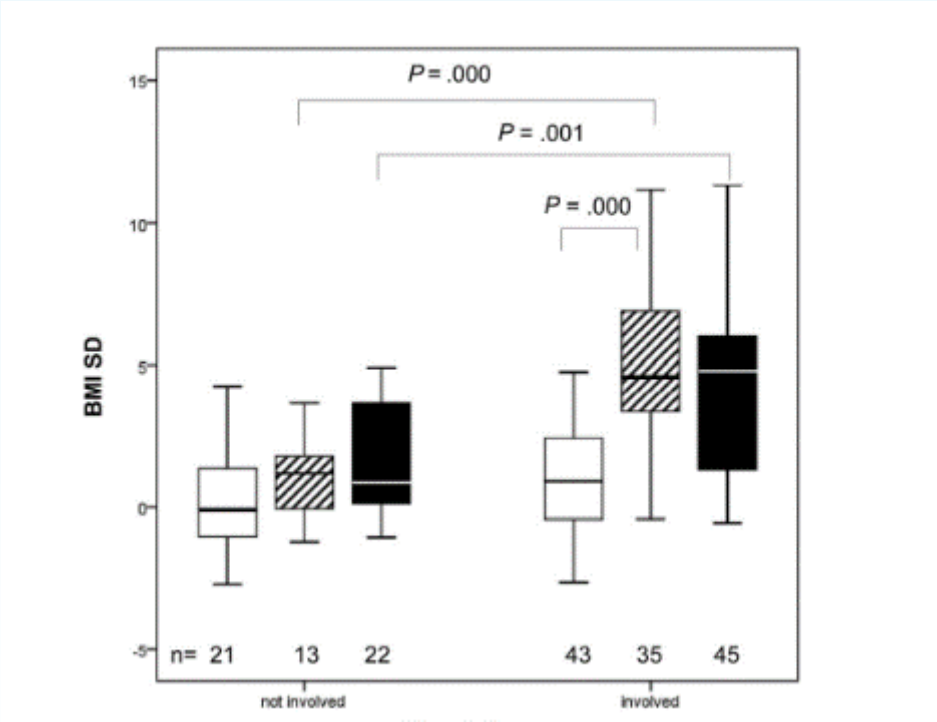
Patients with BBS treated with setmelanotide achieved an average BMI reduction of **–1.5 kg/m²** **(–3.8%)** at Week 14 compared with patients on placebo who saw ***negligible weight loss*** (*P*<0.05)



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

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

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



+0.80

Median change in BMI SD

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

+4.29

Median change in BMI SD

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

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

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

Rhythm® PHARMACEUTICALS

Phase 3 Trial Setmelanotide Achieved Clinically Meaningful Improvements in Health-related Quality of Life (HRQOL) in Patients with BBS

85% of patients reported clinically meaningful improvements or preserved non-impaired health related quality of life status

Impact of Setmelanotide on HRQOL		
	Adults (≥18 years old)	Children (8-17 years old)
Patients, n	11	9
	IWQOL-Lite total score*	PedsQL total score**
Baseline, mean (standard deviation)	74.9 (12.6)	67.2 (18.9)
Change at week 52, mean (SD)	**+12.0 (10.8)**	**+11.2 (14.4)**

***Impact of weight on quality of life or IWQOL:** Is a zero to 100 range, with zero being the worst possible and 100 best possible score. A total score increase of 7.7 to 12 is considered clinically meaningful improvement; Pre-defined ranges are: Impairment: <71.8 = severe, 71.9-79.4 = moderate, 79.5-87.0 = mild, 87.1-94.6 = none.
****Pediatric quality of life inventory or PedsQL:** Also zero to 100, with zero being the worst and 100 best possible score. A total score increase of 4.44 or greater is considered clinically meaningful. Impairment is defined as a score < 68.2.

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

Raymond A. Wood foundation

FDA Patient Listening Session on Hypothalamic Obesity

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

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

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

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

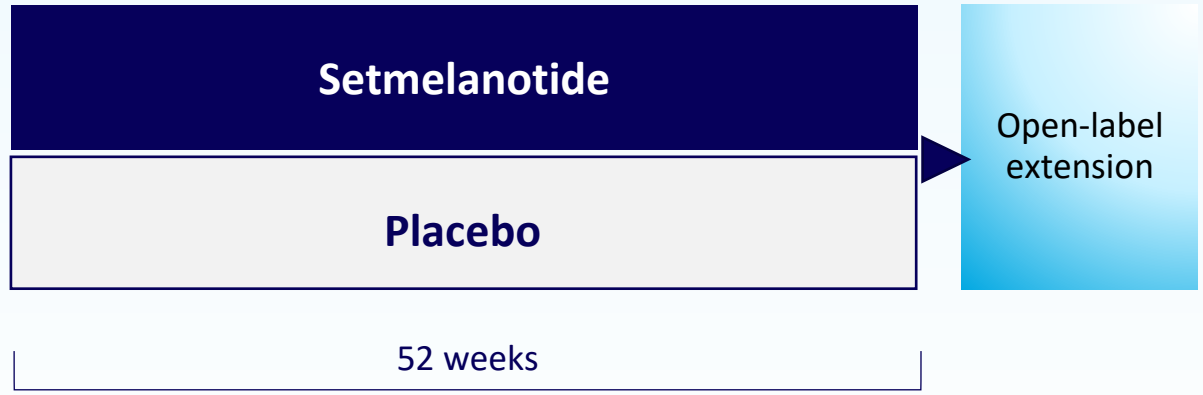
Phase 3 EMANATE Trial Comprised of Four Independent Sub-studies

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

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

Enrollment 12-18 Months

Each sub-study: Patients randomized 1:1



Endpoints

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

* VUS – Variant of uncertain significance.

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

HETs Obesity

POMC/PCSK1/LEPR Heterozygous Insufficiency

34.3%

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

Responses to setmelanotide were maintained through 6 and 9 months

SRC1 Deficiency Obesity

30%

of patients **(9/30)** achieved the primary endpoint of **≥5% weight loss** or **≥0.15 reduction in BMI Z score** from baseline at Month 3

SH2B1 Deficiency Obesity

42.9%

of patients **(15/35)** achieved the primary endpoint of **≥5% weight loss** or **≥0.15 reduction in BMI Z score** from baseline at Month 3

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

HETs Obesity
POMC/PCSK1/LEPR
Heterozygous Deficiency

-8.7%
mean BMI reduction
(n=17)
at **12 months**
on therapy

SRC1 Deficiency Obesity

-10.1%
mean BMI reduction
(n=8)
at **12 months**
on therapy

SH2B1 Deficiency Obesity

-9.7%
mean BMI reduction
(n=14)
at **12 months**
on therapy

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

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

Heterozygous POMC/PCSK1 and LEPR sub-studies are 90% powered to show >8% treatment effect vs. placebo

SRC1 and SH2B1 sub-studies are 90% powered to show >7% treatment effect vs. placebo

Assumption to achieve mean treatment effect v placebo:

- The placebo group is not expected to lose weight, even with lifestyle intervention
- The placebo group may even gain 2% over 52 weeks
- Setmelanotide non-responders demonstrate treatment effect (weight loss, BMI reduction) relative to placebo
- Setmelanotide responders anticipated to demonstrate >10% treatment effect at 52 weeks
- Setmelanotide mean treatment effect (weighted responder and non-responder) anticipated to be >8% at 52 weeks

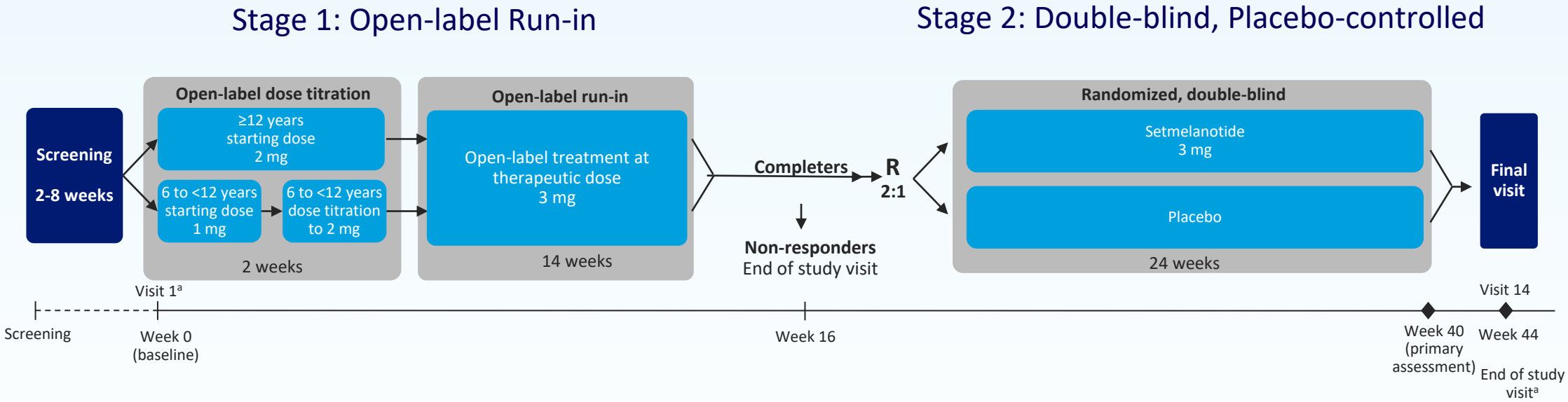
PLP: pathogenic, likely pathogenic or suspected pathogenic

EMANATE Secondary Endpoints to Illustrate Effect on Weight and Hunger

Secondary endpoints

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

DAYBREAK 2-Stage Design: 16-Week Run-in Followed by 24-week Randomized Withdrawal and Double-blind, Placebo-controlled



Eligibility criteria:

- Genetic confirmation in patients 6-65 years
- Obesity: BMI ≥40 kg/m2 (adults ≥18 years) or BMI ≥97th percentile for age and sex (children <18 years)

Primary Endpoint: proportion of patients by genotype who achieve a BMI reduction of ≥5% from baseline in response to setmelanotide at the end of Stage 1

[a]Virtual visit. R, randomization.

Validated Gene Selection Methodology[1,2] Led to Initial Selection of ~30 Genes for Exploratory Phase 2 DAYBREAK Study

Gene expression

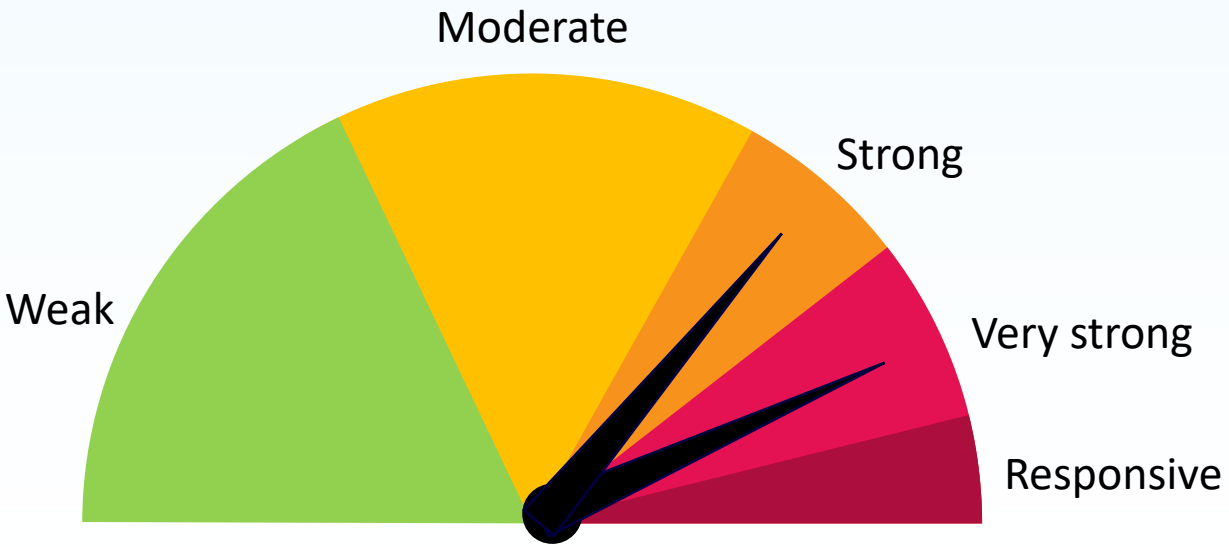
Cellular and molecular function

Physiological function

Functional rescue

Obesity-related epidemiology

Clinical response



MC4R, melanocortin-4 receptor.

1. Strande et al. *Am J Hum Genet.* 2017;100:895-906. **2.** Vogel et al. Poster presented at: American College of Medical Genetics and Genomics (ACMG)Annual Clinical Genetics Meeting; March 22-26, 2022.

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

Primary endpoint is the proportion of patients by gene who enter Stage 2 and are responders compared to placebo

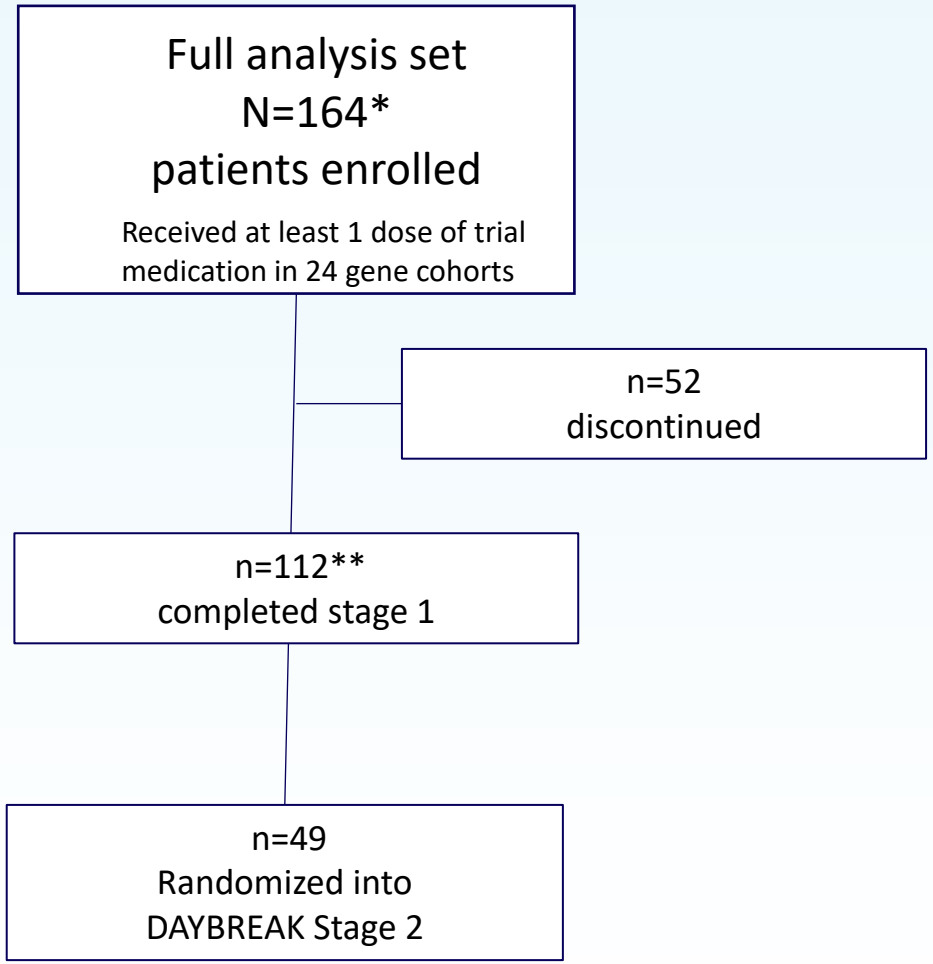
- Responders ≥18 years who achieve 10% or greater body weight reduction from baseline
- Responders <18 years who achieve BMI reduction of > 0.3 from baseline

Secondary endpoints by gene

- Proportion of patients who meet 5% weight loss criteria to enter Stage 2 compared to historic rate of 5%
- Mean change and percent change in body weight in patients ≥18 years of age compared to placebo
- Mean BMI-Z change in patients <18 years of age compared to placebo
- Mean change in waist circumference in patients ≥12 years of age compared to placebo
- Mean % change in weekly average hunger
- Overall safety and tolerability

Other secondaries: physical functioning scores and quality of life measures vs placebo

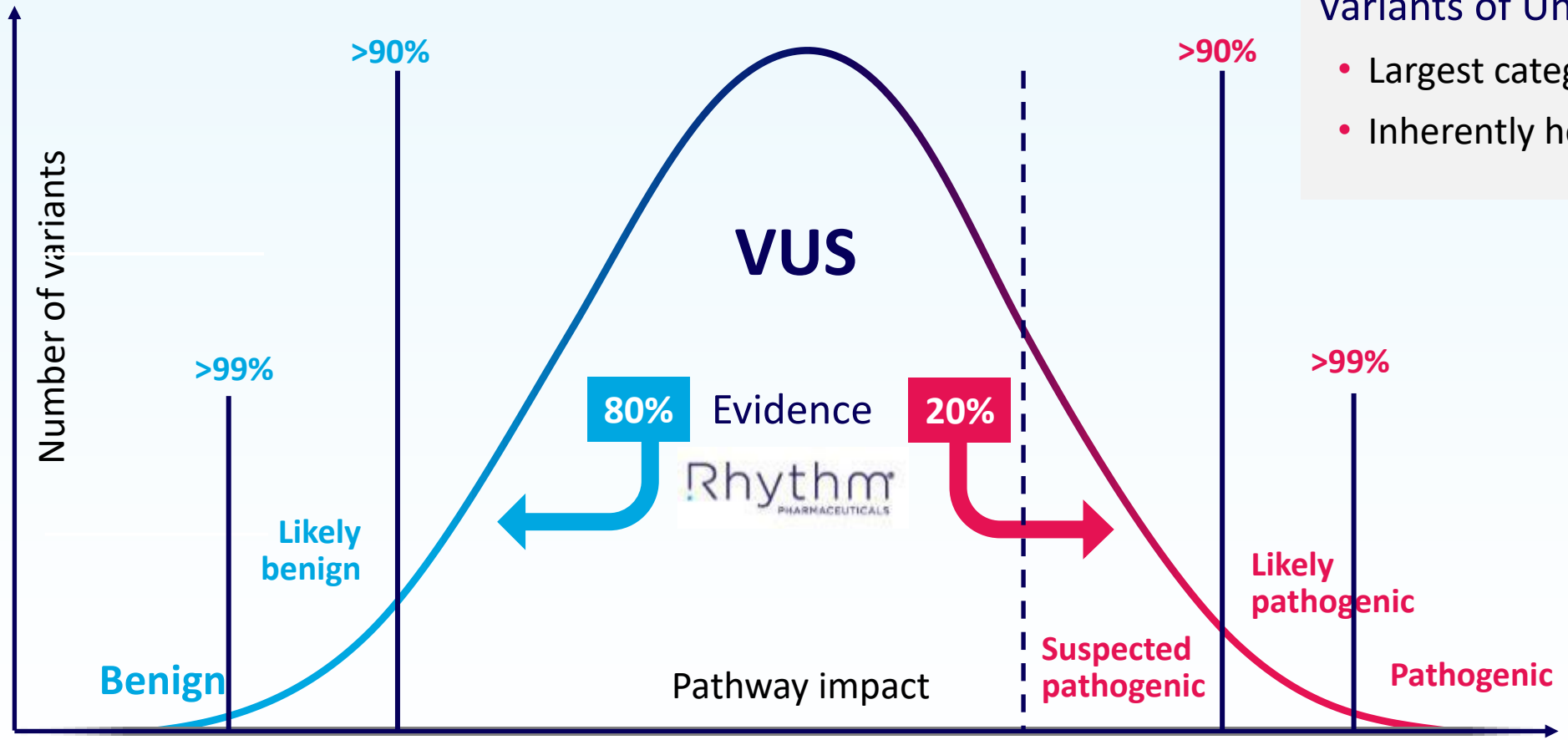
DAYBREAK Patient Dispositions



*165 patients consented and enrolled and one discontinued before 1 dose;

** Includes 12 discontinued patients who withdrew prior to week 16 but had their end-of-study visit within 2 weeks of 16; their data is included in completer analyses.

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



Variants of Uncertain Significance

- Largest category of rare variants
- Inherently heterogeneous

*ACMG Guidelines Richards et al, 2015

Ad Hoc Analysis of Primary Endpoint, Responder Rate of Participants with Week 16 Data with BMI Reduction ≥5% at Week 16

Gene	Response rate of Completers	PG ACMG reconfirmation	Estimated US prevalence*	Presentation
Overall	43.8% (n=112)	45.6% (48.5%) **(n=101)**	-	---
SEMA3 family	61% (n=26)	72% **(n=21)**	~25,000	Monogenic [1]
PHIP	69.2% (n=13)	69.2% **(n=13)**	~4,000	Chung-Jansen Syndrome [2]
TBX3	66.7% (n=3)	66.7% (100%) **(n=3 or (2))**	~2,300	Ulnar-Mammary Syndrome [3]
PLXN family	44% (n=27)	44% **(n=27)**	~34,000	Monogenic [1]

*U.S. prevalence estimates based on results from Rhythm's Uncovering Rare Obesity genetic program with samples from more than 36,000 participants, classification of variants for pathogenic, likely pathogenic and 20% of VUS and applied to established estimate of approximately 5 million people in the US with early-onset obesity; **1.** van der Klaauw et al. *Cell*. 2019;176:729-742.e18. **2.** Marenne et al. *Cell Metab.* 2020;31:1107-1119.e12. **3.** Bamshad et al. *Am J Hum Genet.* 1999;64:1550-1562 **4.** Patak et al. *Clin Genet.* 2019;96:493-505. **5.** McCarthy et al. *Am J Med Genet A.* 2018;176:2564-2574. **6.** Ackinci et al. *J Clin Res Pediatr Endocrinol.* 2019;11:341-349. **7.** Swarbrick et al. *Obesity.* 2011;19:2394-2403

Pediatrics 2-<6yo Phase 3 Trial Baseline Demographics and Disposition

Parameter	Statistic	POMC or LEPR Deficiency	BBS	Total
Enrolled patients	n	7	5	**12**
Male	n (%)	5 (71.4%)	2 (40.0%)	**7 (58.3%)**
Female	n (%)	2 (28.6%)	3 (60.0%)	**5 (41.7%)**
BMI at Baseline (kg/m^2)	Mean (SD)	34.347 (7.0673)	23.716 (3.5184)	**29.918 (7.8559)**
BMI-Z score at Baseline	Mean (SD)	10.749 (3.8400)	4.233 (1.0742)	**8.034 (4.4408)**

Dispositions

N=12
patients enrolled

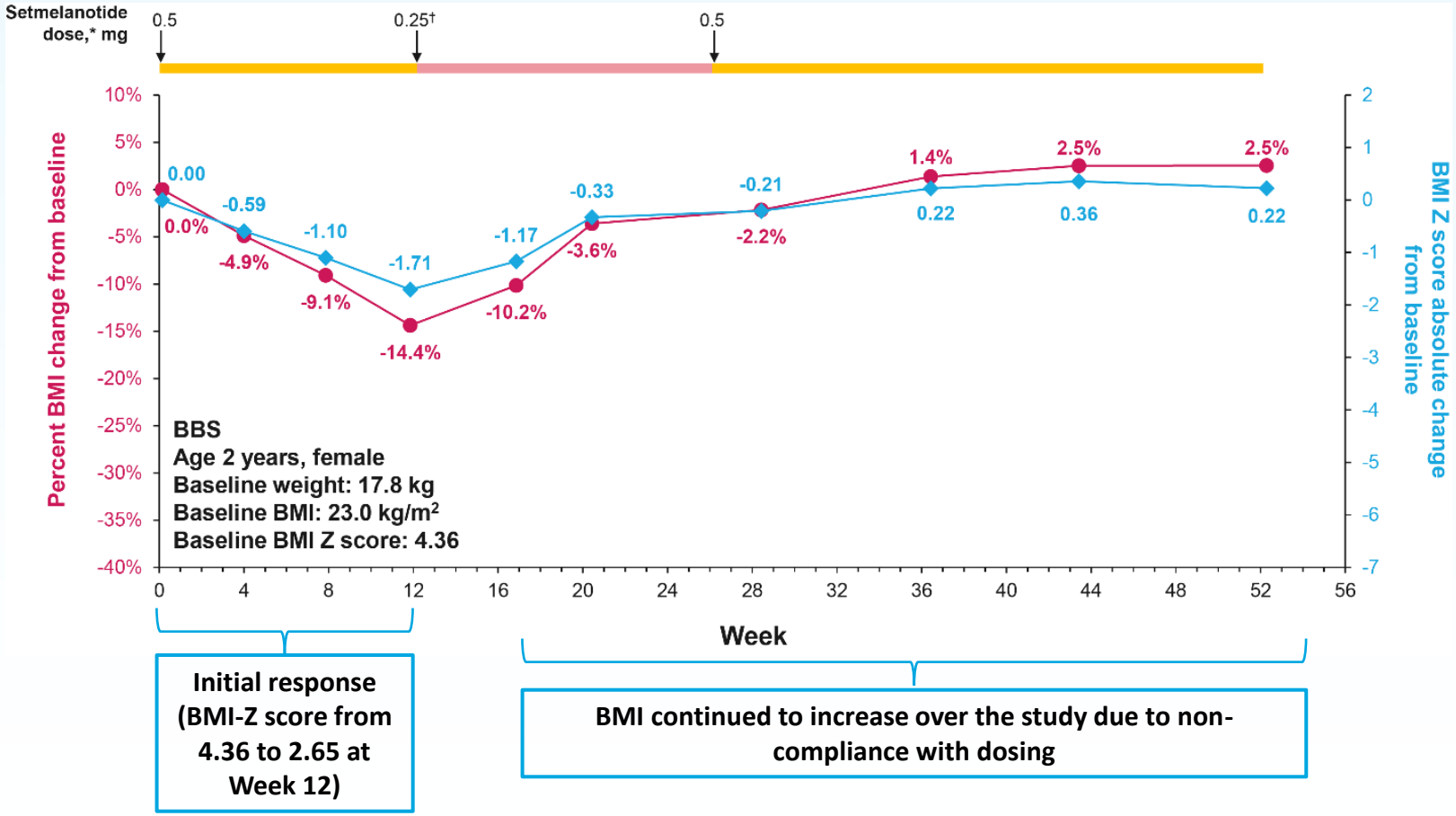
- 3 POMC deficiency
- 4 LEPR deficiency
- 5 BBS

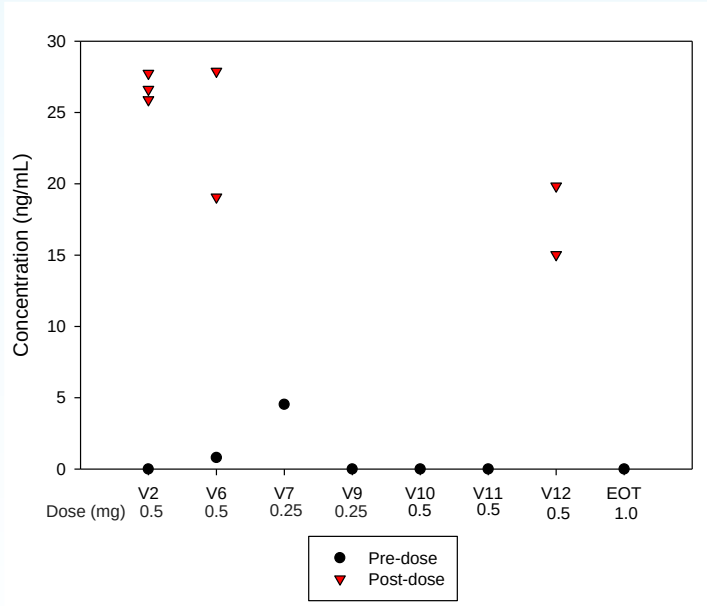
n=1
discontinued
Lost to follow up (LEPR) at week 7

n=11
completers

Patient Who Did Not Achieve ≥0.2 BMI-Z Score Reduction at Week 52

Dose reduced due to unrelated AE





Safety Profile in Patients 2-<6yo Consistent with Past Trials Evaluating Setmelanotide in Patients 6 years old and older

AE	POMC or LEPR Deficiency	BBS	Total
Skin hyperpigmentation	5 (71.4%)	4 (80.0%)	9 (75.0%)
Injection site bruising	1 (14.3%)	3 (60.0%)	4 (33.3%)
Injection site pruritus	1 (14.3%)	3 (60.0%)	4 (33.3%)
Vomiting	2 (28.6%)	1 (20.0%)	3 (25.0%)
Abdominal pain	1 (14.3%)	1 (20.0%)	2 (16.7%)

Safety analysis set is defined as all patients who received ≥1 dose of study drug. TEAE, treatment emergent adverse event.

Setmelanotide Demonstrated Safety, Tolerability and Consistent, Clinically Meaningful BMI, BMI-Z Reductions in Patients 2-<6yo

Clinically meaningful reductions in BMI and BMI-Z

Generally well-tolerated and safe, as seen in older patients

Doses of 0.5mg to 2.5mg proposed for patients <6yo

All 11 patients remain on therapy*

8 patients enrolled in bridging program

3 patients who are now 6yo or older are on commercial therapy.

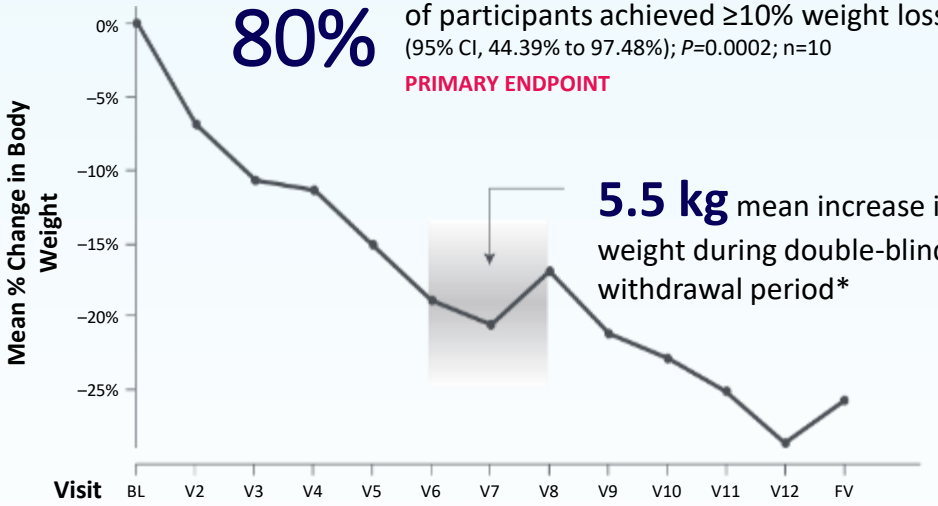
* As of Dec. 5, 2023

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

POMC/PCSK1

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

PRIMARY ENDPOINT

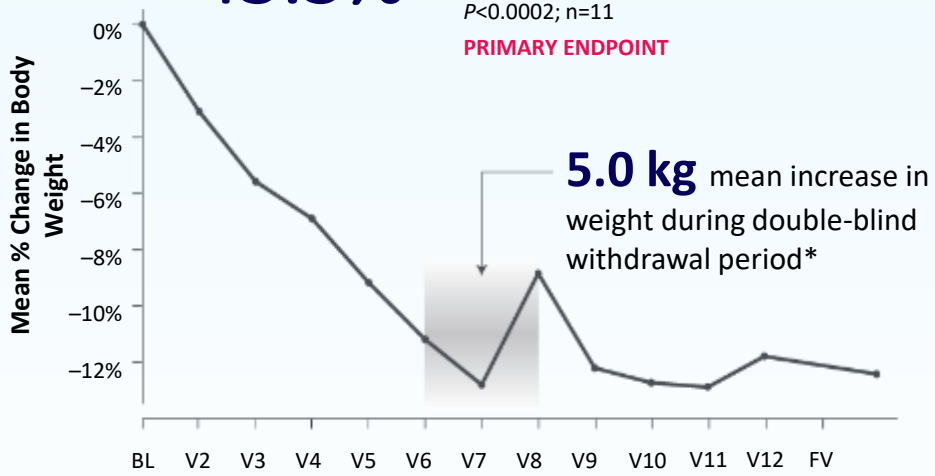


5.5 kg mean increase in weight during double-blind withdrawal period*

LEPR

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

PRIMARY ENDPOINT



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

Supplemental patients:

- 100% of POMC (n=4) and LEPR (n=4) supplemental patients achieved >10% weight loss*

Long-term extension study:

- 12 of 15 eligible POMC patients enrolled *
- 12 of 15 eligible LEPR patients enrolled *

PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; V, visit; FV, final visit. **Reference:** IMCIVREE Prescribing Information; * Data as of Nov. 16, 2020 cutoff as presented on Dec. 22, 2020 corporate conference call.

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