Rhythm Pharmaceuticals

January 2025

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, Bivamelagon (formerly LB54640), and RM718, 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 our other product candidates, the announcement of data from our clinical trials, including our global Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity, the ongoing enrollment of patients in our clinical trials, the potential benefits of any of the Company's products or product candidates for any specific disease indication or at any dosage, 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, our anticipated financial performance for any period of time, including preliminary unaudited net revenues, for the fourth quarter and full year ending December 31, 2024, and the timing of any of the foregoing. 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 global events 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.

Financial Disclosure Advisory

This presentation contains certain estimated preliminary financial results for the fourth quarter and fiscal year ended December 31, 2024. These estimates are based on the information available to the Company at this time. The Company's financial closing procedures for the fourth quarter and full year 2024 are not yet complete and, as a result, actual results may vary from the estimated preliminary results presented here due to the completion of the Company's financial closing and audit procedures. The estimated preliminary financial results have not been audited or reviewed by the Company's independent registered public accounting firm. These estimates should not be viewed as a substitute for the Company's full interim or annual financial statements. Accordingly, you should not place undue reliance on this preliminary data.

Rhythm's Value Drivers

1. Significant **expansion opportunity in hypothalamic obesity** (both acquired and congenital)
2. Continued **BBS global commercial execution**
3. **Driving life-cycle management** with bivamelagon and RM-718
4. **Advancing setmelanotide clinical development** in Prader-Willi syndrome and genetically-defined MC4R pathway diseases

What's New?

Announced preliminary unaudited net revenues from global sales of IMCIVREE

~$42 million *for Q4 24*

$130 million *for FY2024*

On track *to report topline data from pivotal, Ph3 trial in acquired* ***hypothalamic obesity*** *in H1 25*

Completed enrollment in ***supplemental Japanese cohort*** *of Ph 3 trial of setmelanotide in acquired* ***hypothalamic obesity***

Completed enrollment in two substudies in ***Phase 3 EMANATE trial*** *in genetically-caused MC4R pathway diseases*

Plans to initiate ***new Phase 2 trial*** *exploring setmelanotide in* ***Prader-Willi syndrome*** *in Q1 25*

Continued Growth in IMCIVREE Global Sales

~$42M
Q4 2024

~$130M
FY 2024

Preliminary unaudited net revenues from global sales of **IMCIVREE®** (setmelanotide)

+26% **QoQ** increase from Q3 2024

74% of **4Q** revenues **from U.S.**

73% of **FY '24** revenues **from U.S.**

Drivers of QoQ growth

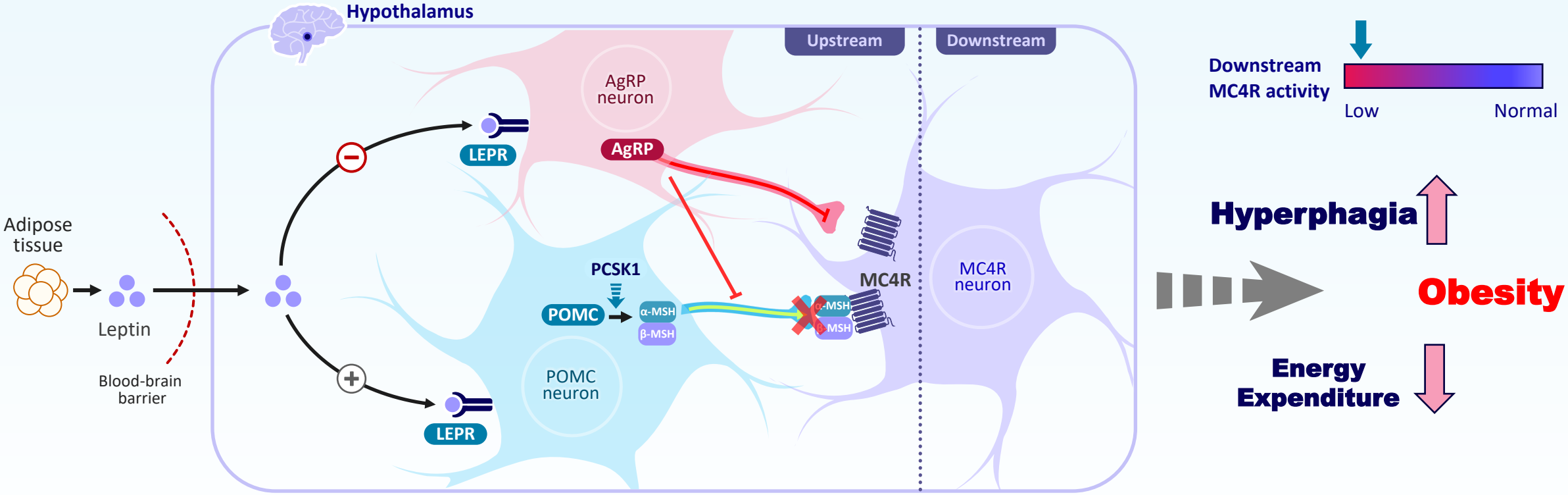
evenly split among two factors:

1. Increase in number of patients on **reimbursed therapy**

2. **Inventory growth:** Excess of vials shipped to specialty pharma over vials dispensed to patients

The Company plans to report fourth quarter and full year 2024 financial results in late February

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

~29,000**
EMANATE
Lead 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). **Estimated prevalence in United States of SH2B1 and POMC and/or PCSK1 cohorts.

Well Capitalized: Cash Sufficient to Fund Planned Operations into 2026

$298.4M

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

Guidance

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

61.2 Million

Common shares outstanding as of Sept. 30, 2024

Analyst coverage[1]

BofA Securities; Canaccord Genuity; Guggenheim; HC Wainwright; Jefferies; JMP Securities; Morgan Stanley; Needham; Oppenheimer; Stifel; TD Cowen; Wells Fargo

[1]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. Goldman Sachs temporarily suspended coverage.

Multiple Anticipated Milestones

Q1 2025	Complete enrollment in **Ph2 trial** evaluating **bivamelagon (LB54640)** in acquired hypothalamic obesity
Q1 2025	Begin dosing patients with acquired hypothalamic obesity in **Part C** of **Ph1 trial evaluating RM-718**
Q1 2025	Begin dosing patients in **Ph3 congenital hypothalamic obesity substudy** evaluating setmelanotide
Q1 2025	Begin dosing patients in exploratory **Ph2 Prader-Willi trial** evaluating setmelanotide
H1 2025	Topline data from **Ph3 acquired hypothalamic obesity trial**
H1 2026	Topline data from **Ph3 EMANATE trial** evaluating setmelanotide in four genetically-defined, rare MC4R pathway diseases

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

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

Jennifer Lee
Executive Vice President, Head of North America

SANOFI GENZYME
Krystal

20-plus years leading global commercial strategy in rare diseases

Yann Mazabraud
Executive Vice President, Head of International

SANOFI GENZYME
trevi THERAPEUTICS

20-plus years leading global commercial strategy in rare diseases

Joe Shulman
Chief Technology Officer

Ra Pharma
novelion THERAPEUTICS

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

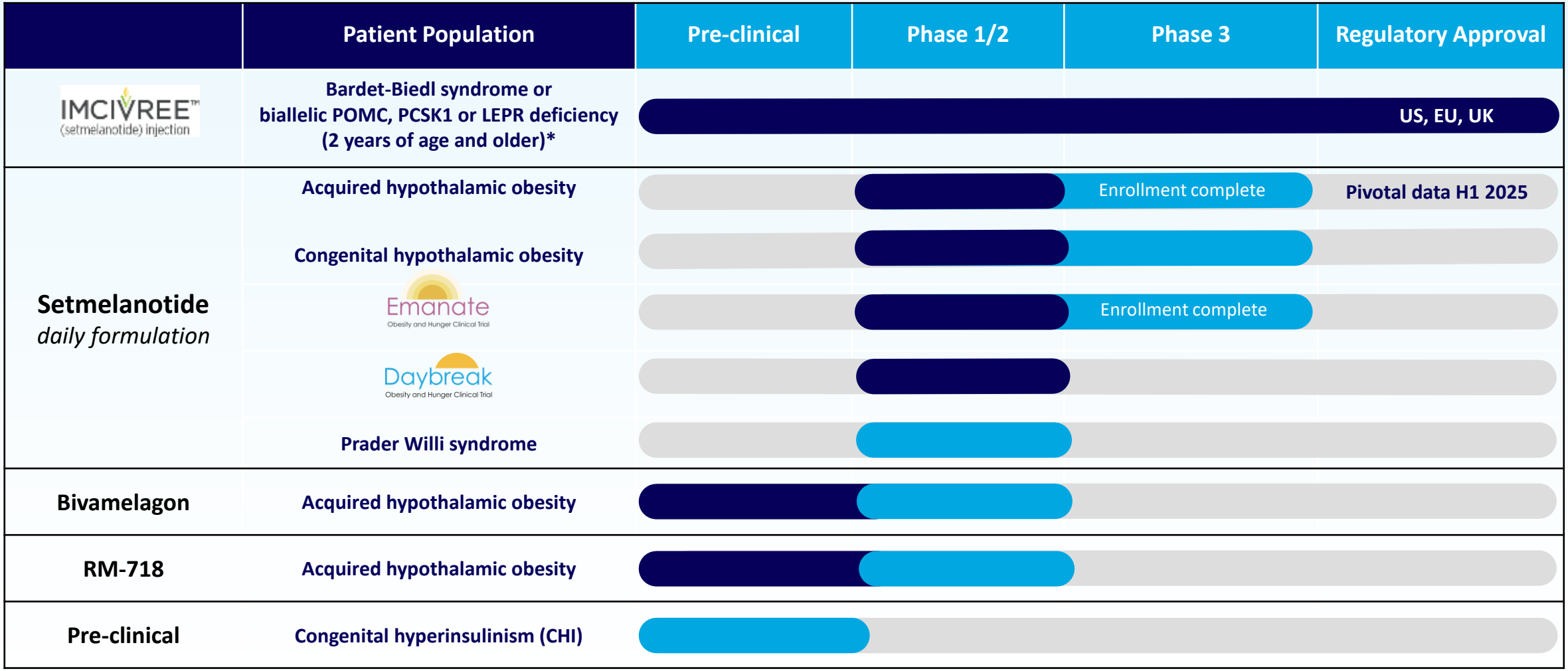
Alastair Garfield, PhD
Chief Scientific Officer

RECTIFY PHARMA
Pfizer

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

Rhythm® PHARMACEUTICALS

Expanding Pipeline in Rare Neuroendocrine Diseases



*IMCIVREE approved in Israel & Canada (6 years of age and older).
LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

Hypothalamic Obesity

Acquired and Congenital

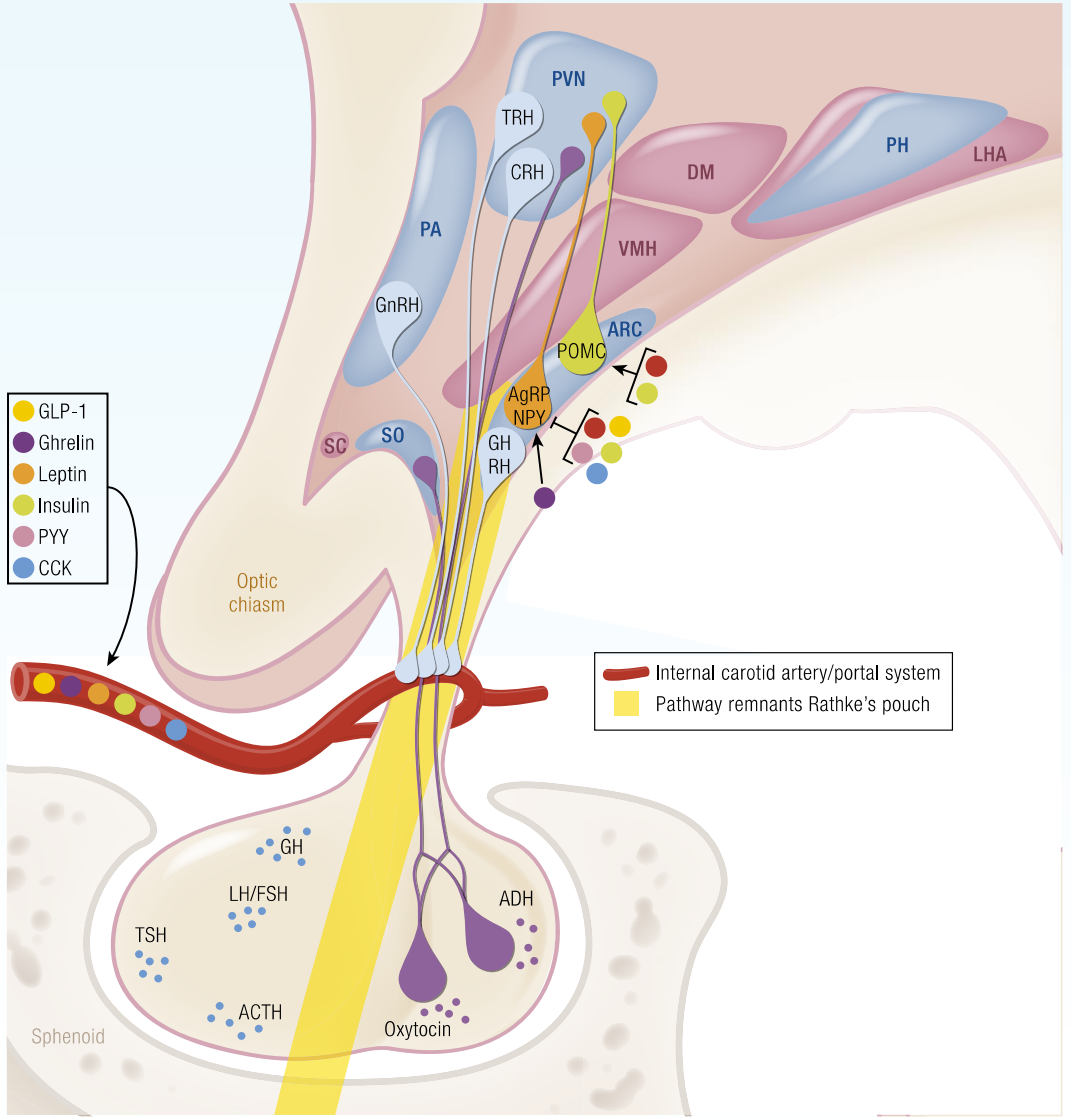
Setmelanotide, bivamelagon and RM-718

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

Hypothalamic Obesity: A Transformative Opportunity for Rhythm

5,000 – 10,000*
estimated U.S. prevalence

~500*
Estimated U.S. incidence

3,500 – 10,000**
estimated European prevalence

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

5,000 – 8,000£
estimated Japanese prevalence

✓ Unmet medical need is high

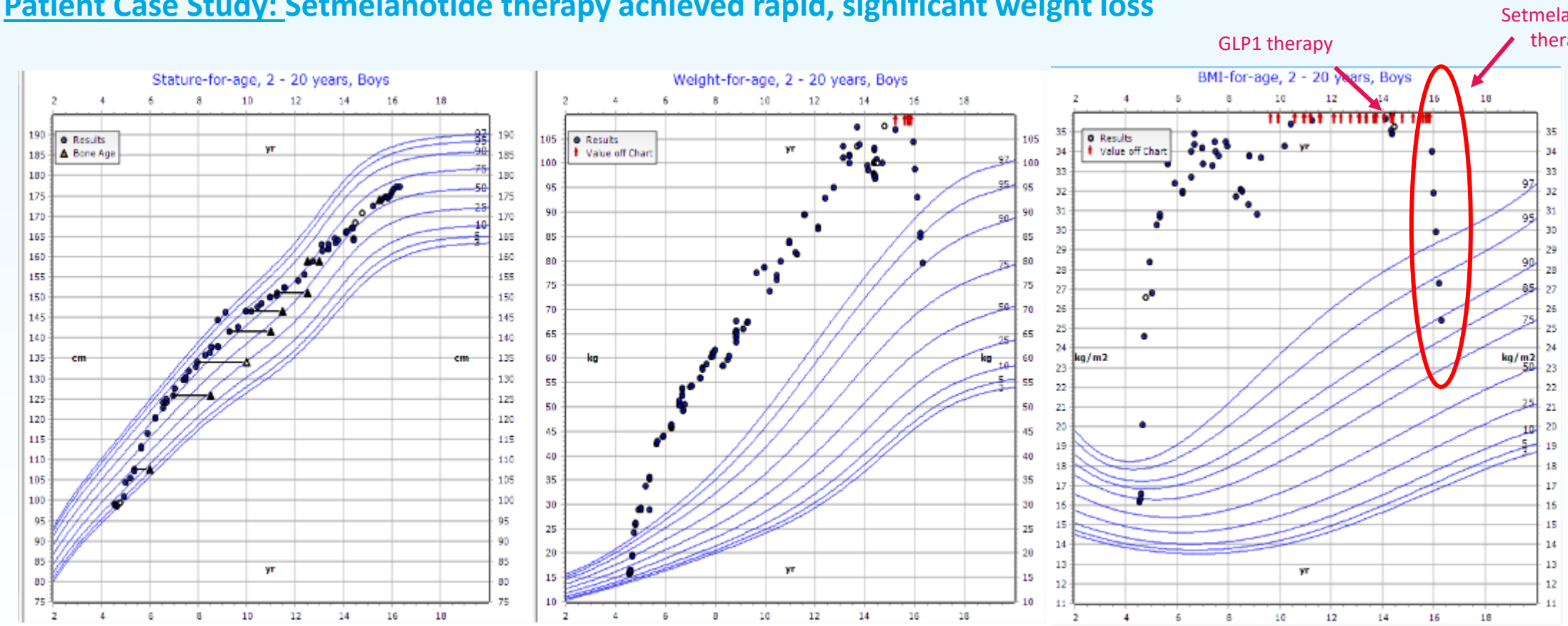
✓ Patients are identified

✓ Patients engaged with system

*U.S. estimates based on reported incidence of hypothalamic obesity following craniopharyngioma and long-term survival rates, (Zacharia, et al., *Neuro-Oncology* 14(8):1070–1078, 2012. doi:10.1093/neuonc/nos142; and Muller, et al., *Neuro-Oncology* 17(7), 1029–1038, 2015 doi:10.1093/neuonc/nov044.); **European estimates limited to the EU4 (Germany, France, Spain, Italy), UK and the Netherlands and prevalence of 0.1-0.3 in 10,000 patients; £ Rhythm estimates the prevalence of acquired hypothalamic obesity in Japan to be approximately 5,000 to 8,000 based on our review of tumor registries and claims data; Prevalence is 2-3 times higher than in the USA & Europe due to a higher frequency of craniopharyngioma been reported.

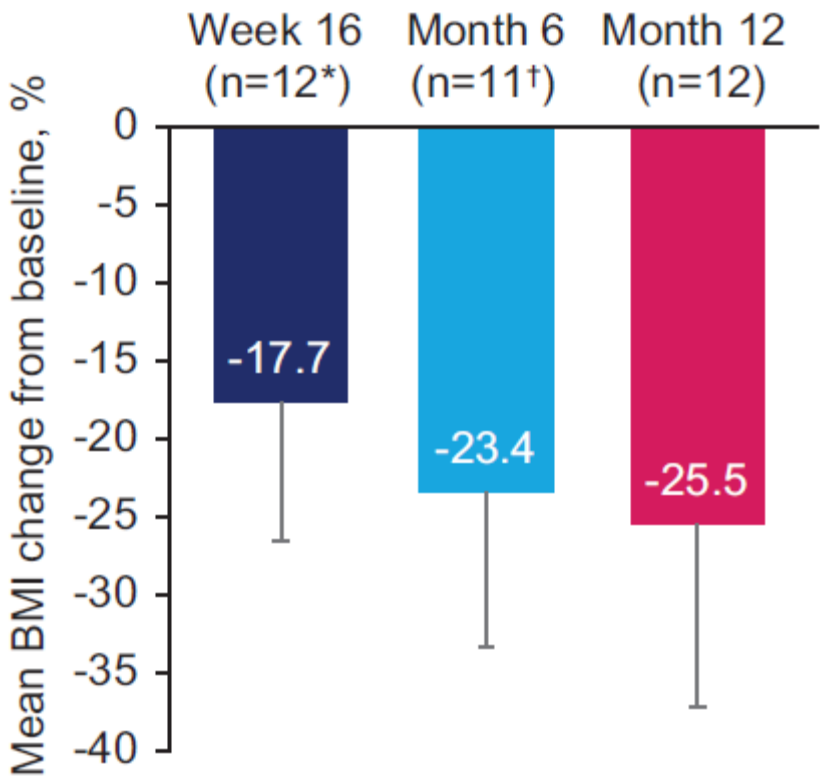
HO: Aggressive, Rapid Weight Gain follows Therapy for CP

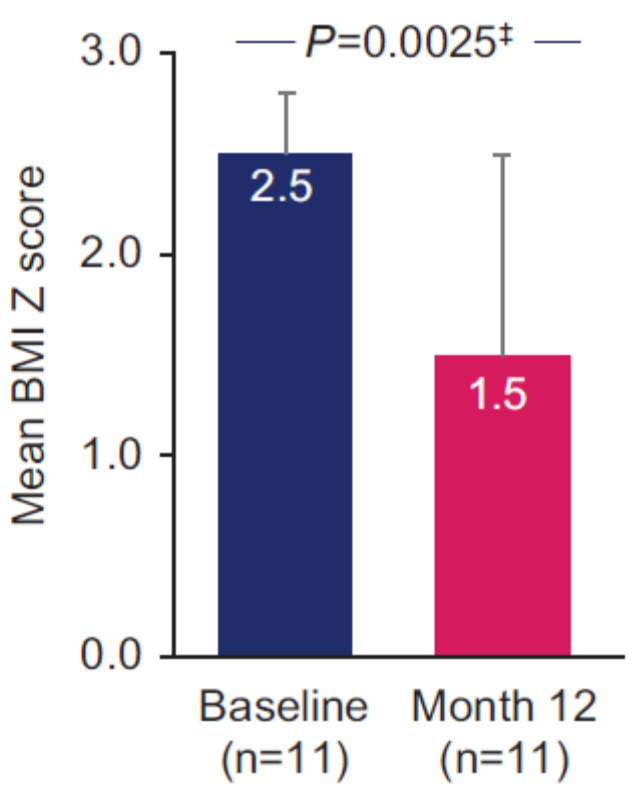
Patient Case Study: Setmelanotide therapy achieved rapid, significant weight loss

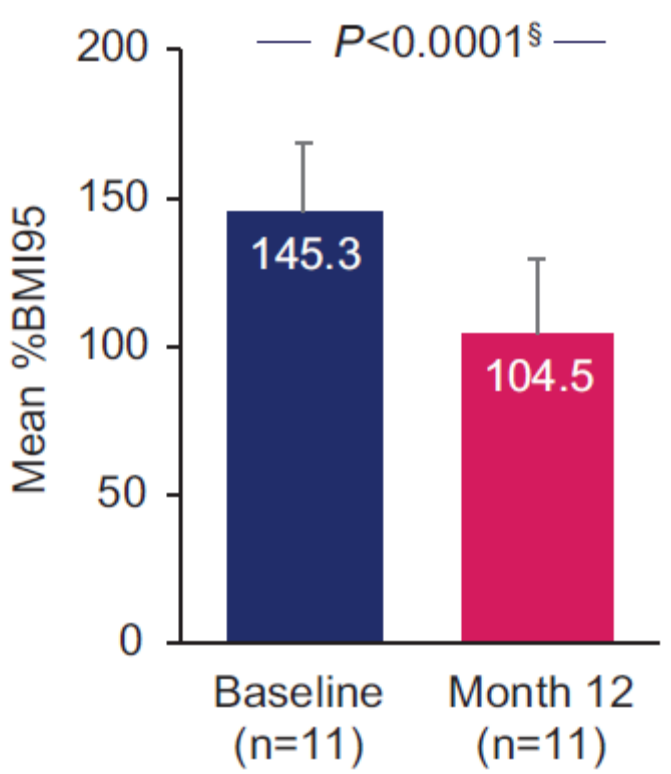


Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota

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

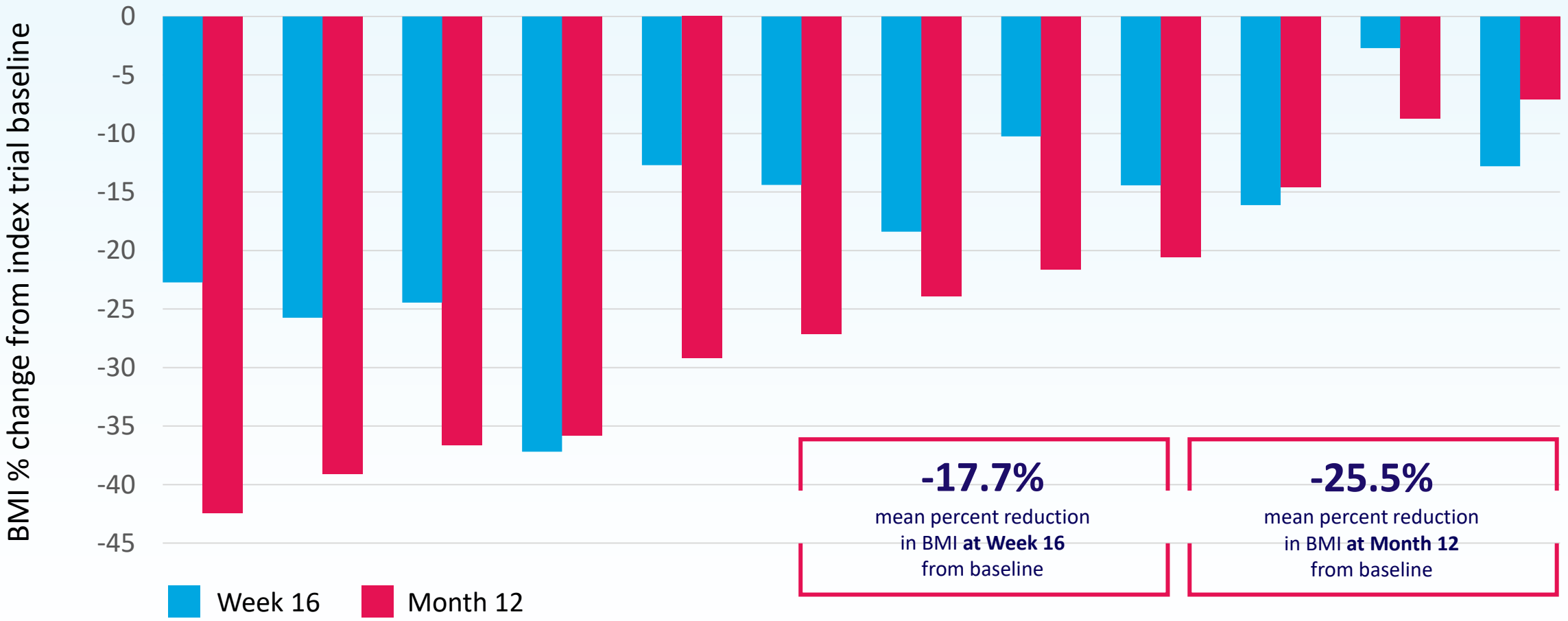






Error bars are the standard deviation. *Includes all patients who received 16 weeks of setmelanotide in the index trial and ≥12 months of treatment in the long-term extension. †One patient did not complete a Month-6 visit. ‡One sample *t*-test with 2-tailed *P*-values. §Paired *t*-test with 2-tailed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

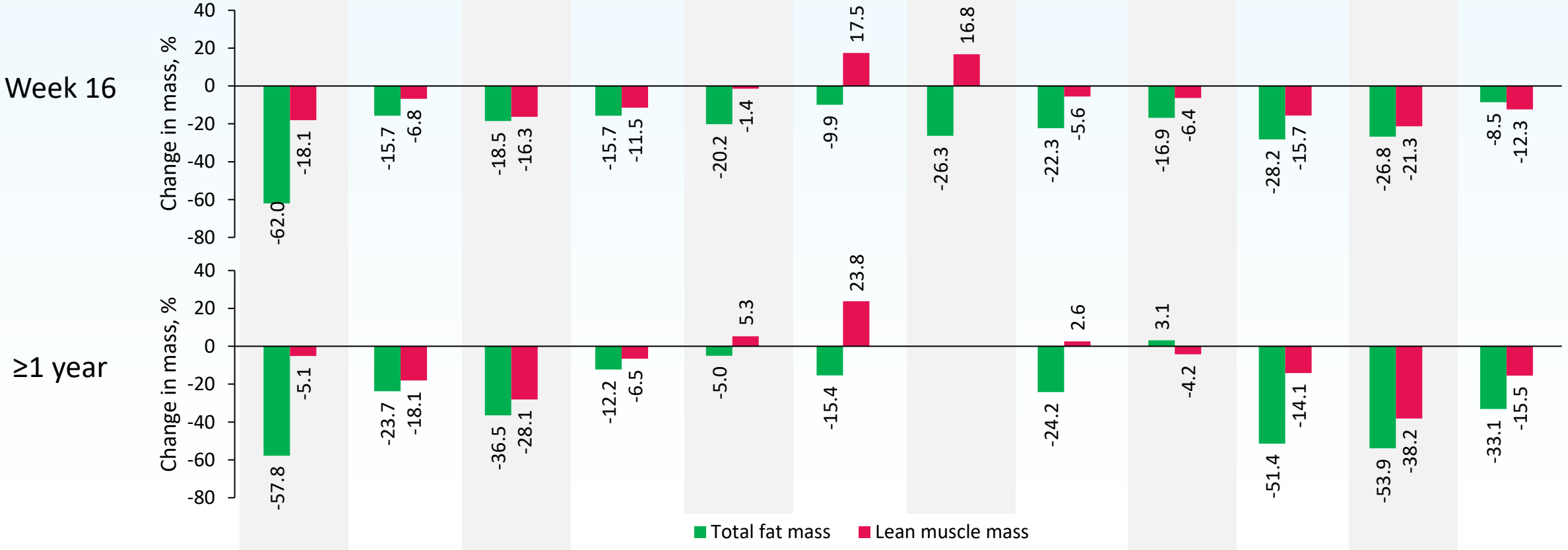


Adapted from data presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.

Rhythm® PHARMACEUTICALS

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.

Positive Real-world Setmelanotide Data Reported from French Early-access Program in Adult Patients with Acquired Hypothalamic Obesity

N=8*
patients

19.3 years
Mean age at resection

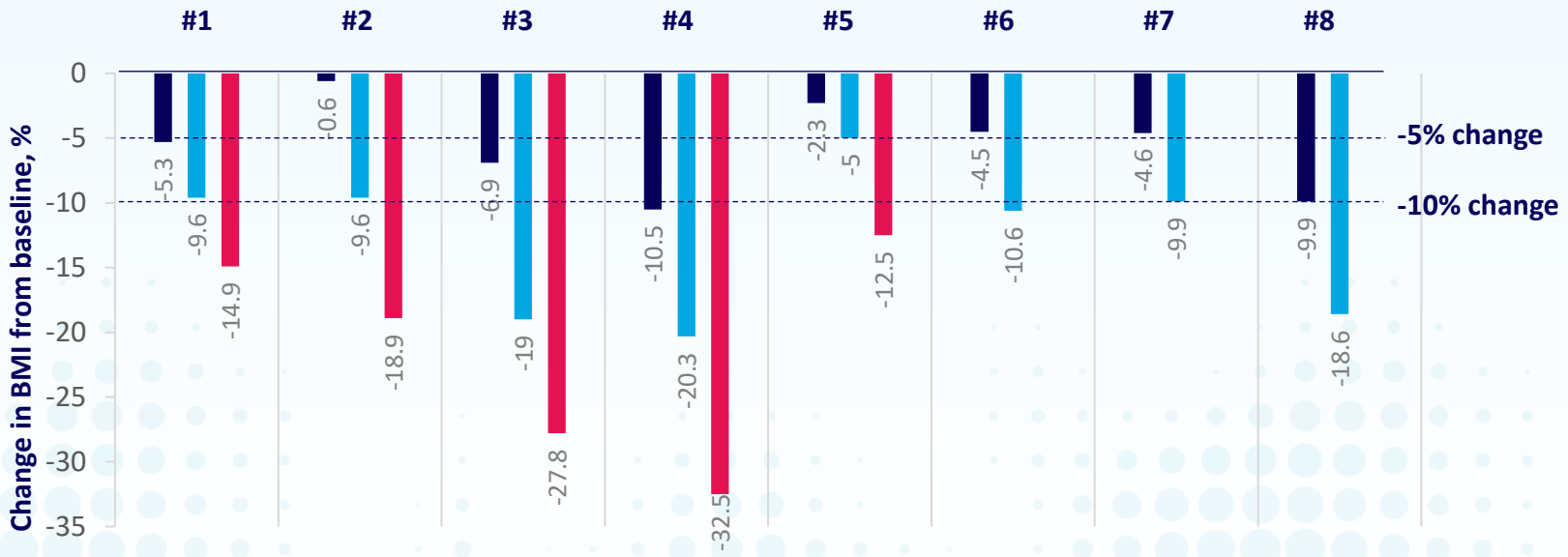
31.4 years
Mean age at initiation of setmelanotide therapy

44.1 kg/m²
Mean BMI at baseline

-5.6%
Mean BMI reduction
■ **Month 1**

-12.8%
Mean BMI reduction
■ **Month 3**

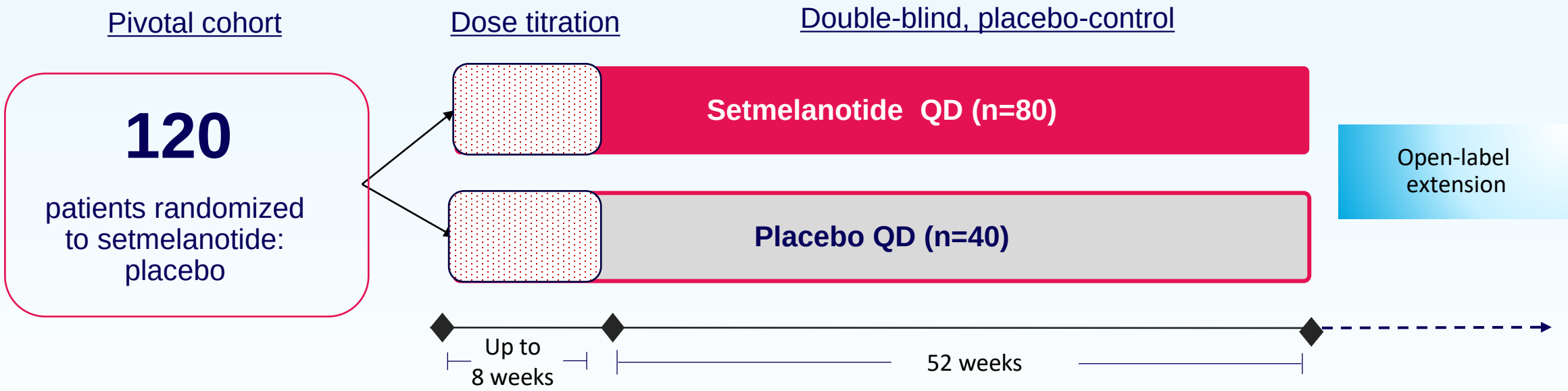
-21.3%
Mean BMI reduction
■ **Month 6**



*50% male; all aged ≥18 years, with a previous resection of craniopharyngioma (n=7) or of Rathke cleft cyst (n=1); Adapted from "3-Month Real-World Setmelanotide Hunger and Weight Outcomes in Patients with Hypothalamic Obesity" poster presented ObesityWeek®; November 3-6, 2024, in San Antonio, TX, USA.

Rhythm® PHARMACEUTICALS

Phase 3 Hypothalamic Obesity Trial: Enrollment Complete, Top-line Data Expected in H1 2025



+12 Japanese patients enrolled supplemental cohort; Data from this supplemental cohort will serve as the basis for a regulatory submission in Japan.

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

Congenital HO Represents Additional Opportunity with Significant Unmet need

Congenital HO occurs due to **dysfunction or damage to the hypothalamus from birth**, with patients often experiencing **hyperphagia** and difficulty managing their weight

The weight gain and appetite changes accompanying HO are often **unresponsive to existing therapies** for obesity

No approved therapies for congenital HO

>1,000 patients

estimated prevalence
in each
the United States
and Europe

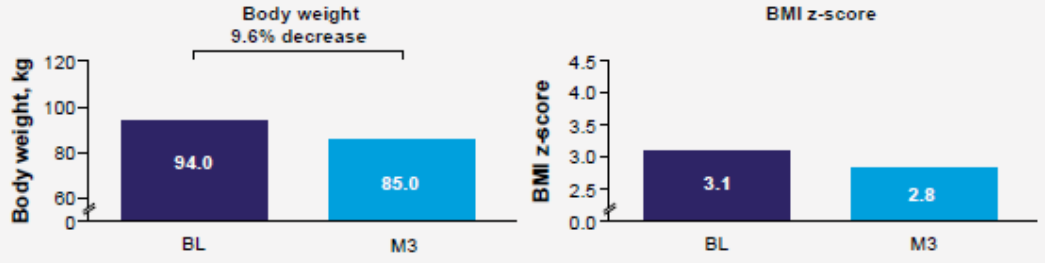
Real-world Case Reports from French Early-access Program Suggest Setmelanotide may be Effective Treatment for Congenital HO

Case reports presented at 62nd annual meeting of the European Society for Paediatric Endocrinology (EPSE)

Case Report 3 (Congenital HO)

- Patient 3, female, had septo-optic dysplasia (SOD), combined pituitary hormone deficiency and valgus foot as co-morbidity. Age of onset of obesity was not reported
- Setmelanotide treatment was started at 15 years of age, with dose escalation from 0.5 mg at BL to 1 mg at M3
  - As ongoing treatment, patient was on hormonal replacement therapy
- Patient had a 9.6% decrease in body weight and -0.3 BMI z-score change at M3 of treatment **(Figure 3)**

Figure 3:

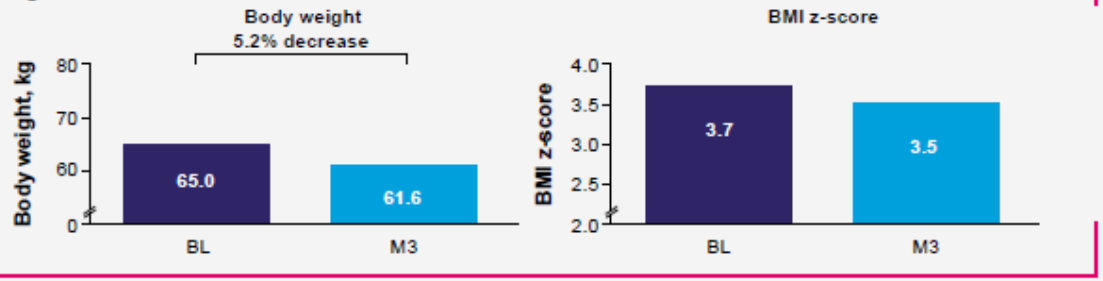


- For the 4 questions included in the scoring of hunger scores, the reported change was 5-5-0-6 (BL) to 5-5-0-5 (M3). Physician noted difficulty in interpretation and scoring with the questionnaire
- During treatment, patient reported injection site reaction and intermittent diarrhoea at 2 weeks of treatment which was resolved. Angina, sore throat and hyperpigmentation was reported at M3

Case Report 4 (Congenital HO)

- Patient 4, male, 2.5 years at onset of obesity, had pituitary stalk interruption syndrome (PSIS), corticotropic, thyrotropic and growth hormone (GH) deficiency as co-morbidity
- Setmelanotide treatment was started at 9 years of age, with dose escalation from 0.5 mg at BL to 2 mg at M3
  - As ongoing treatment, patient was on hormonal replacement therapy
- Patient had a 5.2% decrease in body weight and -0.2 BMI z-score change at M3 of treatment **(Figure 4)**

Figure 4:



- For the hunger outcomes, patient reported a qualitative improvement rather than quantitative, as normally reflected by hunger scores. Initially, the patient described feeling moderately hungry at BL, slightly hungry at M1, and not hungry at all by M3 of treatment
- During treatment, no adverse events were reported for the patient

Adapted from '3-Month real-world setmelanotide hunger and weight outcomes in four French paediatric patients with acquired or congenital hypothalamic obesity,' presented at ESPE on November 18, 2024, by Dr. Ahlam Azar-Kolakez, et al.

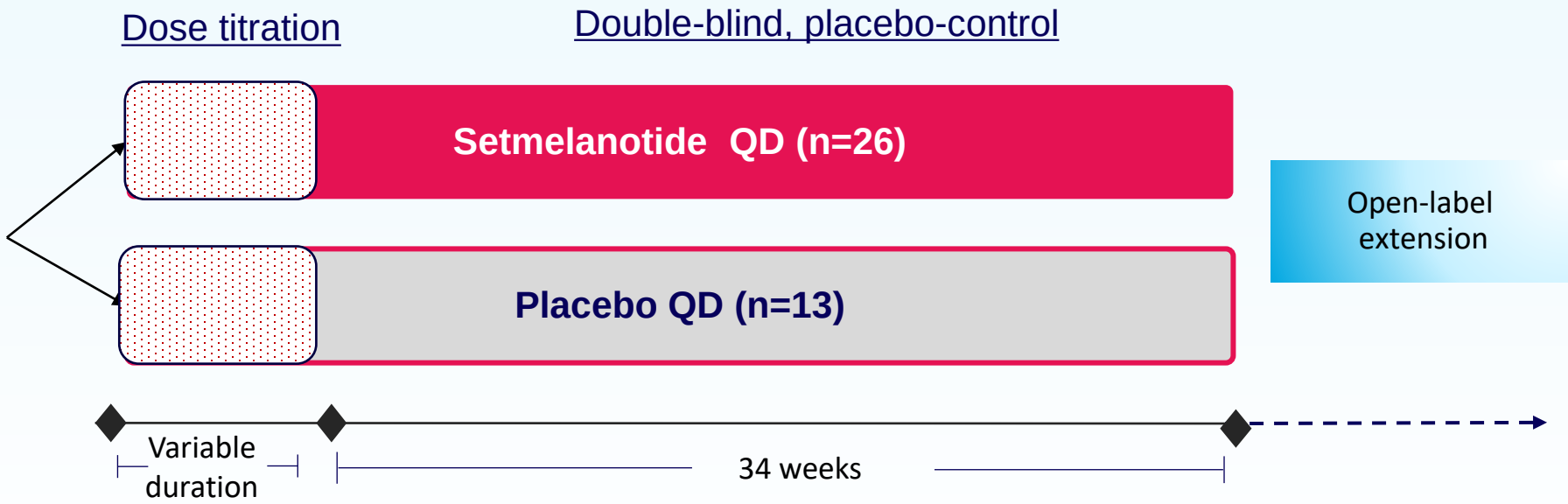
Rhythm® PHARMACEUTICALS

34-week Substudy in Congenital Hypothalamic Obesity Added to Pivotal, Ph3 HO Study

Independent substudy leverages existing Ph3 trial infrastructure; Enrollment expected to begin in Q1 2025

39

patients randomized
2:1
setmelanotide:
placebo



~90% power to detect a treatment difference (treatment - placebo) of -12% in percent change of BMI from baseline after 26 weeks on a therapeutic regimen (up to 34 weeks) at 2-sided alpha of 0.05

Rhythm® PHARMACEUTICALS

Advancing Next-generation MC4R Agonists in Acquired HO Clinical Trials

Efficient signal finding possible due to sensitivity of acquired HO to MC4R agonism

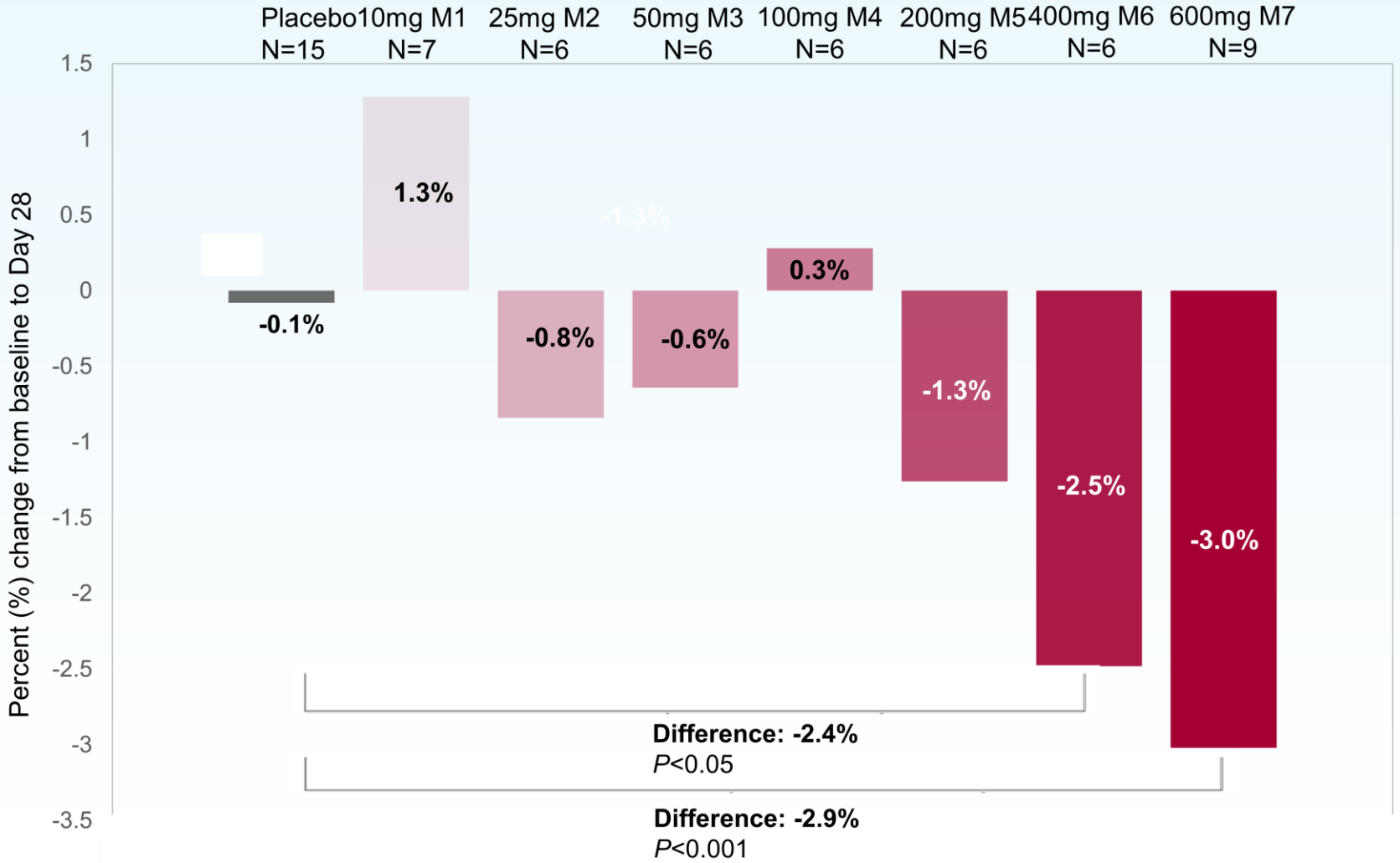
Bivamelagon (LB54640)

- Global rights acquired from LG Chem in January 2024
- Daily oral, highly selective MC4R agonist
- Compelling Phase 1 data in healthy, obese volunteers
- No hyperpigmentation observed
- IP protection out to 2045, assuming patent term extension

RM-718

- Developed in-house based on setmelanotide
- 7-amino acid peptide administered QW
- In vivo results: supportive of no off-target cardiovascular effects, like setmelanotide; No hyperpigmentation observed
- In vivo results suggest potential efficacy for body weight reduction, hyperphagia reduction
- IP protection out to 2040, assuming patent term extension

Bivamelagon Showed Dose-response Body Weight Loss Healthy Volunteers with General Obesity



Favorable safety profile

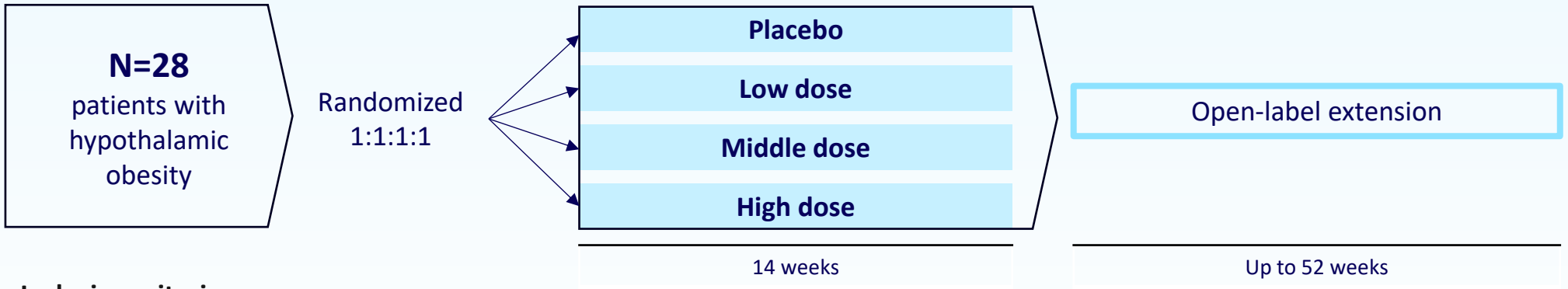
- No serious adverse events
- No skin pigmentation, adrenal, or genitourinary adverse events observed
- Mild to moderate nausea, diarrhea, vomiting most common

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

Rhythm® PHARMACEUTICALS

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

Enrollment to be complete in Q1 2025



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

Three-part Phase 1 Study Evaluating RM-718 QW Ongoing

Part C dosing of patients with acquired HO expected to begin in Q1 2025

Part A: SAD
RM-718 QW

Screening: 28 days
9 cohorts X 6 subjects ≥18yo
n=54
Randomized 2:1 (RM-718: Placebo)
Single ascending doses 3mg - 80mg*
Safety follow up 28 days

Part B: MAD
RM-718 QW 4 doses

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

Part C: MAD Hypothalamic Obesity RM-718 QW 16 weeks

Screening: 28 days
1 cohort X up to 30 patients
≥12yo
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. In Part C, Dosing will initiate in patients ≥18 years of age. Based on the ongoing evaluation of safety, tolerability, and available PK data (including 8-week dosing data from a minimum of 6 patients ≥18 years of age), dosing may proceed in patients <18 years of age. 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.

EMANATE and DAYBREAK

Genetically-defined MC4R Pathway Diseases

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 — **Study completed in 2024**

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;

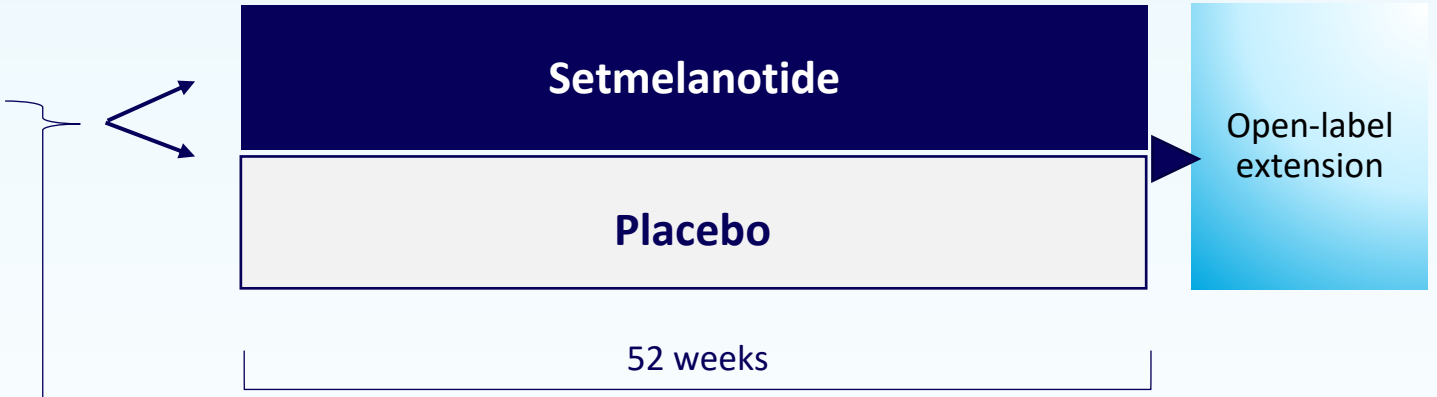
Phase 3 EMANATE Trial Comprised of Four Independent Sub-studies

Enrollment completed in 4Q 2024; Topline data anticipated in H1 2026

Genetic substudy	Enrolled patients	ACMG Classification
POMC/ PCSK1*	**n=79**	• Pathogenic • Likely pathogenic • VUS*-Suspected pathogenic
LEPR*	**n=23**	• Pathogenic • Likely pathogenic • VUS-Suspected pathogenic
SRC1	**n=73**	• All VUS
SH2B1	**n=121**	• Pathogenic • Likely pathogenic • VUS

* VUS = Variant of uncertain significance;

Each sub-study: Patients randomized 1:1

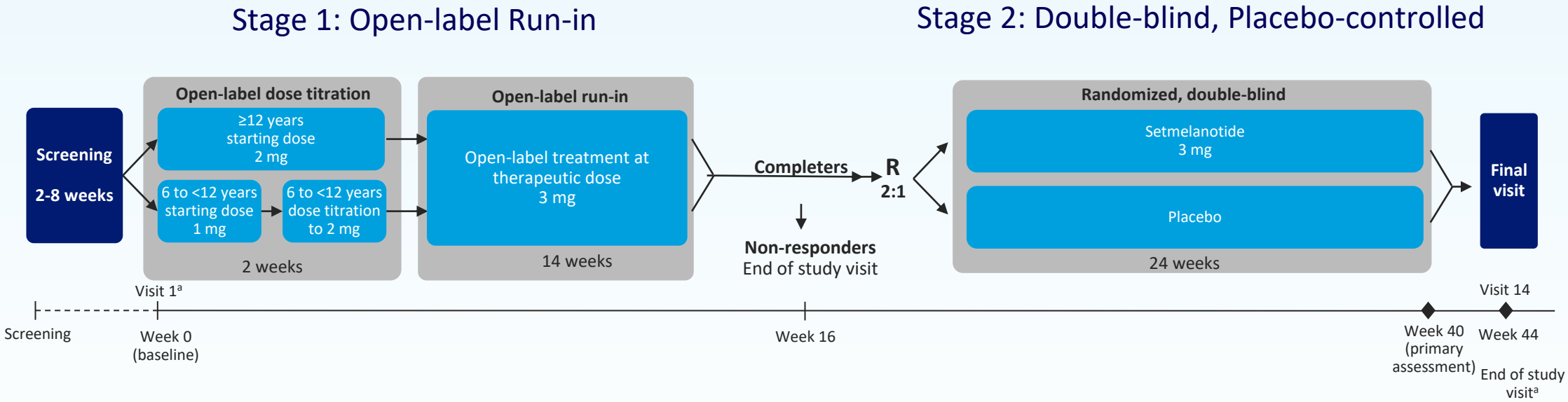


Endpoints

- 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

NOTE: The SRC1 and LEPR substudies are currently under-enrolled, so additional studies may be necessary in order to seek regulatory approval. We believe the SH2B1 and POMC/PCSK1 substudies are fully enrolled and powered and could enable Rhythm to seek registration, pending success.

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)

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

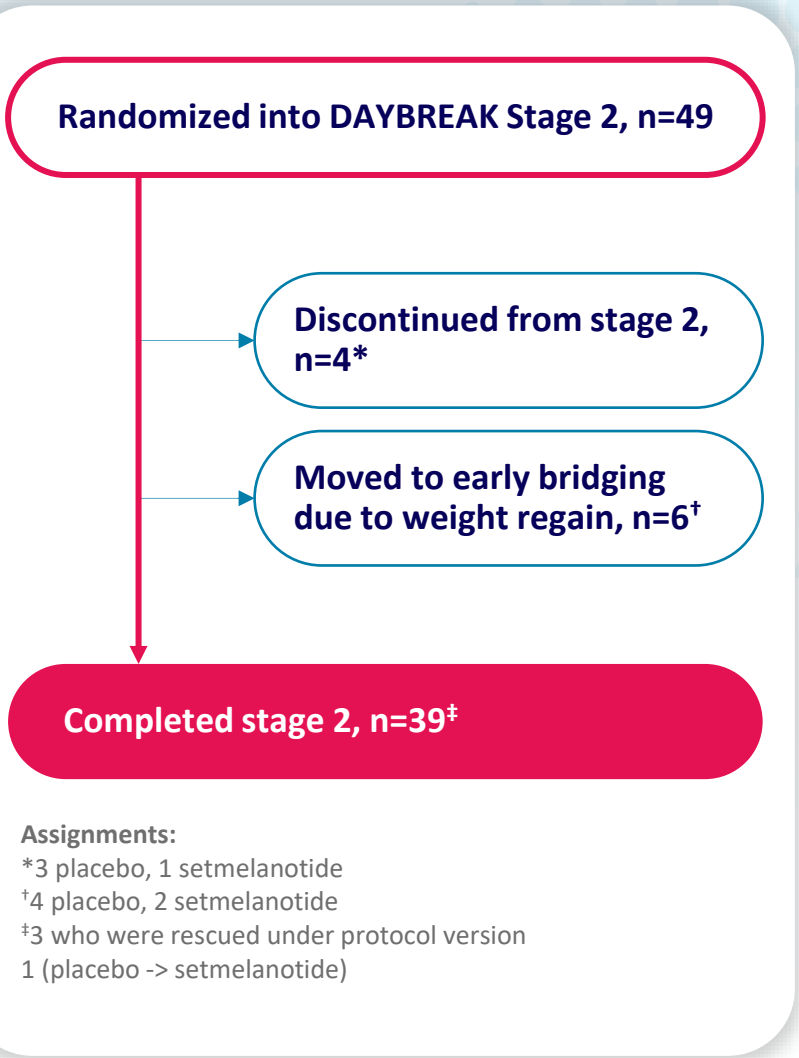
S2 Eligibility Criteria Reduction at end of S1, from baseline: Adult: Reduction of ≥3% BMI; Pediatric: reduction of ≥3% BMI OR of ≥0.05 BMI Z-score

[a]Virtual visit. R, randomization.

DAYBREAK Baseline Demographics

Sex, N=49	All	<18 yrs	≥18 yrs
Male n (%)	22 (44.9)	10 (45.5)	12 (54.5)
Female n (%)	27 (55.1)	14 (51.9)	13 (48.1)

N=49	n	Mean (SD)	Range	% of S1 starters
BMI, kg/m^2				
Adult Baseline	25	46.1 (7.2)	40.4 - 69.9	23%
Adult Stage 2 start	25	42.6 (7.0)	36.2 - 66.3	-
BMI-Z (CDC)				
Pediatric Baseline	24	2.5 (0.3)	1.83 - 2.97	44%
Pediatric Stage 2 start	24	2.25 (0.4)	1.48 - 2.92	-



Assignments:
*3 placebo, 1 setmelanotide
†4 placebo, 2 setmelanotide
‡3 who were rescued under protocol version 1 (placebo -> setmelanotide)

Data Highlights from Stage 2 of DAYBREAK Phase 2 Trial

-12.4%

Mean BMI change from baseline
(SD: 8.0%; range 1.2%-35.0%)

n=32

patients on continuous
setmelanotide therapy*

84%

or **27 of 32**

patients on

setmelanotide

vs.

29%

or **5 of 17**

patients on

placebo

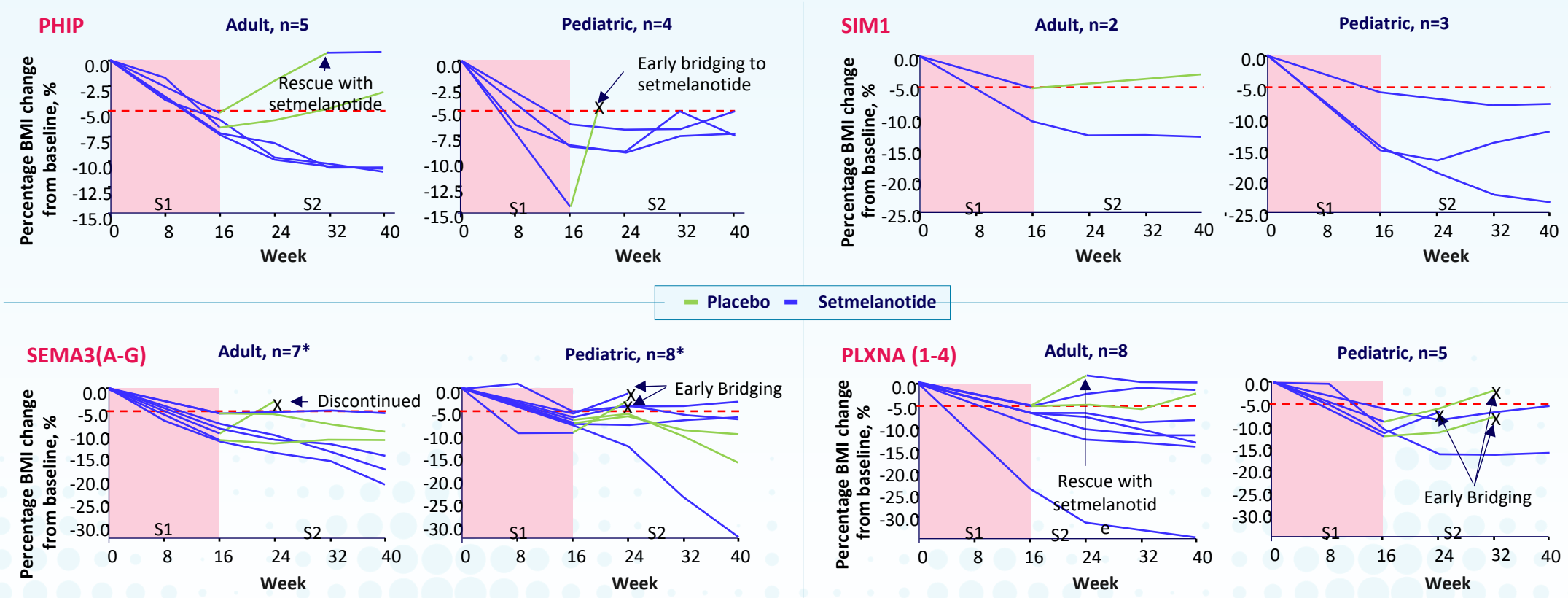
achieved or maintained
>5% BMI reduction from baseline

P=0.001

* Analyses were limited by the small number of PBO-treated pts

Variable Responses Observed in DAYBREAK Stage 2 in Different Genetic Cohorts

Several genetically defined subgroups may merit further study with next-generation MC4R agonists



*One adult and one pediatric SEMA3G patient dropped out of S2 prior to having any data and are not shown

Prader-Willi Syndrome

Revisiting Prader-Willi Syndrome

PWS is a **complex, multi-system** disorder

Constant sense of hunger usually begins at 2yo; if not managed by stringent food restrictions and environmental controls, often **results in life-threatening obesity**

Currently **no approved therapies** that effectively reduce the **extreme hyperphagia** or address **low resting energy expenditure**

Prior setmelanotide study evaluated **low doses** (up to 2.5mg daily) for **only 4 weeks**; results were not statistically significant

~20,000 patients

estimated
U.S. prevalence

~400,000

Estimated world-wide prevalence

In 2016, Rhythm completed a Phase 2 trial (NCT02311673) that evaluated setmelanotide in patients with PWS 16-65 years of age. The study had co-primary endpoints of weight and hyperphagia after 4 weeks of placebo or setmelanotide (doses up to 2.5 mg). No statistically significant treatment differences were observed for the co-primary endpoints

Initiating Exploratory Phase 2, Open-label Trial of Setmelanotide in PWS in Q1 2025

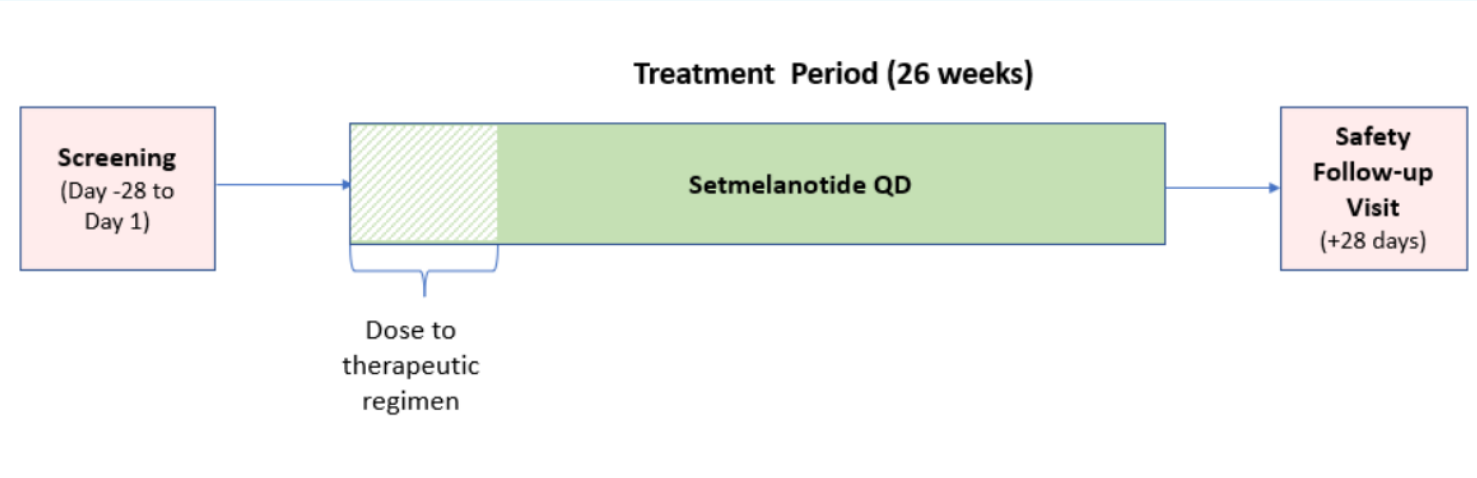
Single, US-site

Up to **20 patients** with PWS and obesity aged 6 to 65 years old

Daily dose of setmelanotide escalated to **5 mg/day** as tolerated for **26 weeks**

Primary endpoints: safety and tolerability

Key secondaries: assessments on **weight, hyperphagia, behavior** and pharmacokinetics



IMCIVREE Global Commercial Execution

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

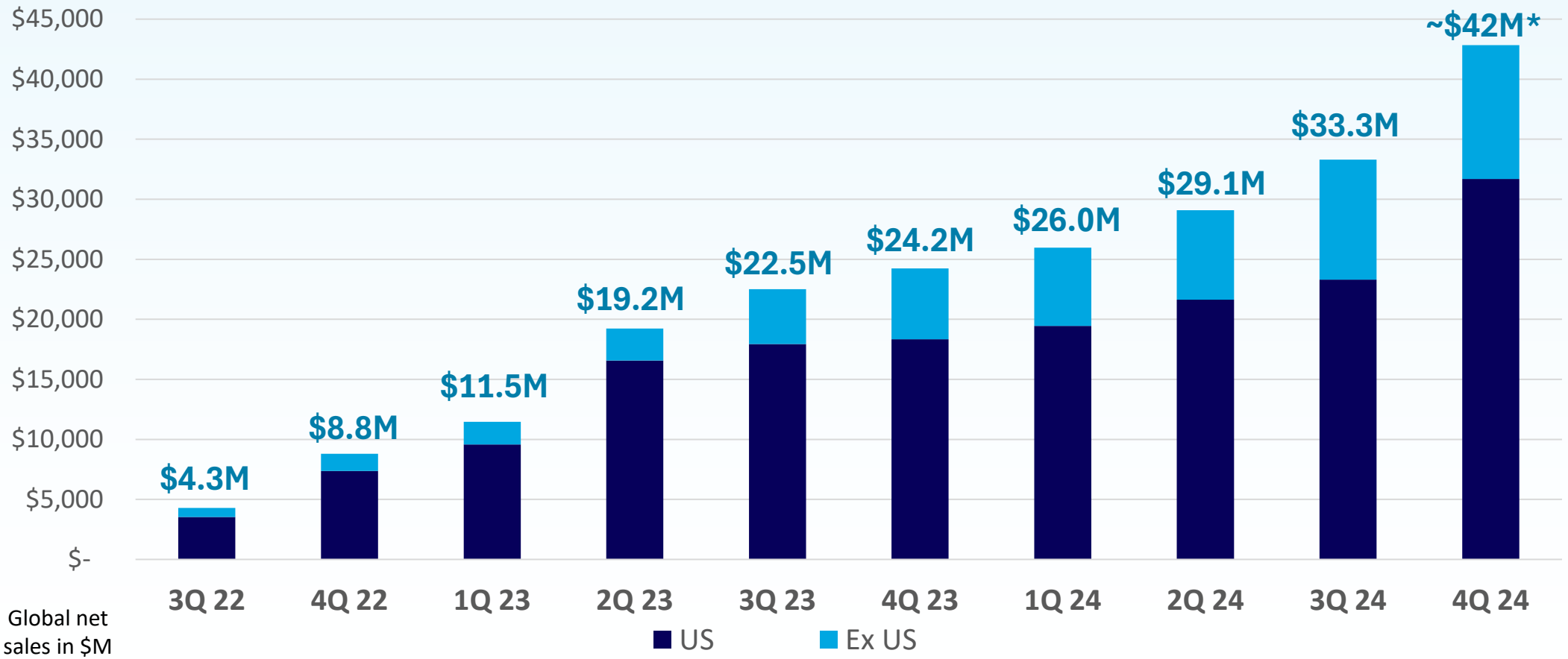
IMCIVREE™
(setmelanotide) injection

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

- **Bardet-Biedl syndrome** (BBS)
- 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)

Steady Growth in Net Product Revenues since BBS Launch

FDA approved IMCIVREE for BBS in June 2022



Global net sales in $M

* Q4 2024 revenues are preliminary and unaudited as of Jan. 10, 2024. The Company plans to report its fourth quarter and full year 2024 financial results in late February 2025.

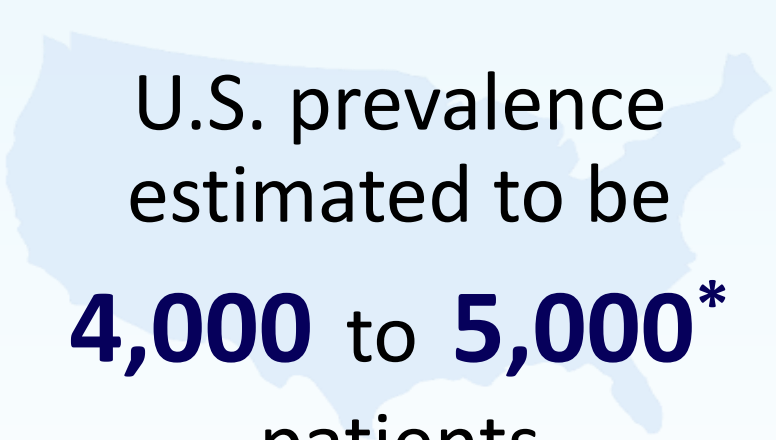
Rhythm® PHARMACEUTICALS

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

U.S. prevalence estimated to be

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

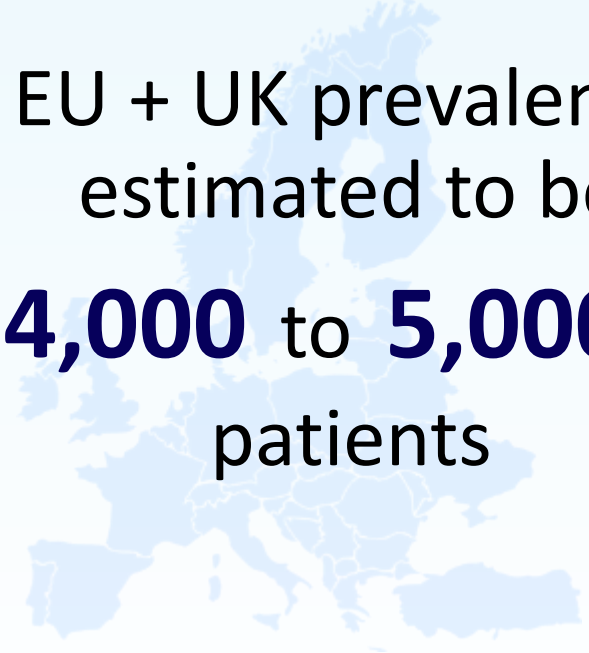
patients



EU + UK prevalence estimated to be

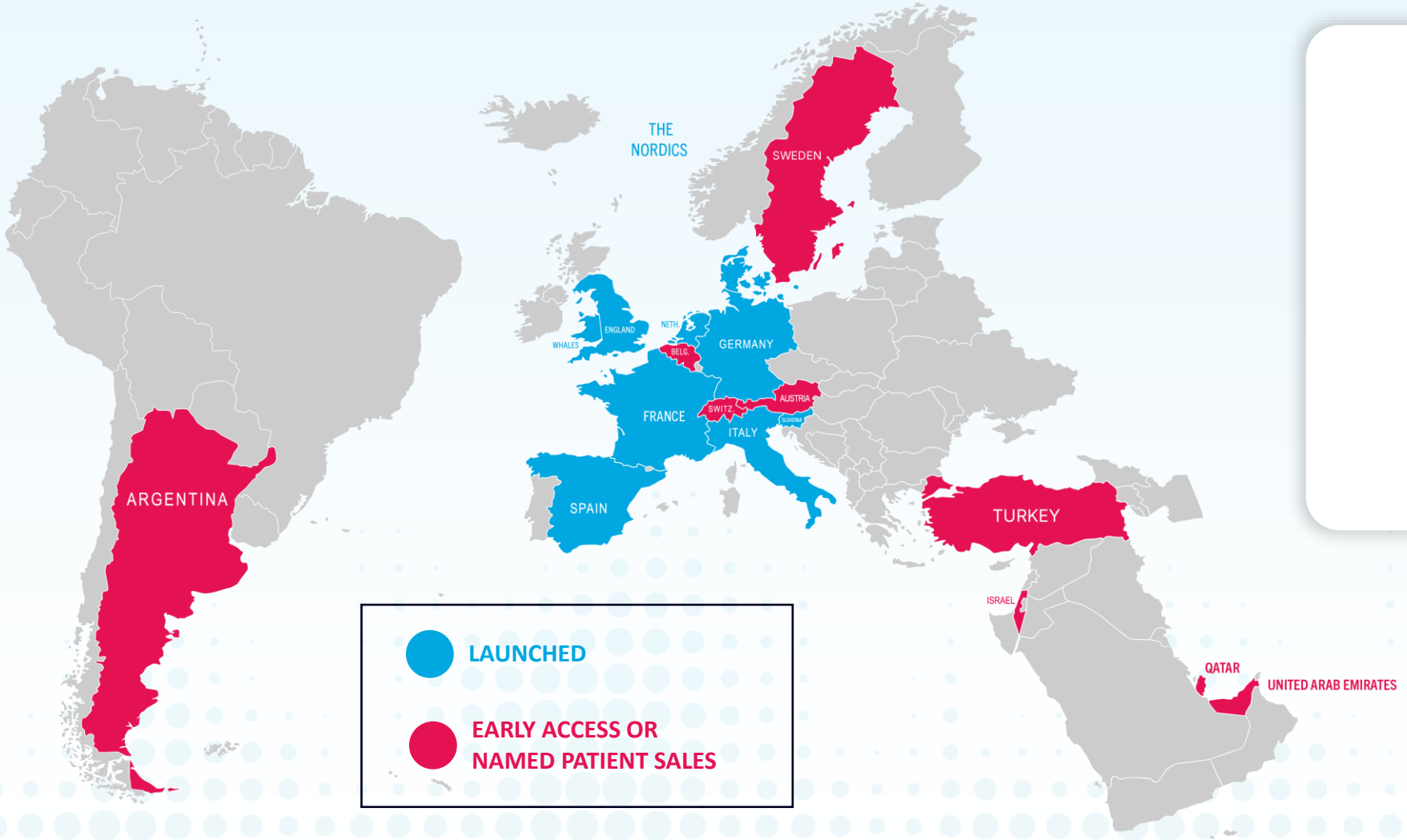
4,000 to **5,000** *

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.

Continued Progress in Securing Market Access for IMCIVREE



IMCIVREE
is available in
>15 countries
outside the
United States

Rhythm® PHARMACEUTICALS

Setmelanotide Benefiting Patients with Hypothalamic Obesity through Reimbursed Early-access Programs in France and Italy

France

- Steady uptake since first available in early 2024
- Access granted by joint federal multidisciplinary committee monthly
- Positive responses reported in adult patients at 2024 ObesityWeek® in San Antonio, TX

Italy

- Eligibility: patients between 6-24 yo with HO caused by craniopharyngioma
- Physician makes request for access directly to Italian MoH
- First patients beginning therapy

BBS Commercial Launch Underway in England and Wales in Q4 2024

England and Wales

- NICE recommended NHS reimbursement for patients younger than 18yo with BBS
- 4 NHS BBS specialized clinics:
  2 for adult patients, 2 for pediatric patients
- Patients to be trained in hospital setting with at-home nursing support

Thank you