# Rhythm Pharmaceuticals

## Corporate Presentation

**September 2026**

# Forward-looking Statements

This presentation and the accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding the safety, efficacy, potential benefits of, and clinical design or progress of any of our products or product candidates at any dosage or in any indication, including, setmelanotide, bivamelagon, and RM-718; the use of setmelanotide in patients with acquired hypothalamic obesity (HO) and the success of our commercial launch; our expectations surrounding potential regulatory submissions, progress, or approvals and timing thereof for any of our product candidates, including anticipated launch in Japan and launches in the European Union and the timing thereof; the commercial growth of IMCIVREE; the estimated market size and addressable population for our drug products, including setmelanotide for the treatment of acquired HO; the future announcement of data from our ongoing clinical trials, including the substudy evaluating setmelanotide for patients with congenital hypothalamic obesity, Part C and Part D of the Phase 1 trial evaluating RM-718, and the open-label Phase 2 trial evaluating setmelanotide in patients with PWS, and ongoing enrollment in our clinical trials; existing or future collaboration agreements; the Company's business strategy and plans; our anticipated financial performance and financial position for any period of time, including our estimated Non-GAAP Operating Expenses for the year ending December 31, 2026; and the sufficiency of our cash, cash equivalents and short-term investments to fund our operations for at least 24 months; and the timing of any of the foregoing. Statements using words such as "expect", "anticipate", "believe", "may", "will", "aim" 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 design and outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, our ability to successfully commercialize setmelanotide, our liquidity and expenses, our ability to retain our key employees and consultants, and to attract, retain and motivate qualified personnel, and general economic conditions, and the other important factors, including those discussed under the caption "Risk Factors" in Rhythm's Quarterly Report on Form 10-Q for the quarter ended June 30, 2026 and our other filings 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.

# MC4R Agonism Development Across Three Pillars

**Genetic MC4R Pathway Diseases**

**Hypothalamic Obesity**

**Prader-Willi Syndrome**

| Next-generation MC4R agonists | |
|---|---|
| RM-718 (weekly injection) | Bivamelagon (daily oral) |

IMCIVREE® (setmelanotide) injection

**Global commercial foundation established by IMCIVREE in BBS**

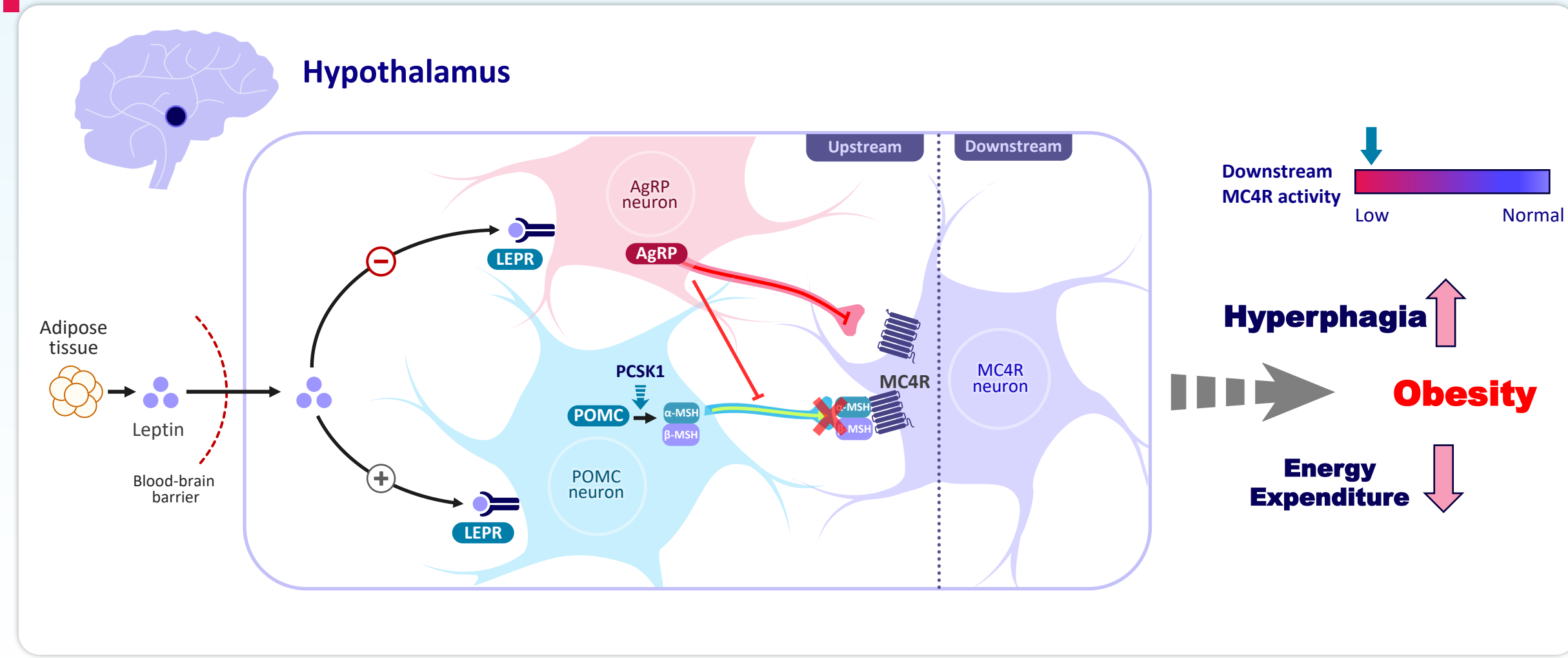
# IMCIVREE: First and Only Therapy Approved for Acquired HO

- ✓ U.S. launch underway following March 19th FDA Approval
- ✓ Japan's MHLW Granted Marketing Authorization; launch anticipated by year-end 2026
- ✓ European Commission Granted Marketing Authorization; country-level launches expected to begin in 2027




NOTE: Approved for patients with HO 4 years old and older; See US FDA-approved package insert and EC-authorized SmPC for more information;
MHLW: Ministry of Health, Labour and Welfare

# MC4R Pathway Biology is Clear




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

# Patient Spotlight: Living with Acquired Hypothalamic Obesity

## Setmelanotide Patient Isaac

*"Everything with day-to-day life was harder for him. Dealing with hyperphagia on top of that…he would suffer, his quality of life was not good"*

*"He was so overweight that everything was a struggle."*

- Brenda, mother of Isaac (diagnosed with acquired HO at 6 years old)

**6 YEARS OLD:**

Developed acquired HO following a craniopharyngioma; loses vision as result of tumor

**7-8 YEARS OLD:**

Severe hyperphagia, undergoes 3 brain surgeries

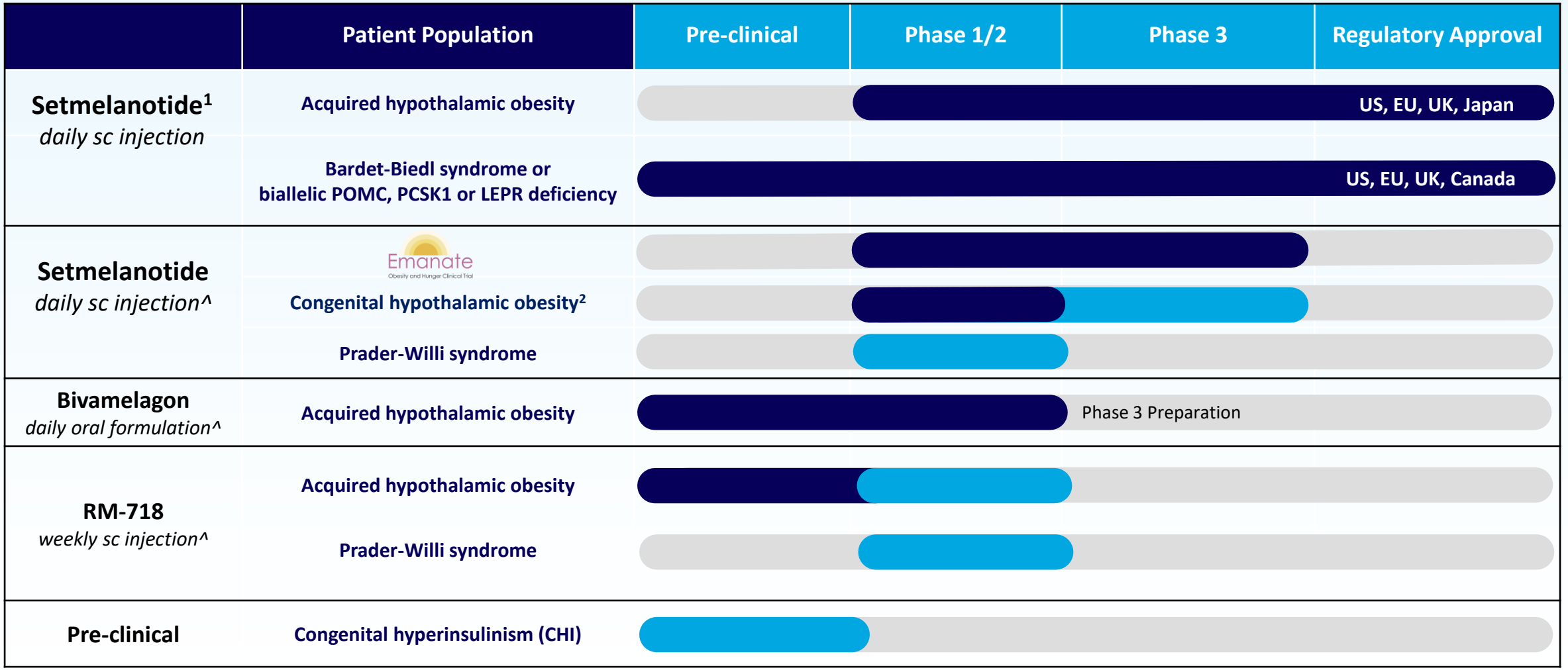
**9 YEARS OLD:**

Hyperphagia, obesity worsen, weight reaches 144 lbs; referred to endo and enrolled in Ph2 trial

**NOW – 13 YEARS OLD:**

Significant reductions in weight and hunger

# Expanding Pipeline in Rare Neuroendocrine Diseases






1. European Commission granted marketing authorization for IMCIVREE for the treatment of obesity and control of hunger in adults and children 4 years of age and above with acquired hypothalamic obesity due to hypothalamic Injury or impairment on May 1, 2026; Approved in Israel & Canada; 2. Setmelanotide is being studied in a proof-of-concept substudy of the Phase 3 TRANSCEND trial; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; sc, sub-cutaneous. ^Currently being studied as

# Significant Market Opportunity for MC4R Agonists

## U.S. patent protection for next-generation assets bivamelagon and RM-718 extends into 2040s

**IMCIVREE approved in U.S., EU,+**

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

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

**IMCIVREE approved in U.S., EU, Japan for acquired HO**

**~10,000**
estimated U.S. prevalence[1]

**~10,000**
estimated European prevalence[2]

**5,000 – 8,000**
estimated Japanese prevalence[3]

**Prader-Willi syndrome**

**8,500 -12,750**
Estimated PWS patients living with hyperphagia/obesity in each of the U.S. and Europe[4-9]

*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.

1. 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.) and company estimates of other tumor types; 2. 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; 3. 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. 4. National Center for Health Statistics (CDC), Final Natality Data (1954–2023); 5. Gallagher L, et al. *A population-based profile of Prader-Willi Syndrome in Ireland*. 2017; 6. Godler DE, et al. *JAMA Netw Open*. 2022; 7. U.S. Prevalence & Mortality of Prader-Willi Syndrome: A Population-Based Study of Medical Claims, JESOCI, Volume 4, Abstract Supplement, 2020; 8. a-population-based-profile-of-prader-willi-syndrome-in-ireland-final-report.pdf; 9. Prader-Willi Syndrome - GeneReviews® - NCBI Bookshelf



Rhythm® PHARMACEUTICALS

# **Well Capitalized:** Cash Sufficient to Fund Planned Operations for at least 24 Months

**$330.9M**

Cash, cash equivalents and short-term investments as of June 30, 2026

**Guidance**

RYTM expects cash to be sufficient to fund planned operations for **at least 24 months**

**68.6 Million**

Common shares outstanding as of June 30, 2026

# 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*

**AJ Joshi, MD**
*Chief Medical Officer*

*20 years of rare disease leadership across clinical development, regulatory strategy and medical affairs*

# Multiple Anticipated Milestones

| | |
|---|---|
| **H2 2026** | Complete enrollment in the **Ph1/2, Part D trial** evaluating **RM-718 (weekly injectable)** in **Prader-Willi syndrome** |
| **H2 2026** | Complete enrollment in **substudy** evaluating **setmelanotide** in **congenital HO** |
| **YE 2026** | Launch **IMCIVREE** for **acquired HO** in **Japan** |
| **YE 2026** | Initiate **pivotal Ph3 trial** evaluating **bivamelagon (daily oral)** in **acquired HO** |
| **2027** | Anticipated **European launches** of **IMCIVREE** for **acquired HO** |

# IMCIVREE Global Commercial Execution

# IMCIVREE available in >25 countries outside the United States for BBS and/or POMC/LEPR Deficiencies

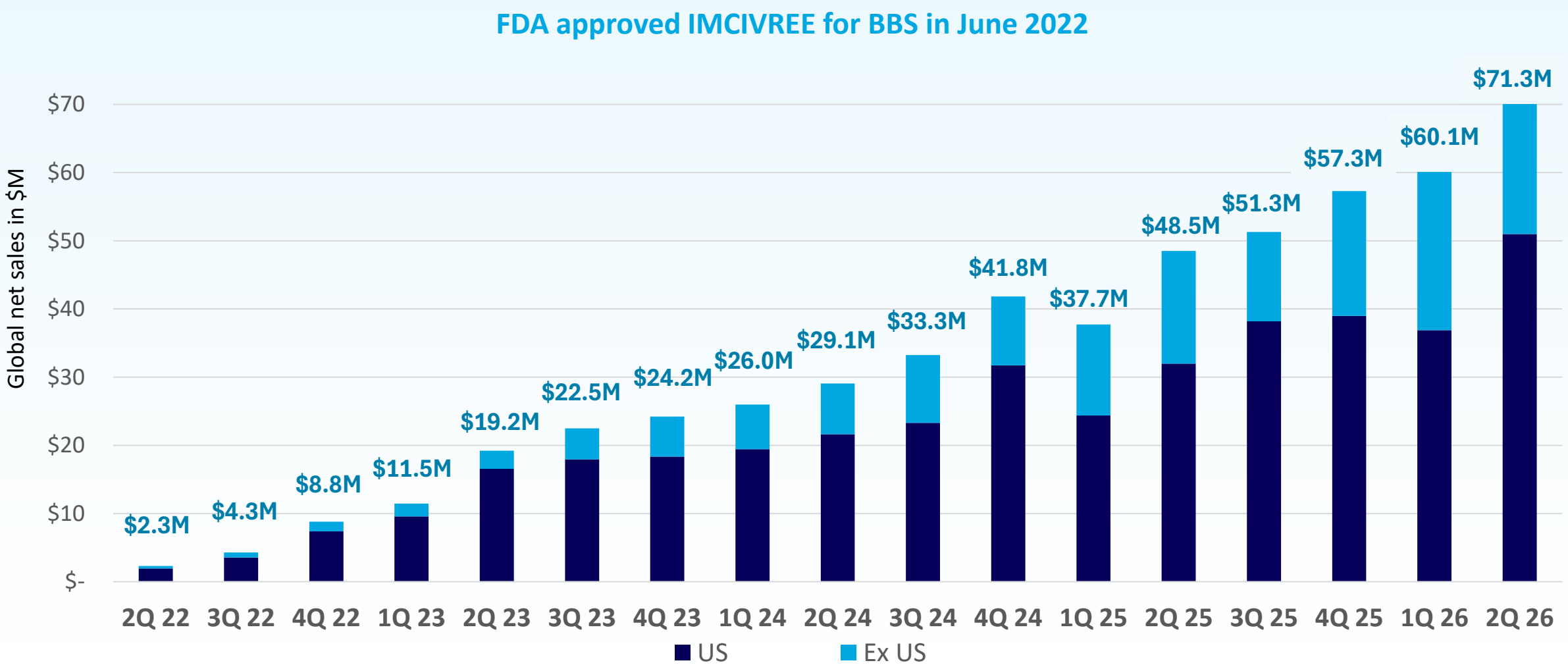
## Supporting Long-Term Growth

**Established global commercial infrastructure**

**Upcoming Ex-US Launches in aHO**

**Focused on reaching more patients globally**

# Steady Growth in Net Product Revenues since BBS Launch



# HO US Launch: Strong Patient Demand and Early Uptake in first 14 weeks

## Start Forms

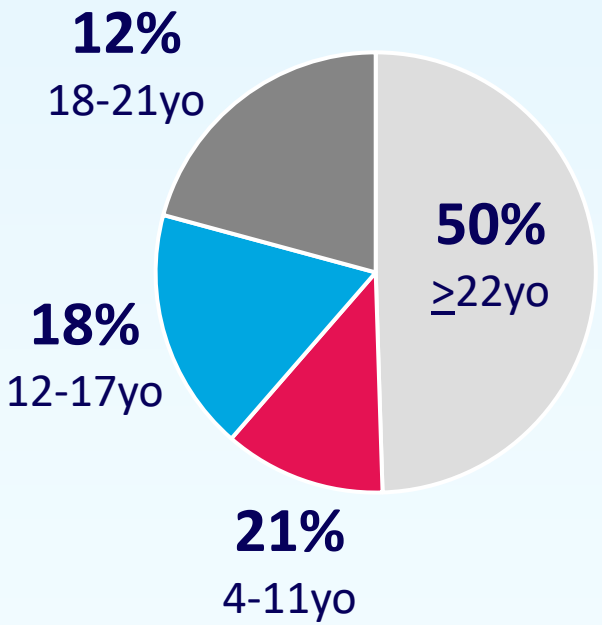
**>400**

Patient Start Forms

Inclusive of **66**

start forms from
clinical trial patients

## Patients by age




## Hypothalamic injury

**~15%**

within two years

**~50%**

>10 years

Note: Between FDA approval on March 19, 2026 and June 30, 2026; yo = years old

# HO US Launch: Broad Prescriber Activation and Engagement

## Prescribers

**~300**

Unique prescribers

**~20%**

Repeat aHO Prescribers

## Specialty

**43%**

Adult Endocrinologist

**37%**

Pediatric Endocrinologist

## Priority Accounts

**~65%**

Activated

**~25%**

of Prescriptions

Note: Between FDA approval on March 19, 2026 and June 30, 2026.

# HO US Launch: Encouraged by Early Payer Engagement

**Majority of early approvals** came **at prior authorization** without aHO specific policy in place

Payer **engagement continues** with majority of P&T meetings expected by year end

## Payers

Positive policies secured

**25%**

of Medicaid covered lives

**35%**

of commercial covered lives

Note: Between FDA approval on March 19, 2026 and June 30, 2026.

# Setmelanotide in Hypothalamic Obesity

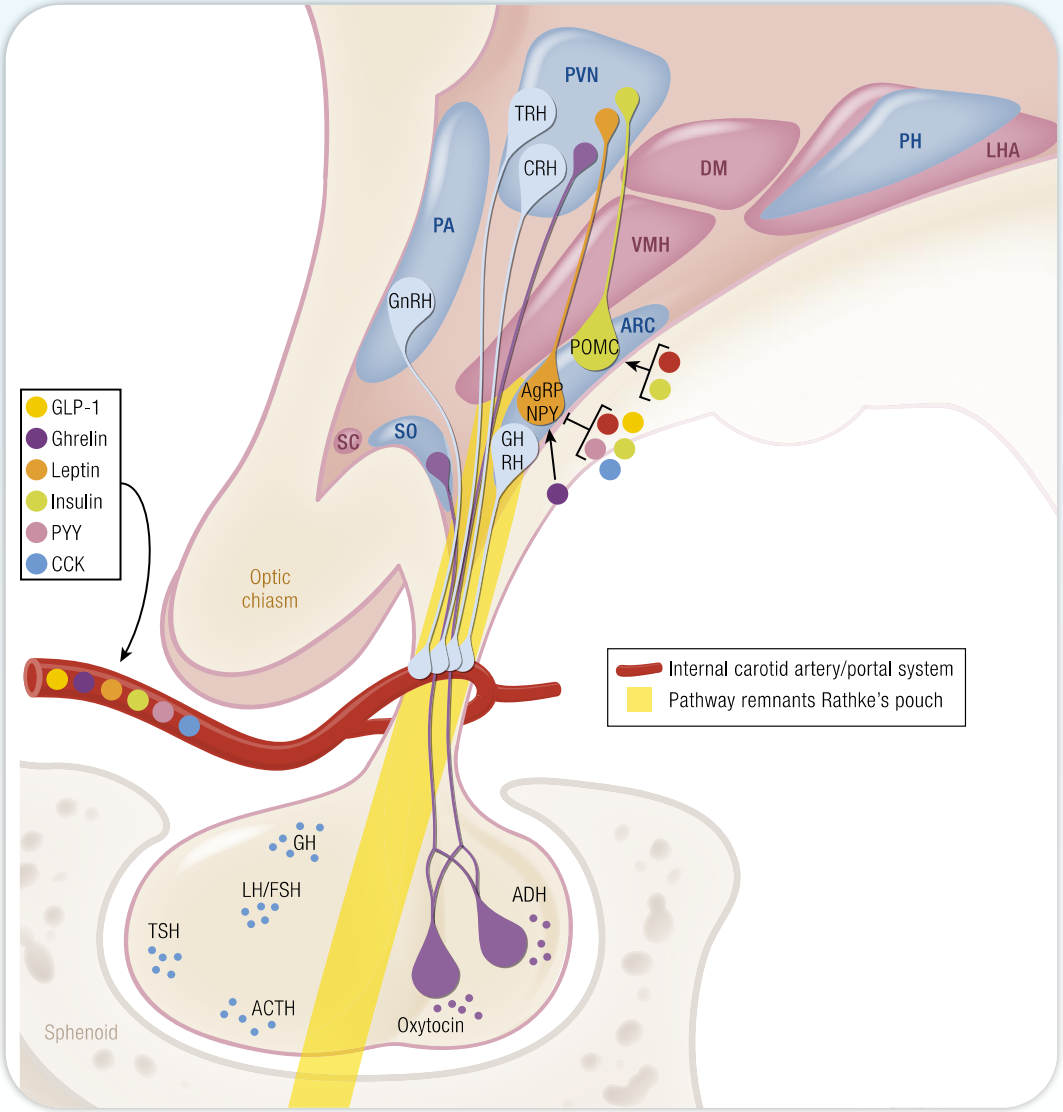
## Acquired and Congenital

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

**Craniopharyngioma** (CP) 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

**IMCIVREE is the only approved treatment for HO**




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

# Severe, Life-long Burden for Patients with Acquired HO

**Frequent visits with multiple specialists, a complex regimen of medications, and hospitalization**

**"Treatment of patients with tumor/treatment-related hypothalamic obesity in the first two years following surgical treatment or radiotherapy"**

**Müller et al., 2025**

scientific reports

**3.7** average hospitalizations during the two years following index;

**23%** included ICU admission in the first year

**12** average number of general practitioner visits and

**20** specialist visits, during the two years following index

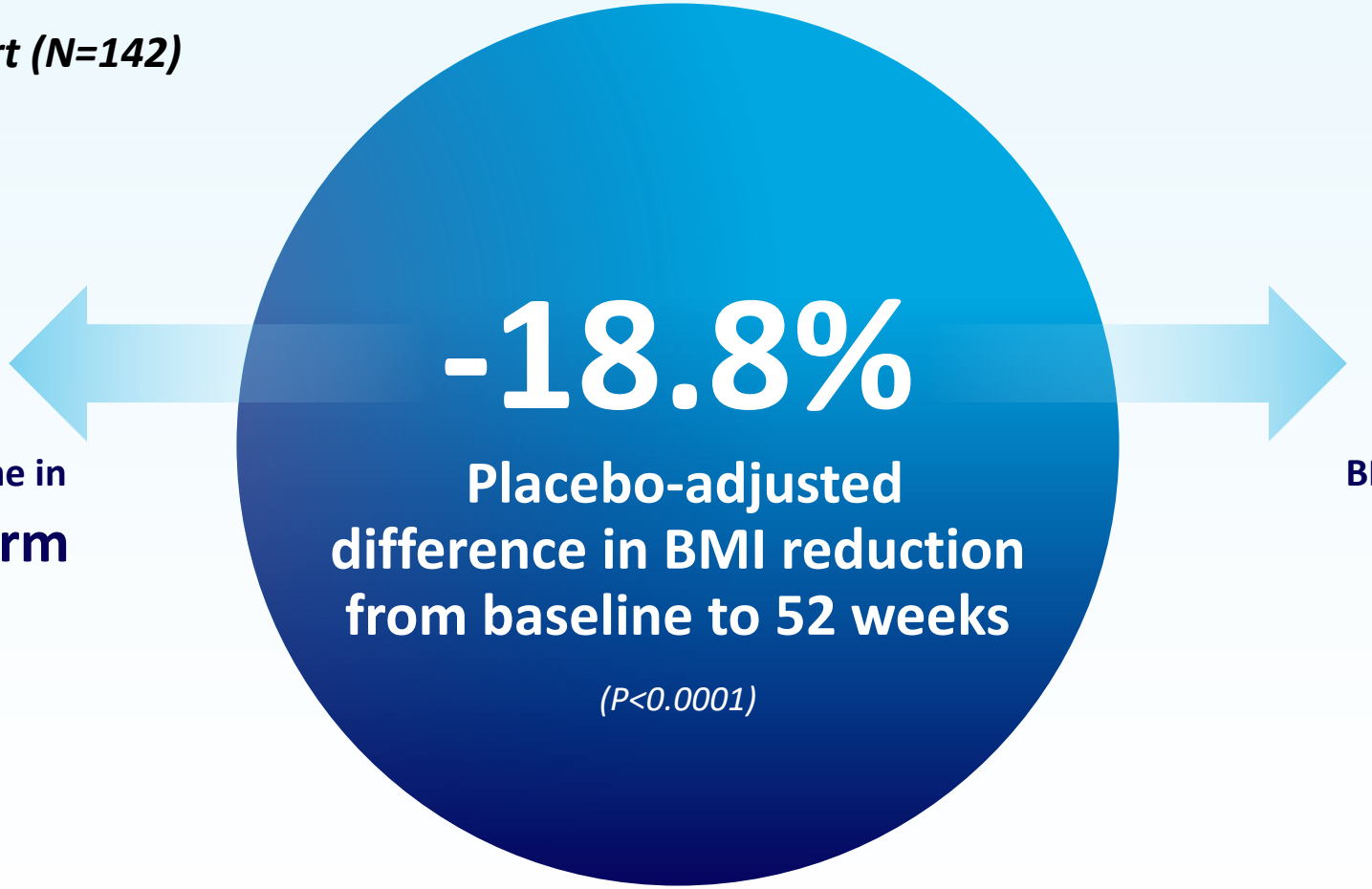
**5.5** average active prescriptions per quarter

**22.1** average number of unique medications over 2 years

**89%** were receiving ≥3 therapies for neuroendocrine dysfunction

# IMCIVREE Approval Supported By Statistically Significant and Highly Clinically Meaningful BMI Reduction in Phase 3 Acquired HO Trial

***Primary analysis cohort (N=142)***




NOTE: Shown are the least square (LS) means for setmelanotide and placebo groups and the LS mean difference in mean percentage change from baseline in BMI at Week 52, obtained from an analysis of covariance (ANCOVA) model. Rubin's Rule was used to provide the overall estimates of differences in LS means and p-value.

# Significant BMI Reductions Observed in Patients Treated with Setmelanotide with Prior Use or Concomitant Use of GLP-1s

**Prior use of GLP-1** *(n=16)*

**-24.7%**

Placebo-adjusted difference in BMI reduction from baseline

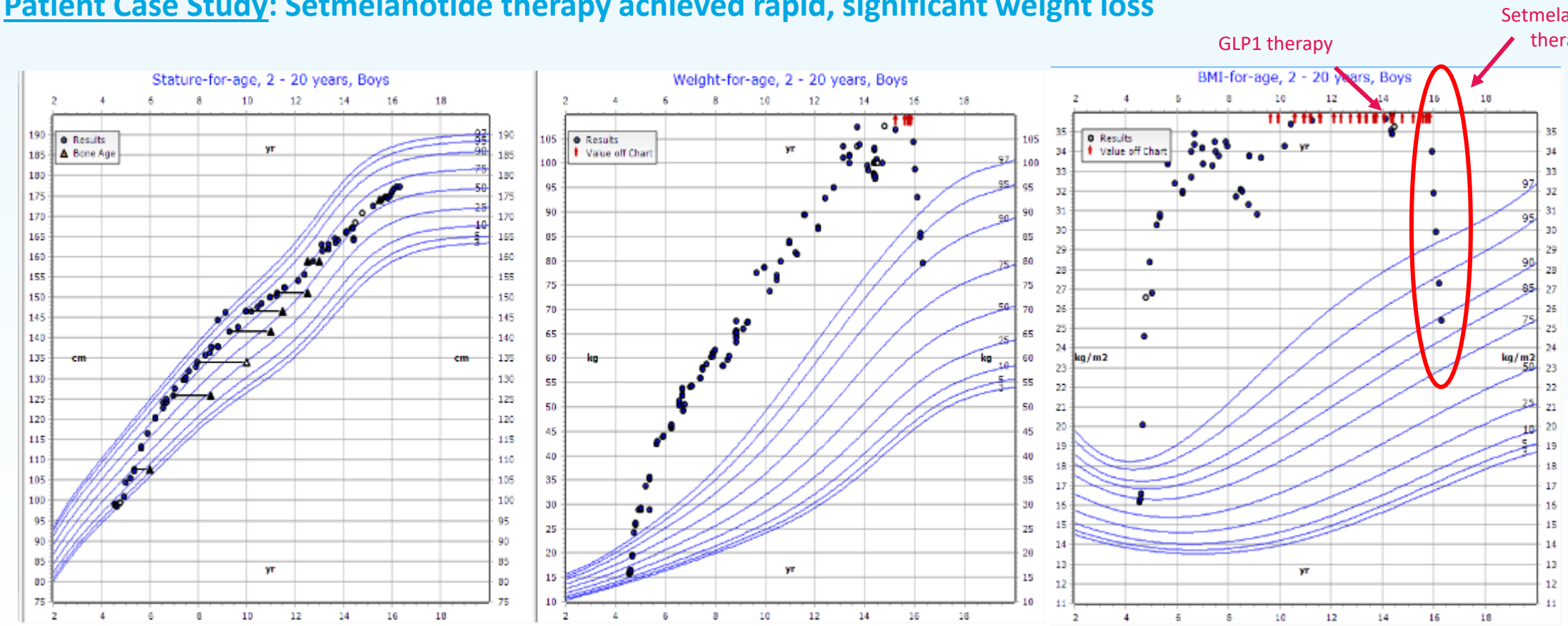
**Concomitant GLP-1** *(n=15)*

**-27.1%**

Placebo-adjusted difference in BMI reduction from baseline

# HO: Aggressive, Rapid Weight Gain follows Therapy for CP

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



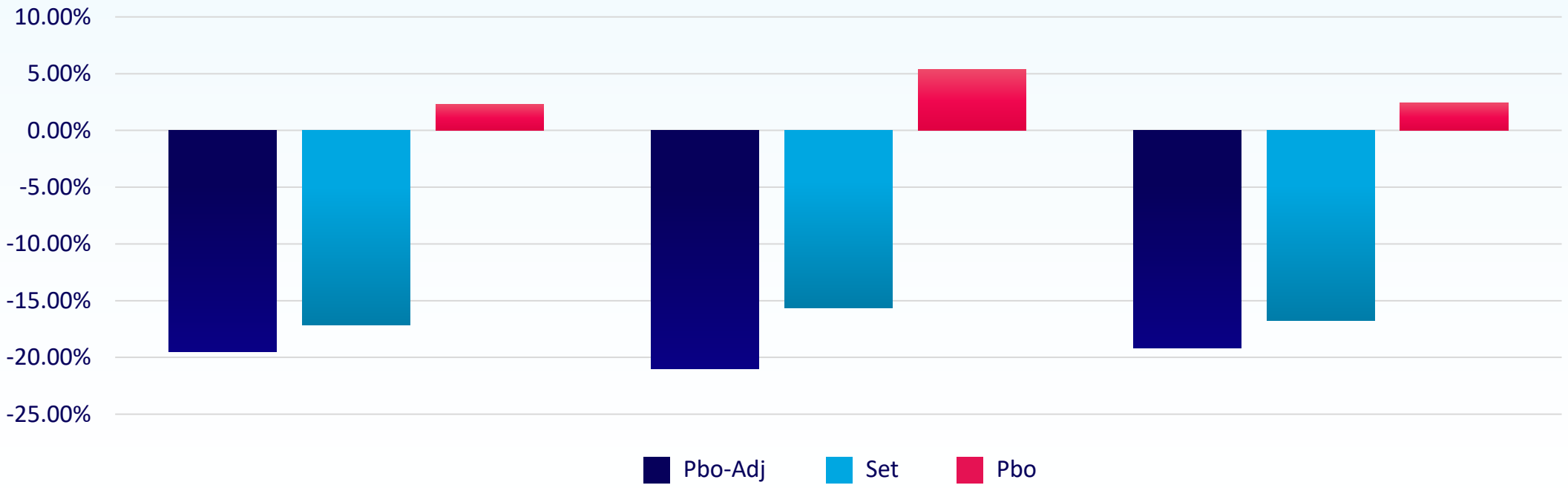

Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota



Rhythm® PHARMACEUTICALS

# Mean BMI Reduction Consistent Across Stratified Age Groups in Phase 3 Trial Evaluating Setmelanotide in Acquired HO

| < 12 Yrs | 12 – < 18 Yrs | ≥ 18 Yrs |
|---|---|---|
| ***-19.5%*** | ***-21.0%*** | ***-19.2%*** |
| ***p <0.0001*** | ***p <0.0001*** | ***p <0.0001*** |
| *(n=31: 20 setmelanotide, 11 placebo)* | *(n=40: 28 setmelanotide, 12 placebo)* | *(n=49: 33 setmelanotide, 16 placebo)* |



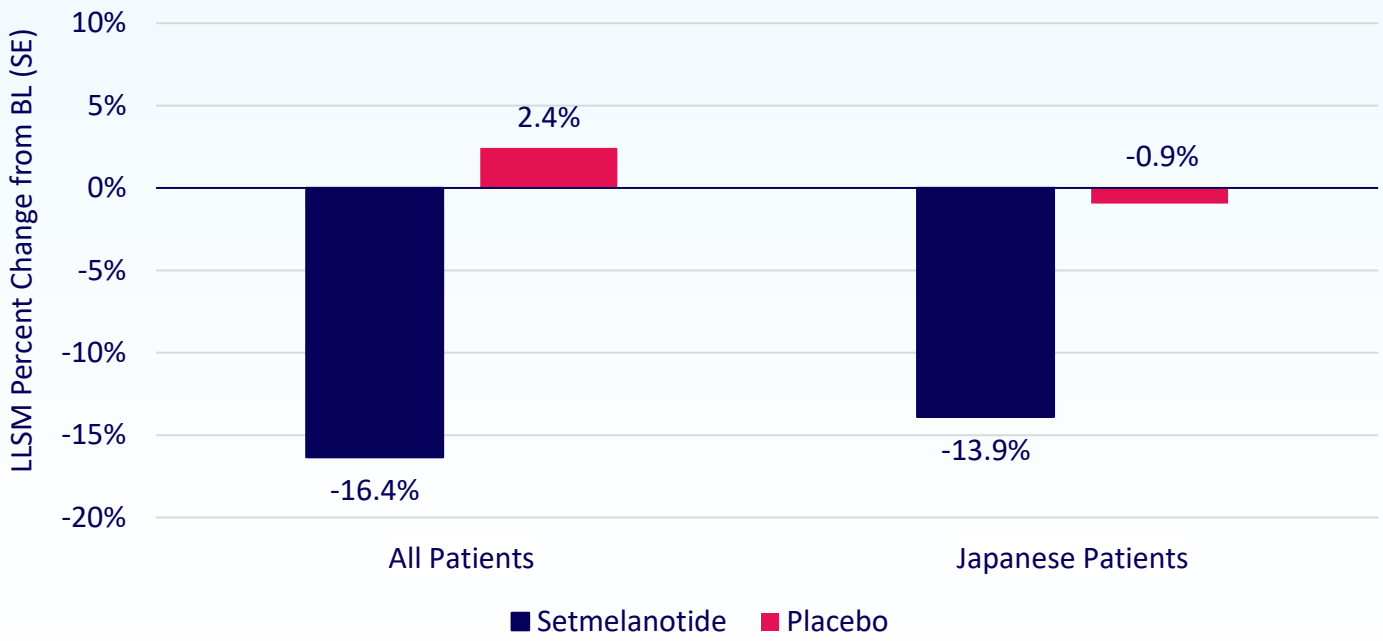
# Phase 3 TRANSCEND Results: Data from 12-patient Japanese Cohort Consistent with Full Data Set

***-18.8%****

***p <0.0001***
*(n=142: 94 setmelanotide, 48 placebo)*

***-13.0%****

***p = 0.0388***
*(n=12: 8 setmelanotide, 4 placebo)*




*LSM Difference (Setmelanotide-Placebo); primary endpoint based on pre-specified statistical analysis plan



Rhythm® PHARMACEUTICALS

# 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

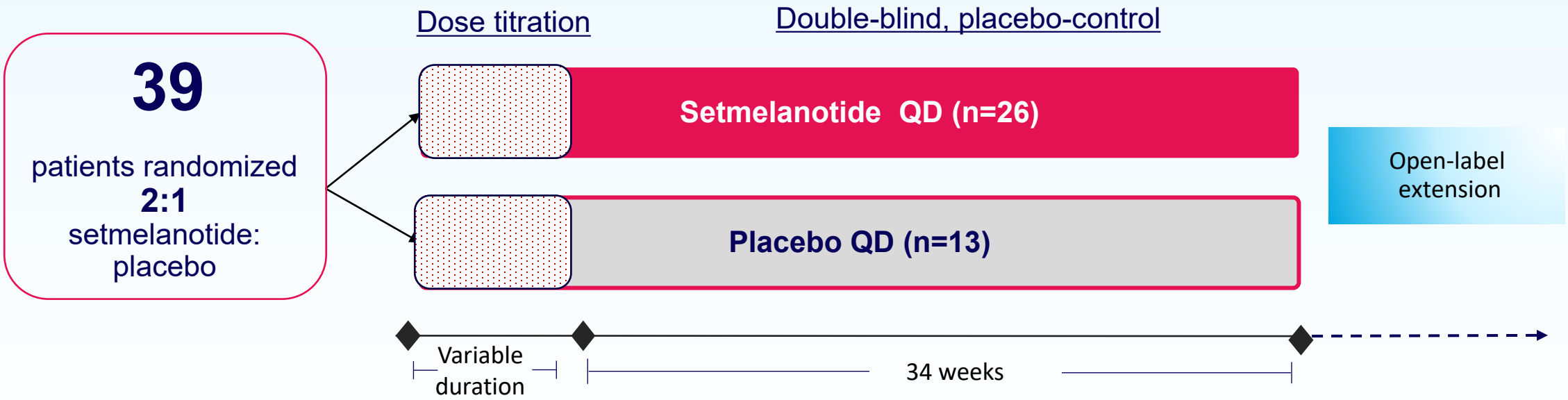
No approved therapies for congenital HO

**>1,000 Patients**

Estimated prevalence in each the United States and Europe

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

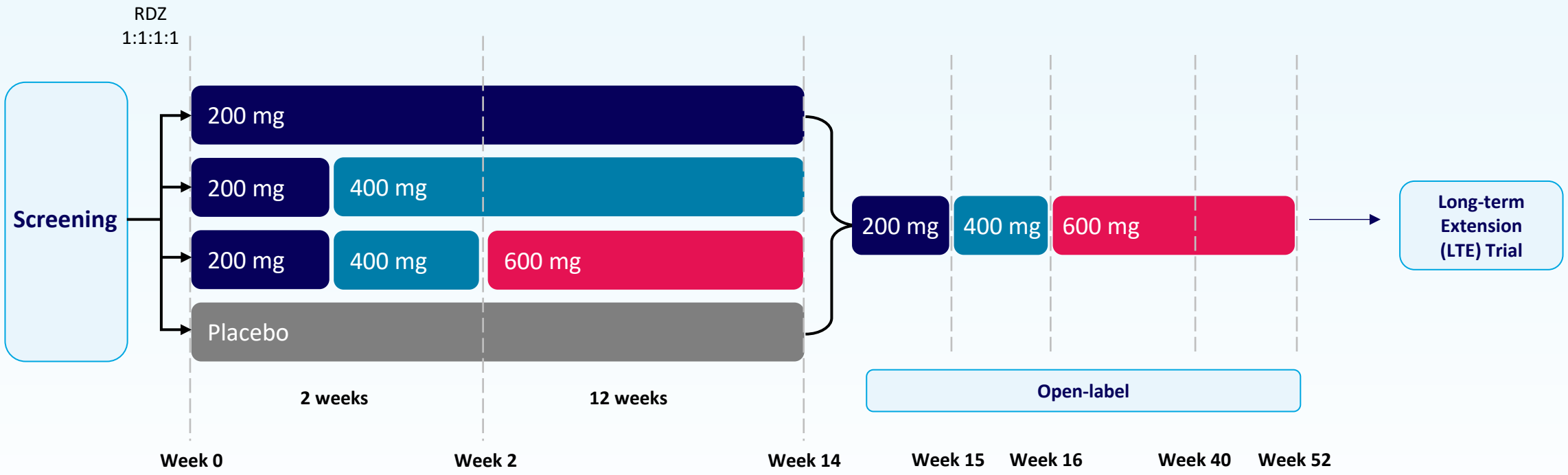
**Independent substudy leverages existing Ph3 trial infrastructure; Enrollment completion expected in H2 2026**




~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

# Bivamelagon (Daily Oral MC4R Agonist) in aHO

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




**Inclusion criteria**

**≥18yo BMI ≥30 kg/m²**

**12-<18 yo ≥95th percentile**

**Setmelanotide-naive**



Rhythm® PHARMACEUTICALS

# Overall Baseline Demographics

**Overall bivamelagon population**

**N=28**

**46.4%**
Female

**25.4yo**
Mean Age
(13 of 28 <18yo)

**38.7 kg/m²**
Mean BMI

**82.1%**
Patients with craniopharyngioma

**7 years**
Mean time from hypothalamic injury to trial enrollment

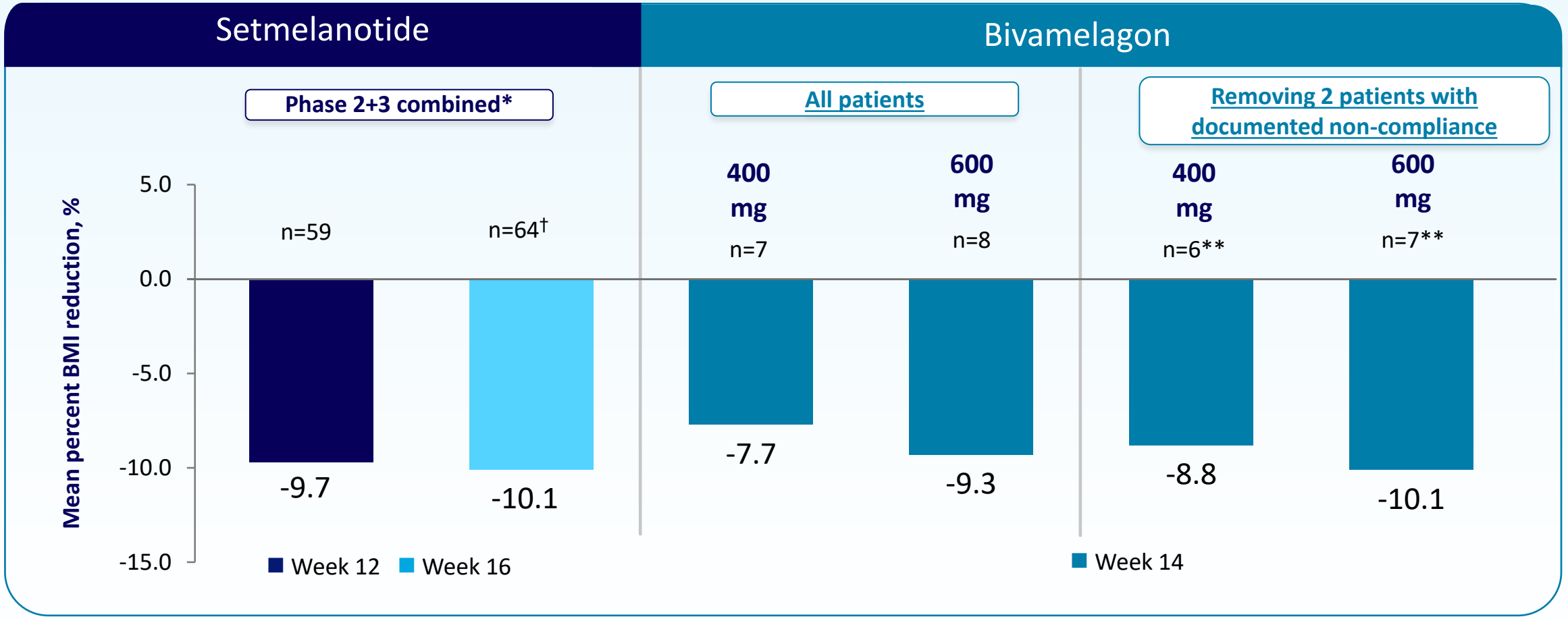
# Bivamelagon Achieved Statistically Significant BMI Reductions at All Doses

| Placebo | 200 mg | 400 mg | 600 mg |
|---|---|---|---|
| **+2.18%** | **-2.68%** | **-7.69%** | **-9.31%** |
| Mean BMI increase from baseline (n=7) | Mean BMI reduction from baseline (n=6) **p-value = 0.0180** | Mean BMI reduction from baseline (n=7) **p-value = 0.0002** | Mean BMI reduction from baseline (n=8) **p-value = 0.0004** |

Note: Arithmetic means and p-values from 2-sided t-test shown above.

Post-hoc analysis:

# Bivamelagon Achieved BMI Reductions Consistent with Setmelanotide




These values represent patients who demonstrated compliance and no concomitant GLP1 therapy (no patients who enrolled in the Phase 2 bivamelagon were on concomitant GLP1 therapy). Patients deemed non-compliant were excluded. †LOCF performed for week 16 only; **1 patient in 400 mg arm and 1 patient in 600 mg arm removed due to Week 1 discontinuation and documented partial compliance respectively.

* LOCF (LOCF not performed for Wk12 , patients not included in those means )



Rhythm® PHARMACEUTICALS

# AEs consistent with MC4R Mechanism, Setmelanotide Trials in Acquired Hypothalamic Obesity

| n (%) | BIVA 200mg (N=6) | BIVA 400mg (N=7) | BIVA 600mg (N=8) | Placebo (N=7) |
|---|---|---|---|---|
| Any AEs | 6 (100) | 7 (100) | 8 (100) | 6 (86) |
| Serious AEs | 0 (0) | 1 (14) | 0 | 1 (14) |
| Treatment-Related AEs | 6 (100) | 7 (100) | 8 (100) | 3 (43) |
| Treatment-Related SAEs | 0 | 1 (14) | 0 | 0 |
| Grade ≥3 AE | 0 | 2 (29) | 0 | 1 (14) |
| AEs Leading to Study Intervention Discontinuation | 0 | 1(14)* | 0 | 0 |
| **AEs with >=10% in all BIVA dosing (N=21)** | | | | |
| Nausea | 6 (100) | 5 (71) | 4 (50) | 2 (29) |
| Diarrhea | 2 (33) | 5 (71) | 3 (37) | 1 (14) |
| Vomiting | 2 (33) | 4 (57) | 4 (50) | 2 (29) |
| Headache | 1 (17) | 5 (71) | 0 (0) | 2 (29) |
| **AEs of Special Interest** | 2 (33) | 3 (43) | 0 | 0 |
| Skin Pigmentation** | 2 (33) | 2 (29) | 0 | 0 |
| Adrenal Adverse Events | 0 | 1 (14) | 0 | 0 |

*Rectal bleeding; ** In addition to the four patients on study drug, one placebo-treated participant had skin hyperpigmentation that was not treatment related and therefore not included as an AE of special interest.

# RM-718 (Weekly Injectable MC4R Agonist) in aHO

# Baseline Demographics

| Parameter | Statistic | Overall (N=11) |
|---|---|---|
| **Age, years** | Mean (SD) (range)<br>≥12 years and <18, n (%)<br>≥18 years old, n (%) | 26.7 (13.1) (12 – 48)<br>4 (36.4)<br>7 (63.6) |
| **Sex, n (%)** | Female / Male | 9/2 (81.8/18.2) |
| **Race, n (%)** | White<br>Black or African American | 10 (90.9)<br>1 (9.1) |
| **BMI, kg/m$^2$** | Mean (SD) | 41.0 (7.1) |

**N=11**
**patients enrolled**

**n=8**
**remain on active therapy***

**n=7**
**reached Week 16**

**n=2**
**discontinued due to AEs**

**1 withdrew from LTE**

**n=2**
**on therapy <4 weeks***

*Data cutoff of July 16, 2026: two (2) patients had not yet reached 16 weeks, and one (1) patient who completed 16 weeks then discontinued from extension due to personal reasons; AE, adverse event; BMI, body mass index; LTE, long-term extension.

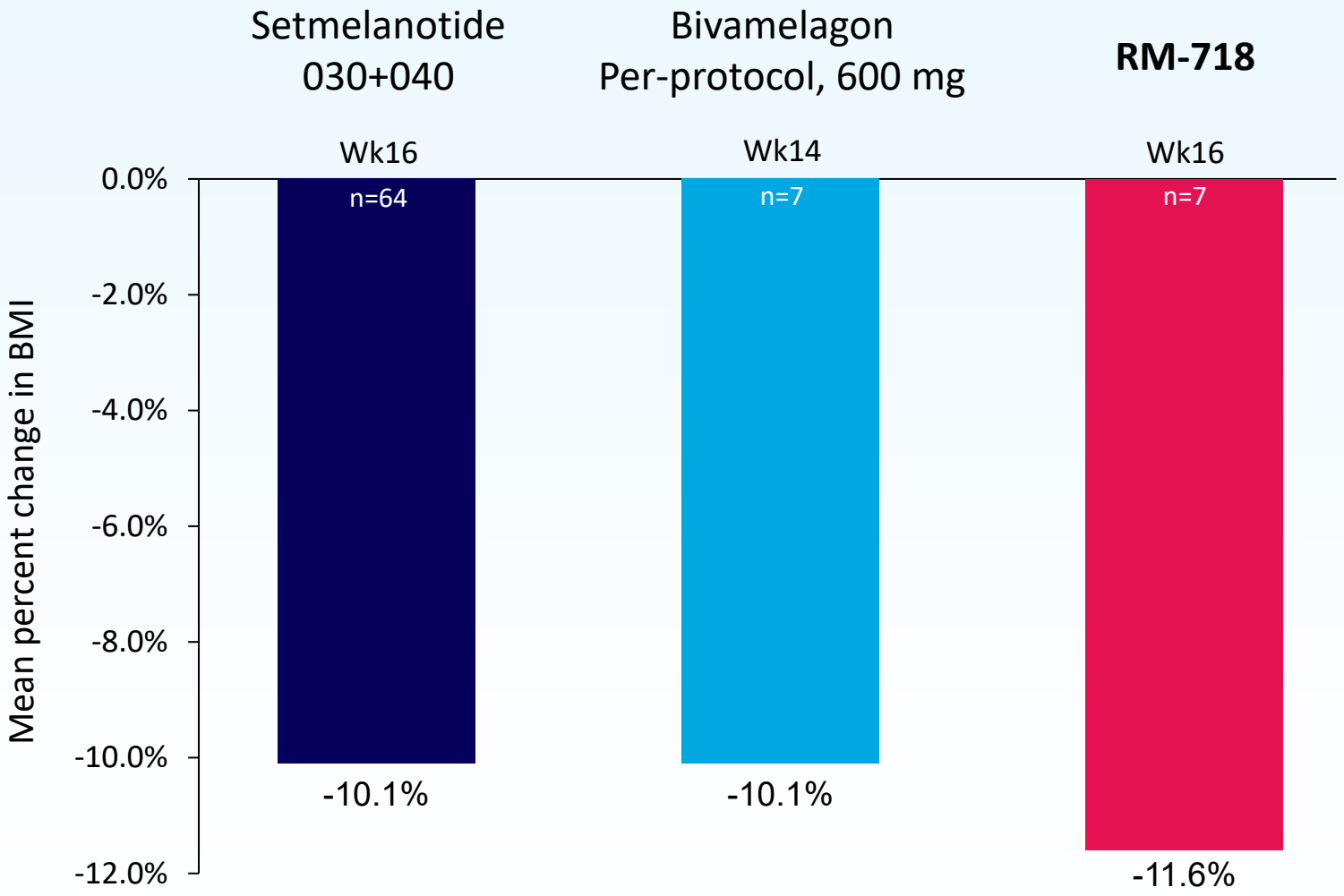
# RM-718 Achieved Clinically Meaningful BMI Reduction in Patients with Acquired HO at Week 16

**-11.6%**

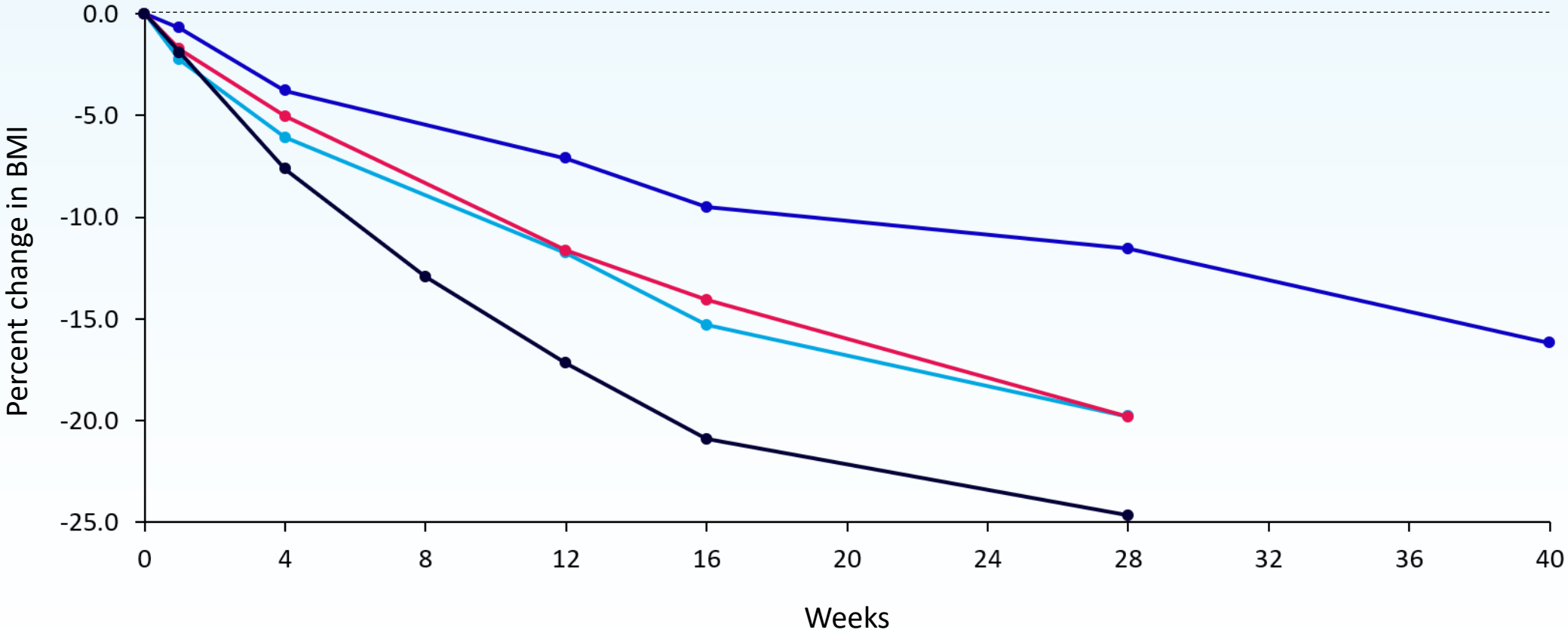
mean BMI reduction
from baseline
at **Week 16**
**(n=7)**

BMI, body mass index.

# RM-718 Exhibited Comparable Reductions to Setmelanotide and Bivamelagon



# Four Patients Achieved Deepening BMI Reductions at 28-40 Weeks on Therapy with RM-718






Rhythm® PHARMACEUTICALS

# Most Common (≥2 Patients) Adverse Events for All Patients (N=11)

| Adverse Events, n (%) | All Patients (N=11) |
|---|---|
| Injection site reactions | 9 (81.8) |
| Nausea | 6 (54.5) |
| Vomiting | 3 (27.3) |
| Abdominal pain | 2 (18.2) |
| Anxiety | 2 (18.2) |
| Cough | 2 (18.2) |
| Decreased appetite | 2 (18.2) |
| Depression | 2 (18.2) |
| Fatigue | 2 (18.2) |
| Headache | 2 (18.2) |
| Nasopharyngitis | 2 (18.2) |
| Oropharyngeal pain | 2 (18.2) |

# Prader-Willi Syndrome

# Significant Unmet Need in Prader-Willi Syndrome


**12,500 – 16,000**

PWS prevalence in each of U.S. and Europe

**8,500 – 12,750**

*PWS patients living with hyperphagia/obesity* in each of U.S. and Europe

1) National Center for Health Statistics (CDC), Final Natality Data (1954–2023); 2. Gallagher L, et al. *A population-based profile of Prader-Willi Syndrome in Ireland*. 2017; 3. Godler DE, et al. *JAMA Netw Open*. 2022; 4. U.S. Prevalence & Mortality of Prader-Willi Syndrome: A Population-Based Study of Medical Claims, JESOCI, Volume 4, Abstract Supplement, 2020; 5. a-population-based-profile-of-prader-willi-syndrome-in-ireland-final-report.pdf; 6. Prader-Willi Syndrome - GeneReviews® - NCBI Bookshelf

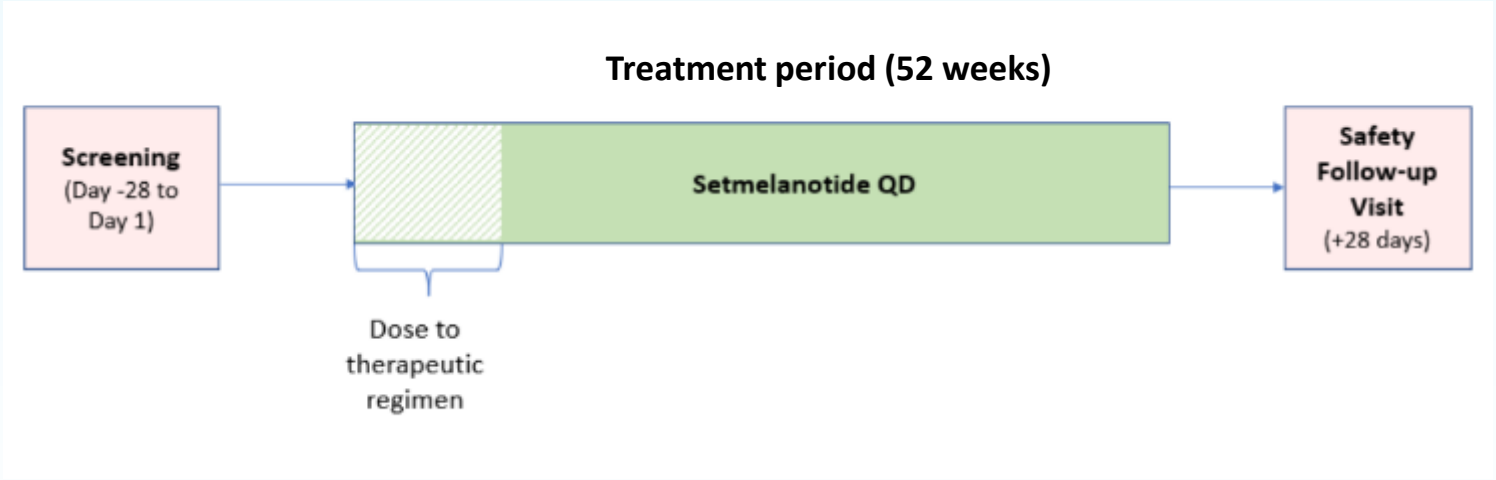
# Exploratory Phase 2, Open-label Trial of Setmelanotide in PWS

**18 patients** with PWS and obesity aged 6 to 65 years old enrolled

Daily dose of setmelanotide escalated up to **5 mg/day** as tolerated for **52 weeks**

**Primary endpoints:** safety and tolerability

**Key secondaries:** assessments on **BMI, hyperphagia, body composition** and pharmacokinetics



# Baseline Demographics

| Parameter | Statistic | Overall (N=18) |
|---|---|---|
| **Age, years** | Mean (SD) (range)<br><12 years old, n (%)<br>≥12 years and <18, n (%)<br>≥18 years old, n (%) | 17.1 (5.6) (6 – 23)<br>3 (16.7)<br>4 (22.2)<br>11 (61.1) |
| **Sex, n (%)** | Female / Male | 8/10 (44.4/55.6) |
| **Race, n (%)** | White<br>Multiple<br>Asian | 15 (83.3)<br>2 (11.1)<br>1 (5.6) |
| **BMI, kg/m²** | Mean (SD)<br>Mean (SD) pts ≥ 18yo | 39.0 (9.3)<br>41.1 (9.6) |
| **BMI z-score in participants aged 4 to <18 y, mean (SD)*** | | 4.15 (1.87) |
| **HQ-CT, mean (SD)** | | 12.83 (8.05) |
| **PADQ, mean (SD)** | | 29.94 (15.12) |

**N=18**
**Patients enrolled**

**n=1**
**discontinued (withdrawal by parent/guardian)**

**n=17**
**patients reached Month 6**

**17**
**patients remain on active therapy[1]**

1. As of June 12, 2026

# Setmelanotide Achieves Compelling, Durable and Consistent Interim Results at Six Months in Phase 2 Trial in Patients with PWS

**-3.06%**

mean BMI reduction from baseline (n=17)

**-3.11%**

mean BMI reduction in **adults (n=10)**

**-0.35**

mean **BMI-Z score** reduction in **pediatrics (n=7)**

**-4.19%**

mean fat loss

**+0.74%**

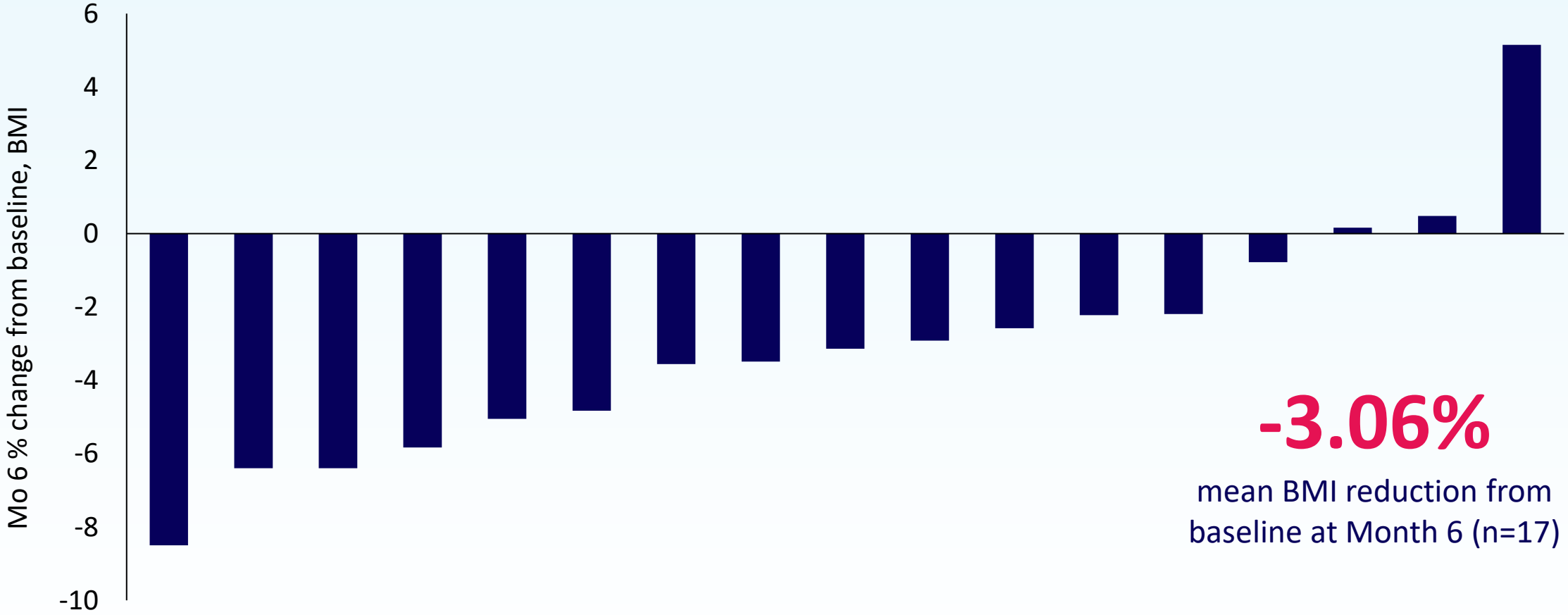
mean gain in lean mass

Showing **preservation of lean mass** in patients with DEXA data (n=16)


**8 of 10 patients** with moderate to severe hyperphagia achieved clinically meaningful improvement defined as a **≥7 point reduction in HQ-CT**

Note: Moderate-to-severe hyperphagia defined as HQ-CT score ≥13 at baseline; Data throughout this presentation are as of a data cut-off date of May 7, 2026.

# Setmelanotide Achieved BMI Reductions from Baseline in 14 of 17 Patients with PWS at Month 6



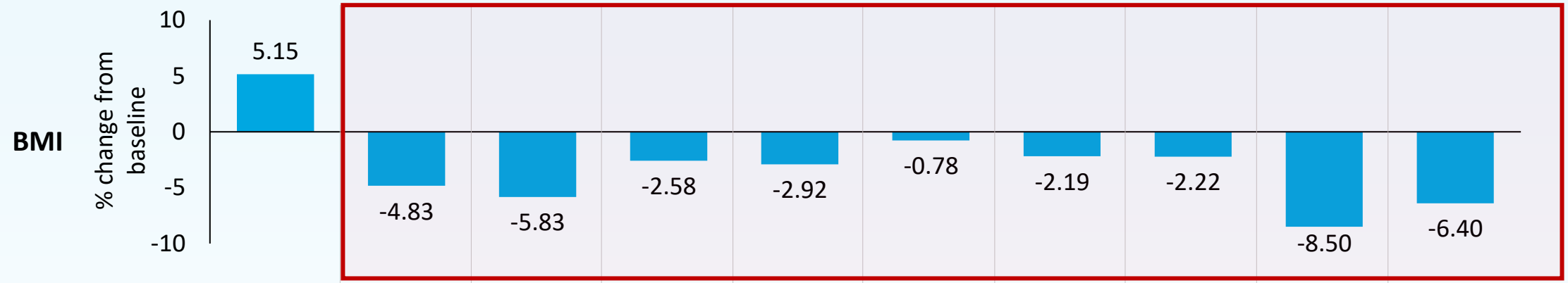

**-3.06%**

mean BMI reduction from baseline at Month 6 (n=17)

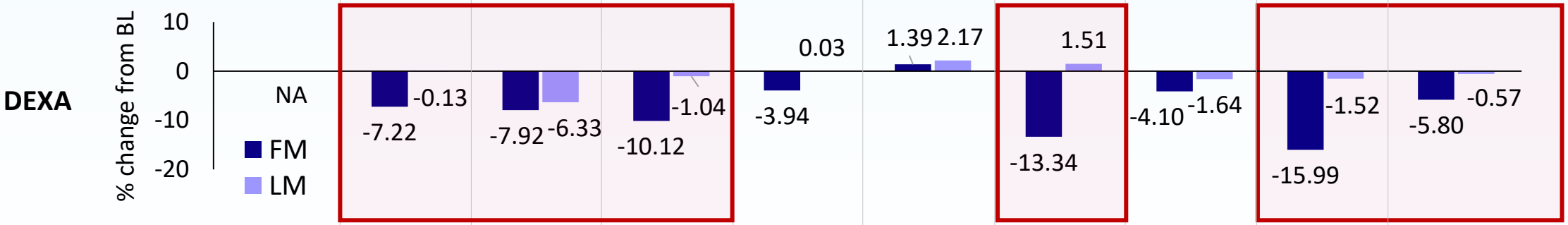
| Patient #: | 13 | 11 | 17 | 3 | 18 | 2 | 15 | 14 | 8 | 7 | 6 | 12 | 10 | 9 | 16 | 5 | 1 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age/sex: | 23/F | 8/F | 22/M | 23/F | 6/M | 18/F | 13/F | 14/M | 12/F | 23/M | 23/M | 20/M | 20/M | 18/F | 9/M | 14/M | 20/F |
| Vykat (Y/N): | Y | Y | Y | N | N | N | Y | Y | N | Y | Y | N | Y | Y | N | N | N |

# Consistent BMI, Fat Mass Reductions Observed in Adult Patients at Month 6

*9/10 patients achieved BMI reduction; mean BMI % change: -3.11% (n=10)*

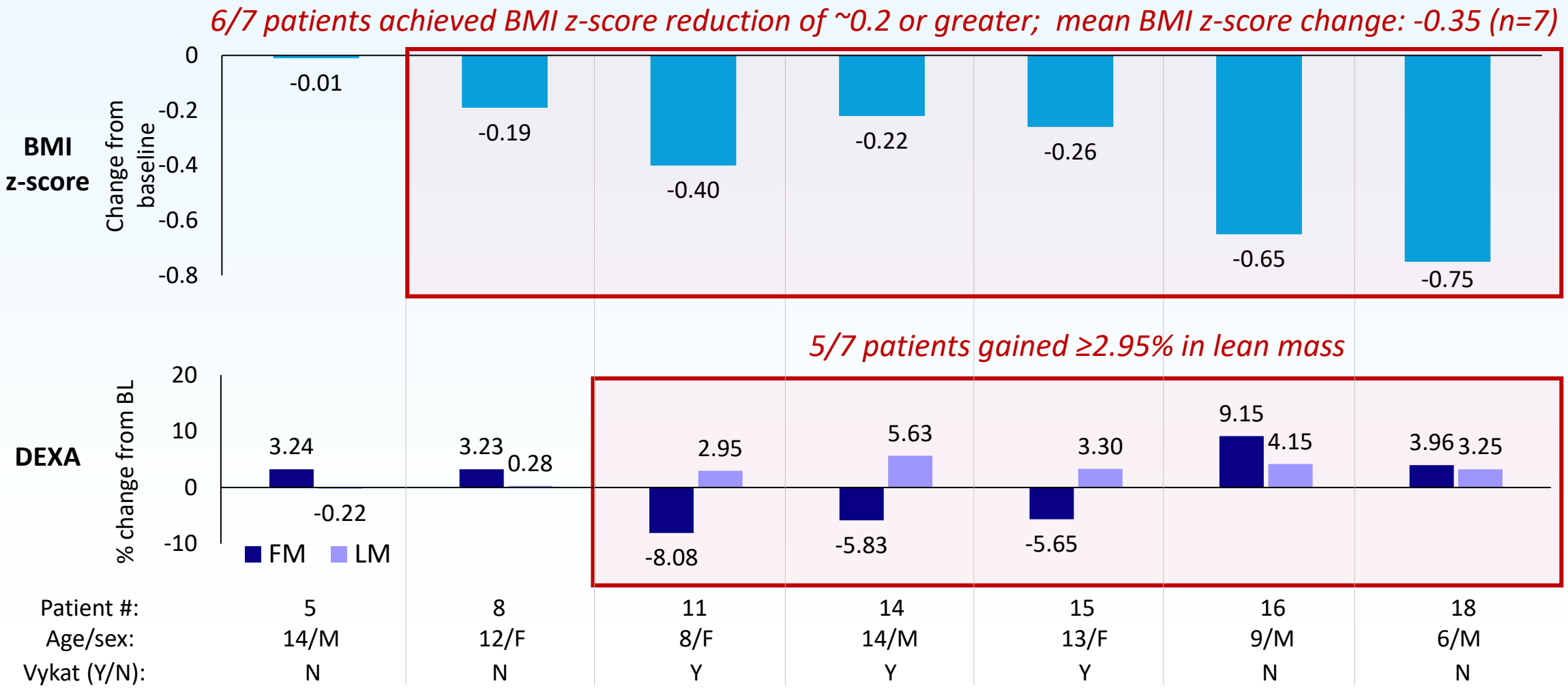



*6/9 patients with DEXA data achieved >5% reduction in fat mass; mean fat mass % change: -7.4% (n=9)*

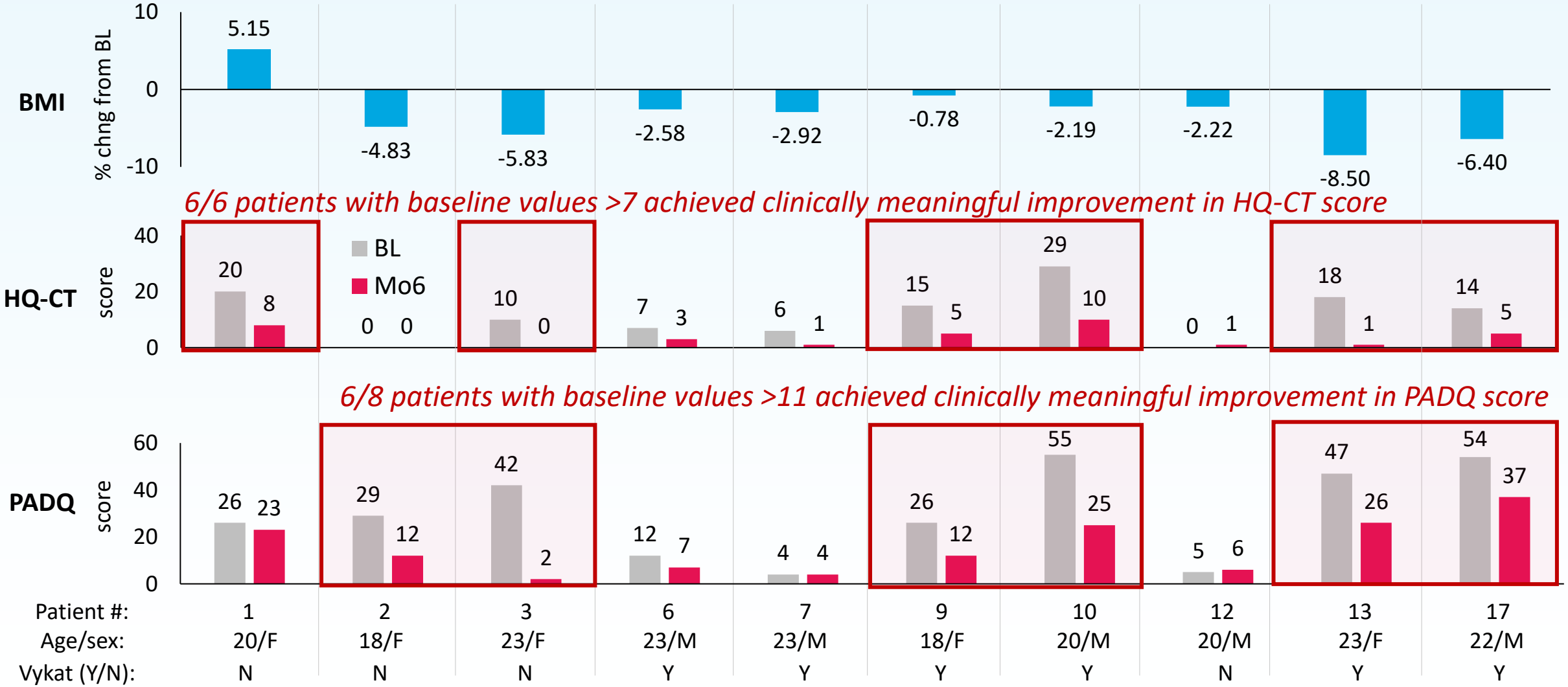



| Patient #: | 1 | 2 | 3 | 6 | 7 | 9 | 10 | 12 | 13 | 17 |
|---|---|---|---|---|---|---|---|---|---|---|
| Age/sex: | 20/F | 18/F | 23/F | 23/M | 23/M | 18/F | 20/M | 20/M | 23/F | 22/M |
| Vykat (Y/N): | N | N | N | Y | Y | Y | Y | N | Y | Y |

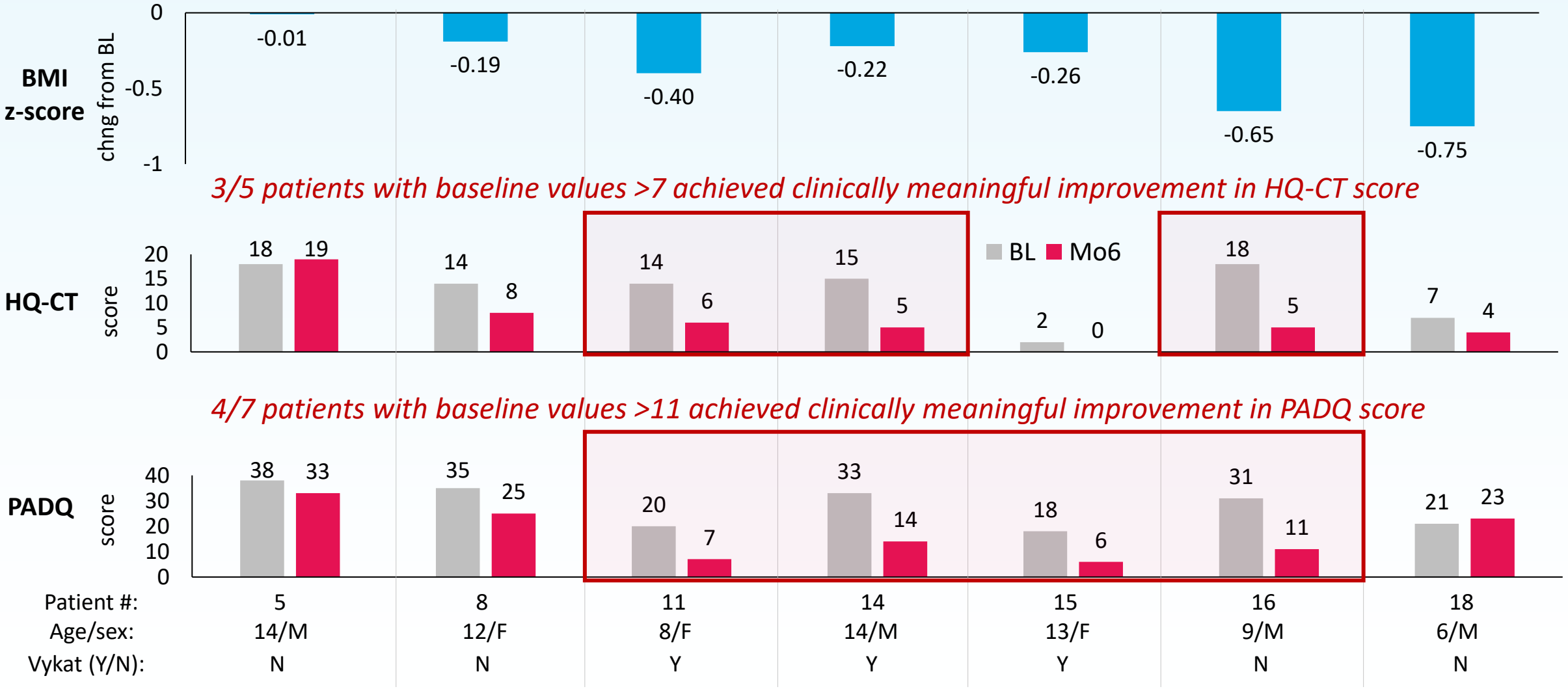
# Consistent BMI Z-Score Reductions and Gains in Muscle Mass Observed in Pediatric Patients at Month 6



# Improvements in Hyperphagia and Anxiety Scores Observed in Adult Patients at Month 6



# Improvements in Hyperphagia and Anxiety Scores Observed in Pediatric Patients at Month 6



# Most Common Adverse Events for All Patients (N=18)

| Adverse Events | Overall n (%) *(n=18)* |
|---|---|
| Injection site reaction | 11 (61.1) |
| Skin hyperpigmentation | 10 (55.6) |
| Fatigue | 6 (33.3) |
| Norovirus infection | 2 (11.1) |
| Hypothyroidism | 2 (11.1) |
| Diabetes mellitus | 2 (11.1) |

*Note: As of May 7, 2026*

# Appendix

# New Diagnostic Algorithm Supports Diagnosis of BBS

AMERICAN JOURNAL OF medical genetics PART A

REVIEW ARTICLE OPEN ACCESS

## Streamlining Diagnosis of Bardet–Biedl Syndrome: New Diagnostic Algorithm With Updated Criteria

Jeremy J. Pomeroy[1] | Jesse Richards[2] | Brooke R. Sweeney[3] | Seema Kumar[4] | Katie E. Queen[5] | Joshua Zarlisky[6] | Carl H. Cramer[7] | Elias I. Traboulsi[8] | Britini A. Scruggs[9] | Erica E. Davis[10,11] | Ekaterina Kefer[1] | Emma McGibbon[12] | Timothy Ogden[13] | Bendert De Graaf[14] | Tonia Hymers[15] | Elizabeth Forsythe[16,17] | Philip Beales[18]

[1]Marshfield Clinic Research Institute, Marshfield, Wisconsin, USA | [2]Department of Internal Medicine, University of Oklahoma School of Community Medicine, Tulsa, Oklahoma, USA | [3]Children's Mercy Kansas City, Center for Children's Healthy Lifestyles & Nutrition, Kansas City, Missouri, USA | [4]Division of Pediatric Endocrinology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA | [5]Our Lady of the Lake Children's Health Weight and Nutrition Center, Baton Rouge, Louisiana, USA | [6]Department of Nephrology, Phoenix Children's Hospital, Phoenix, Arizona, USA | [7]Division of Pediatric Nephrology and Hypertension, Department of Pediatric and Adolescent Medicine, Mayo Clinic, Rochester, Minnesota, USA | [8]Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio, USA | [9]Department of Ophthalmology and Department of Pediatrics, Mayo Clinic, Rochester, Minnesota, USA | [10]Stanley Manne Children's Research Institute, Ann & Robert H. Lurie Children's Hospital of Chicago, Chicago, Illinois, USA | [11]Department of Pediatrics, Cell and Developmental Biology, Flenberg School of Medicine, Northwestern University, Chicago, Illinois, USA | [12]Wolfson Neurodisability Service, Great Ormand Street Hospital NHS Foundation Trust, London, UK | [13]Bardet Biedl Syndrome Foundation, Unionville, Pennsylvania, USA | [14]Bardet-Biedl Stichting, Kampen, the Netherlands | [15]Bardet-Biedl Syndrome UK, Essex, UK | [16]Clinical Genetics Department, Guys and St. Thomas' Hospitals, London, UK | [17]National Bardet-Biedl Syndrome Clinics, Great Ormond Street Hospital, London, UK | [18]Genetics and Genomic Medicine Programme, University College London Great Ormond Street Institute of Child Health, London, UK

**Correspondence:** Philip Beales (p.beales@ucl.ac.uk)

**Received:** 20 February 2026 | **Revised:** 2 May 2026 | **Accepted:** 5 May 2026

**Keywords:** Bardet–Biedl syndrome | ciliopathies | diagnostic algorithm | diagnostic criteria | genetics | obesity

**ABSTRACT**

Considerable advances have been made in our understanding of Bardet–Biedl syndrome (BBS), particularly in its core clinical features and molecular genetics, warranting an update to the existing diagnostic criteria framework. Using a rigorous, evidence-based, and consensus-driven process, a multidisciplinary group of international experts and patient-led organizations developed an updated diagnostic algorithm. This algorithm provides practical, updated guidance for clinicians, including a pathway for accurately incorporating genetic findings into the diagnostic process. We recommend that a clinical diagnosis requires either 4 major criteria or 3 major and 2 minor criteria. Revised major criteria are retinal dystrophy, obesity (or overweight in individuals <2 years old), congenital anomalies of the kidney and urinary tract or chronic kidney disease, hypogonadism/genital anomalies, neurodevelopmental/neurocognitive manifestations, and postaxial polydactyly. The diagnosis can also be established with a positive genetic testing result in patients exhibiting ≥ 1 major criterion, provided that genetic findings should be interpreted in the context of the patient's clinical presentation, age, family history, and overlap with related ciliopathies. These consensus criteria offer a simple algorithm incorporating updated definitions for major and minor criteria and genetic testing to support a timely

Expert consensus, evidence-based diagnostic algorithm

Supports earlier recognition and diagnosis

Aligns around current clinical and genetic evidence



Rhythm® PHARMACEUTICALS

# German Investigator-led Observational Study Showed Setmelanotide associated with Improvement in Measures of MASLD, Kidney Function in Patients with BBS

**26 patients with BBS completed six months on setmelanotide therapy.**


**100%**

of patients (N=26) with both BBS and metabolic dysfunction-associated steatotic liver disease (MASLD)

**>80%**

of patients exhibited either resolution of MASLD or stabilization at grade S1*

Adapted from Hühne, T., *et al.* (2025). *Impact of the melanocortin-4 receptor agonist setmelanotide on MASLD and kidney function in Bardet-Biedl syndrome*. The Journal of Clinical Endocrinology & Metabolism. https://doi.org/10.1210/clinem/dgaf483; * MASLD improvement was correlated with only liver size, not BMI reduction; This study was funded by the German Federal Ministry of Research and Education and by Rhythm Pharmaceuticals.



Rhythm® PHARMACEUTICALS

# 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

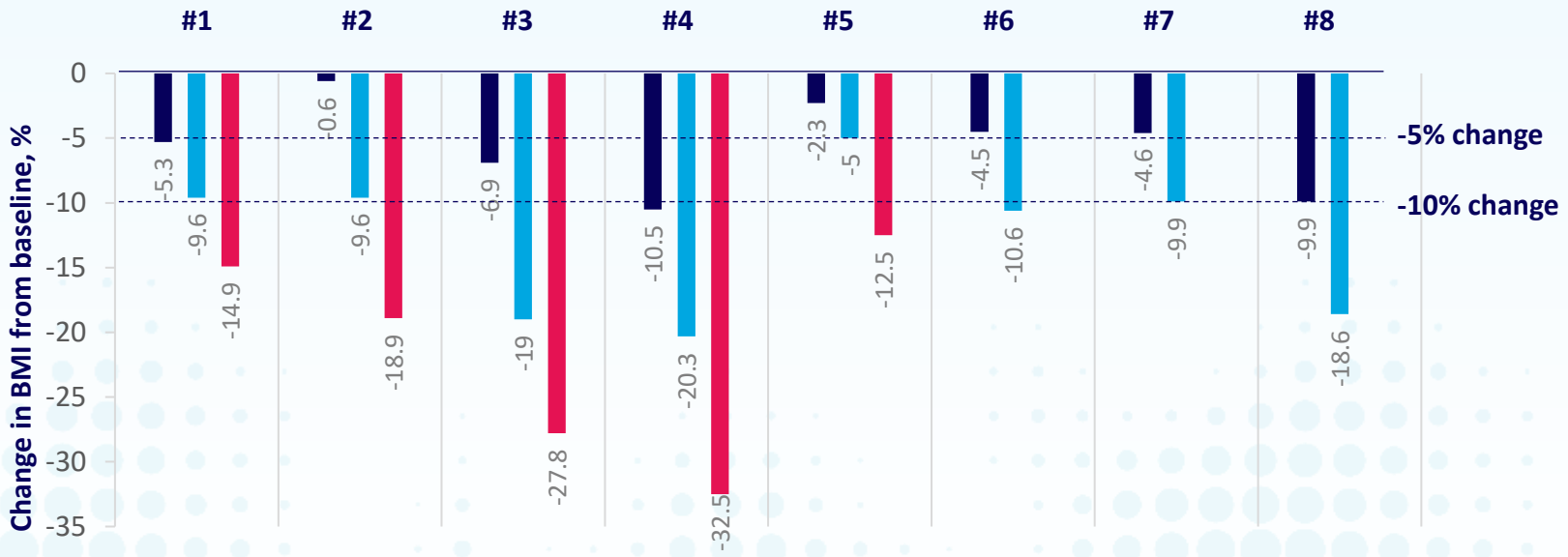
**31.4 years**
Mean age at initiation of setmelanotide therapy

**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

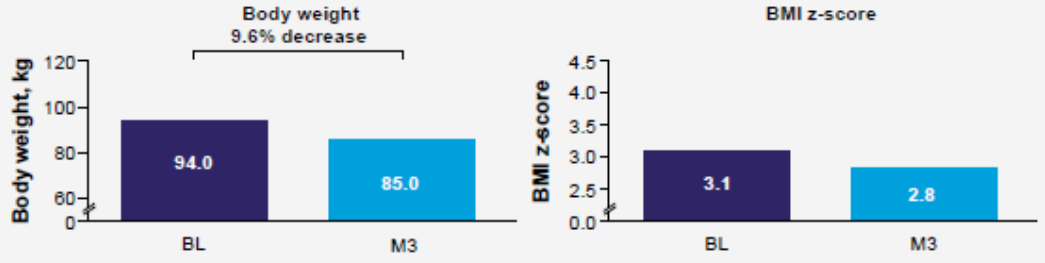
# Real-world Case Reports from French Early-access Program Suggest Setmelanotide may be Effective Treatment for Congenital HO

## 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:**

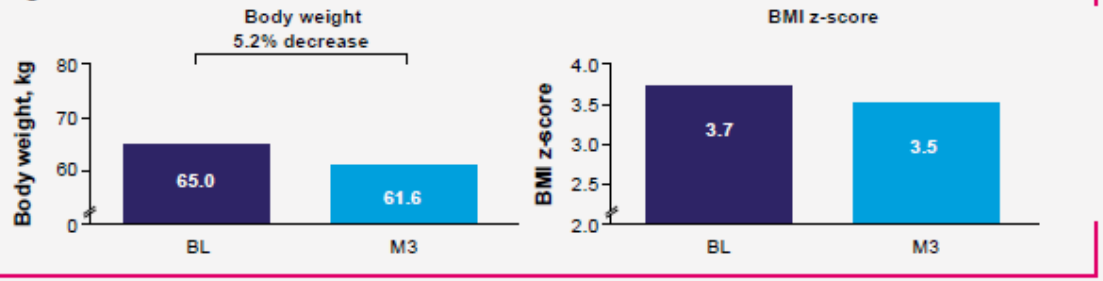



- For the 4 questions included in the scoring of hunger scores, the reported change was 5-5-0-6 (BL) to 5-5-0-5 (M3). Physician noted difficulty in interpretation and scoring with the questionnaire
- During treatment, patient reported injection site reaction and intermittent diarrhoea at 2 weeks of treatment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



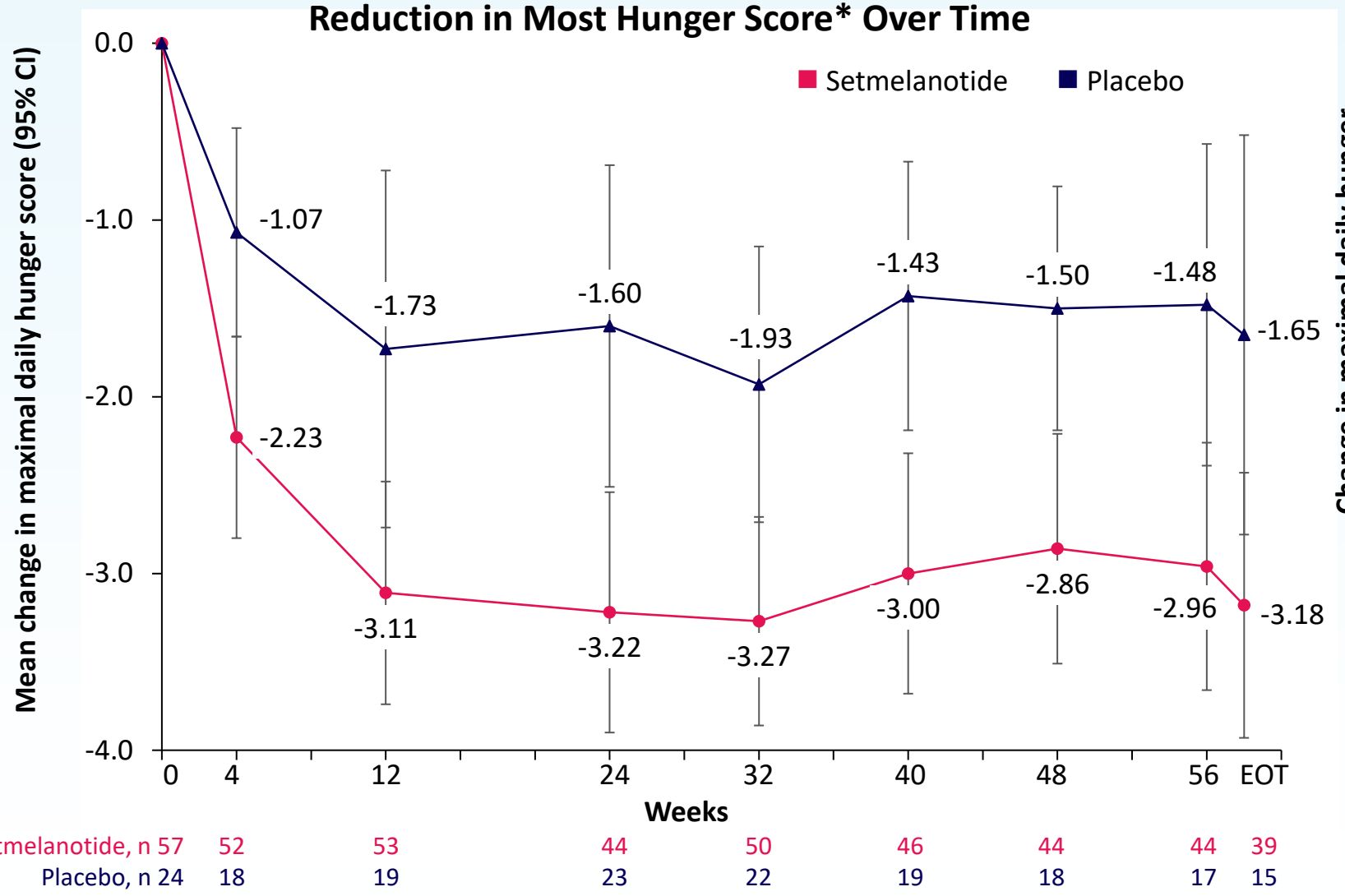

- For the hunger outcomes, patient reported a qualitative improvement rather than quantitative, as normally reflected by hunger scores. Initially, the patient described feeling moderately hungry at BL, slightly hungry at M1, and not hungry at all by M3 of treatment
- During treatment, no adverse events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

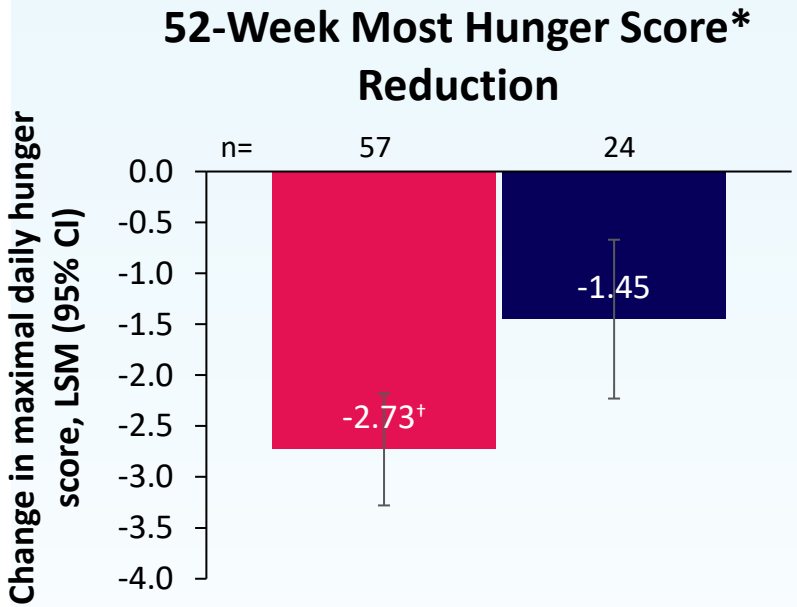
Adapted from '3-Month real-world setmelanotide hunger and weight outcomes in four French pediatric patients with acquired or congenital hypothalamic obesity,' presented at ESPE on November 18, 2024, by Dr. Ahlam Azar-Kolakez, et al.



Rhythm® PHARMACEUTICALS

# Rapid and Statistically Significant Hunger Reduction in Patients with HO Aged ≥12 Years




**PBO-adjusted difference** **-1.28**

†*P*=0.0086 vs placebo.

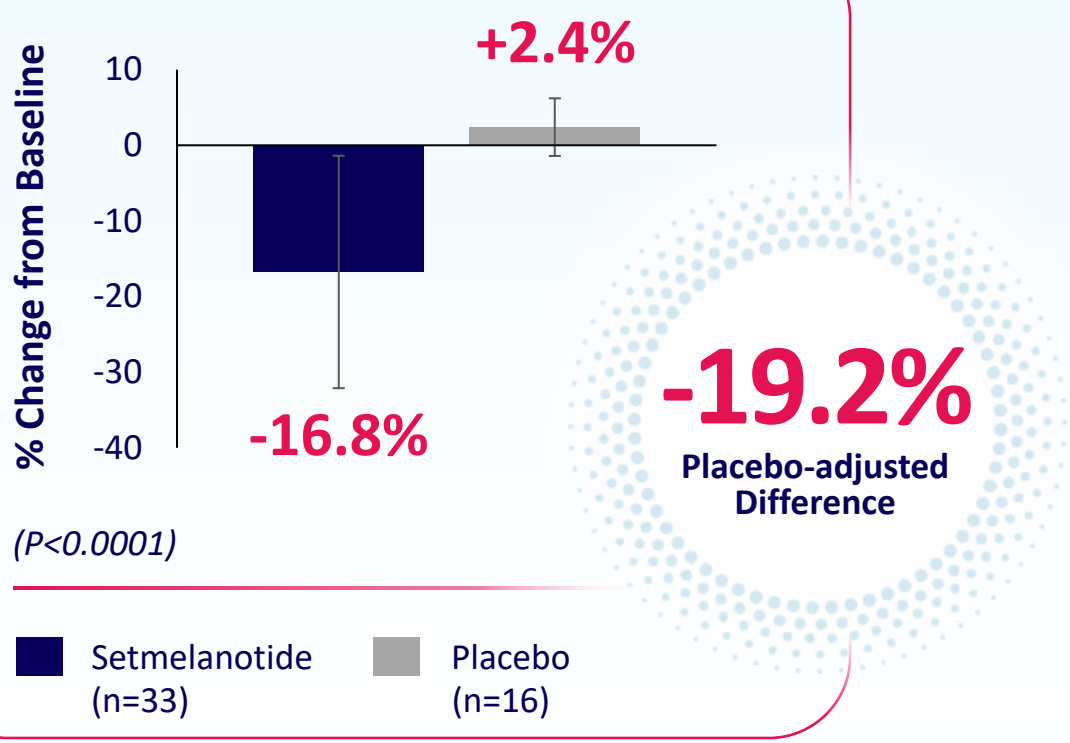
As presented at ENDO 2025



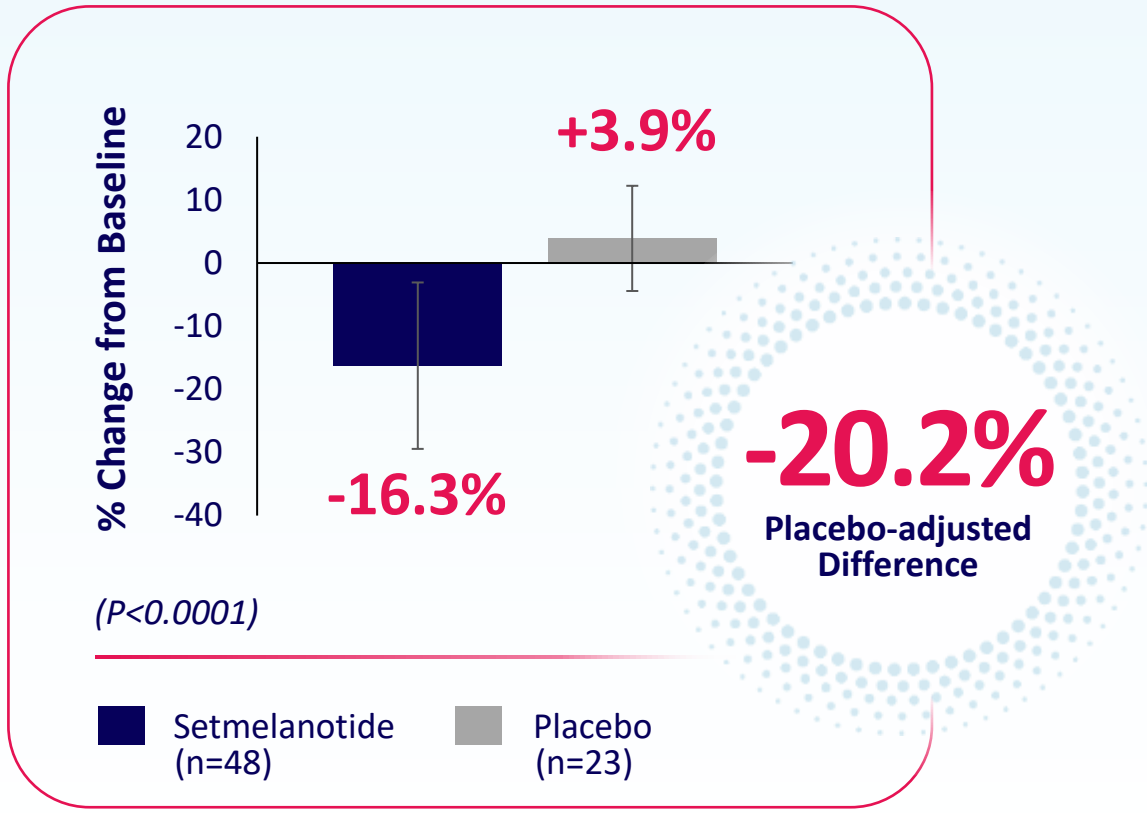
*Weekly average of daily scores. participants ≥12 years of age who were able to self-report were administered the questionnaire. Participants were asked to rate their most hunger on an 11-point numerical rating scale from 0 to 10, where 0 = not hungry at all and 10 = hungriest possible via the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" CI, confidence interval; LSM, least squares mean.

# Significant Reductions in BMI Observed in both Adults and Children in Phase 3 Trial Evaluating Setmelanotide in Acquired HO

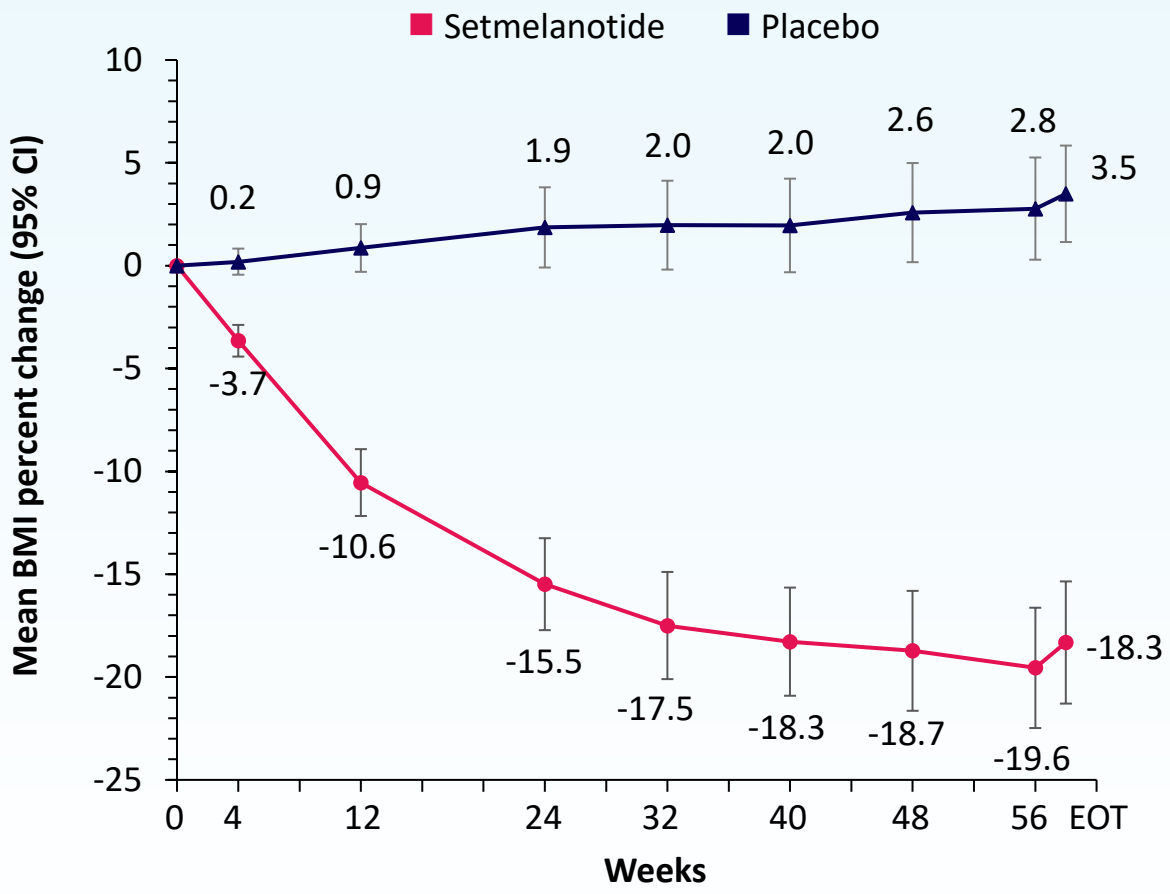
## ≥18 Years Old *(n=49)*




## <18 Years Old *(n=71)*

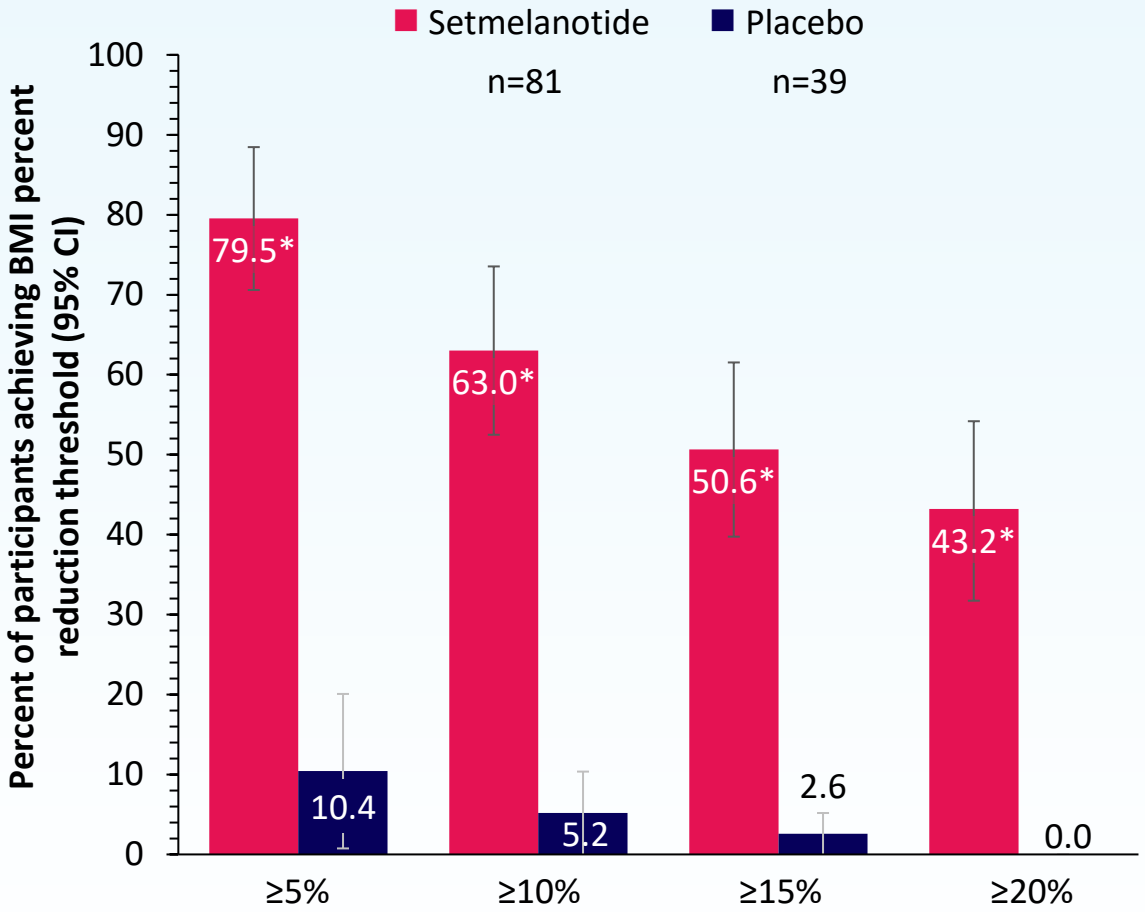


# Rapid and Significant BMI Percent Reduction Starting at Week 4




| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Setmelanotide, n | 81 | 81 | 77 | 75 | 68 | 73 | 68 | 69 | 71 |
| Placebo, n | 39 | 38 | 37 | 38 | 34 | 36 | 33 | 35 | 37 |

# A Higher Proportion Achieved Percent BMI Reductions for All BMI Thresholds




BMI percent reduction from baseline

*$P$<0.0001 vs placebo.

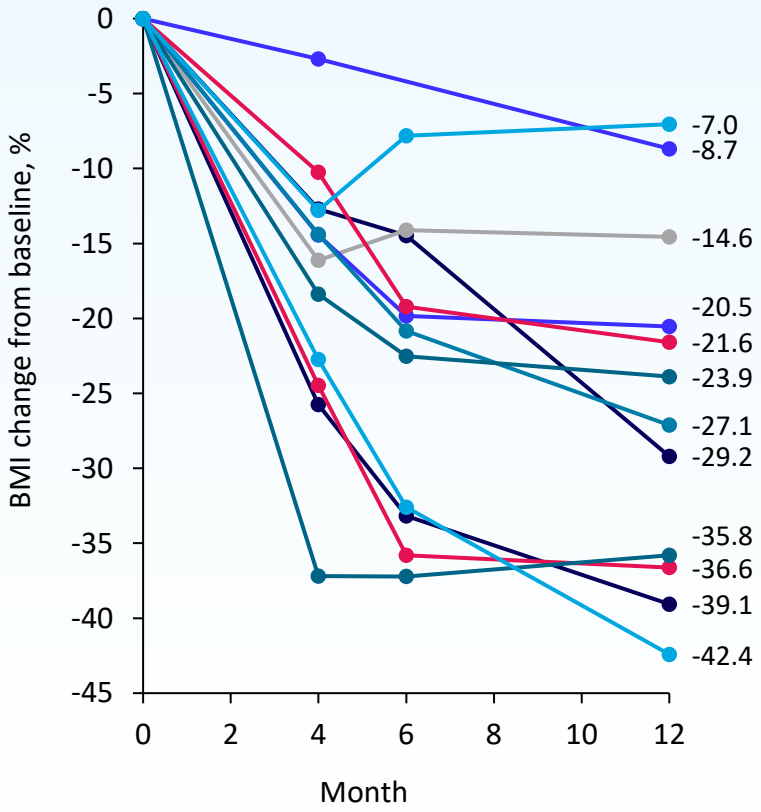
As presented at ENDO 2025



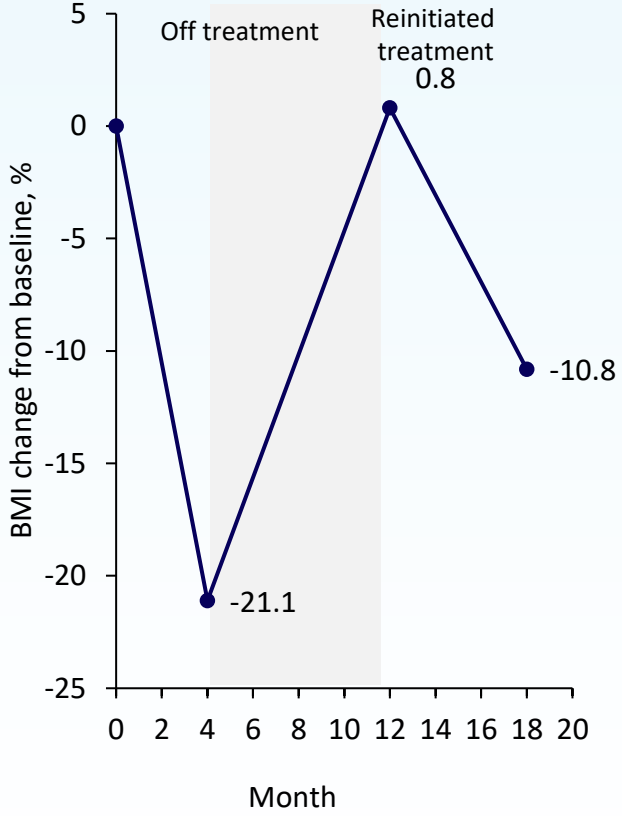
BMI, body mass index; CI, confidence interval.

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

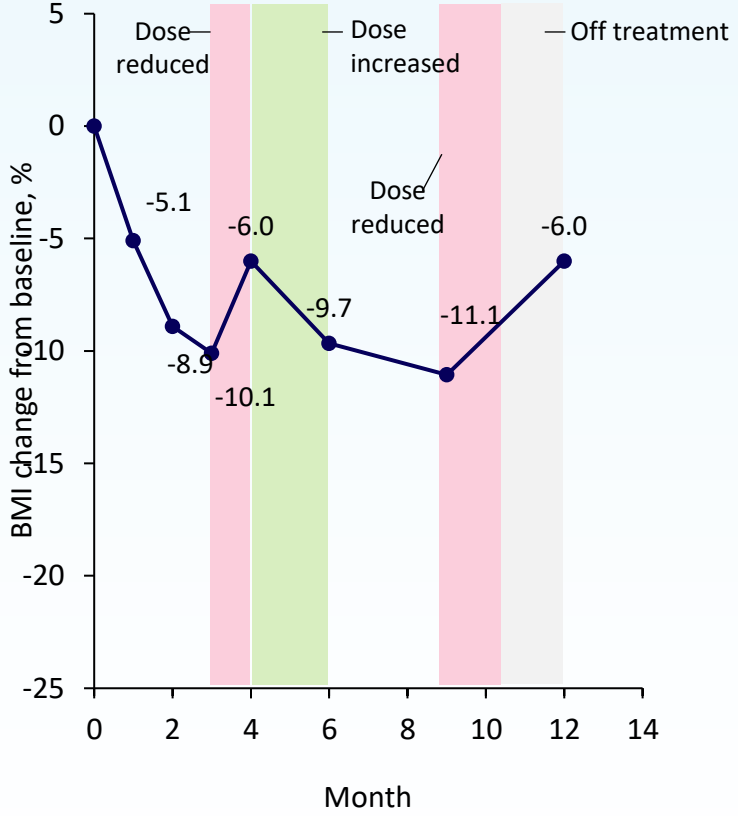
Patients on treatment at Month 12 (n=12)




Patient lost to follow-up (n=1)




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



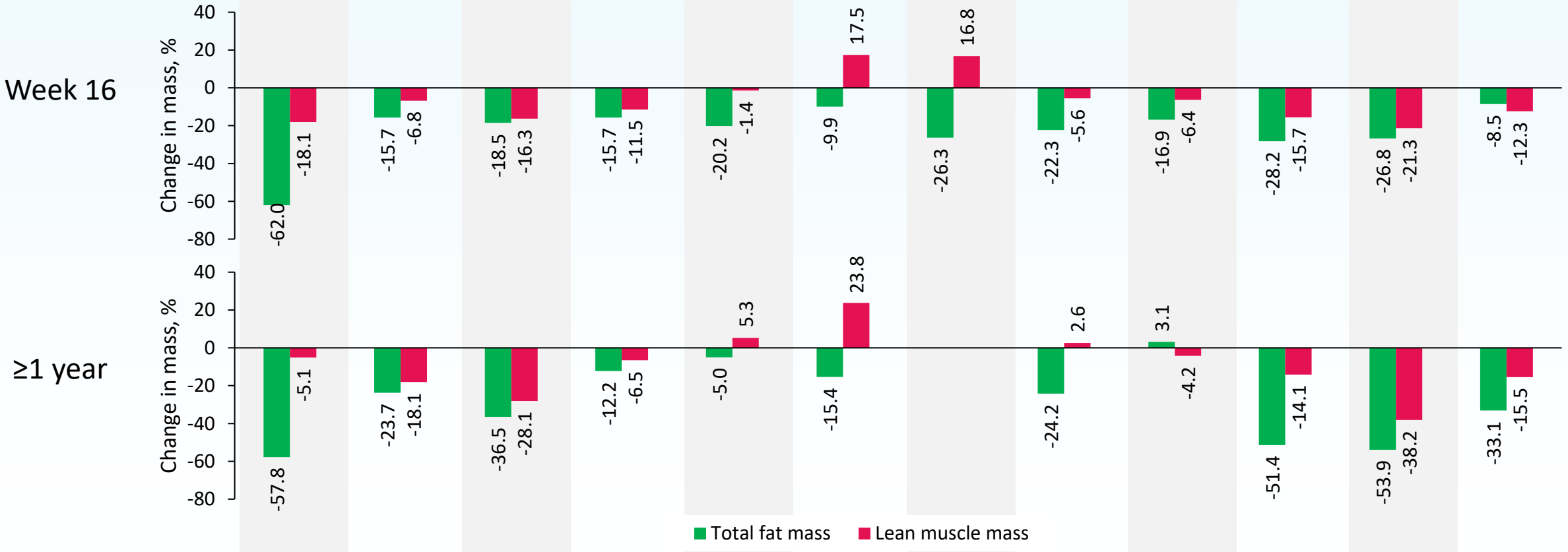

As presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.



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 |



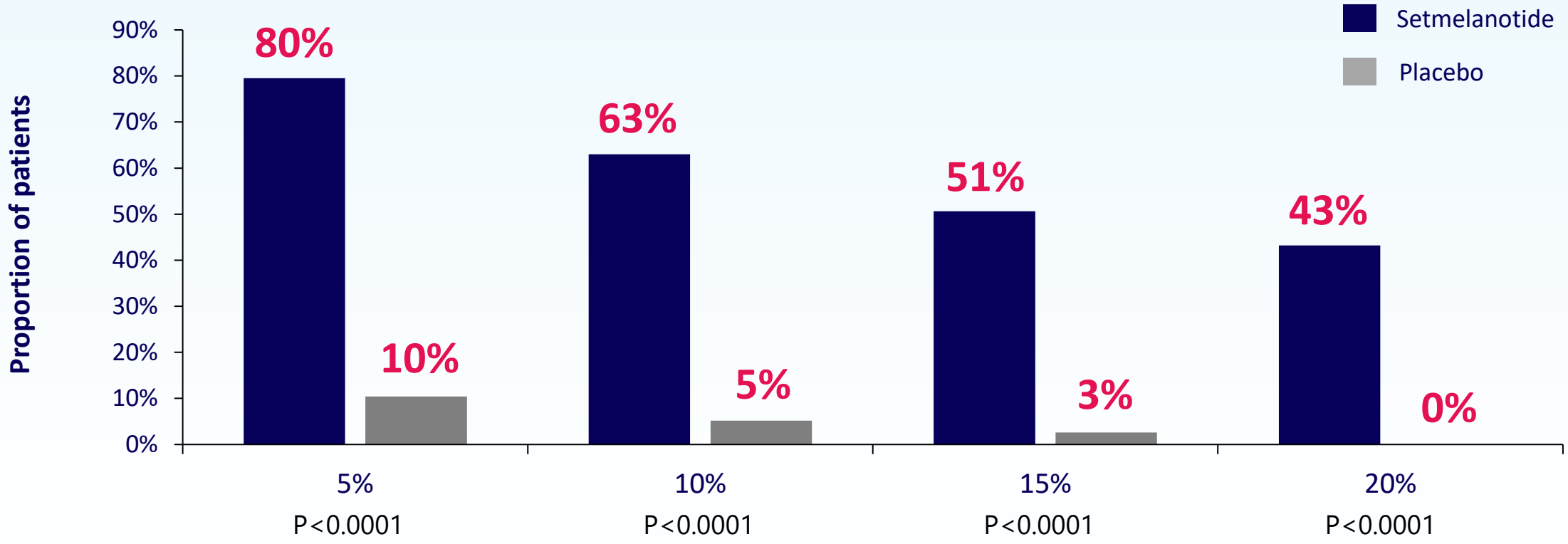
# All Patients Achieved a Decrease in Obesity Severity at One Year

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

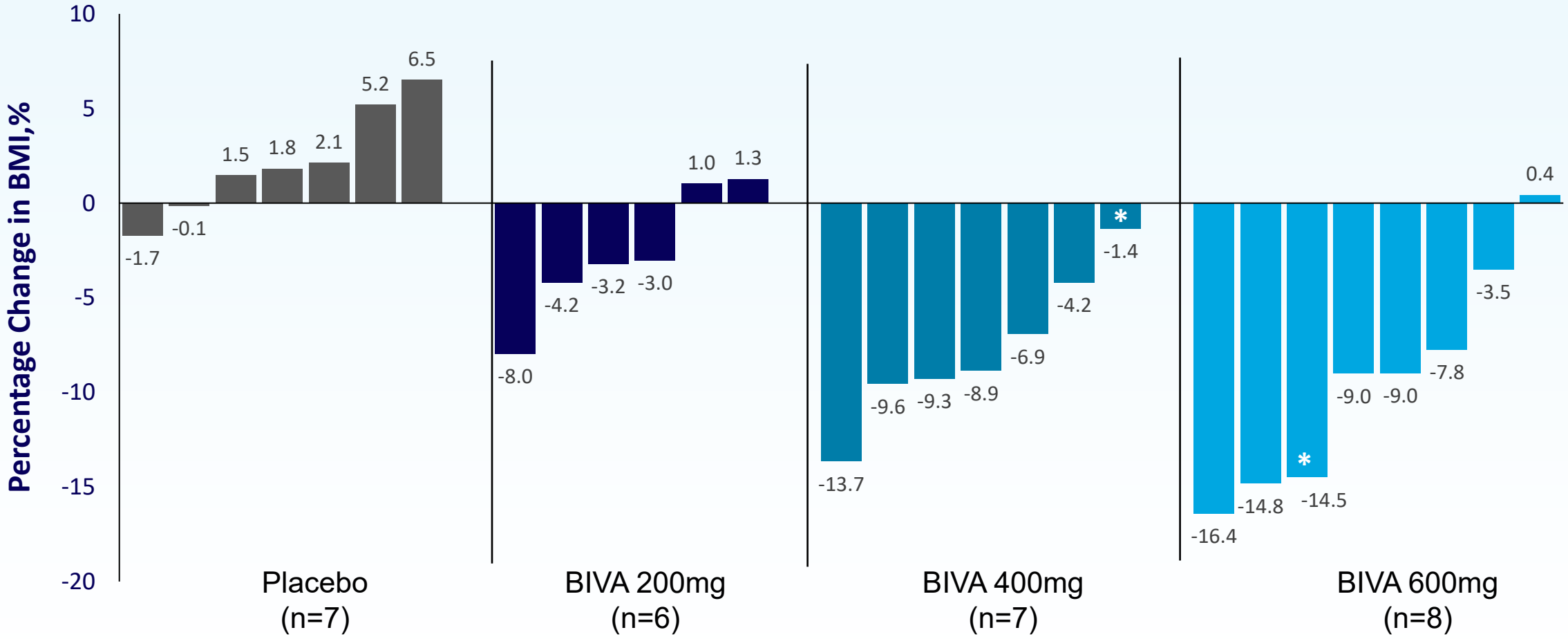
| BMI, kg/m$^2$ | Adults (n=1) | WHO Classification (NIH[5]) | Pediatric patients (n=11)* | | | | | | | | | | | BMI percentile[6] | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ≥50 | 50 | Obesity class III (extreme) | | | 157 | 166 | | | | | 190 | 158 | | ≥140%† | ≥95th percentile |
| ≥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 | 86 | 89 | | | | | ≥95% to <120%§ | |
| ≥25 to <30 | | Overweight | | | | | | | | | | | | ≥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.

# Consistent Response to Setmelanotide Therapy Observed across Majority of Patients in Phase 3 Trial in Acquired HO



# Individual Percentage Change in BMI from Baseline to Week 14

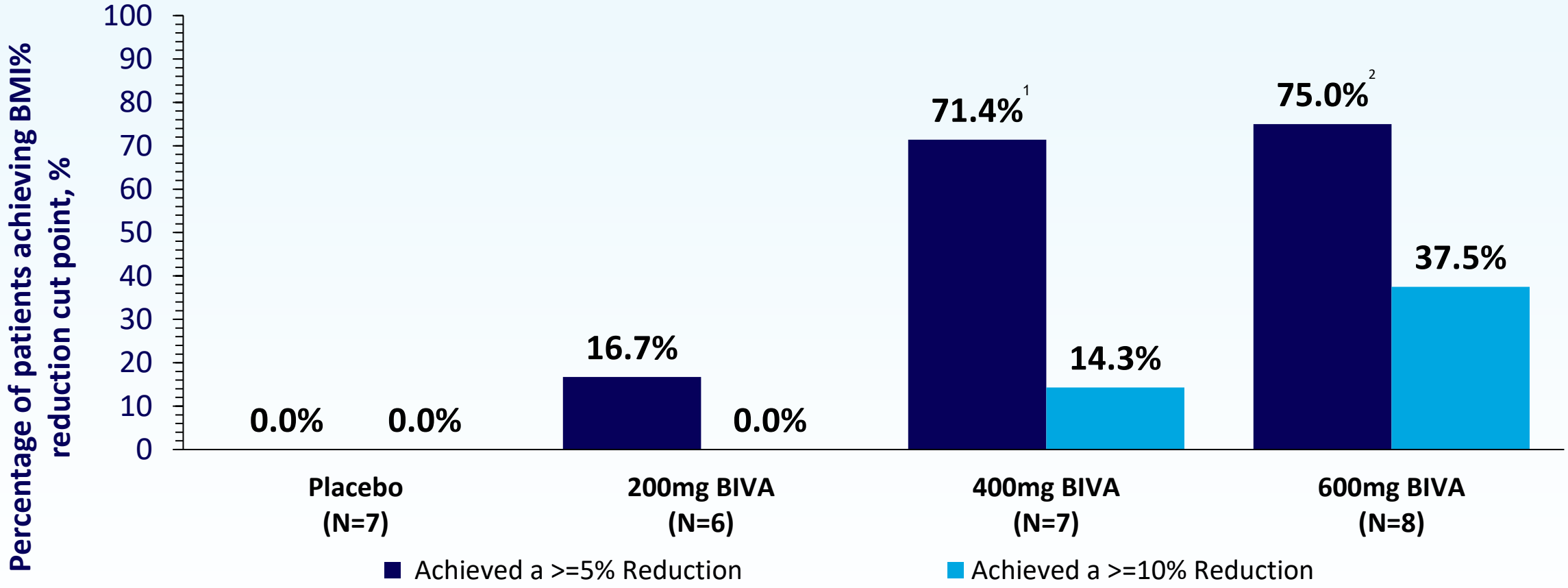



* Last observation carried forward (LOCF): One patient in 400mg cohort discontinued therapy at week one.



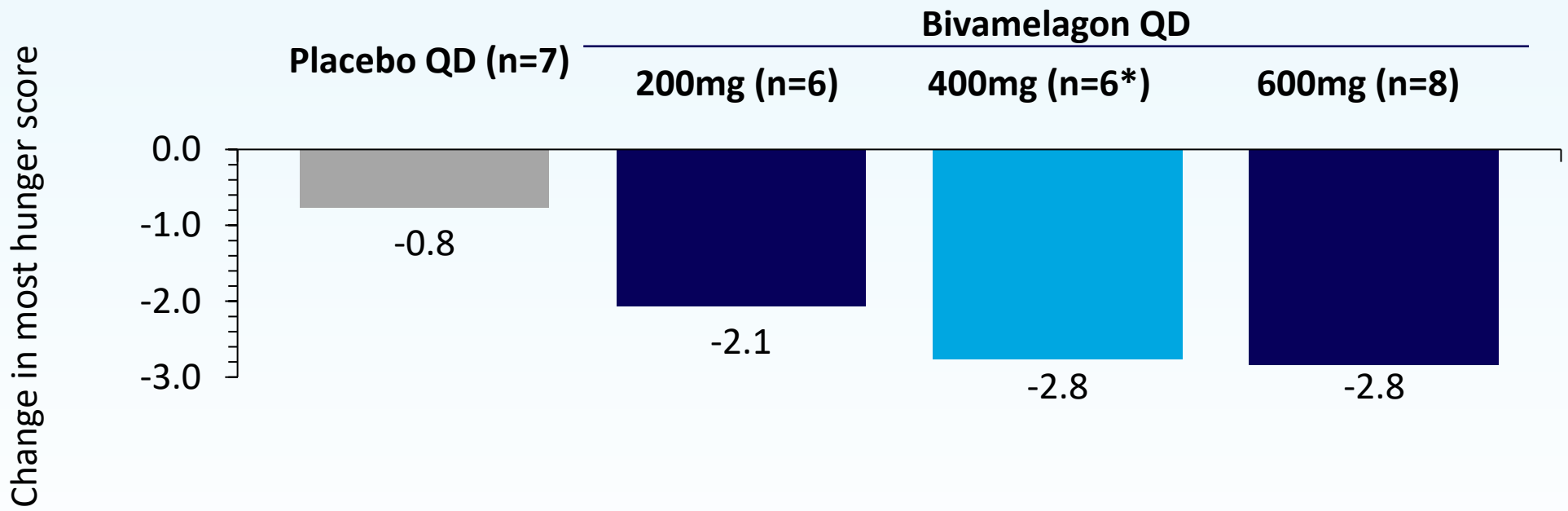
*LOCF (BIVA 400mg participant discontinued Tx Week 1, BIVA 600mg participant Week 10). BIVA, Bivamelagon.

# Patients Achieved BMI Reductions of at least 5%, 10% at Week 14




1. P=0.0105
2. P= 0.0056 vs placebo

# Bivamelagon Achieved Meaningful Reductions in ‘Most’ Hunger Scores at Week 14




Weekly average of daily scores on a 10-point scale with 10 being ‘most’ hungry.
*One patient 400mg bivamelagon who did not complete trial did not have Week 14 score and is not included

# Thank you