Rhythm Pharmaceuticals

Corporate Presentation

April 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 approval and use of setmelanotide in patients with acquired hypothalamic obesity and its availability for patients; the commercial growth of IMCIVREE; our expectations surrounding potential regulatory submissions, progress, or approvals and timing thereof for any of our product candidates, including the Type II variation request to the European Medicines Agency and the anticipated decision by the Committee for Medicinal Products for Human Use to issue an opinion to the European Commission and a potential marketing authorization in the second half of 2026; as well as the Company's engagement with Japan's Pharmaceuticals and Medical Devices Agency and plans to seek authorization for setmelanotide to treat acquired hypothalamic obesity in Japan; the estimated market size and addressable population for our drug products, including setmelanotide for the treatment of hypothalamic obesity in the United Sates, the European Union and Japan; the future announcement of data from our ongoing clinical trials, including the Japanese cohort of our Phase 3 trial evaluating setmelanotide for patients with acquired hypothalamic obesity, the substudy evaluating setmelanotide for patients with congenital hypothalamic obesity, Part C of the Phase 1 trial evaluating RM-718, and the open-label Phase 2 trial evaluating setmelanotide in patients with Prader-Willi syndrome; the ongoing enrollment in and potential progress or outcomes of our clinical trials; the presentation of the full data from the TRANSCEND study at an upcoming medical meeting; and the content, date 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 ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, failure to identify and develop additional product candidates, 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, the impact of competition, risks relating to product liability lawsuits, 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 Annual Report on Form 10-K for the year ended December 31, 2025 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 press release, whether as a result of new information, future developments or otherwise.

Well Positioned to Deliver Long-term, Sustained Growth

Global commercial infrastructure to drive growth with IMCIVREE® (setmelanotide) available **>25 countries** for BBS, POMC, LEPR deficiencies

Acquired hypothalamic obesity (HO): IMCIVREE FDA approval in March 2026 with near-term growth opportunities in Europe and Japan

Setmelanotide, MC4R agonism advancing to address significant unmet need in **Prader-Willi syndrome (PWS)** and additional genetic causes of rare MC4R pathways diseases

Next-generation MC4R-specific agonists, weekly RM-718 and oral bivamelagon, with global patent protection extending into 2040s

IMCIVREE: First and Only Therapy Approved for Acquired HO

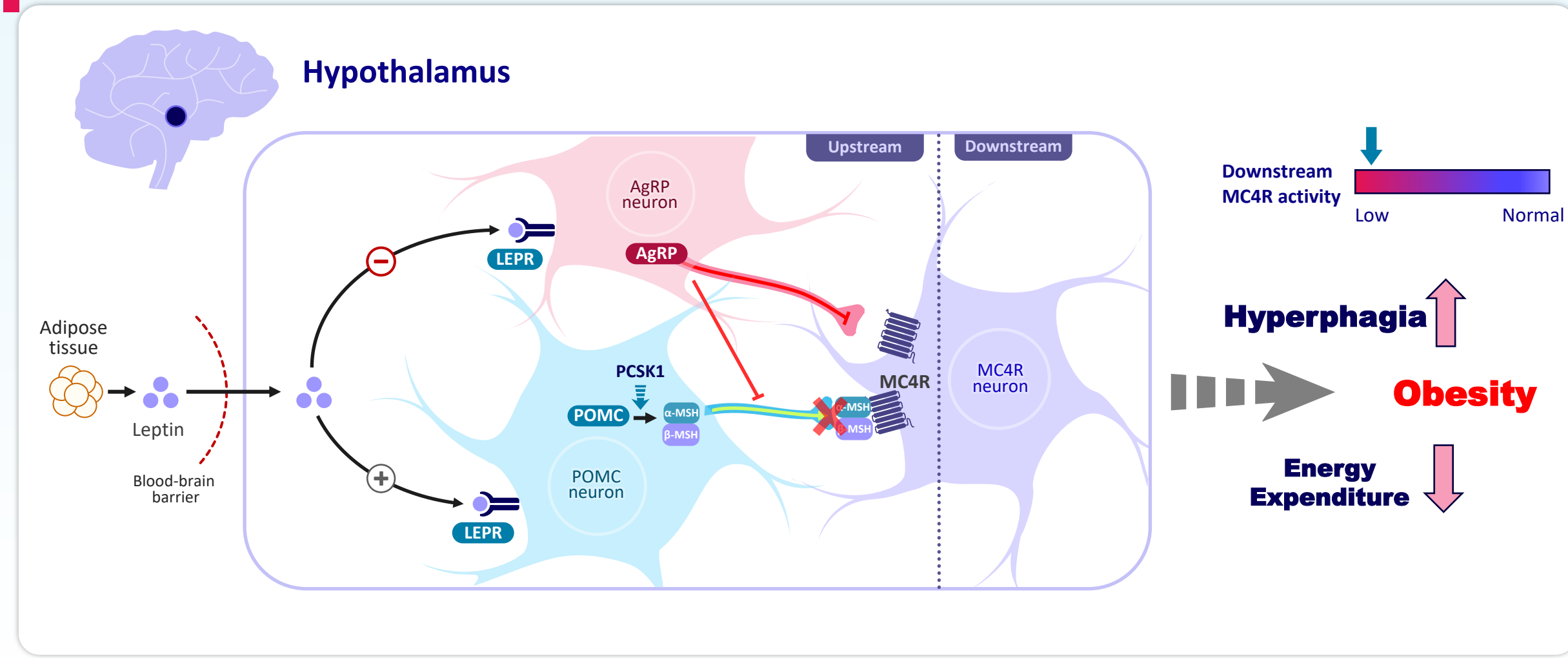
U.S. launch underway following March 19th FDA Approval

IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated to reduce excess body weight and maintain reduction long term in adults and pediatric patients aged:

- 4 years and older with **acquired hypothalamic obesity (HO).**
- 2 years and older with **Bardet-Biedl syndrome (BBS).**
- 2 years and older with pro-opiomelanocortin (**POMC**), proprotein convertase subtilisin/kexin type 1 (**PCSK1**), or leptin receptor (**LEPR**) deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

NOTE: See the full U.S. FDA-approved Package Insert for complete information.

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

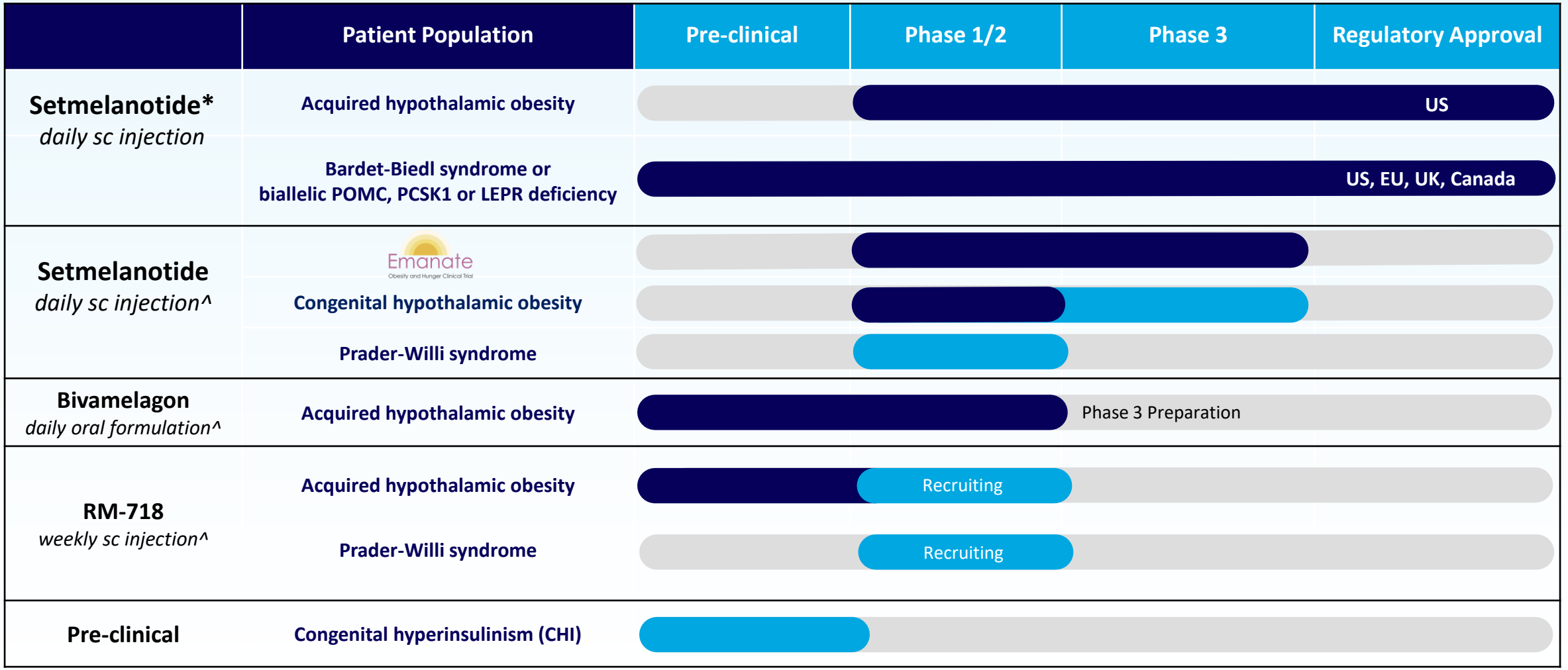
9 YEARS OLD:

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



*Rhythm received a positive CHMP opinion for IMCIVREE for the treatment of obesity and control of hunger in patients with acquired hypothalamic obesity due to hypothalamic Injury or impairment on March 26, 2026; Approved in Israel & Canada LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin. ^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. 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

~20,000
estimated U.S. prevalence[4]

~400,000
estimated worldwide prevalence[4]

*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. Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. In: Adam MP, Bick S, Mirzaa GM, et al, eds. GeneReviews®. 1998:1-41. Updated December 5, 2024. Accessed December 10, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1330/

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

$388.9M

Cash, cash equivalents and short-term investments as of December 31, 2025

Guidance

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

68.3 Million

Weighted average common shares outstanding as of February 24, 2026

Rhythm Leadership – Strong Team with Broad Biopharma Experience

					
David Meeker, MD *Chair, President and Chief Executive Officer*	**Hunter Smith** *Chief Financial Officer*	**Jennifer Lee** *Executive Vice President, Head of North America*	**Yann Mazabraud** *Executive Vice President, Head of International*	**Joe Shulman** *Chief Technology Officer*	**Alastair Garfield, PhD** *Chief Scientific Officer*
SANOFI GENZYME	Celgene	SANOFI GENZYME Krystal	SANOFI GENZYME trevi THERAPEUTICS	Ra Pharma novelion THERAPEUTICS	RECTIFY PHARMA Pfizer
25-plus years; focus on rare genetic disease treatments, including Aldurazyme®, Fabrazyme® and Myozyme®	*20-plus years in finance, M&A, capital markets; financial leadership for Otezla®*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years experience leading CMC, supply chain planning and quality assurance and control*	*20 years experience in neurobiology of appetite /body weight regulation; rare disease drug discovery*

Multiple Anticipated Milestones

Q1 2026	Complete enrollment in **Part C** of **Ph1/2 trial** evaluating **weekly RM-718** in **acquired hypothalamic obesity**
Q2 2026	European Commission decision on **Marketing Authorization Application** for IMCIVREE in **acquired hypothalamic obesity**[1]
Q2 2026	Disclose six-month results from exploratory **Ph2 trial** evaluating **setmelanotide** in **Prader-Willi syndrome**
H2 2026	Complete enrollment in **Ph3 substudy** evaluating **setmelanotide** in **congenital hypothalamic obesity**
H2 2026	Complete enrollment in **Part D** of **Ph1/2 trial** evaluating **RM-718** in **PWS**
YE 2026	Initiate **pivotal Ph3 trial** evaluating **oral bivamelagon** in **acquired hypothalamic obesity**

1. Rhythm Pharmaceuticals received a Positive CHMP Opinion for IMCIVREE for the Treatment of Obesity and Control of Hunger in Patients with Acquired Hypothalamic Obesity due to Hypothalamic Injury or Impairment on March 26, 2026.

IMCIVREE Global Commercial Execution

IMCIVREE available in >25 countries outside the United States

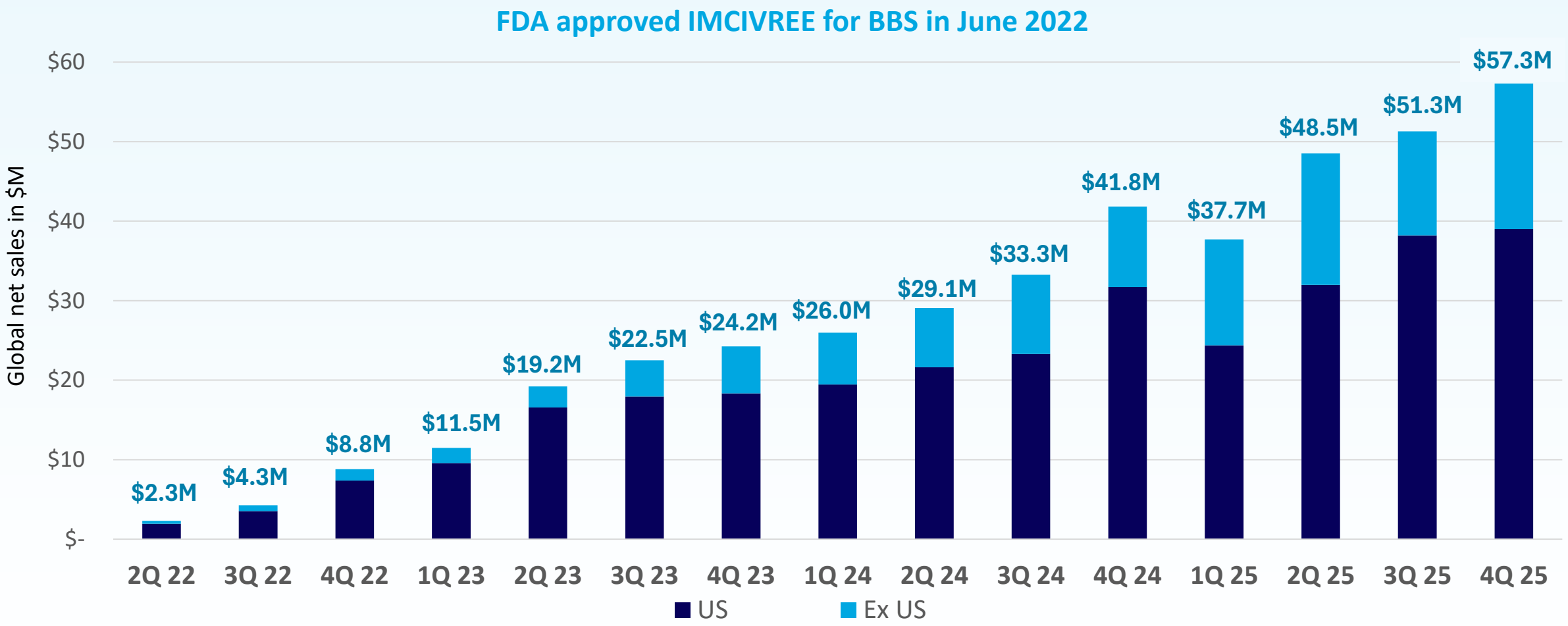
Continued execution

>100 employees in 13 countries

Eight countries added in 2025

64 abstracts at
12 international
scientific congresses

Steady Growth in Net Product Revenues since BBS Launch



Hypothalamic Obesity

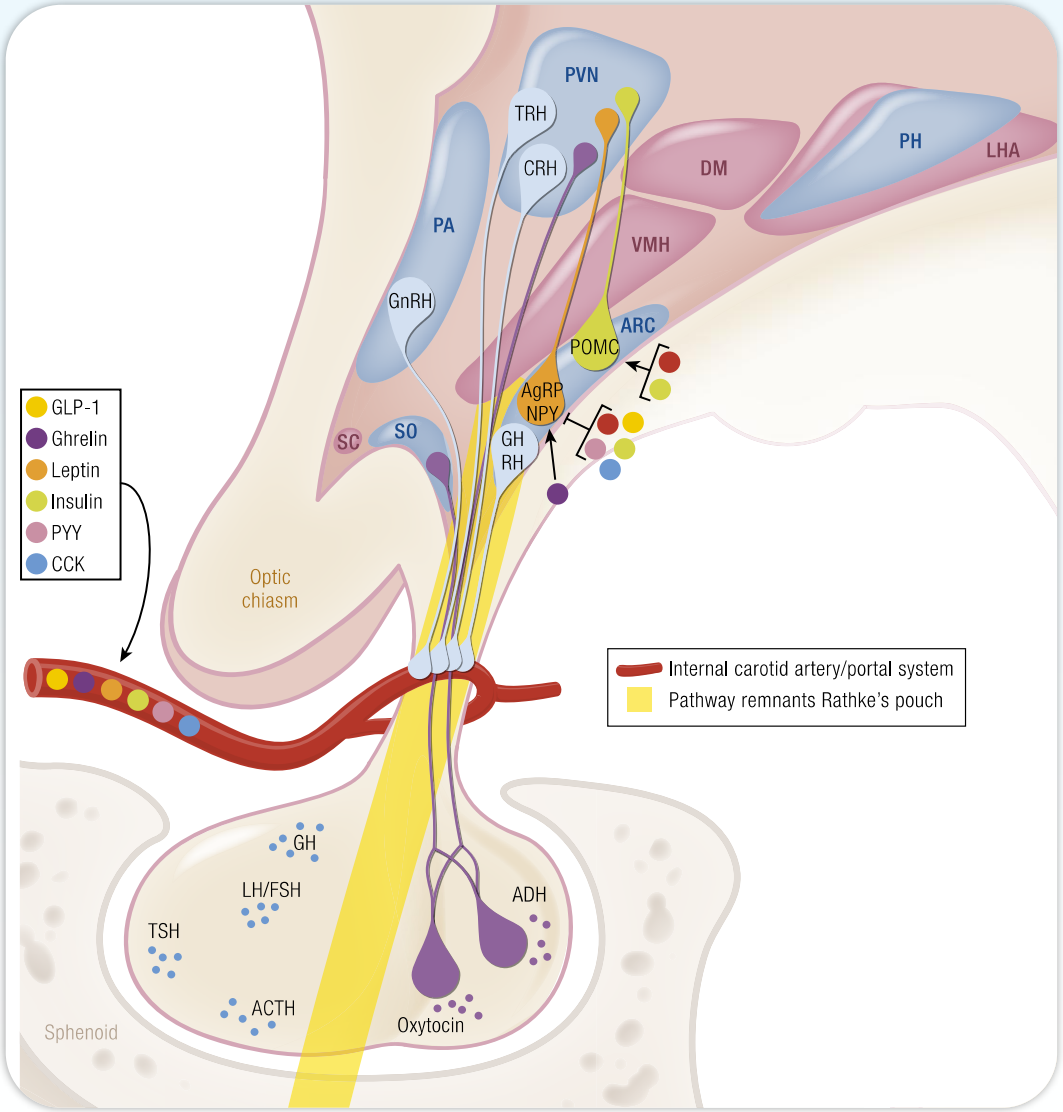
Acquired and Congenital

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

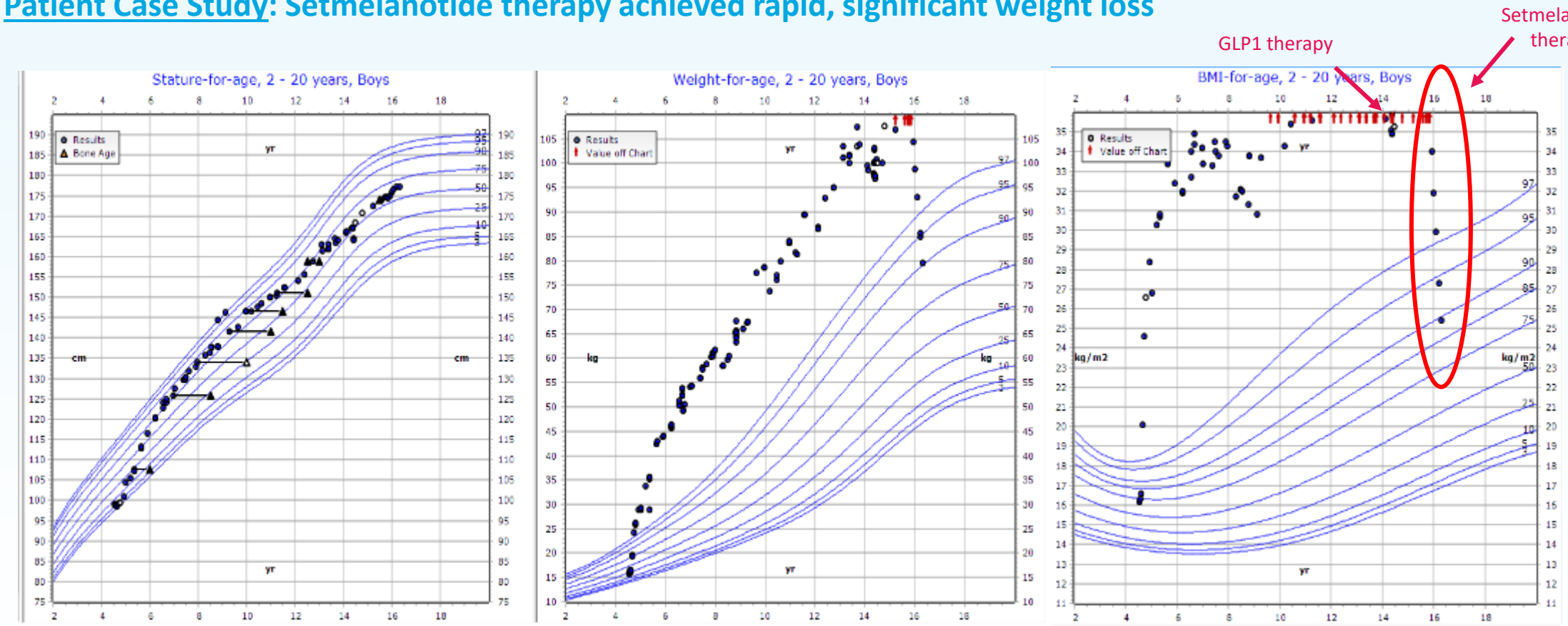
5.5 average active prescriptions per quarter

22.1 average number of unique medications over 2 years

89% were receiving ≥3 therapies for neuroendocrine dysfunction

HO: Aggressive, Rapid Weight Gain follows Therapy for CP

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

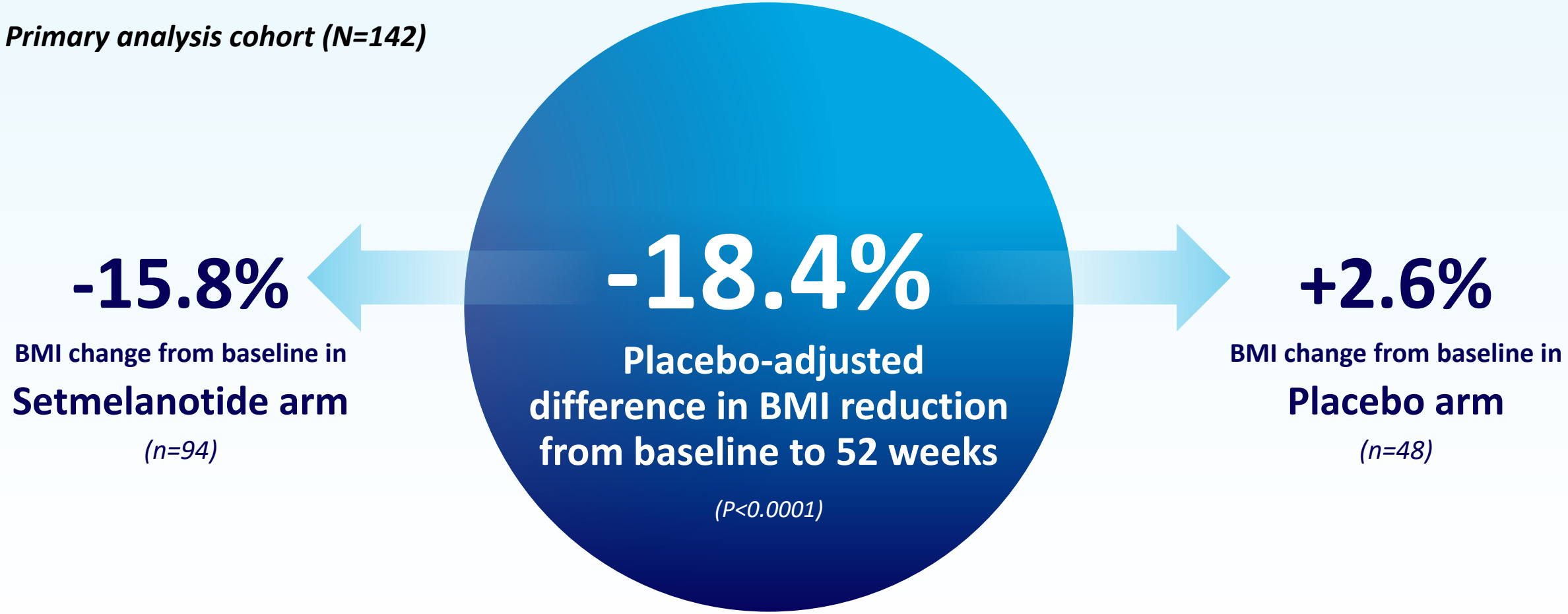


Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota

Rhythm® PHARMACEUTICALS

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 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

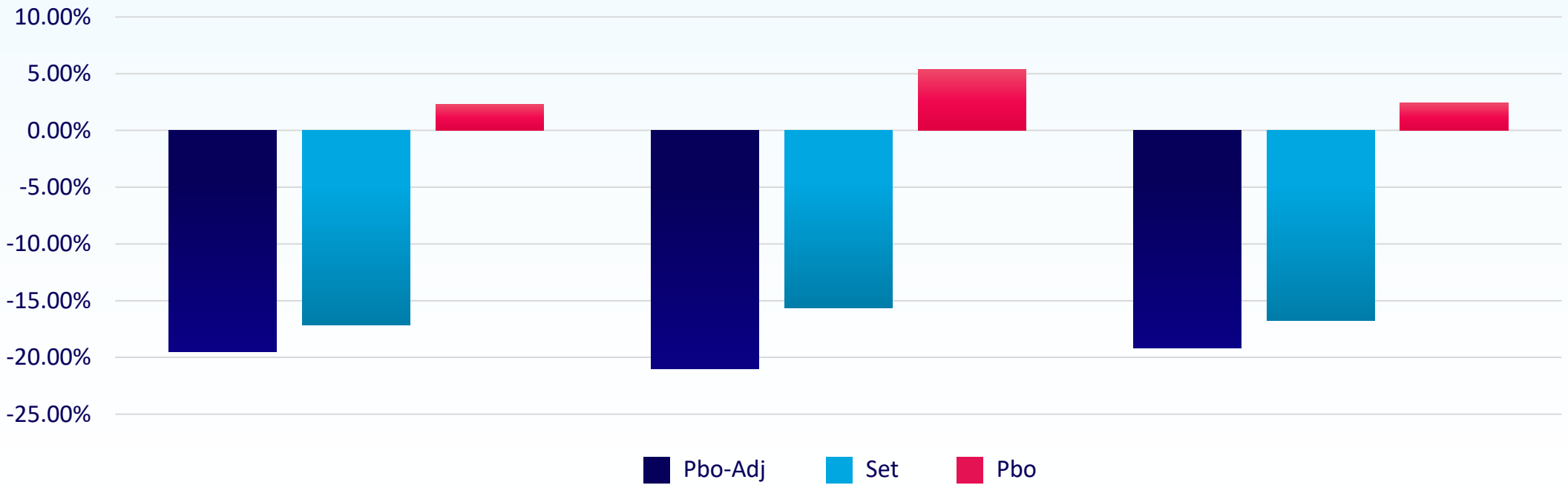
Concomitant GLP-1 *(n=15)*

-27.1%

Placebo-adjusted difference in BMI reduction from baseline

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)*



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

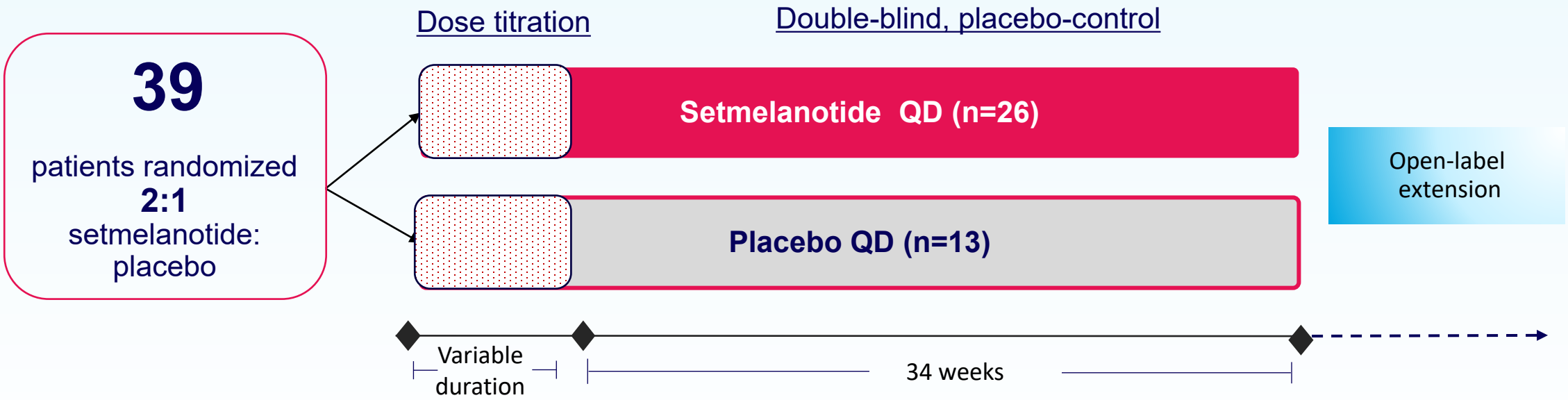
No approved therapies for congenital HO

>1,000 Patients

Estimated prevalence in each the United States and Europe

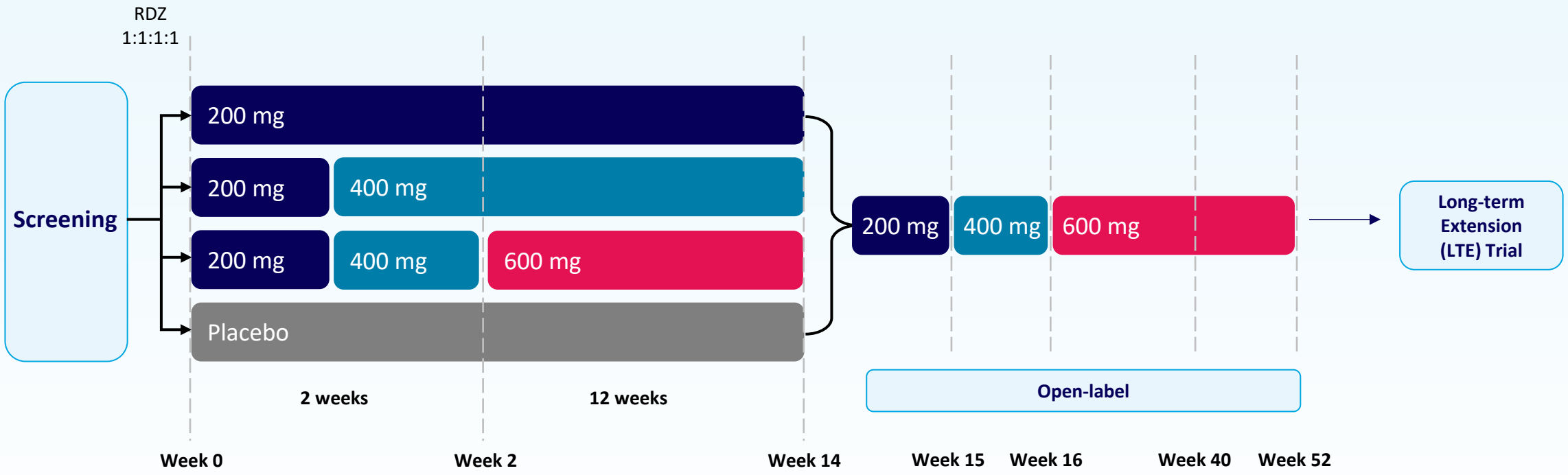
34-week Substudy in Congenital Hypothalamic Obesity Added to Pivotal, Ph3 HO Study

Independent substudy leverages existing Ph3 trial infrastructure; Enrollment completion expected in H1 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

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

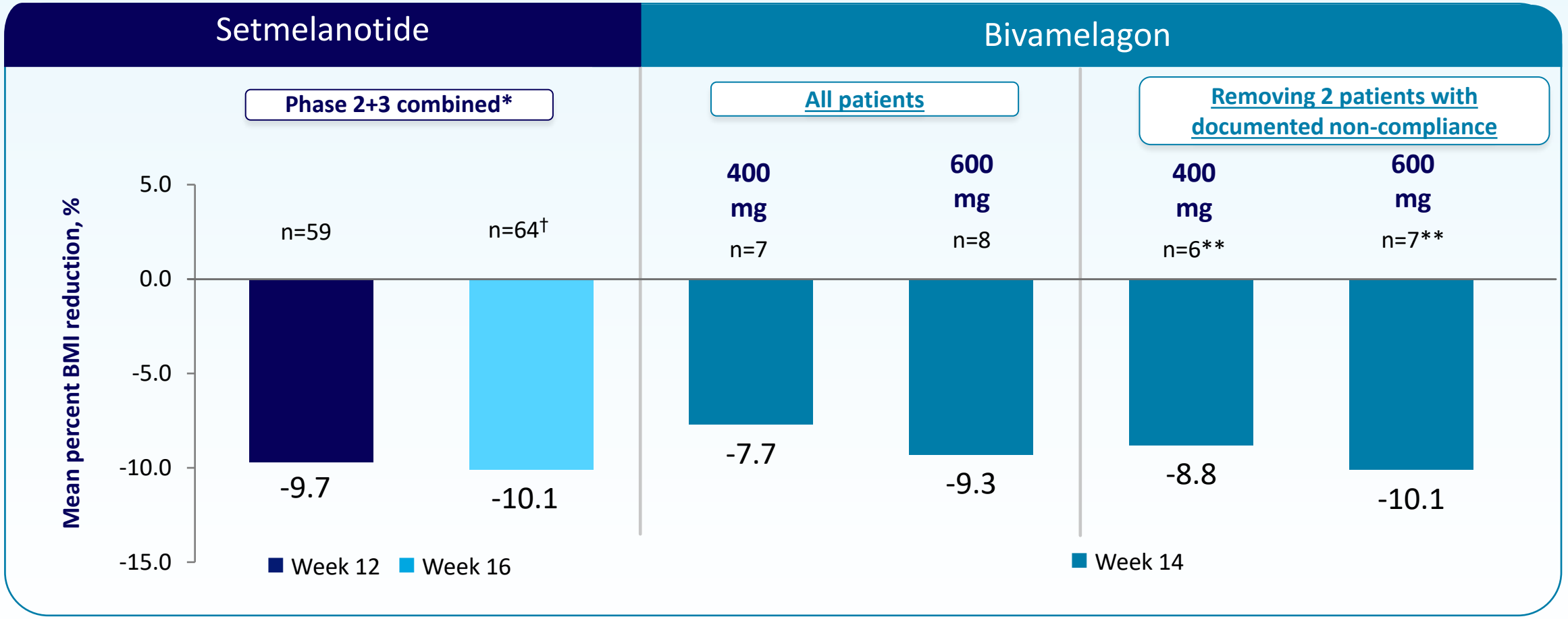
Bivamelagon Achieved Statistically Significant BMI Reductions at All Doses

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.

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 **limited therapeutic options** that effectively reduce the **extreme hyperphagia** and 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 Patients

Estimated worldwide prevalence*

* Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. In: Adam MP, Bick S, Mirzaa GM, et al, eds. GeneReviews®. 1998:1-41. Updated December 5, 2024. Accessed December 10, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1330/

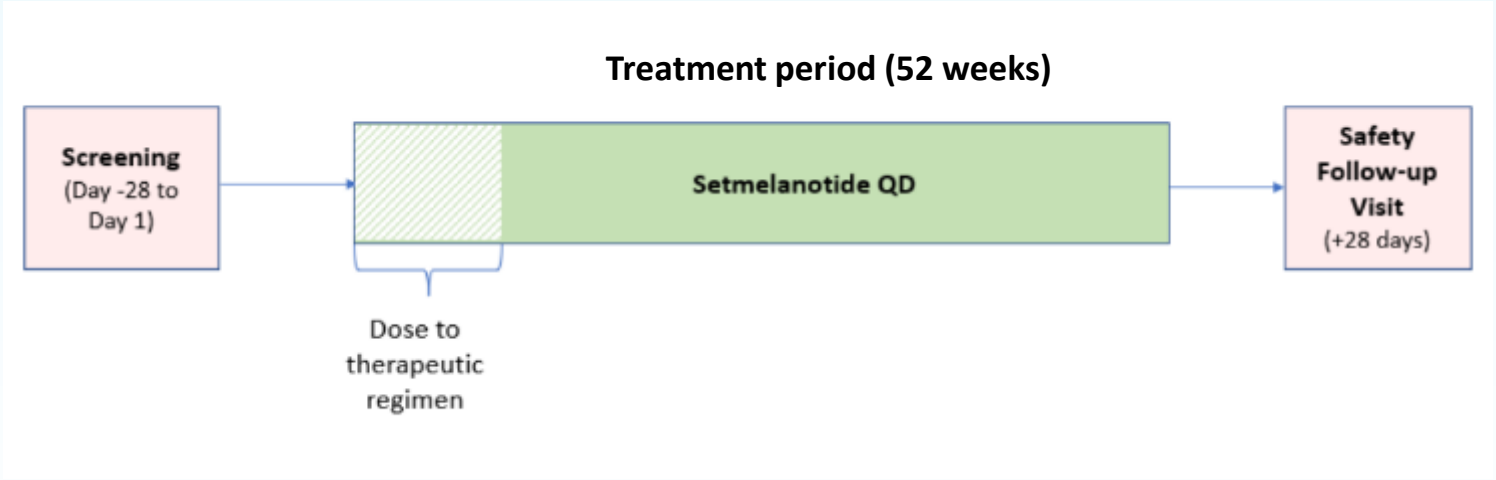
Exploratory Phase 2, Open-label Trial of Setmelanotide in PWS

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) <12 years old, n (%) ≥12 years and <18, n (%) ≥18 years old, n (%)	17.1 (5.6) (6 – 23) 3 (16.7) 4 (22.2) 11 (61.1)
Sex, n (%)	Female / Male	8/10 (44.4/55.6)
Race, n (%)	White Multiple Asian	15 (83.3) 2 (11.1) 1 (5.6)
BMI, kg/m²	Mean (SD) Range	39.1 (9.5) 24.2 – 67.0
BMI, kg/m² (n=8*)	Mean (SD) Range	43.7 (10.3) 32.6 – 67.0

*BMI for the 8 patients with ≥3 months' treatment

N=18
Patients enrolled

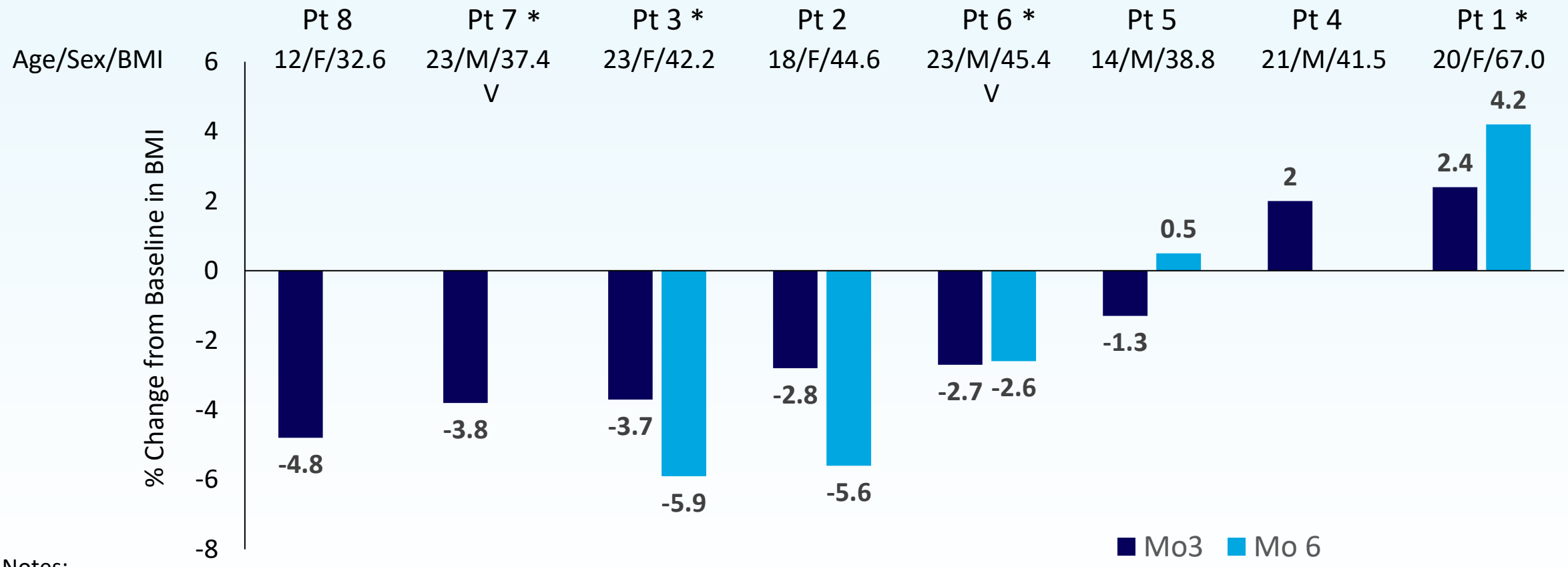
n=8
patients reached Month 3[1]

n=5
patients reached Month 6[1]

17
patients remain on active therapy

1. Data cut-off date is Nov. 14, 2025

Setmelanotide Achieved BMI Reductions from Baseline in Patients with PWS After 3 and 6 Months of Treatment

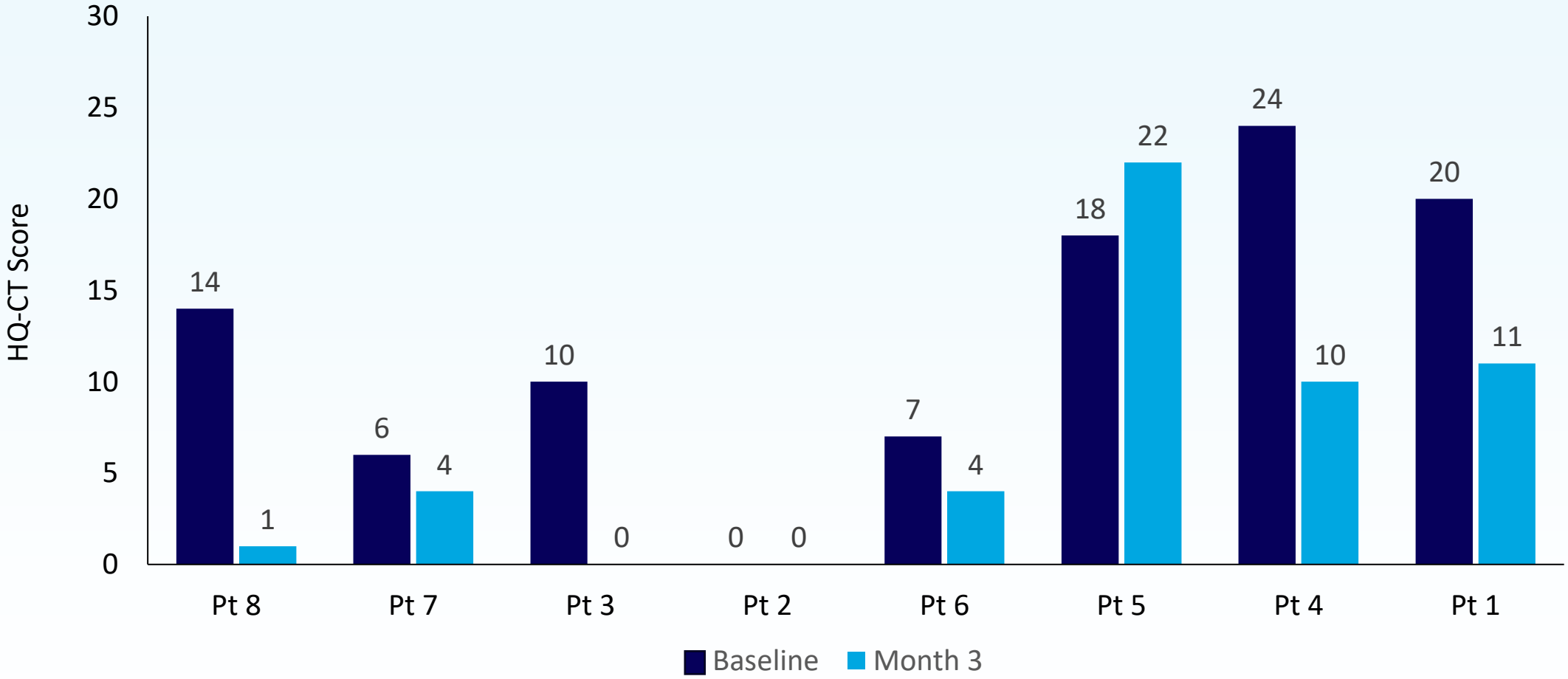


Notes:

V=Patients 7 and 6 are on Vykat™ XR (diazoxide choline); *Patients 7, 3, 6, and 1 have type 2 diabetes.

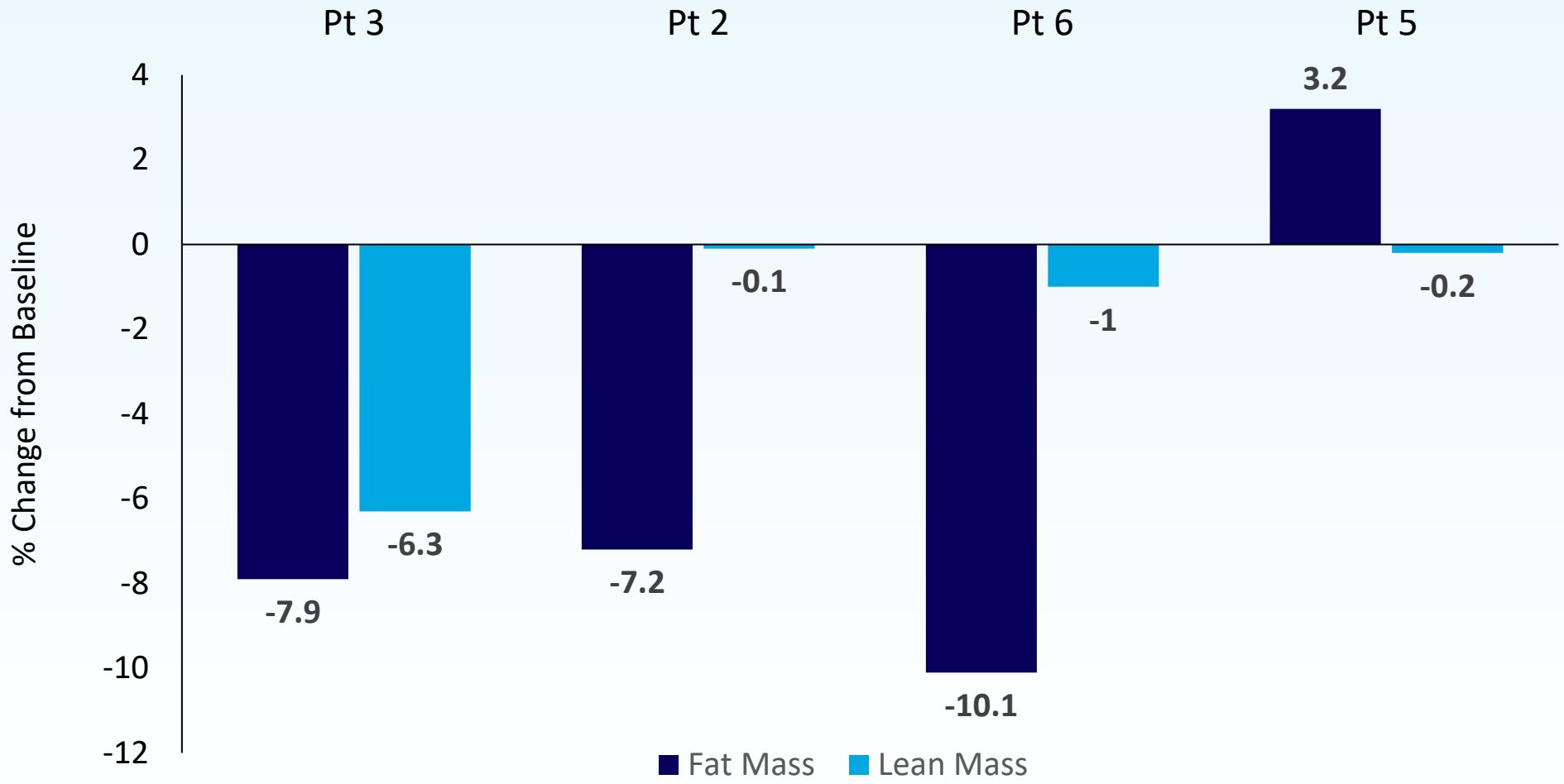
Patient 3: Worsened diabetes control after 13 weeks, started on insulin. **Patient 5:** non compliant after initial response; **Patient 4:** discontinued prior to visit 6. **Patient 1:** poorly controlled diabetes, lipohypertrophy, severe lower extremity lymph edema

HQ-CT[1] Scores Showed Meaningful Hyperphagia Reductions from Baseline Observed in 6 of 7 Evaluable Patients at Month 3



1. The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) is a 9-item, observer-reported outcome measure that assesses changes in hyperphagic behaviors in individuals with PWS. Each item is scored from 0 to 4, for a total possible score of 36.

Positive Body Composition Changes from Baseline to Month 6



Note: There are no DEXA data for Patient 1 (exceeded table's weight limits)

Appendix

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

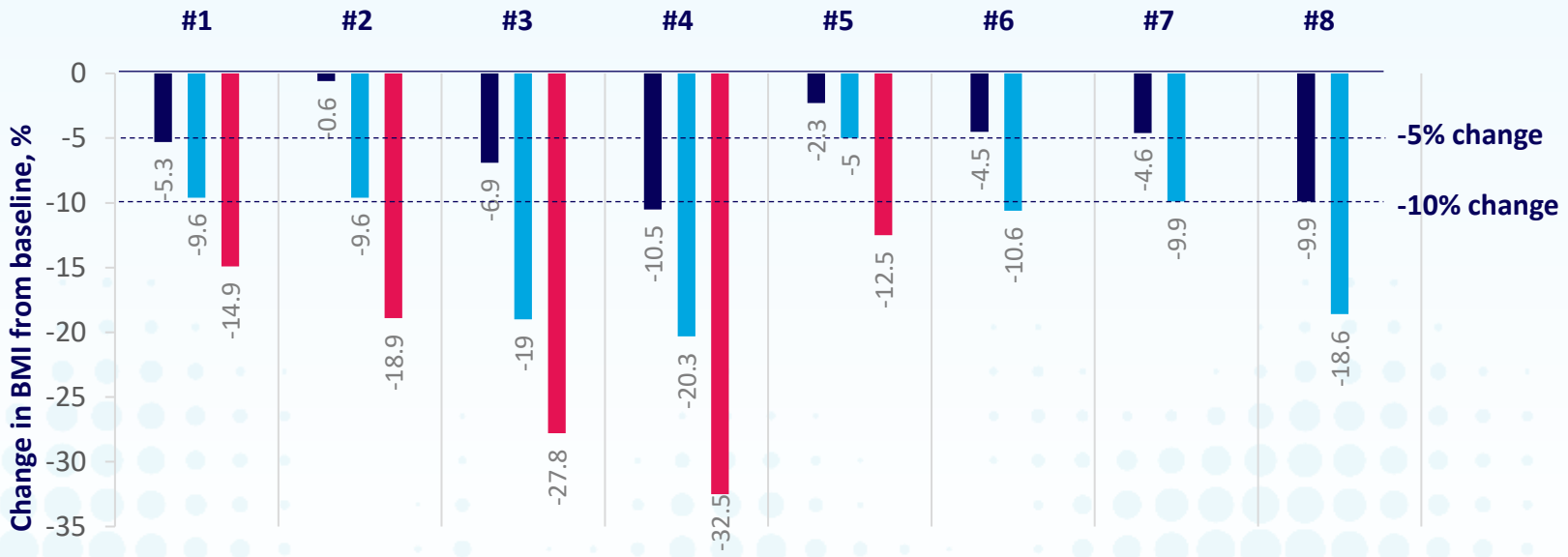
31.4 years
Mean age at initiation of setmelanotide therapy

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

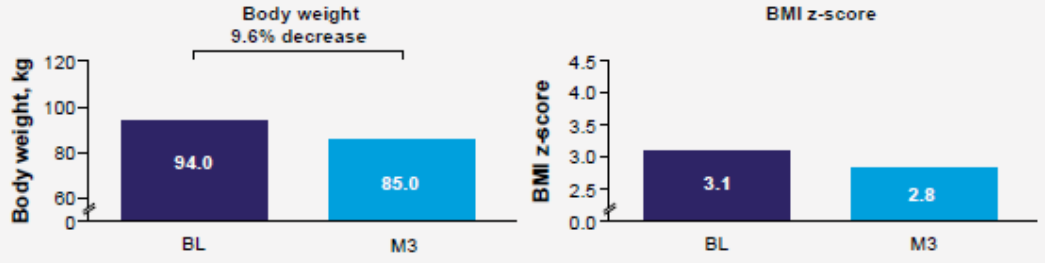
Real-world Case Reports from French Early-access Program Suggest Setmelanotide may be Effective Treatment for Congenital HO

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:

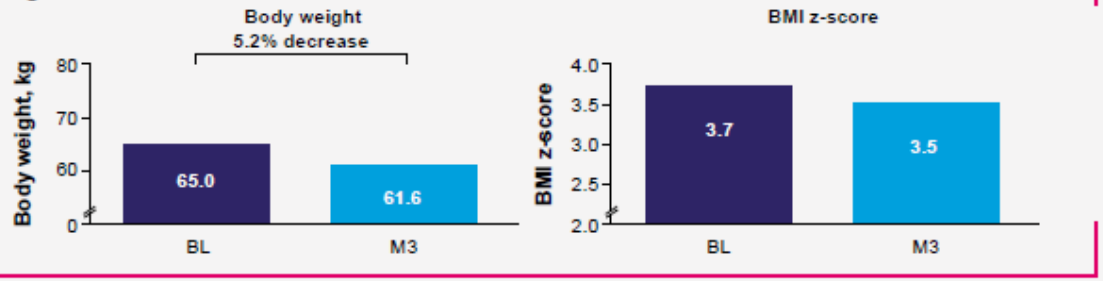


- For the 4 questions included in the scoring of hunger scores, the reported change was 5-5-0-6 (BL) to 5-5-0-5 (M3). Physician noted difficulty in interpretation and scoring with the questionnaire
- During treatment, patient reported injection site reaction and intermittent diarrhoea at 2 weeks of treatment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

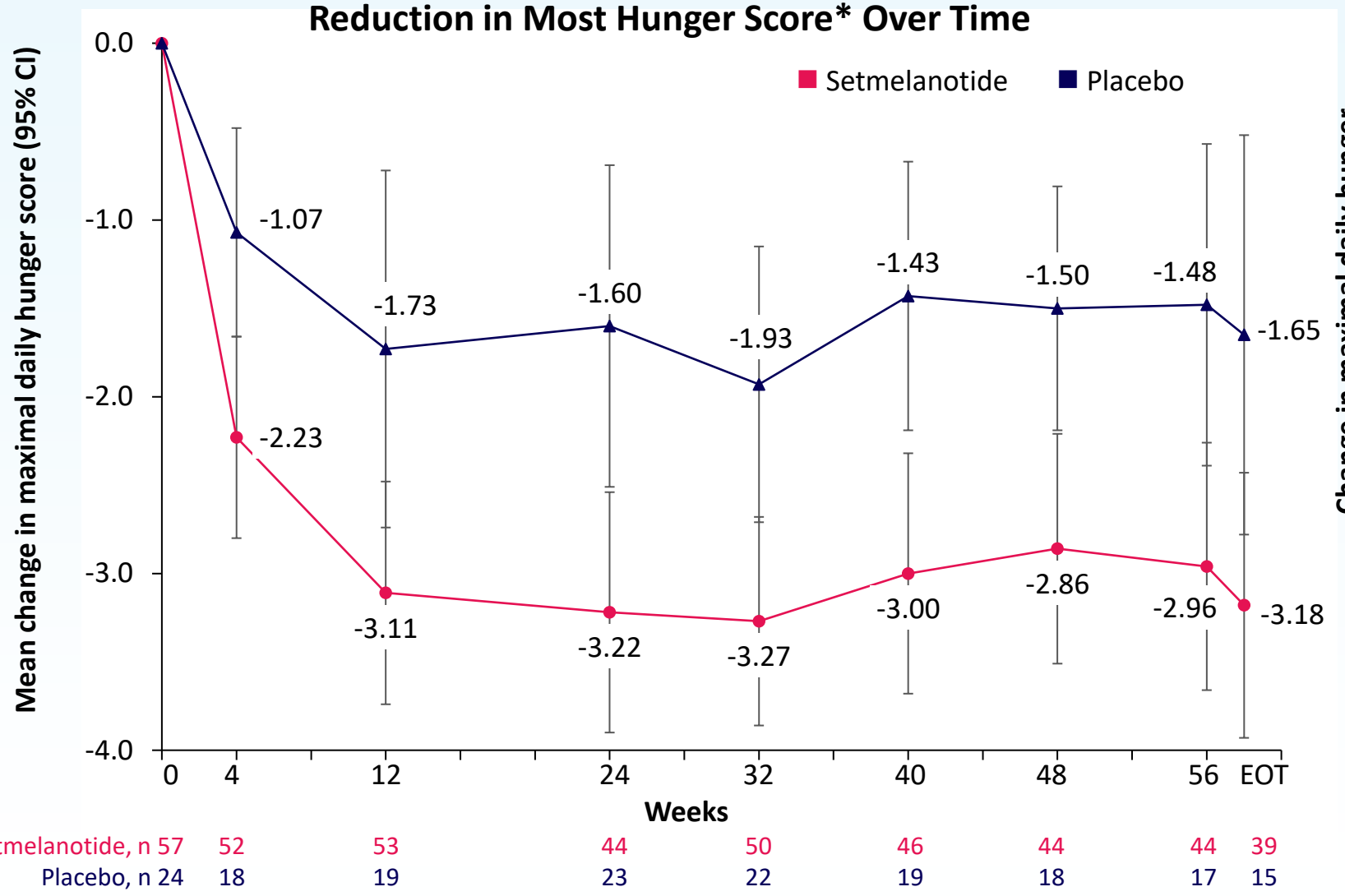


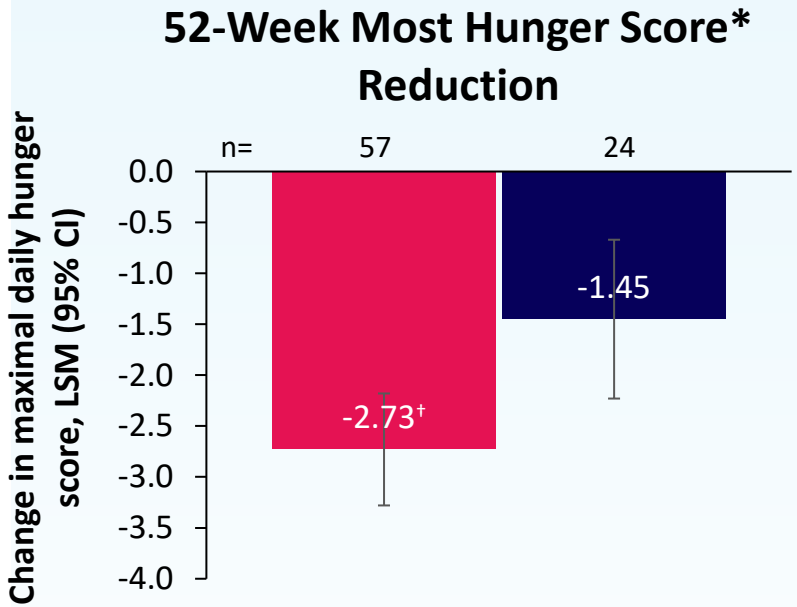
- For the hunger outcomes, patient reported a qualitative improvement rather than quantitative, as normally reflected by hunger scores. Initially, the patient described feeling moderately hungry at BL, slightly hungry at M1, and not hungry at all by M3 of treatment
- During treatment, no adverse events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

Adapted from '3-Month real-world setmelanotide hunger and weight outcomes in four French paediatric 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**

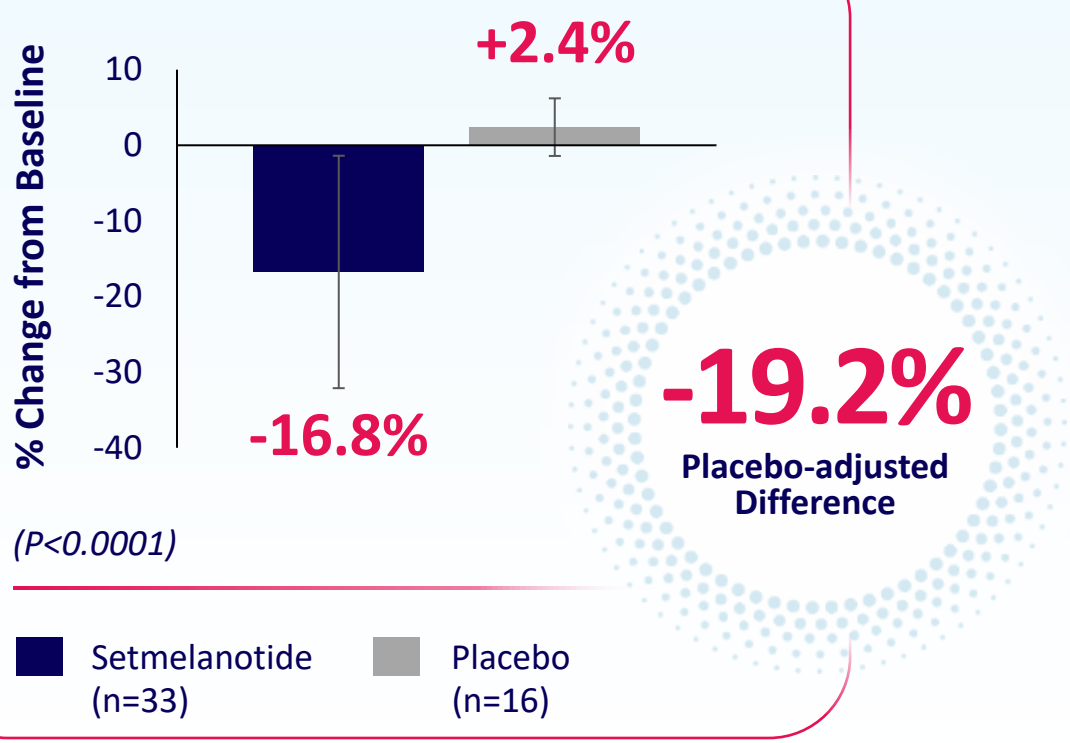
†*P*=0.0086 vs placebo.

As presented at ENDO 2025

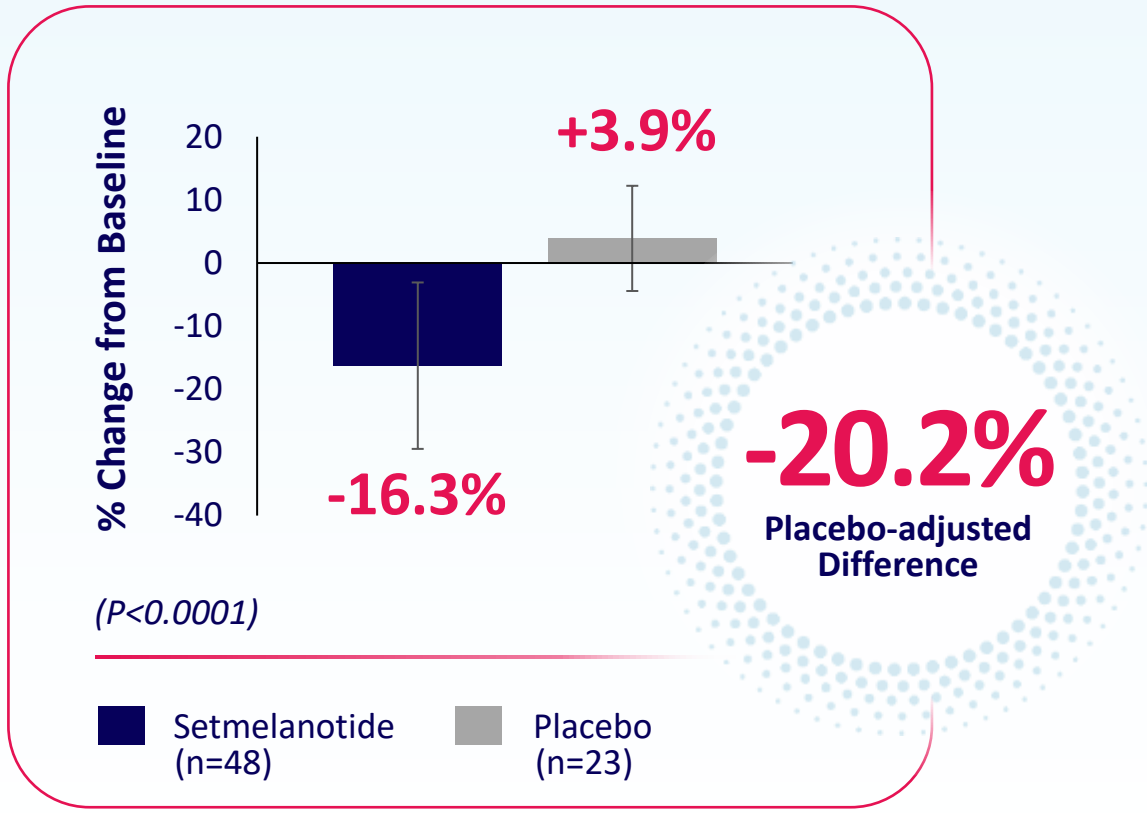
*Weekly average of daily scores. participants ≥12 years of age who were able to self-report were administered the questionnaire. Participants were asked to rate their most hunger on an 11-point numerical rating scale from 0 to 10, where 0 = not hungry at all and 10 = hungriest possible via the question, "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

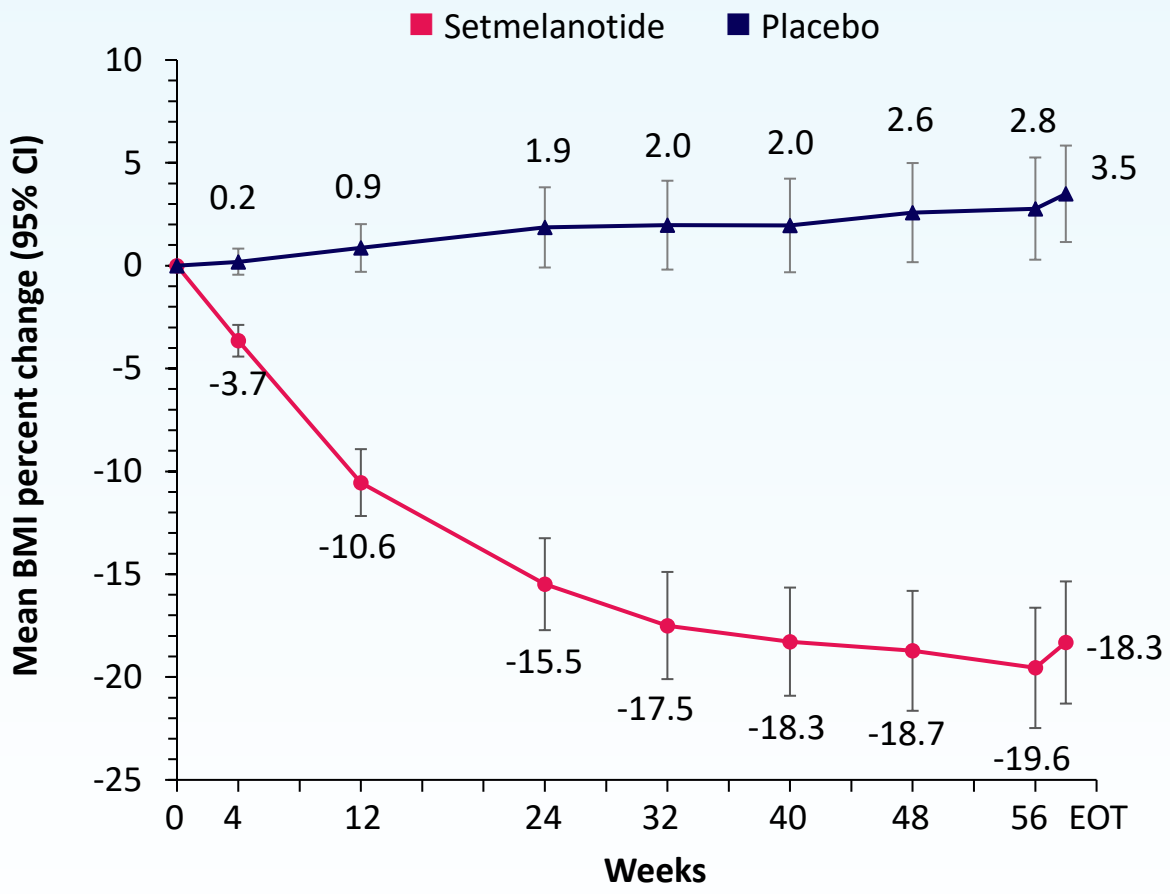
≥18 Years Old *(n=49)*



<18 Years Old *(n=71)*

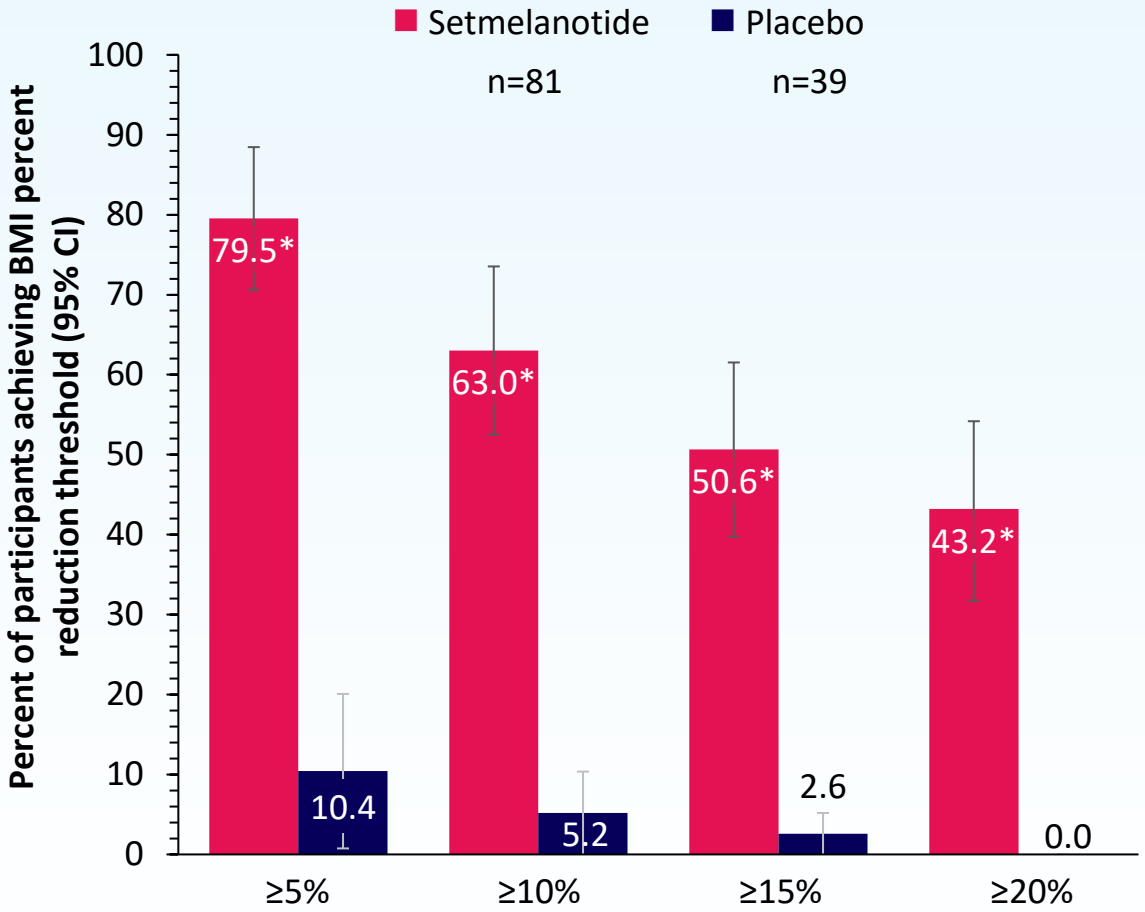


Rapid and Significant BMI Percent Reduction Starting at Week 4



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

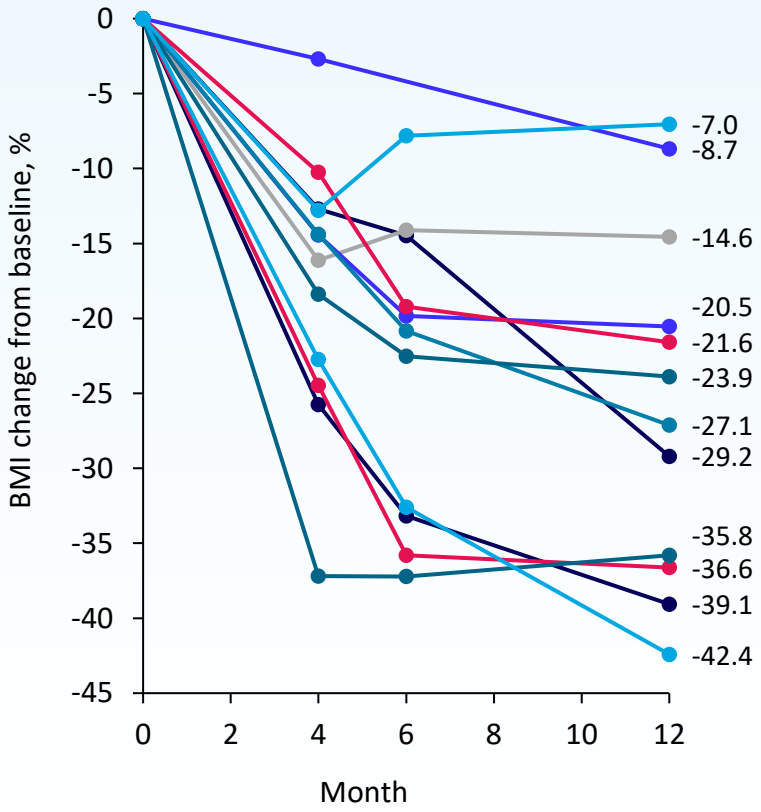
*P<0.0001 vs placebo.

As presented at ENDO 2025

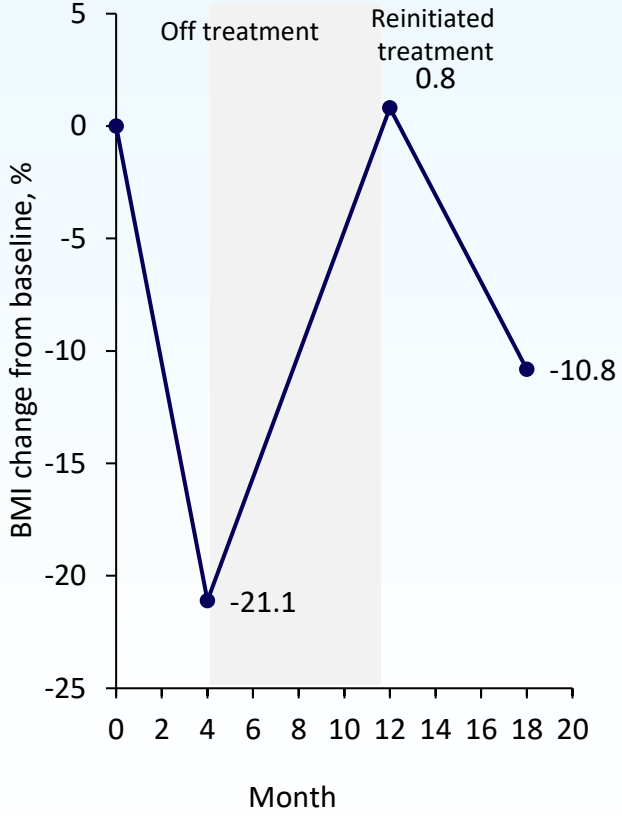
BMI, body mass index; CI, confidence interval.

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

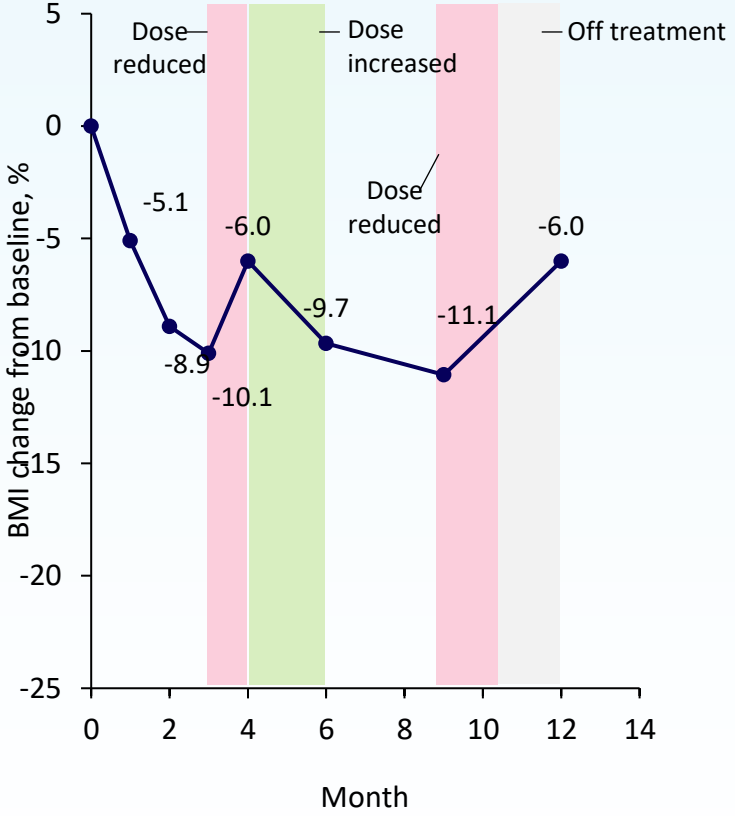
Patients on treatment at Month 12 (n=12)



Patient lost to follow-up (n=1)



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

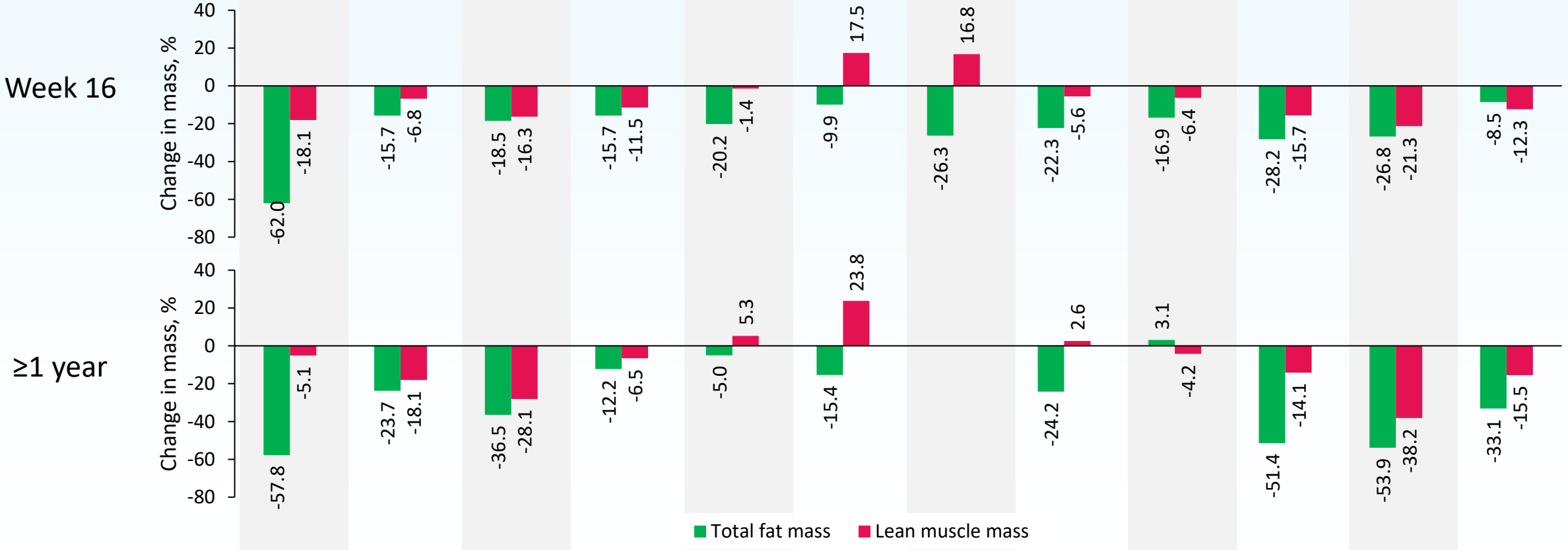


As presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.

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



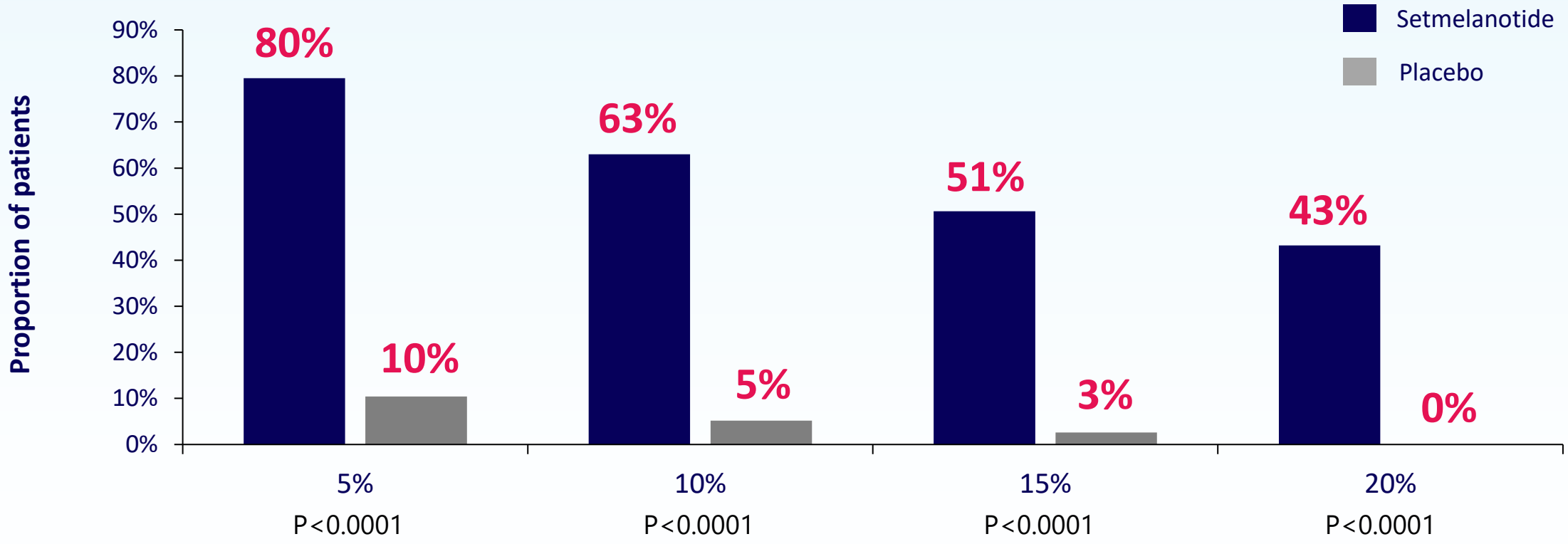
All Patients Achieved a Decrease in Obesity Severity at One Year

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

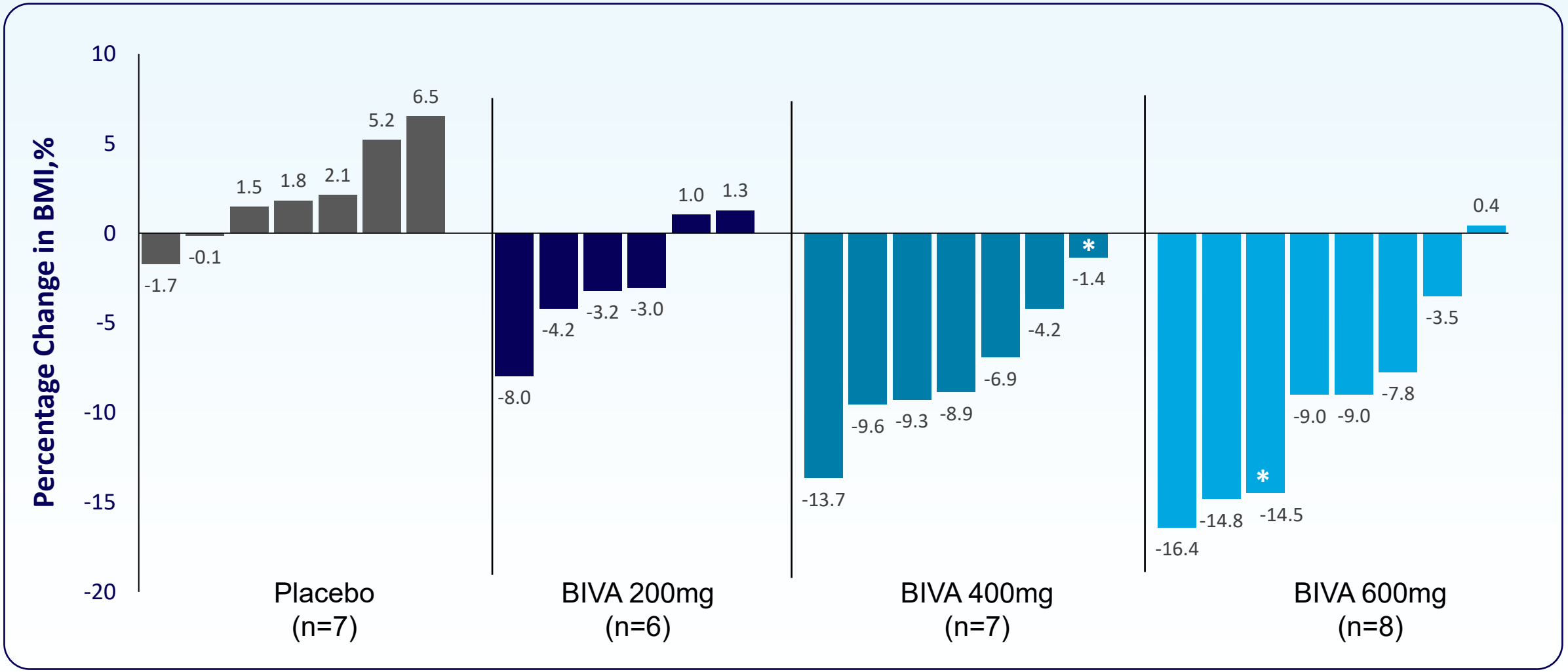
BMI, kg/m^2	Adults (n=1)	WHO Classification (NIH[5])	Pediatric patients (n=11)*											BMI percentile[6]	
≥50	50	Obesity class III (extreme)			157	166					190	158		≥140%†	≥95th percentile
≥45 to <50								149							
≥40 to <45									144			140	141		
≥35 to <40	37	Obesity class II (severe)[5]	139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

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

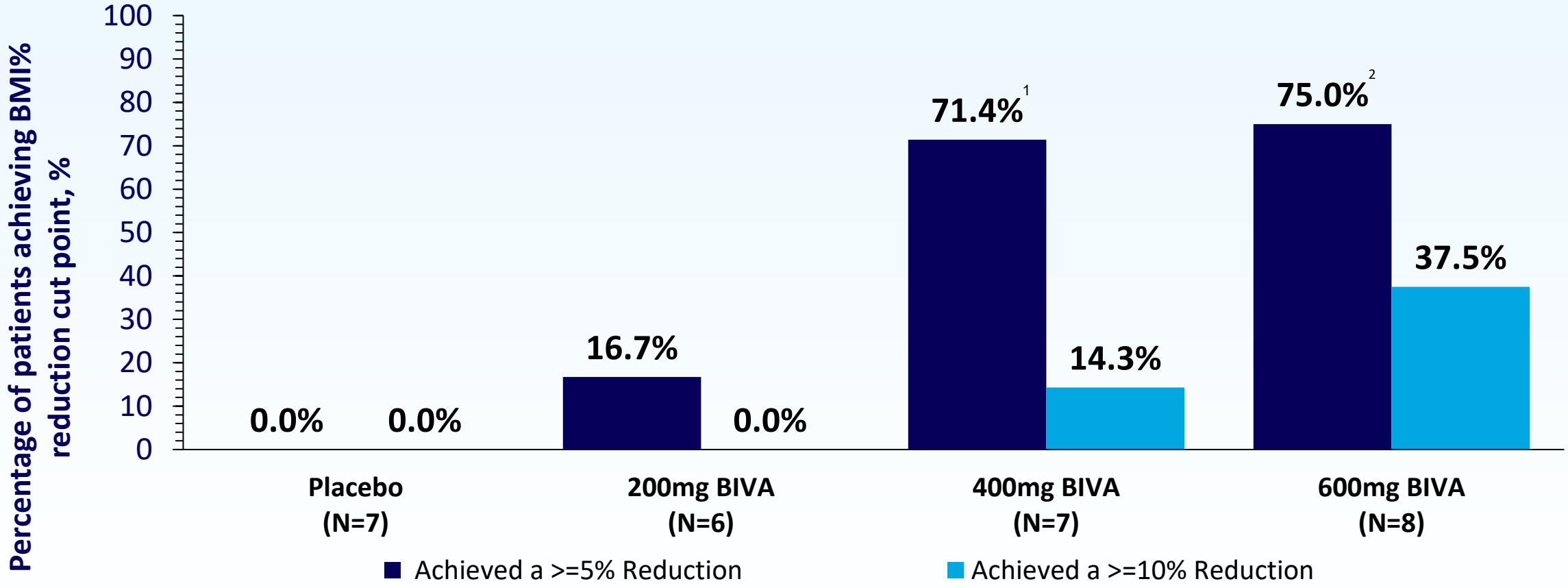


* Last observation carried forward (LOCF): One patient in 400mg cohort discontinued therapy at week one.

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

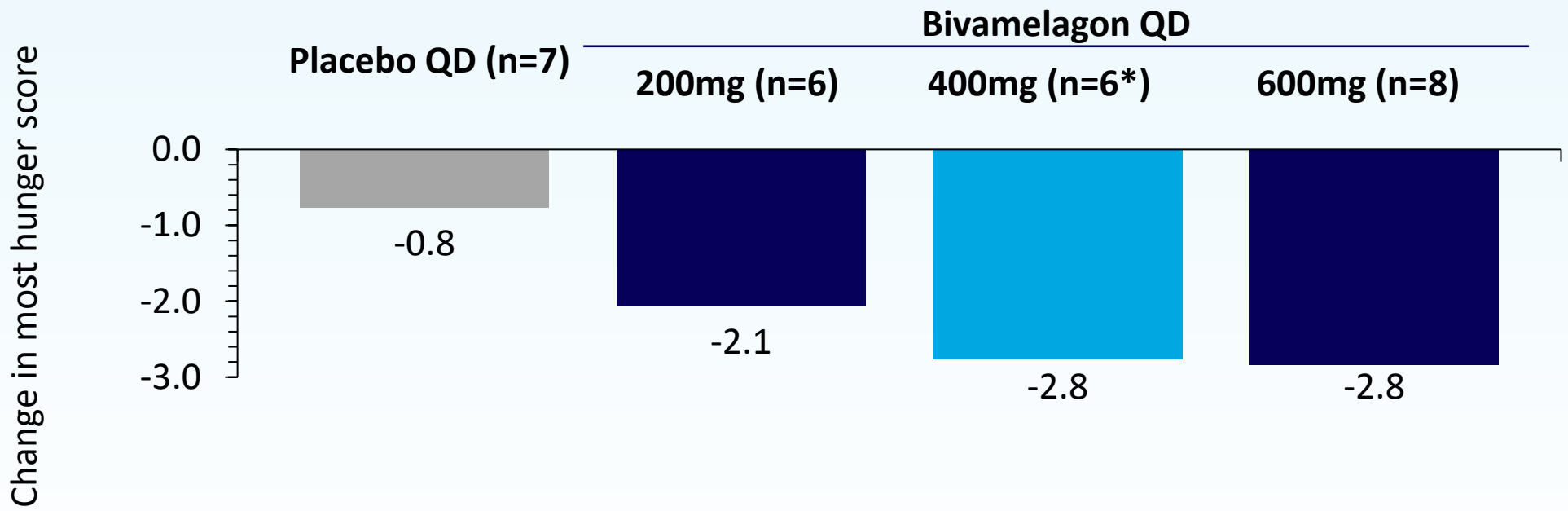
Rhythm® PHARMACEUTICALS

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