Rhythm Pharmaceuticals

Positive Interim Six-month Results from Phase 2 Trial Evaluating Setmelanotide in Patients with Prader-Willi Syndrome

June 13, 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 our ongoing Phase 2 trial of setmelanotide in patients with Prader Willi Syndrome; the safety, efficacy, potential benefits of, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of setmelanotide and other product candidates; the clinical design or progress of any of our products or product candidates at any dosage or in any indication; the potential benefits of any of the Company's products or product candidates for any specific disease indication or at any dosage; our participation in upcoming events and presentations, and the date, time and content thereof; the sufficiency of our cash, cash equivalents and short-term investments to fund our planned operations; and the timing of any of the foregoing. Statements using words such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks, 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, 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 three months ended March 31, 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 release or to update them to reflect events or circumstances occurring after the date of this release, whether as a result of new information, future developments or otherwise.

Industry and Other Data

Unless otherwise indicated, information contained in this presentation concerning our industry and the markets in which Rhythm operates, including its general expectations, market position and market opportunity, is based on its management's estimates and research, as well as industry and general publications and research, surveys and studies conducted by third parties. While we believe the information from these third-party publications, research, surveys and studies is reliable, it does not guarantee the accuracy or completeness of such information, and Rhythm has not independently verified this information. Management's estimates are derived from publicly available information, their knowledge of the company's industry and their assumptions based on such information and knowledge, which they believe to be reasonable. This data involves a number of assumptions and limitations which are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in our periodic reports filed with the Securities and Exchange Commission under the captions "Cautionary Note Regarding Forward Looking Statements," "Summary Risk Factors" and "Risk Factors." These and other factors could cause Rhythm's future performance and market expectations to differ materially from its assumptions and estimates.

On Today's Call

David Meeker, MD
Chairman, President & Chief Executive Officer,

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Jennifer Miller, MD
Professor of Pediatric Endocrinology, University of Florida

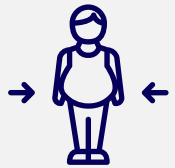
David Meeker, MD

Chairman, President & Chief Executive Officer

Setmelanotide Achieves Consistent Six-Month Results in Phase 2 Trial in Patients with Prader-Willi Syndrome

Further validates MC4R agonism potential to address significant unmet need and treat patients with Prader-Willi syndrome (PWS)

Reduction in BMI and BMI-Z scores



Preservation of lean mass with loss in fat mass

Improvement in hyperphagia and anxiety

Note: Results as of May 7, 2026

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 driven by IMCIVREE in BBS

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; Note: Graphic is not to scale.

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.

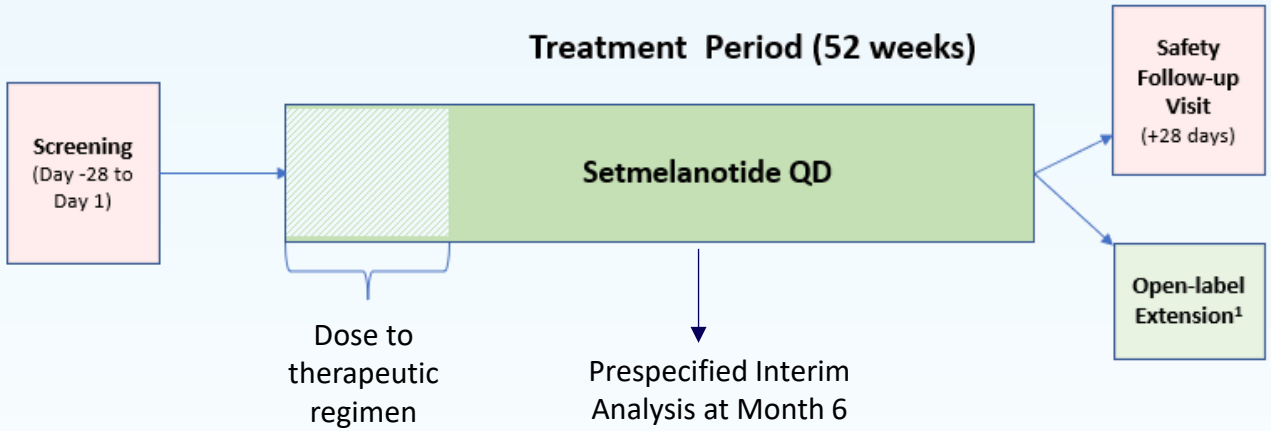
Exploratory Phase 2, Open-label Trial of Setmelanotide in PWS

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

Secondary endpoints: assessments on **BMI, BMI z-score, hyperphagia, body composition** and pharmacokinetics



[1] Open-label extension continues for up to 4 years (or until commercial product is available, or the Sponsor closes the study).

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) Mean (SD) pts ≥ 18yo	39.0 (9.3) 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

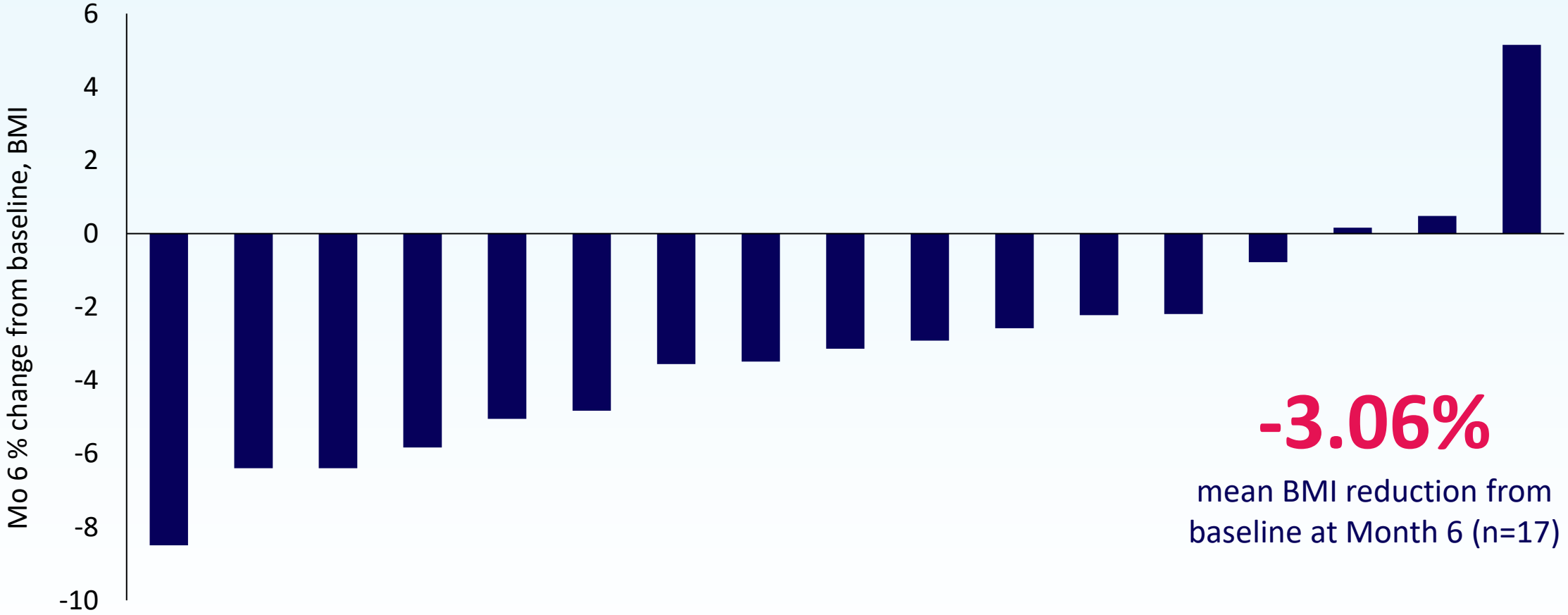
n=1
discontinued (withdrawal by parent/guardian)

n=17
patients reached Month 6

17
patients remain on active therapy[1]

1. As of June 12, 2026

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



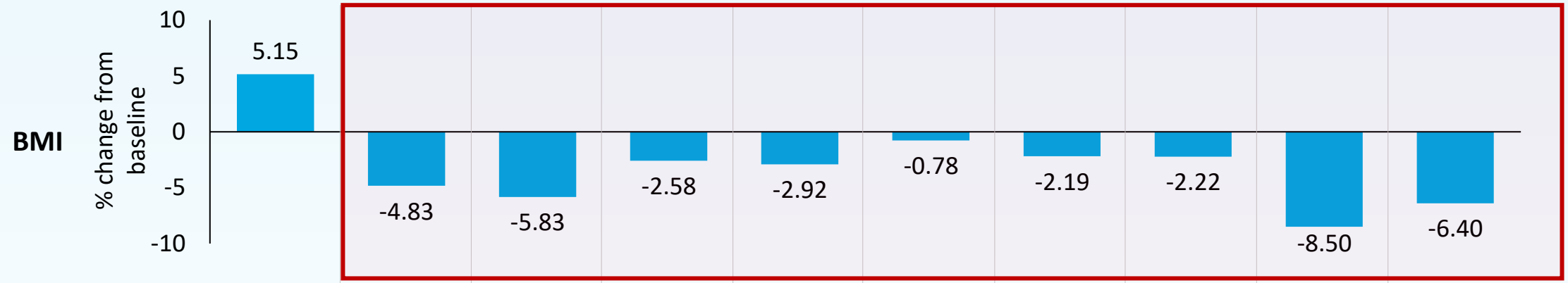
-3.06%

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

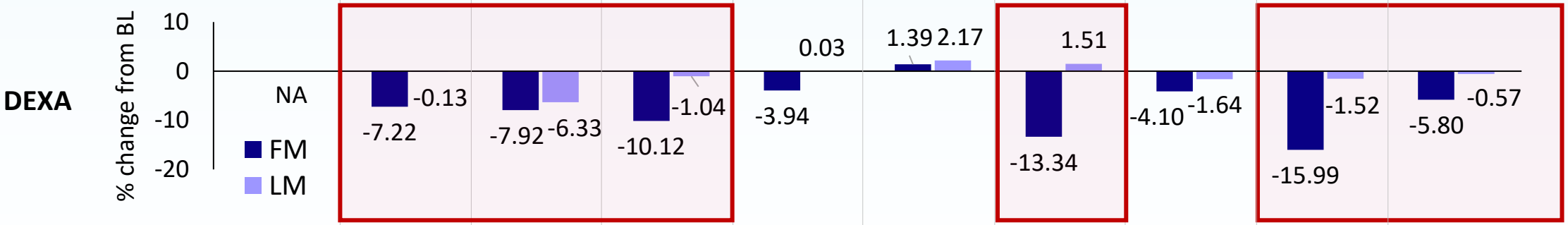
Patient #:	13	11	17	3	18	2	15	14	8	7	6	12	10	9	16	5	1
Age/sex:	23/F	8/F	22/M	23/F	6/M	18/F	13/F	14/M	12/F	23/M	23/M	20/M	20/M	18/F	9/M	14/M	20/F
Vykat (Y/N):	Y	Y	Y	N	N	N	Y	Y	N	Y	Y	N	Y	Y	N	N	N

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)

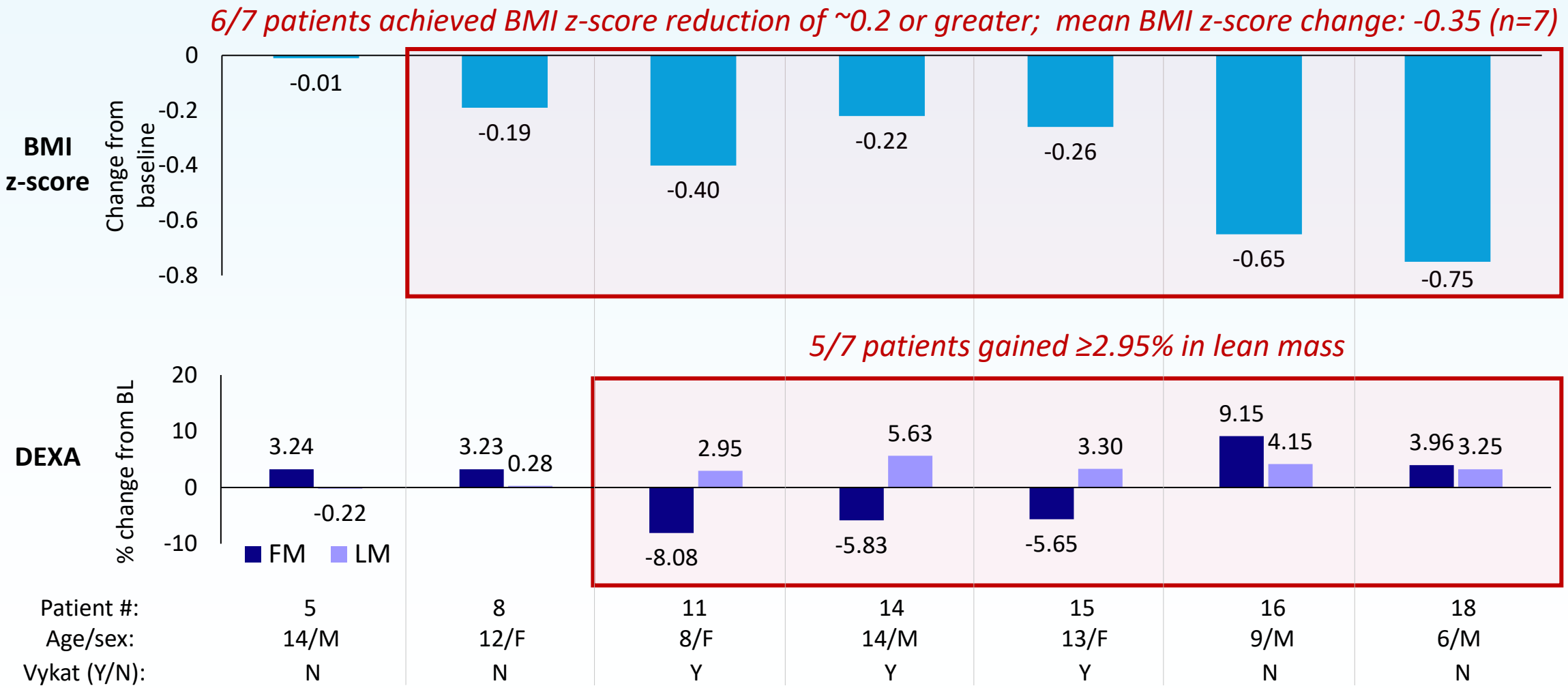


6/9 patients with DEXA data achieved >5% reduction in fat mass; mean fat mass % change: -7.4% (n=9)

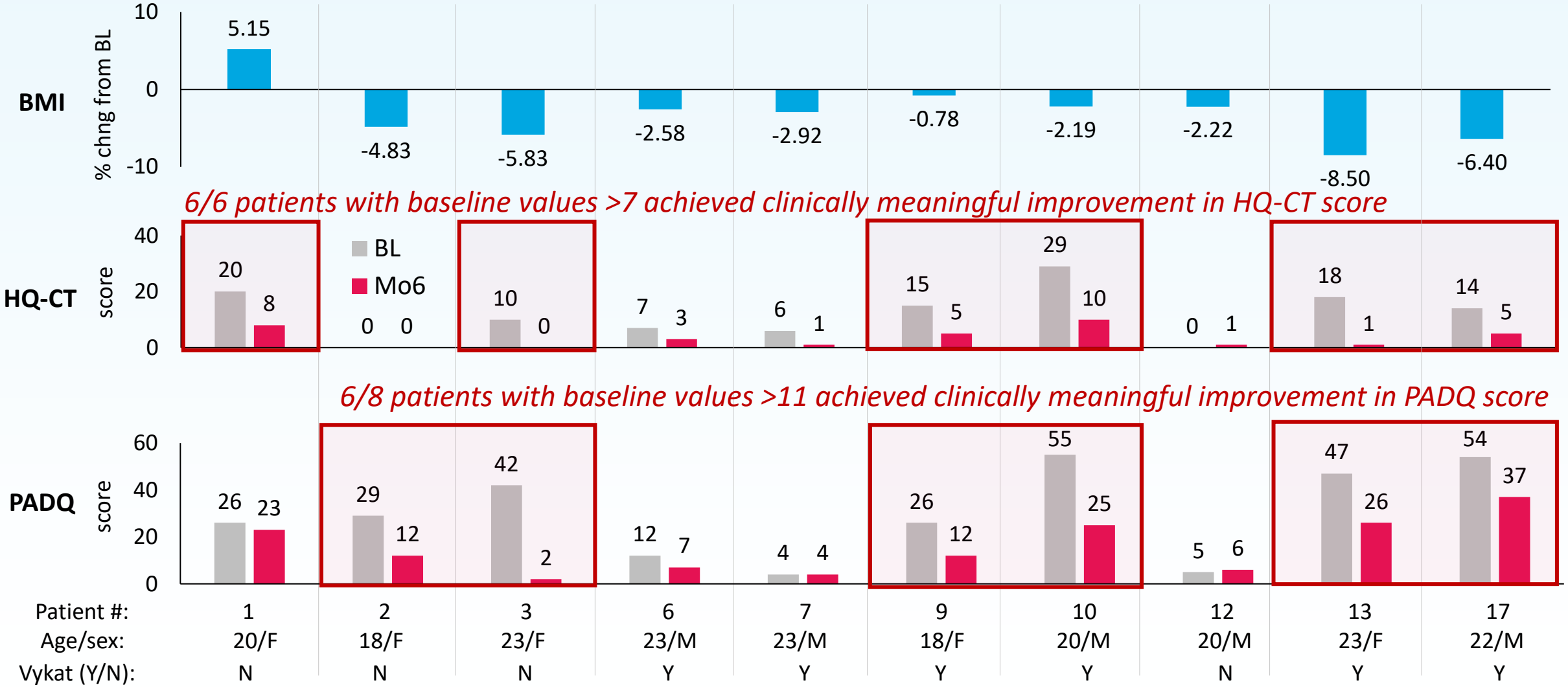


Patient #:	1	2	3	6	7	9	10	12	13	17
Age/sex:	20/F	18/F	23/F	23/M	23/M	18/F	20/M	20/M	23/F	22/M
Vykat (Y/N):	N	N	N	Y	Y	Y	Y	N	Y	Y

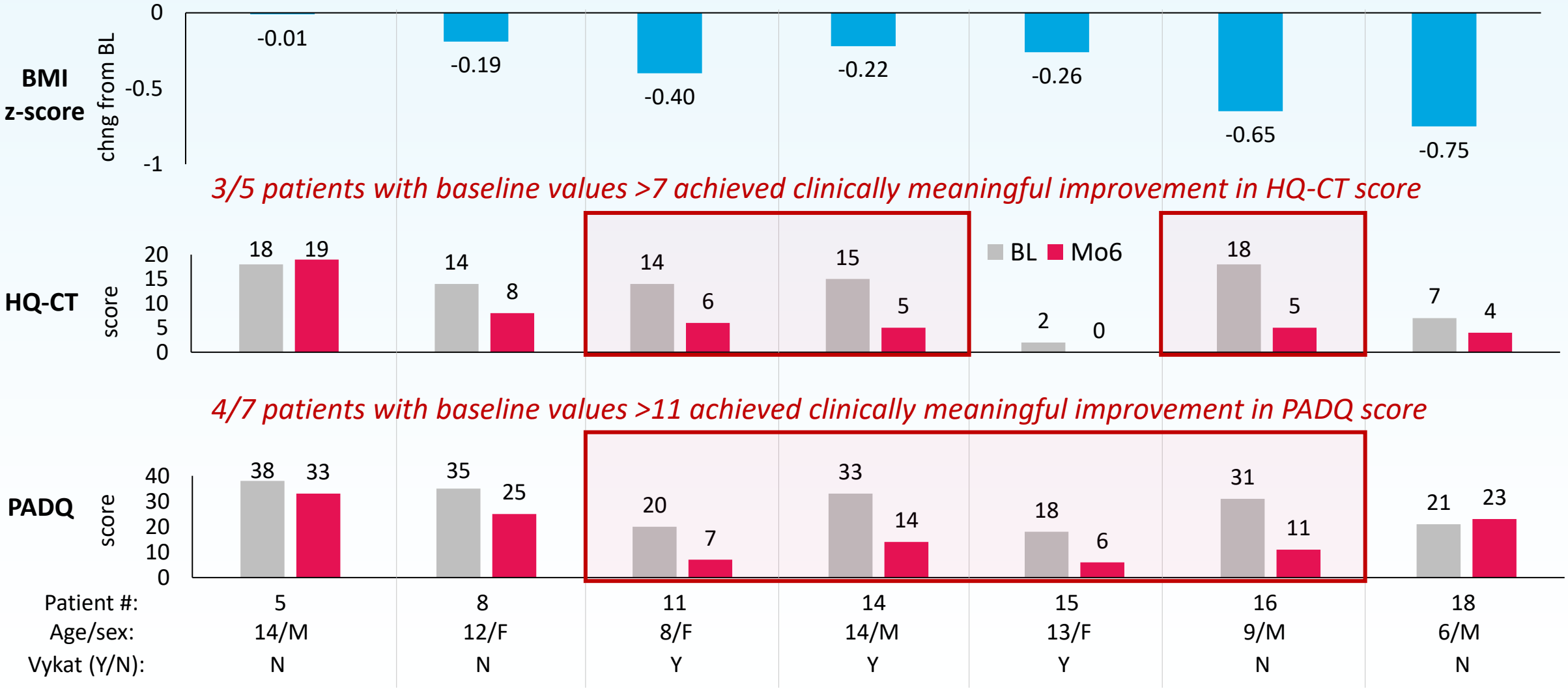
Consistent BMI Z-Score Reductions and Gains in Muscle Mass Observed in Pediatric Patients at Month 6



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



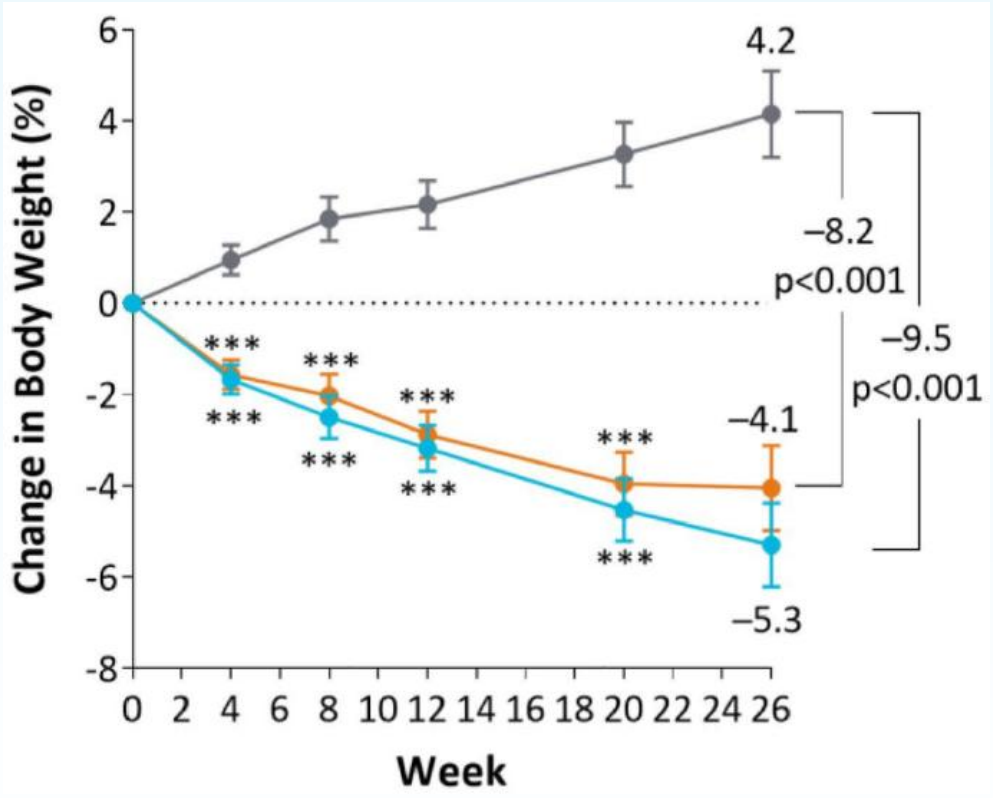
Most Common Adverse Events for All Patients (N=18)

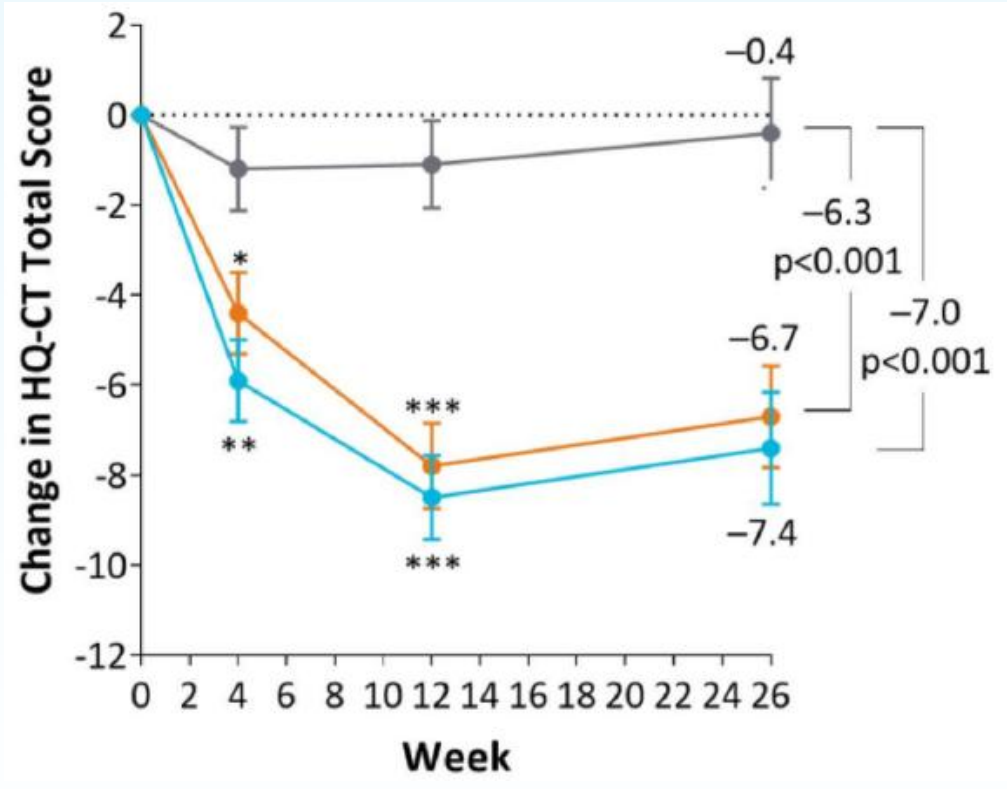
Adverse Events	Overall n (%) *(n=18)*
Injection site reaction	11 (61.1)
Skin hyperpigmentation	10 (55.6)
Fatigue	6 (33.3)
Norovirus infection	2 (11.1)
Hypothyroidism	2 (11.1)
Diabetes mellitus	2 (11.1)

Note: As of May 7, 2026

Discussion with Dr. Jennifer Miller

Historical Context: Beloranib Trial Results in PWS: Changes in Weight, HQ-CT Scores at Week 26





Placebo (N=34) 1.8 mg Beloranib (N=36) 2.4 mg Beloranib (N=37)

Diabetes Obes Metab. 2017;19:1751–1761.

Rhythm® PHARMACEUTICALS

Questions?

Appendix

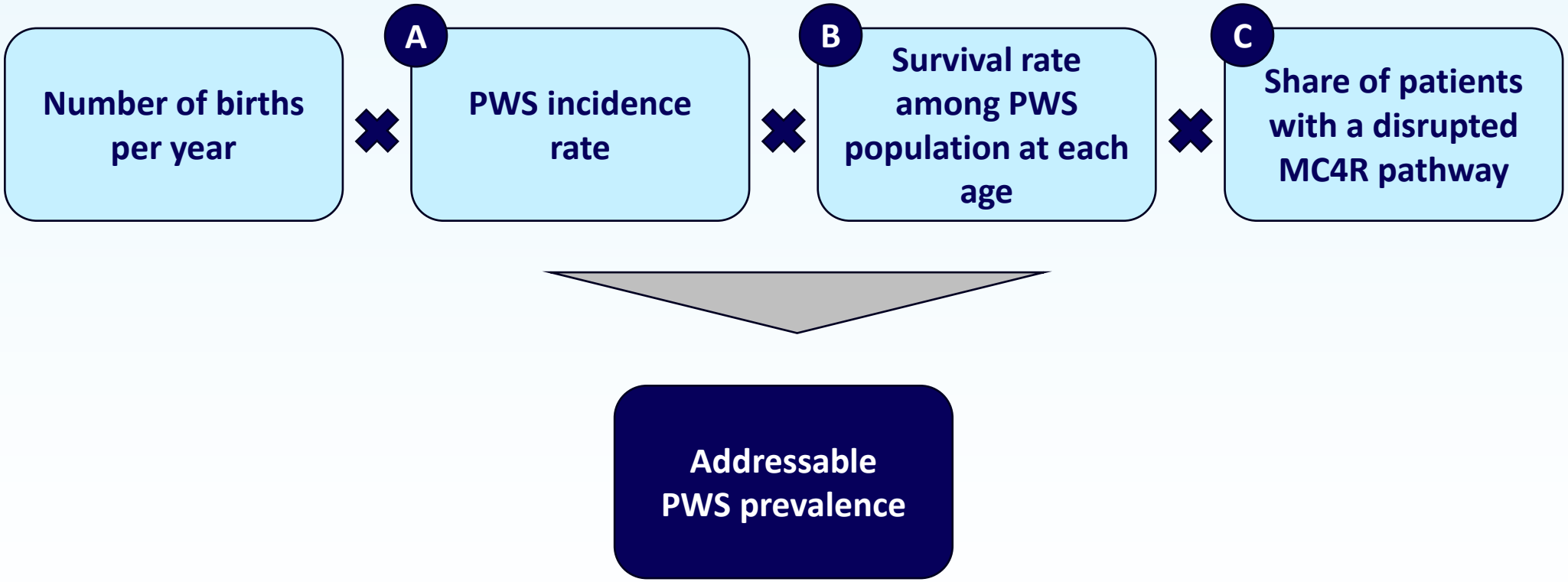
Published Epidemiology Estimates for PWS Are Readily Available, With Some Considerations

- Estimates are **relatively consistent**, but often because of **iterative referencing** rather than citing primary epidemiology studies
- Estimates most often cite **birth incidence**, which cannot be directly used to extrapolate population prevalence because of the differences in **PWS mortality rates** compared to the general population
- When **population prevalence** is cited, typically **wide ranges** (e.g. 2 to 12 per 100,000 individuals[1-3]) are provided and sources can be unclear

Notable public benchmarks	
FOUNDATION FOR PRADER-WILLI RESEARCH	**1:15,000 births**
Prader-Willi SYNDROME ASSOCIATION | USA SAVING AND TRANSFORMING LIVES	**1:15,000-25,000 births 350,000 worldwide**
IPWSO International Prader-Willi Syndrome Organisation	**1:15,000-25,000 births**
NORD® National Organization for Rare Disorders	**1:10,000-30,000 incidence 350,000-400,000 worldwide**

1. Hughes BM et al. *Orphanet J of Rare Diseases*. 2024. 2. Butler MG, et al. *J Med Genet*. 2019. 3. Whittington JE, et al. *J Med Genet*. 2001.

To Estimate The Addressable PWS Prevalence, We Leverage The PWS Incidence Combined with Survival Rate



A Published PWS Incidence Rates Are Very Broad But When Leveraging Primary Studies, The PWS Incidence Is Estimated at 1:8,000 to 1:10,000

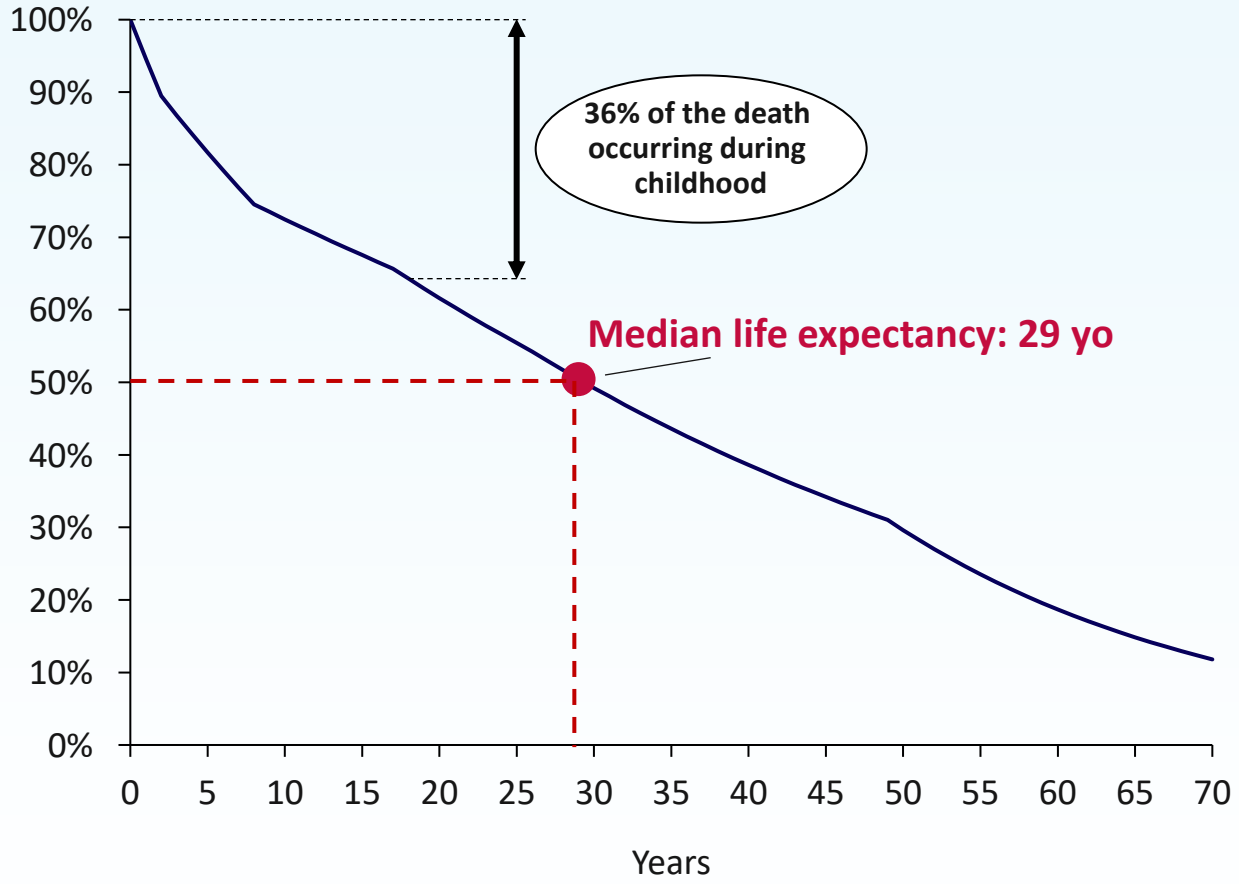
- Published PWS birth incidence rates most often cited in a range of **1:10,000-30,0000**[1-5]
  - Reviews and publications often utilize overlapping references from older primary sources and include a range of populations (ex: Australia, France, UK, Sweden, US)[6-10]

- Several recent primary studies report the following estimates:
  - Birth incidence **1:11,000** (Ireland; 2017)[11]
  - Birth incidence **~1:8,290** (Included sites in Australia, Chile, US, Italy; 2022)[12]

1. Miller J, et al. *Paediatr Drugs*. 2025. 2. Dempsey D et al. *Orphanet J Rare Dis*. 2025. 3. Giesecke J, et al. *J Clin Med*. 2025. 4. Hughes BM, et al. *Orphanet J Rare Dis*. 2024. 5. Bellis SA, et al. *Eur J Med Genet*. 2022. 6. Smith A, et al. *Arch Dis Child*. 2003. 7. Bar C, et al. *Orphanet J Rare Dis*. 2017. 8. Whittington JE, et al. *J Med Genet*. 2001. 9. Akefeldt A,. *Dev Med Child Neurol*. 1991. 10. Burd L, et al. *Am J Med Genet*. 1990. 11. Gallagher L, et al. *A population-based profile of Prader-Willi Syndrome in Ireland*. 2017. 12. Godler DE, et al. *JAMA Netw Open*. 2022.

B Mean Life Expectancy Is Estimated To Be Around 30 Years With 25-35% of The Death Occurring During Childhood

Kaplan-Meier survival estimates derived from age-based mortality rates[1]



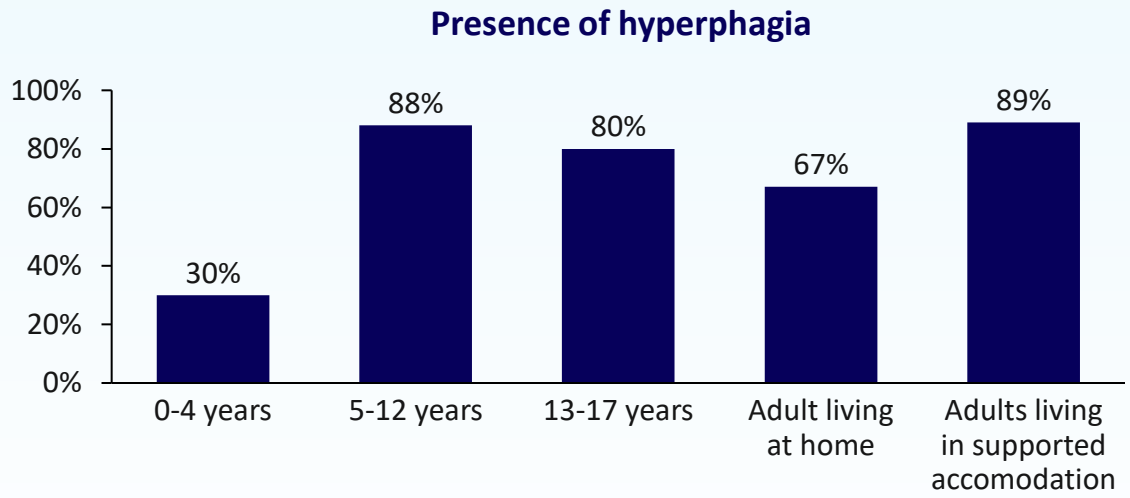
The **premature death** is patients with PWS has been **consistently reported** in several studies:

- French expert center[2]:
  - Median age at death: **30 years** (N=104 death)
  - Yet, childhood death has been reported at a lower rate **25% of the death** occurring **before the age of 20 yo**
- USA 40-years mortality survey[3]:
  - Mean age at death: **29.5 years** (N=486 death)
  - **30% of the death reporter during childhood/adolescence**
- Literature review[4]:
  - **Mean mortality ages ranged from 23 to 32 years**

1) U.S. Prevalence & Mortality of Prader-Willi Syndrome: A Population-Based Study of Medical Claims, JESOCI, Volume 4, Abstract Supplement, 2020
2) Causes of death in Prader-Willi syndrome: lessons from 11 years' experience of a national reference center, Orphanet Journal of Rare Diseases (2019) 14:238
3) Causes of death in Prader-Willi syndrome: Prader-Willi syndrome association (USA) 40-year mortality survey. Genet Med. 2017;19(6):635–42.
4) The burden of illness in Prader-Willi syndrome: a systematic literature review, Orphanet Journal of Rare Diseases (2025) 20:374

C Share of Addressable Patients with Hyperphagia and Obesity is Estimated to Be 80% - 90% With An Age of Onset Between 4 - 6 Years

- Few sources are consistently reporting hyperphagia frequency across different age groups, yet the Irish patient association has reported a survey (N=61)[1]:

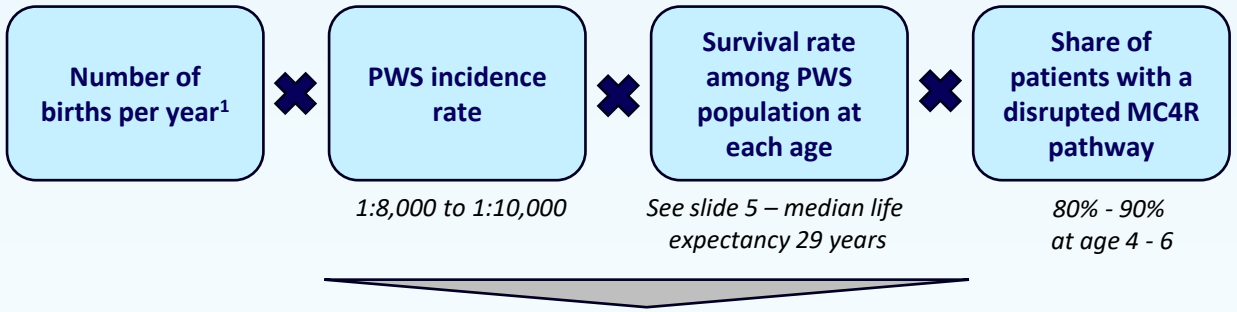


Given the difficulties in assessing hyperphagia and biased for patients in recognizing it (*cf hyperphagia in BBS – UK study*), the **share of patients with an impaired MC4R pathway is estimated to be 80% - 90% by the age of 4 - 6 onwards**

- In different reviews, the **rate of hyperphagia/obesity** is reported in the range of **90%-100%**[2]

1) a-population-based-profile-of-prader-willi-syndrome-in-ireland-final-report.pdf
2) Prader-Willi Syndrome - GeneReviews® - NCBI Bookshelf

The Estimated Addressable PWS Prevalence is Estimated to be 8,500 – 12,750 in the US & EU with Children Accounting for ~34%

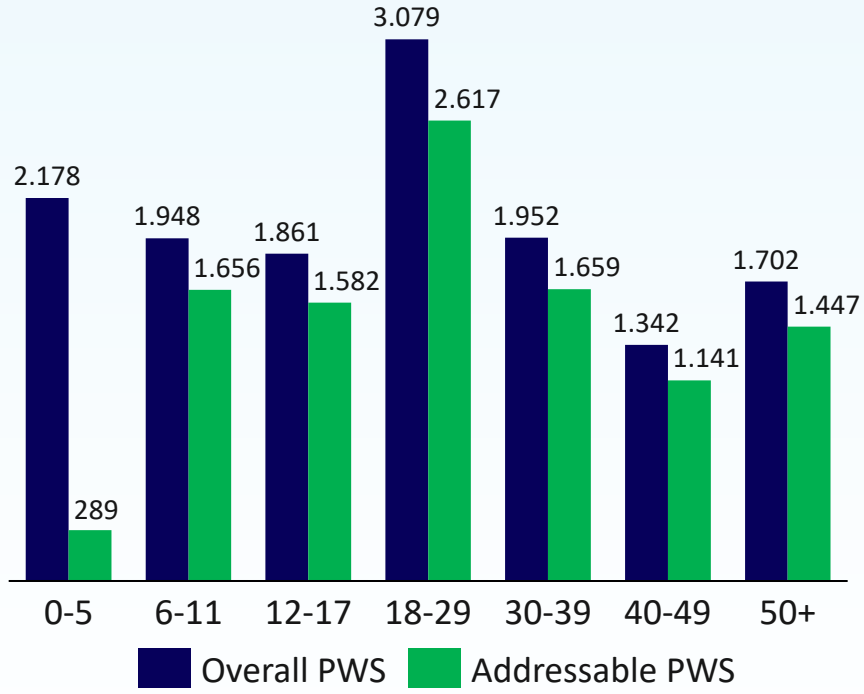


PWS prevalence is estimated to be: **12,500 – 16,000** with an **addressable prevalence** of 8,500 – 12,750 *(pts with PWS living with hyperphagia/obesity)*

In **absence** of any **evidence** supporting any **ethnics differences**, the **addressable prevalence** is expected to be the **same across** different **geographies**

Addressable prevalence is estimated to be 30 pts/million inhabitants or 1/24,250

Breakdown of the prevalence by age group



Children (<18y) account for 34% of the addressable prevalence

1) National Center for Health Statistics (CDC), Final Natality Data (1954–2023)