

# Rhythm at ObesityWeek® 2023

Data presentations in hypothalamic obesity and more  
as presented at ObesityWeek

Oct. 18, 2023





## On Today's Call

David Connolly, Executive Director of Investor Relations and Corporate Communications

David Meeker, MD, Chair, President and Chief Executive Officer

Hunter Smith, Chief Financial Officer

# Forward Looking Statements

This presentation contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, and that involve risks and uncertainties, including without limitation statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide and our other preclinical investigational candidates, including with respect to our open-label, long-term extension studies evaluating setmelanotide in individuals with hypothalamic obesity, BBS or obesity due to POMC or LEPR deficiencies, and the potential benefits of setmelanotide for patients, including those with BBS and hypothalamic obesity, and our business strategy and plans, including regarding commercialization of setmelanotide. Statements using words such as "expect", "anticipate", "believe", "may" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including but not limited to, our ability to enroll patients in clinical trials, the outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our liquidity and expenses, the impact of the COVID-19 pandemic on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and other reports we file with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this presentation or to update them to reflect events or circumstances occurring after the date of this presentation, whether as a result of new information, future developments or otherwise.

# Rhythm at ObesityWeek® 2023



October 14-17, 2023 • Dallas

Weight Reduction  
in Patients with  
Hypothalamic  
Obesity Treated  
With Setmelanotide  
for 12 Months

3-Year  
Setmelanotide  
Weight Outcomes  
in Patients with  
Bardet-Biedl  
Syndrome and  
Obesity

Cardiac, Renal, and  
Endocrine/Diabetes  
Mellitus Outcomes  
in Children with  
Bardet-Biedl  
Syndrome

Impact of  
Setmelanotide on  
Metabolic  
Syndrome Risk in  
Patients With  
Bardet-Biedl  
Syndrome

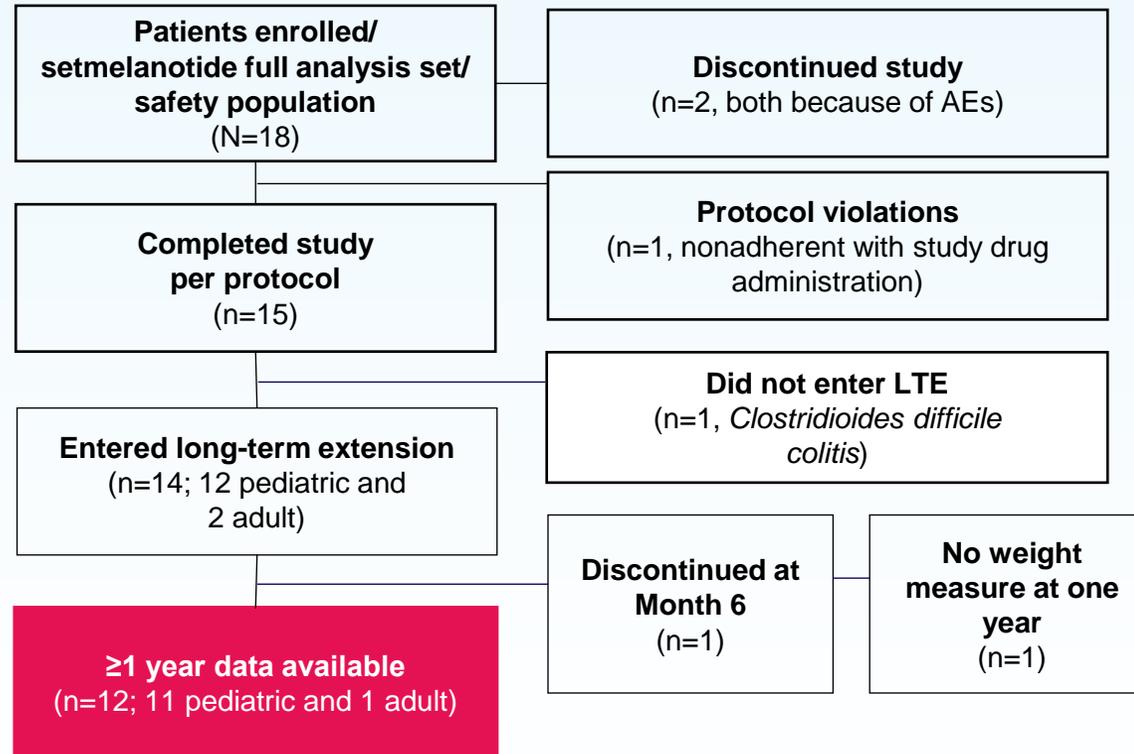
4-Year  
Setmelanotide  
Weight Outcomes  
of Patients With  
POMC and LEPR  
Deficiency Obesity

Impact of  
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Deficiency

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# Weight Reduction in Patients with Hypothalamic Obesity Treated With Setmelanotide for 12 Months

# Patient Dispositions: Phase 2 to Open-label, Long-term Extension Trial

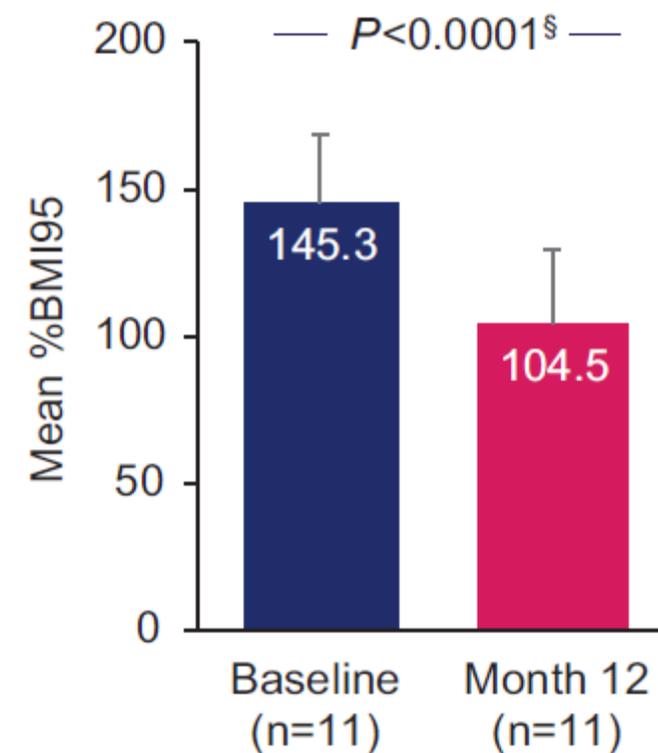
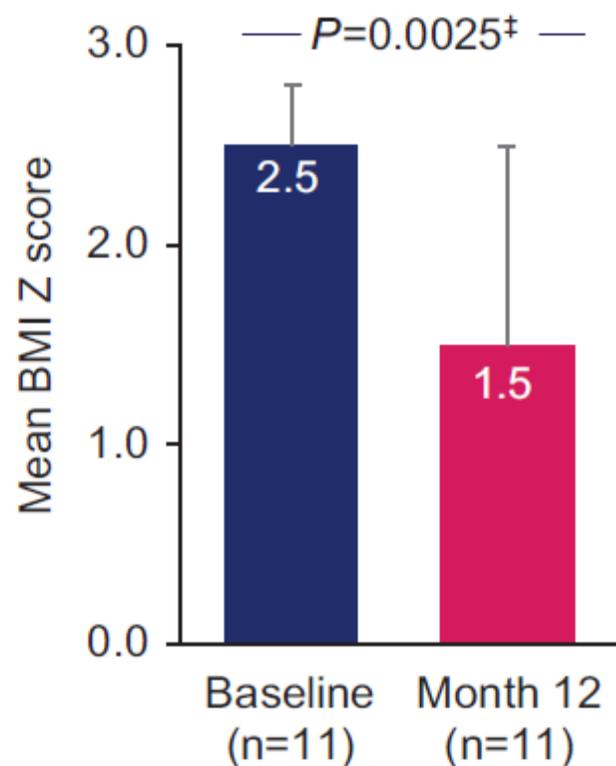
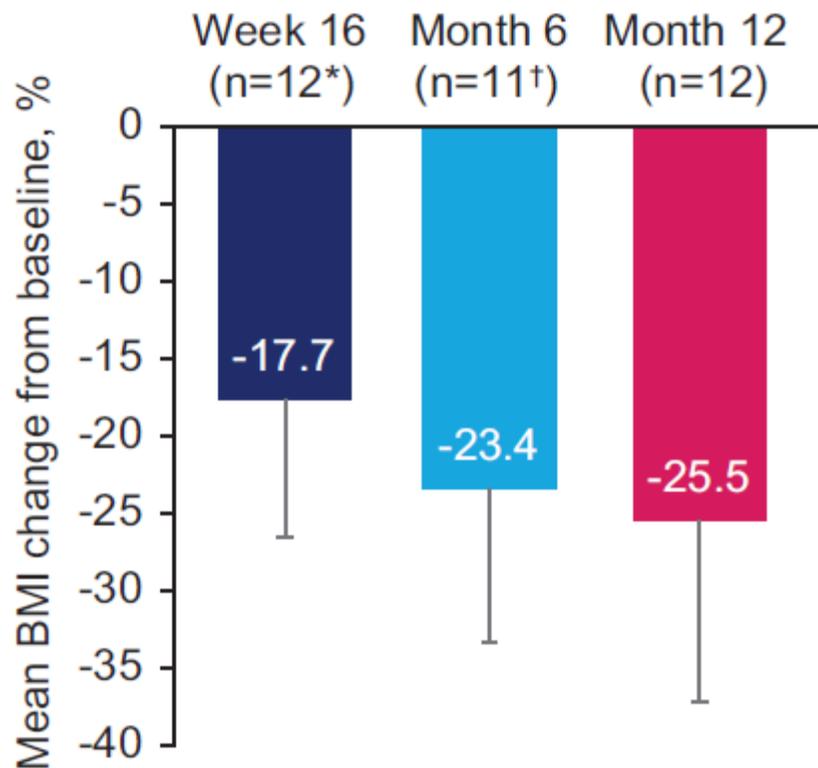


# Demographics and Baseline Characteristics

	Total (n=14)
<b>Age, mean (SD), y</b>	13.6 (5.0)
<b>Age range, n (%), y</b>	
Adults >18	2 (14.3)
Children 10-18	12 (85.7)
<b>Sex, n (%)</b>	
Female	4 (28.6)
Male	10 (71.4)
<b>Tumor type, n (%)</b>	
Craniopharyngioma	11 (78.6)
Hypothalamic hamartoma	2 (14.3)
Juvenile pilocytic astrocytoma	1 (7.1)
<b>Waist circumference, mean (SD), cm</b>	112.0 (17.9)
<b>Weight, mean (SD), kg</b>	99.1 (32.7)
<b>BMI, mean (SD), kg/m<sup>2</sup></b>	37.0 (7.1)
<b>BMI Z score, mean (SD)<sup>¶</sup></b>	2.5 (0.3)
<b>%BMI95, mean (SD)<sup>#</sup></b>	145.3 (22.8)

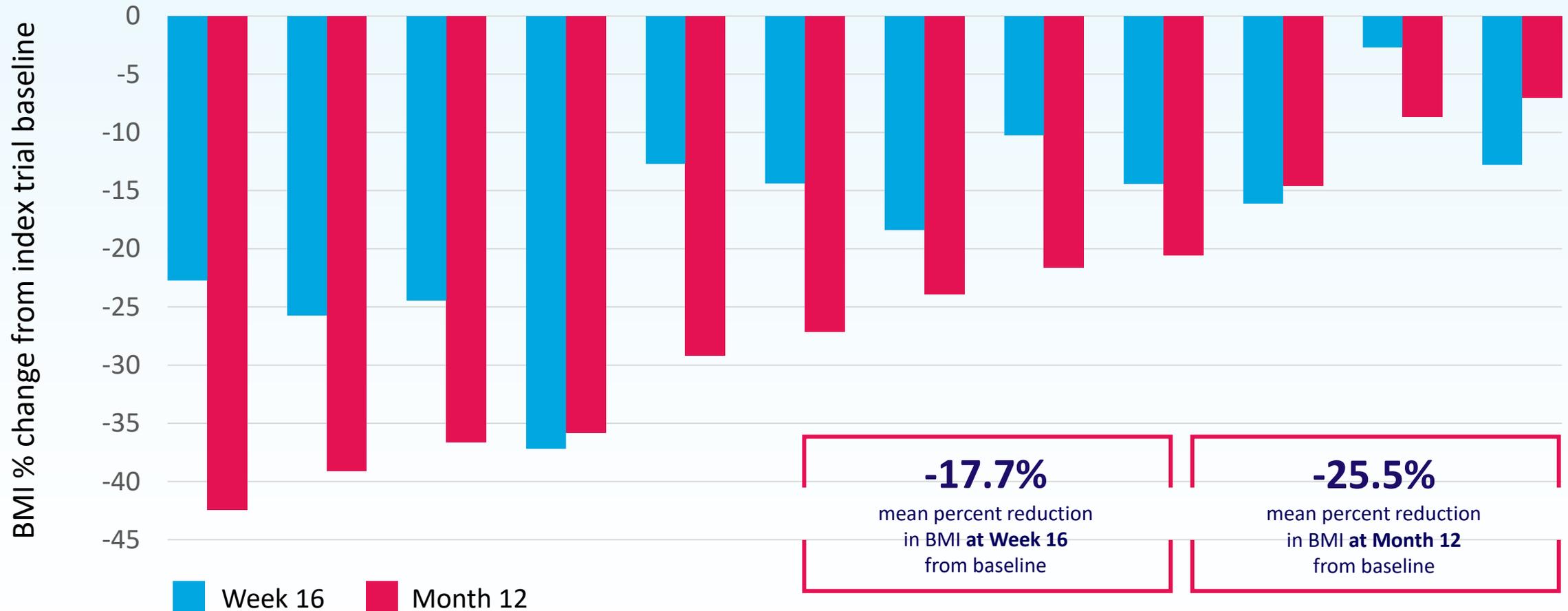
¶BMI Z score was calculated for patients aged <18 years (n=11) using the Centers for Disease Control and Prevention 2022 methodology; #Based on 11 pediatric patients. AE, adverse event; %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; LTE, long-term extension; SD, standard deviation.

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



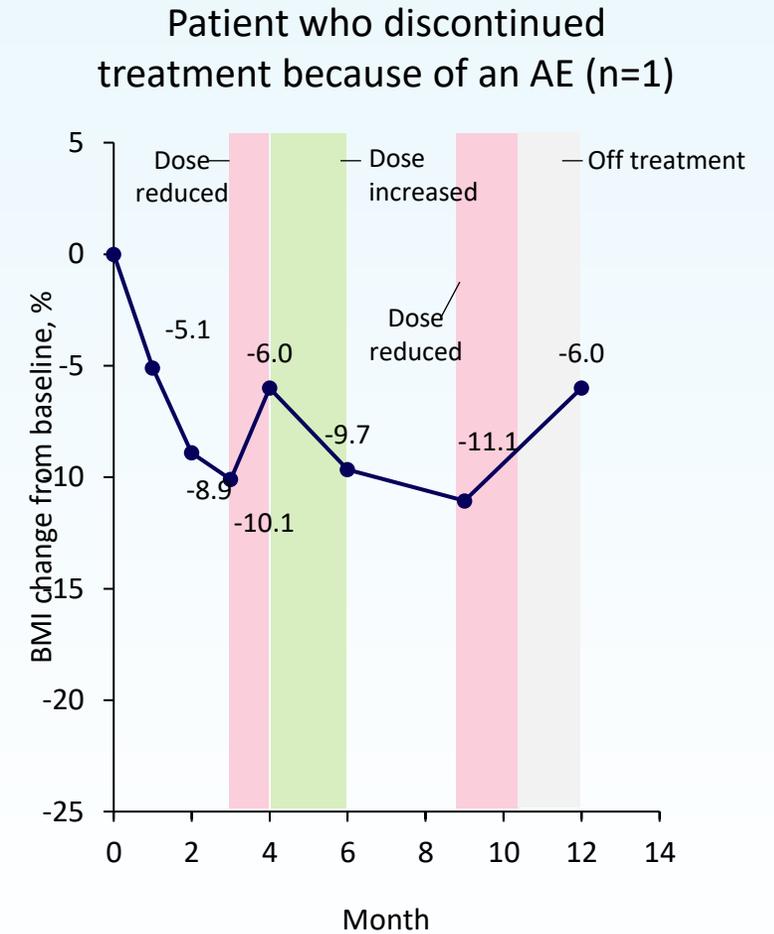
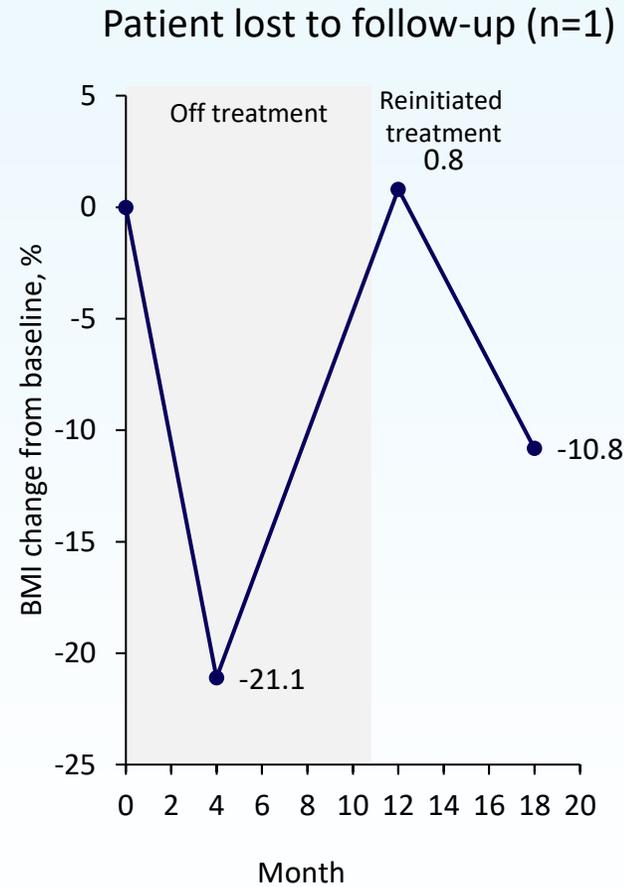
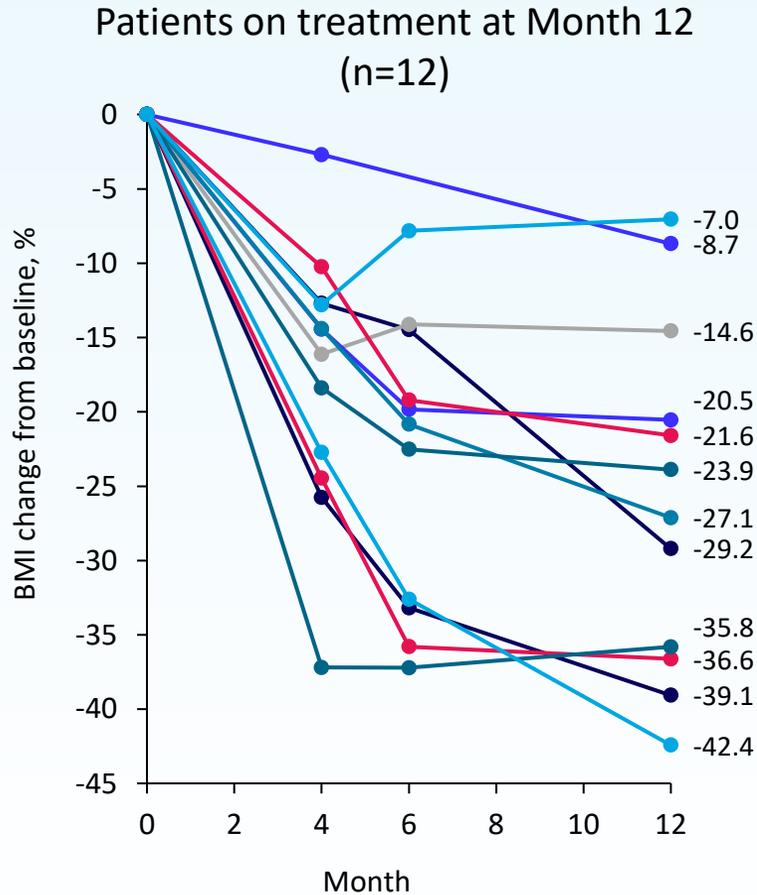
Error bars are the standard deviation. \*Includes all patients who received 16 weeks of setmelanotide in the index trial and  $\geq 12$  months of treatment in the long-term extension. †One patient did not complete a Month-6 visit. ‡One sample *t*-test with 2-tailed *P*-values. §Paired *t*-test with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

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



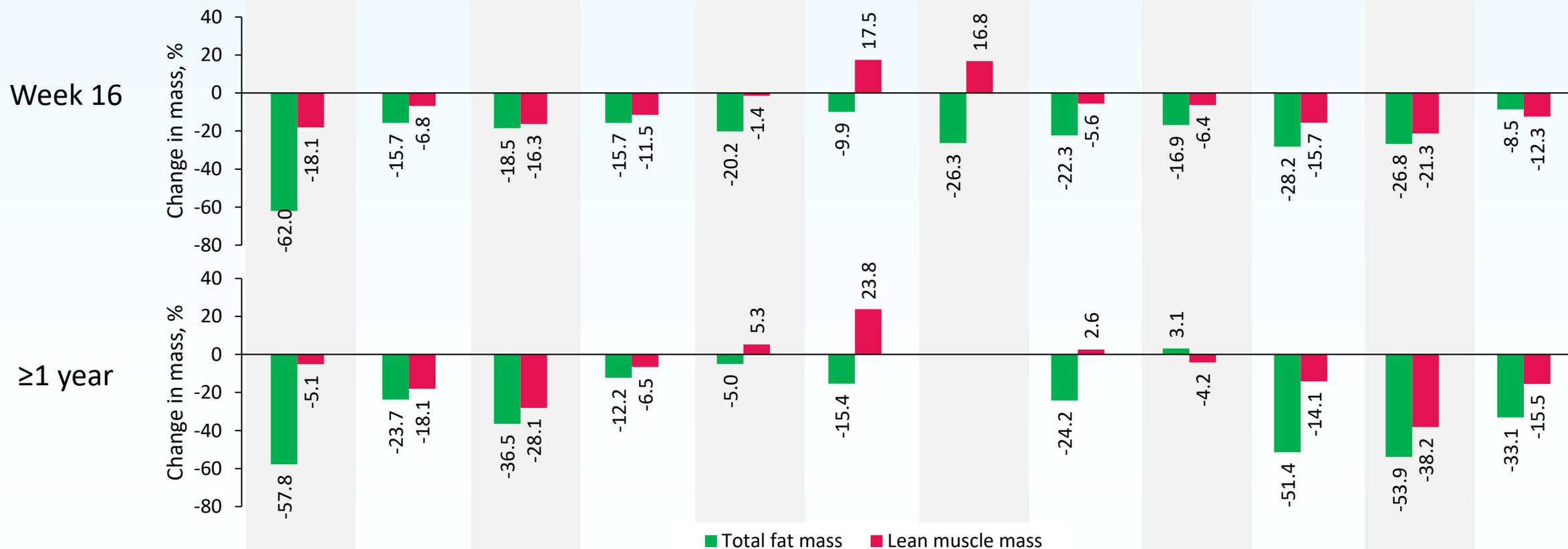
Adapted from data presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.

# All Patients Achieved $\geq 5\%$ BMI Reduction at One Year



# 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 <sup>2</sup>	Adults (n=1)	WHO Classification (NIH <sup>5</sup> )	Pediatric patients (n=11)*											BMI percentile <sup>6</sup>	
≥50	50	Obesity class III (extreme)											190	≥140% <sup>†</sup>	≥95th percentile
≥45 to <50					157	166							158		
≥40 to <45							149						140		
≥35 to <40	37	Obesity class II (severe) <sup>5</sup>	139	124	131	126						120	138	≥120% to <140% <sup>‡</sup>	
≥30 to <35		Obesity class I	96	109			109								≥95% to <120% <sup>§</sup>
≥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/m<sup>2</sup> (whichever is lower). ‡Or BMI ≥35 to <40 kg/m<sup>2</sup> (whichever is lower). §Or BMI ≥30 to <35 kg/m<sup>2</sup> (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; NIH, National Institutes of Health; WHO, World Health Organization.

# Setmelanotide and Hypothalamic Obesity: A Transformative Opportunity for Rhythm

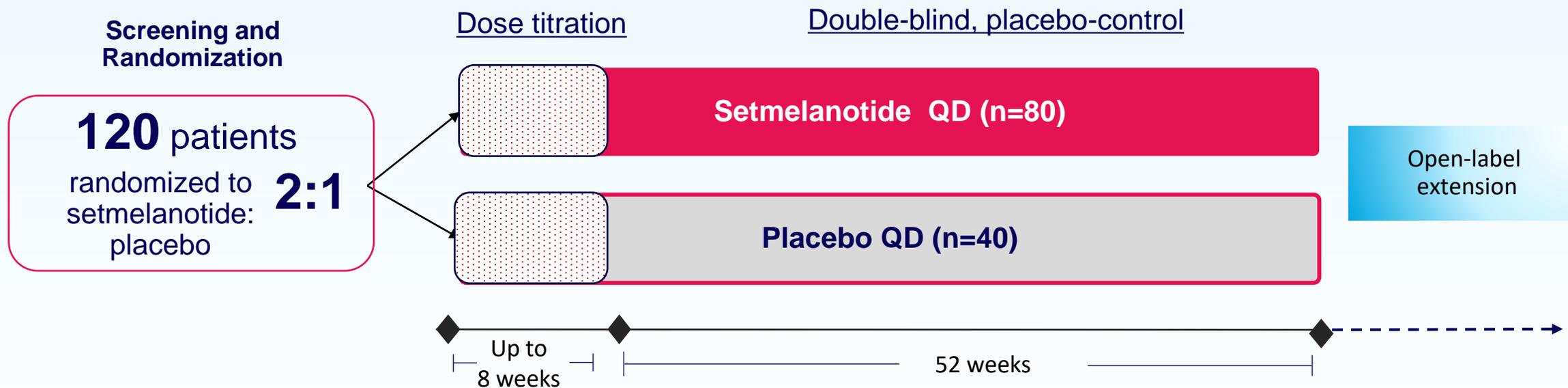
**5,000 – 10,000\***  
patients  
Estimated U.S. prevalence

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

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

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

# Hypothalamic Obesity: Expect to Complete Enrollment by the end of 2023 in Ph3 Trial



Starting dose for all patients is 0.5mg QD; Maximum dose for patients <6yo is between 1.5mg QD and 3.0mg QD based on body weight; maximum dose for patients >6yo with a body weight of 30 kgs or more is 3.0mg QD.

BMI, body mass index; QD, once daily.

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

# Questions



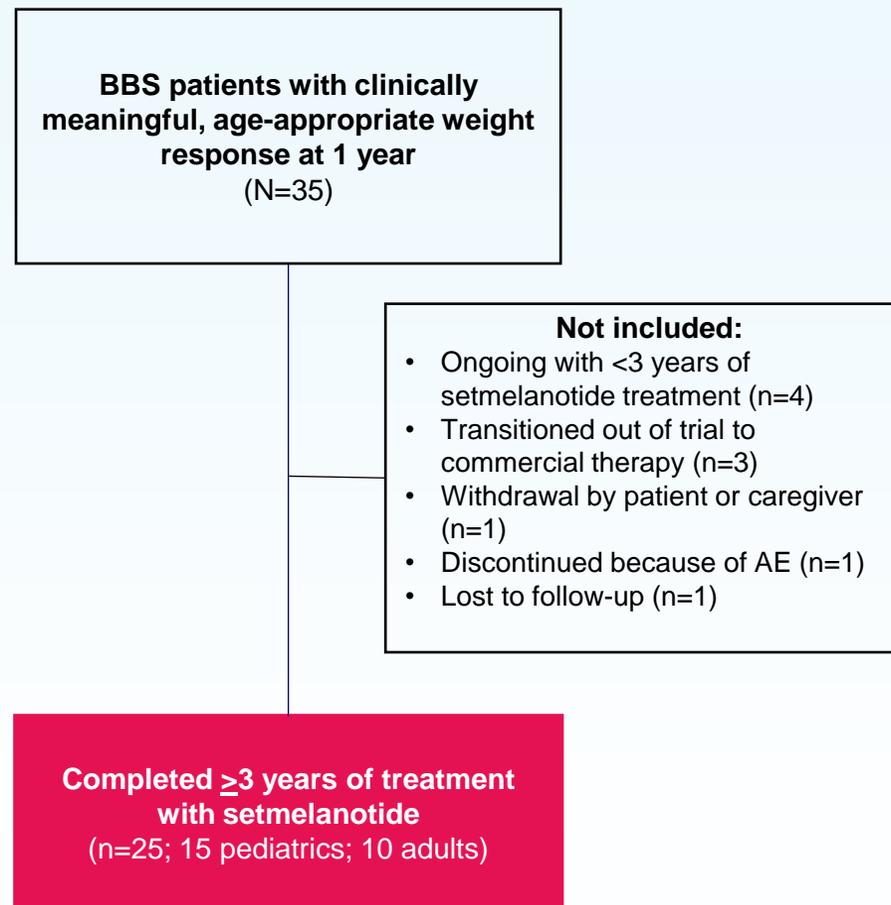
Appendix:

Additional TOS 2023 presentation summaries

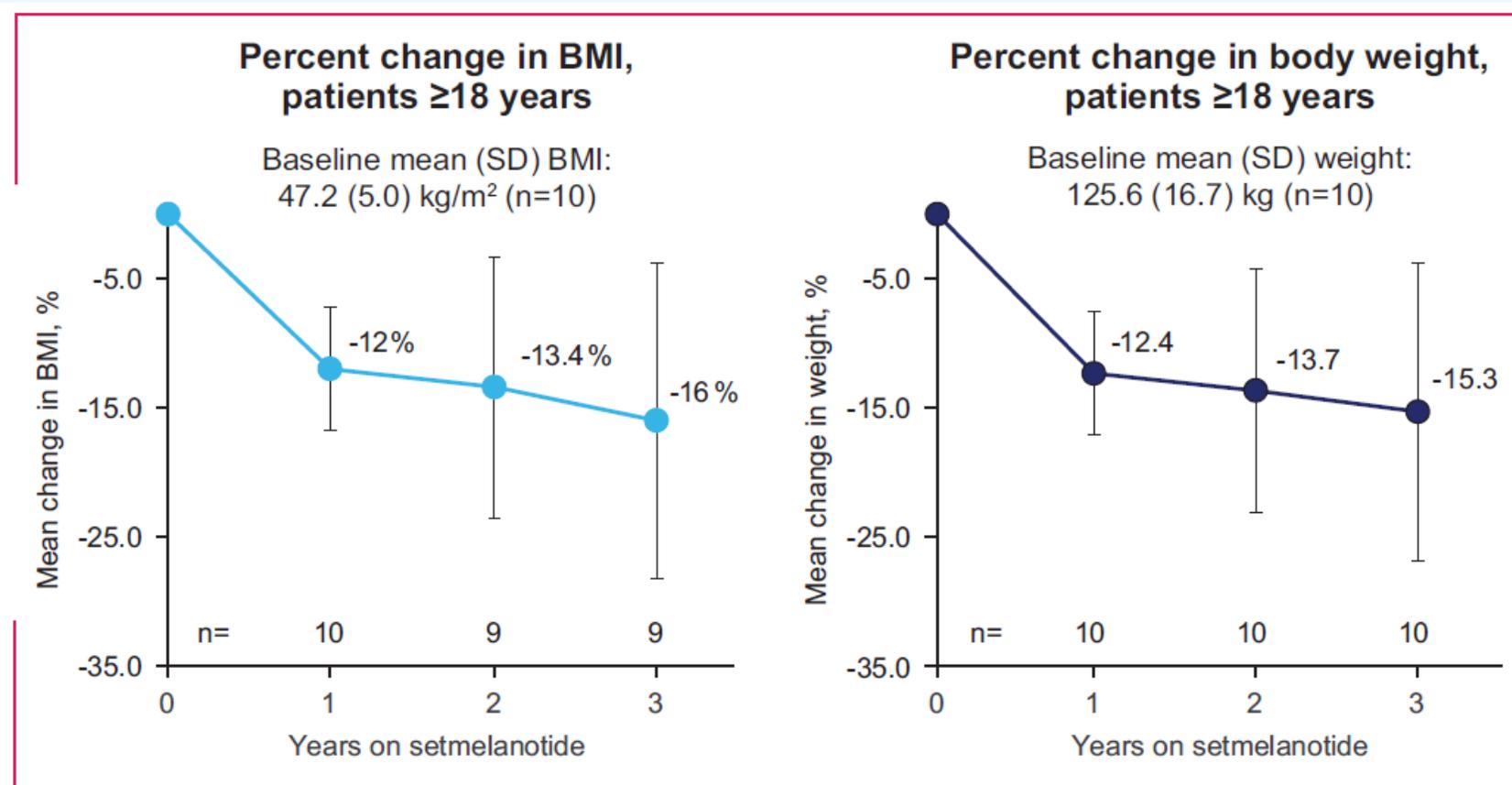
# Patient Baseline Demographics and Dispositions Related to TOS 2023 Long-term Data Readout in Patients with BBS

	Patients (n=25)
Age, mean (SD; range), years	21.4 (13.62; 7-61)
Age range, n (%), years	
≥18	10 (40.0)
<18	15 (60.0)
Sex, n (%)	
Male	9 (36.0)
Female	16 (64.0)
Race	
White	22 (88.0)
Black or African American	1 (4.0)
Other	2 (8.0)
Weight, mean (SD), kg	108.3 (29.2)
BMI, mean (SD), kg/m <sup>2</sup>	41.7 (9.2)
BMI Z score, mean (SD)*	3.1 (1.4)
%BMI95, mean (SD), percentage points*	147.2 (37.0)
Waist circumference, mean (SD), cm	115.3 (18.7)

BMI, body mass index; %BMI95, percent of the 95th BMI percentile; SD, standard deviation. \*Calculated based on Centers for Disease Control and Prevention (CDC) 2022 methodology for children (aged <18 years) only (n=15).

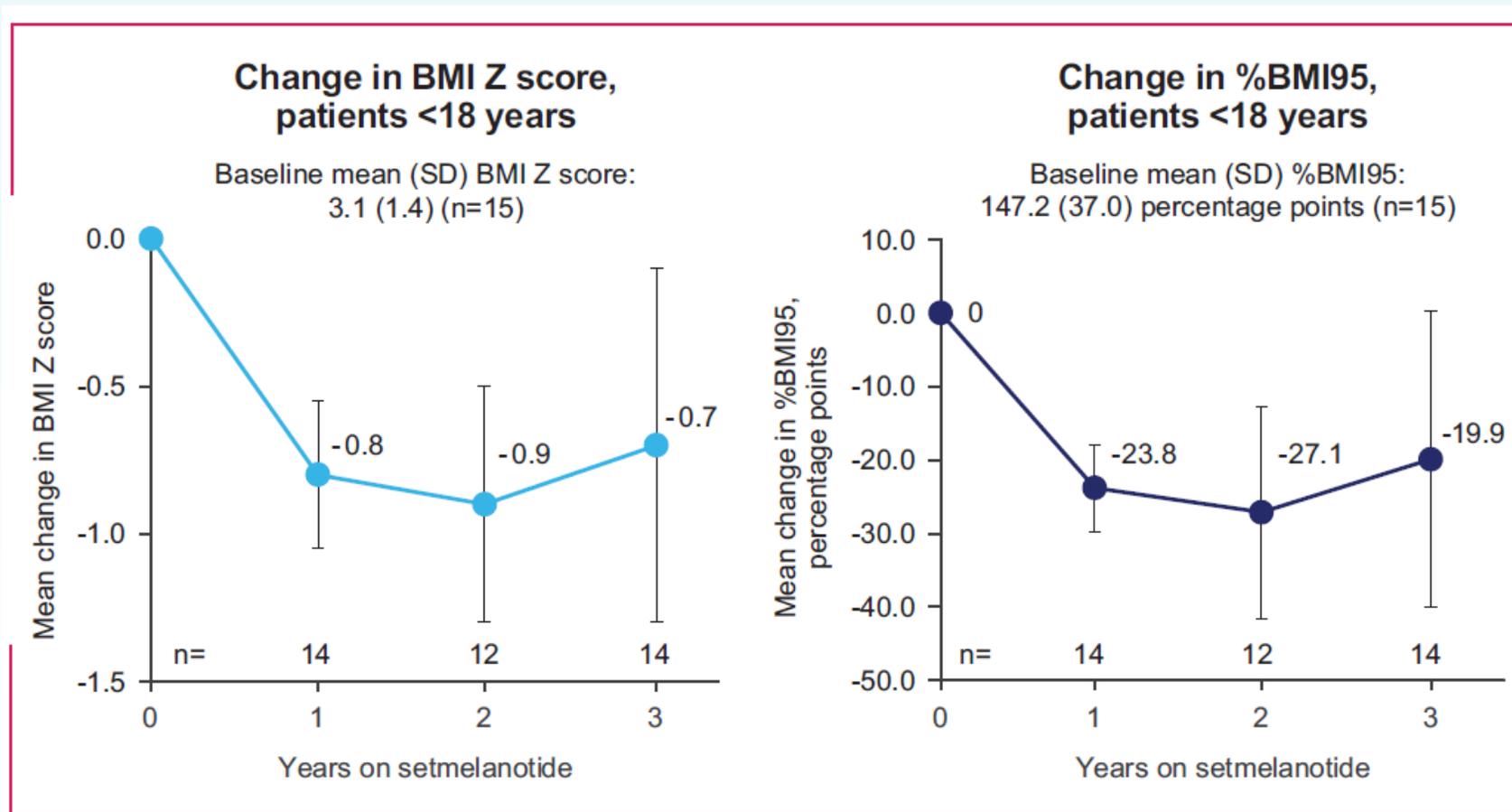


# 16% BMI Reduction in Adult Patients with BBS on Setmelanotide Therapy at Three Years



Error bars are the SD. BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

# Reduction of 0.7 in Mean BMI Z Achieved in Pediatric Patients at Three Years of Setmelanotide Therapy



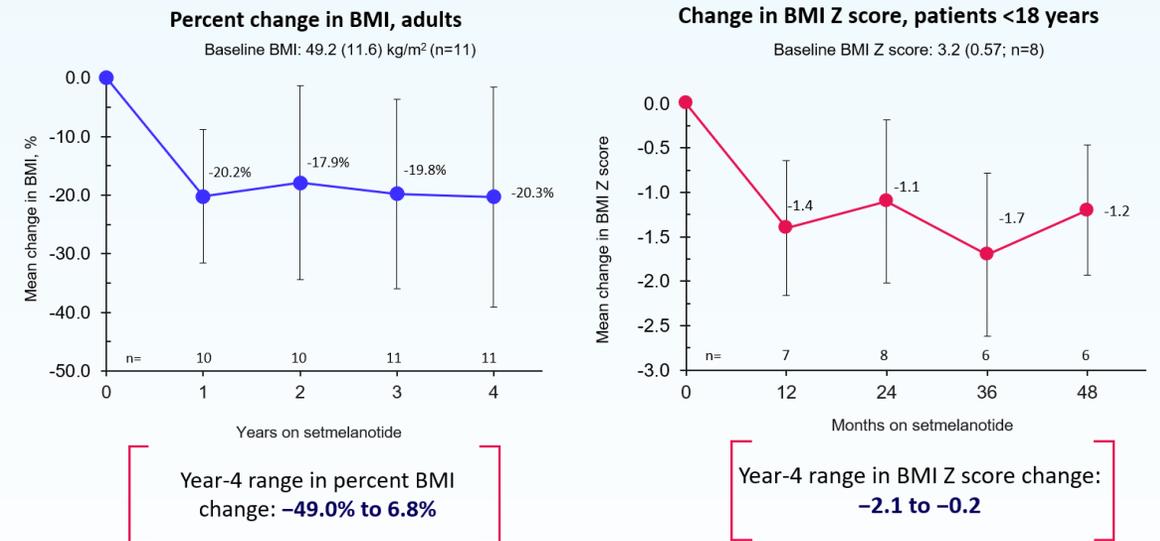
Error bars are the SD. %BMI95, percent of the 95th BMI percentile; BBS, Bardet-Biedl syndrome; BMI, body mass index; SD, standard deviation.

# 4-Year Setmelanotide Weight Outcomes of Patients With POMC and LEPR Deficiency Obesity

## Key takeaways

- The long-term efficacy of setmelanotide was analyzed in patients with POMC and LEPR deficiency who had a clinically meaningful weight response at Year 1 and who had long-term, on-treatment outcomes at Year 4 (n=19)
- Long-term treatment demonstrated sustained weight-related efficacy in adult (aged  $\geq 18$  years; n=11) and pediatric (aged  $< 18$  years; n=8) patients with POMC or LEPR deficiency
  - In adult patients, mean percent changes from baseline at Year 4 in body weight and BMI were  $-20.2\%$  and  $-20.3\%$ , respectively
  - In pediatric patients, mean changes from baseline at Year 4 in BMI Z score and %BMI95 were  $-1.2$  and  $-35.8$  percentage points, respectively
- **Long-term treatment with setmelanotide demonstrated sustained weight-related efficacy in pediatric and adult patients with POMC or LEPR deficiency**
- **The safety profile of setmelanotide was consistent with previous studies**

## Weight measures over 4 years of treatment\*



Presentation Number: Oral-084

Presenting Author: Dr James Swain

%BMI95, percent of the 95th BMI percentile; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation.

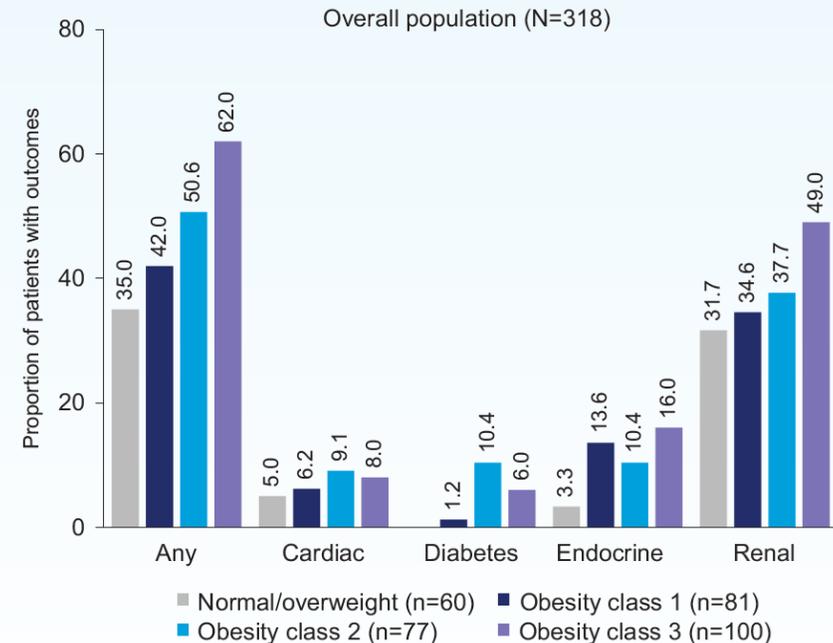
\*Error bars are the SD.

# Cardiac, Renal, and Endocrine/Diabetes Mellitus Outcomes in Children with Bardet-Biedl Syndrome

## Key takeaways

- The prevalence of cardiac, endocrine/diabetes, and renal outcomes was examined in children (aged  $\leq 17$  years) with BBS with varying levels of obesity severity who were enrolled in CRIBBS (N=318)
- Approximately half of all patients (156/318 [49.1%]) reported a health outcome of interest, and the prevalence of any cardiac, endocrine, diabetes, or renal outcome increased with obesity class
  - Cardiac, endocrine, diabetes-related, and renal outcomes were reported in 23 patients (7.2%), 37 patients (11.6%), 15 patients (4.7%), and 125 patients (39.3%), respectively
- Health outcomes occurred early in childhood; among patients aged 0 to <6 years (n=93), outcomes of interest were reported in 46.2%, 48.0%, 52.0%, and 56.7% of those with normal or overweight, obesity class 1, obesity class 2, and obesity class 3, respectively

Prevalence of cardiac, endocrine, diabetes, and renal outcomes in the overall population



**Presentation Number: Poster-129**

**Presenting Author: Caroline Huber**

# Impact of Setmelanotide on Metabolic Syndrome Risk in Patients With Bardet-Biedl Syndrome

## Key takeaways

- The change in MetS risk as assessed through the MetS-Z-BMI score was quantified in patients with BBS following 1 year of setmelanotide treatment (N=22)
  - Patients were classified as 1-year weight threshold achievers (n=13) or nonachievers (n=9) on the basis of weight outcomes
- One year of treatment was associated with decreased MetS-Z-BMI scores in most patients, suggesting that MC4R pathway-targeted treatment in this patient population may reduce the risk of future MetS, CVD, and T2DM
  - The mean decrease in MetS-Z-BMI score in 1-year weight threshold achievers was significantly greater than that in nonachievers (difference, 0.72;  $P=0.0043$ )
- All but 1 patient showed stabilization or decrease in their BMI or BMI Z score, even if not achieving the weight threshold
- Despite not meeting weight-related clinical response thresholds, 5 of 9 clinical nonachievers exhibited a reduction in MetS-Z-BMI score, highlighting the potential impact of setmelanotide treatment beyond weight outcomes alone
- These data suggest that 52 weeks of setmelanotide treatment in patients with BBS may result in MetS improvements beyond traditional weight-related measures**

MetS-Z-BMI score\* at baseline and week 52



Presentation Number: Oral-066

Presenting Author: Dr Sonali Malhotra

BBS, Bardet-Biedl syndrome; BMI, body mass index; CVD, cardiovascular disease; MC4R, melanocortin-4 receptor; MetS, metabolic syndrome; MetS-Z-BMI, metabolic syndrome score based on BMI; T2DM, type 2 diabetes mellitus.; \*MetS-Z-BMI score was calculated using confirmatory factor analysis. †BMI Z score was calculated according to the Centers for Disease Control and Prevention 2022 method only in patients <18 years of age.

# Impact of Setmelanotide on Metabolic Syndrome Risk in Patients With POMC and LEPR Deficiency

## Key takeaways

- The change in MetS risk as assessed through the MetS-Z-BMI score was quantified in patients with POMC (n=10 [POMC, n=9; PCSK1, n=1]) and LEPR (n=8) deficiency following 1 year of setmelanotide treatment (N=18)
  - Patients were classified as 1-year weight threshold achievers (n=14) or nonachievers (n=4) on the basis of weight outcomes
- One year of treatment was associated with decreased MetS-Z-BMI scores in most patients, suggesting intervention with setmelanotide may reduce the risk of future CVD and T2DM in those with MC4R pathway diseases, as observed with changes in MetS severity scores of other populations
  - The mean MetS-Z-BMI score decrease in 1-year weight threshold achievers was significantly greater than that in nonachievers (difference, -1.1;  $P=0.0187$ )
- These data suggest that 52 weeks of setmelanotide treatment in patients with POMC or LEPR deficiency may result in MetS improvements beyond traditional weight-related measures**

BMI, body mass index; CVD, cardiovascular disease; T2DM, type 2 diabetes mellitus; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MetS, metabolic syndrome; MetS-Z-BMI, metabolic syndrome score based on BMI; POMC, proopiomelanocortin. \*MetS-Z-BMI score was calculated using confirmatory factor analysis. †BMI Z score was calculated according to the Centers for Disease Control and Prevention 2022 method only in patients <18 years of age.

MetS-Z-BMI score\* at baseline and week 52



Presentation Number: Oral-065

Presenting Author: Dr James Swain