



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

Presenting author: Sonali Malhotra

Andrea M. Haqq,¹ Christine Poitou,^{2,3} Wendy K. Chung,⁴ Anoop Iqbal,⁵ Elizabeth Forsythe,⁶ Sonali Malhotra,⁷⁻⁹ Nicolas Touchot,⁸ Karine Clément,^{2,3} Jesús Argente^{10,11}

¹Division of Pediatric Endocrinology, University of Alberta, Edmonton, AB, Canada; ²Nutrition Department, Assistance Publique Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris, France; ³Sorbonne University, Inserm, Nutrition and Obesity, Systemic Approaches (NutriOmique) Research Group, Paris, France; ⁴Division of Molecular Genetics, Department of Pediatrics, Columbia University, New York, NY, USA; ⁵Department of Clinical Research, Marshfield Clinic Research Institute, Marshfield, WI, USA; ⁶Clinical Genetics Department, Guys and St. Thomas' Hospitals, London, and National Bardet-Biedl Syndrome Clinics, Great Ormond Street Hospital, London, UK; ⁷Rhythm Pharmaceuticals, Inc., Boston, MA, USA; ⁸Massachusetts General Hospital, Boston, MA, USA; ⁹Harvard Medical School, Boston, MA, USA; ¹⁰Department of Pediatrics and Pediatric Endocrinology, Universidad Autónoma de Madrid, University Hospital Niño Jesús, CIBER "Fisiopatología de la obesidad y nutrición" (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain; ¹¹IMDEA Food Institute, Madrid, Spain



Objective: to quantify the change in MetS risk as assessed through the MetS-Z-BMI Score^{1,2} following 1 year of setmelanotide treatment



- Data were obtained from patients with BBS who completed a Phase 3 trial of setmelanotide (NCT03746522)^{3,*}



- Inclusion criteria for this analysis included
 - Necessary values needed to calculate MetS-Z-BMI score at baseline and Week 52
 - Identification of age, sex, and race/ethnicity to determine appropriate MetS-Z-BMI coefficients



- Patients were classified as 1-year weight threshold achievers or nonachievers on the basis of weight outcomes[†]
 - Achievers were defined as achieving $\geq 10\%$ weight reduction for adults or ≥ 0.3 -point BMI Z score[‡] reduction for pediatric patients after 52 weeks of setmelanotide treatment⁴⁻⁶
 - A 2-sided 2-sample *t*-test was used to determine the mean difference significance between achievers and nonachievers and should be interpreted with caution

*Primary analysis data published previously. Patients missing height data at Week 52 were included using baseline value carried forward to maximize the number of patients in the analysis. [†]P-value for mean MetS-Z-BMI difference between 1-year weight threshold achievers vs nonachievers was calculated from a 2-sided 2-sample *t*-test and should be interpreted with caution. [‡]BMI Z score calculations for weight response were calculated using the World Health Organization 2007 method. 1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128. 2. Gurka et al. *Metabolism*. 2018;83:68-74. 3. Haqq et al. *Lancet Diabetes Endocrinol*. 2022;10:859-868. 4. Knowler et al. *N Engl J Med*. 2002;346:393-403. 5. Reinehr et al. *J Clin Endocrinol Metab*. 2016;101:3171-3179. 6. US Preventative Services Task Force. *JAMA*. 2016;317:2417-2426.



Demographic and Baseline Characteristics of Patients With BBS

Baseline characteristics	Total (N=22)	BBS1 (n=10)	BBS10 (n=9)	Other* (n=3)
Age, mean (standard deviation [SD]), y	20.3 (11.2)	17.8 (8.0)	21.4 (13.1)	25.3 (16.7)
Age range, n (%), y				
Adults ≥18	13 (59.1)	6 (60.0)	6 (66.7)	1 (33.3)
Children 10-18	9 (40.9)	4 (40.0)	3 (33.3)	2 (66.0)
Sex, n (%)				
Female	13 (60.1)	5 (50.0)	5 (55.6)	3 (100)
Male	9 (40.9)	5 (50.0)	4 (44.4)	0
Weight, mean (SD), kg	112.9 (28.5)	113.4 (28.8)	116.6 (31.4)	100.4 (23.4)
Waist circumference, mean (SD), cm	118.2 (17.9)	120.7 (16.8)	116.8 (21.6)	113.8 (12.4)
Diabetes diagnosis, n (%)				
Prediabetes	4 (18.2)	4 (40)	0	0
T2DM	2 (9.1)	0	1 (11.1)	1 (33.3)
Receiving medication for hypertension, n (%)	7 (31.8)	3 (30.0)	2 (22.2)	2 (66.7)
Receiving medication for dyslipidemia, n (%)	2 (9.1)	0	1 (11.1)	1 (50.0)

Characteristics used in MetS-Z-BMI Score Calculation	Total (N=22)	BBS1 (n=10)	BBS10 (n=9)	Other* (n=3)
BMI, mean (SD), kg/m ²	42.2 (9.9)	41.0 (10.0)	43.5 (11.5)	42.4 (5.1)
BMI Z score, mean (SD) [†]	2.5 (0.4)	2.4 (0.5)	2.5 (0.4)	2.6 (–)
Waist circumference, mean (SD), cm	118.2 (17.9)	120.7 (16.8)	116.8 (21.6)	113.8 (12.4)
Systolic blood pressure, mean (SD), mm Hg	112.9 (9.4)	116.3 (9.1)	110.2 (10.1)	109.6 (6.8)
HDL cholesterol, mean (SD), mg/dL	41.5 (6.3)	38.7 (5.8)	43.8 (6.7)	43.8 (4.4)
Triglycerides, mean (SD), mg/dL	141.3 (67.1)	154.4 (58.4)	107.6 (44.4)	198.7 (114.7)
Fasting glucose, mean (SD), mg/dL	86.4 (17.6)	80.9 (12.1)	88.1 (20.2)	99.7 (22.9)
MetS-Z-BMI score, mean (SD) [‡]	1.2 (0.5)	1.2 (0.3)	1.0 (0.6)	1.4 (0.9)

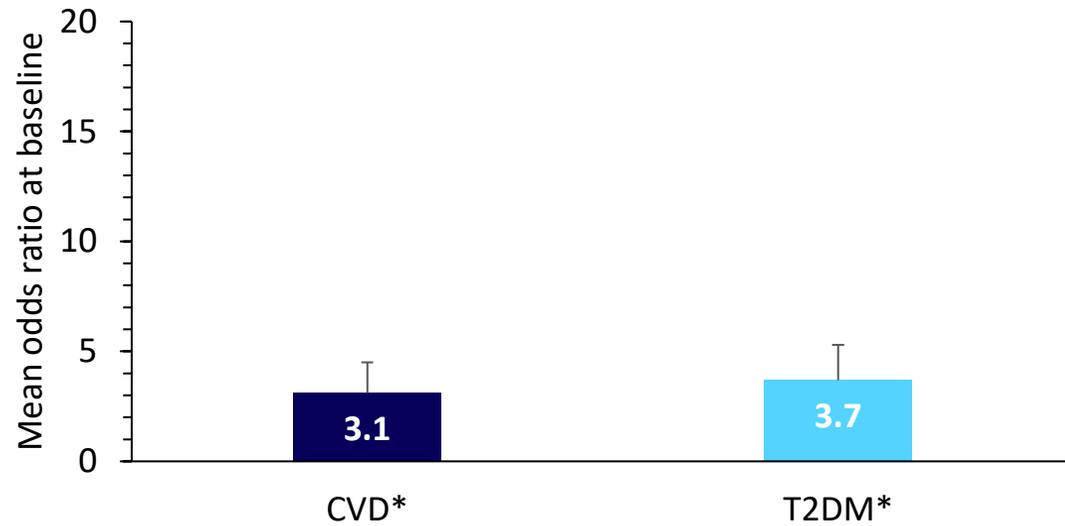
*BBS2 (n=2) and MKKS (n=1). [†]BMI Z score based on Centers for Disease Control and Prevention (CDC) 2022 methodology. [‡]MetS-Z-BMI was calculated using confirmatory factor analysis.¹
 1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128.



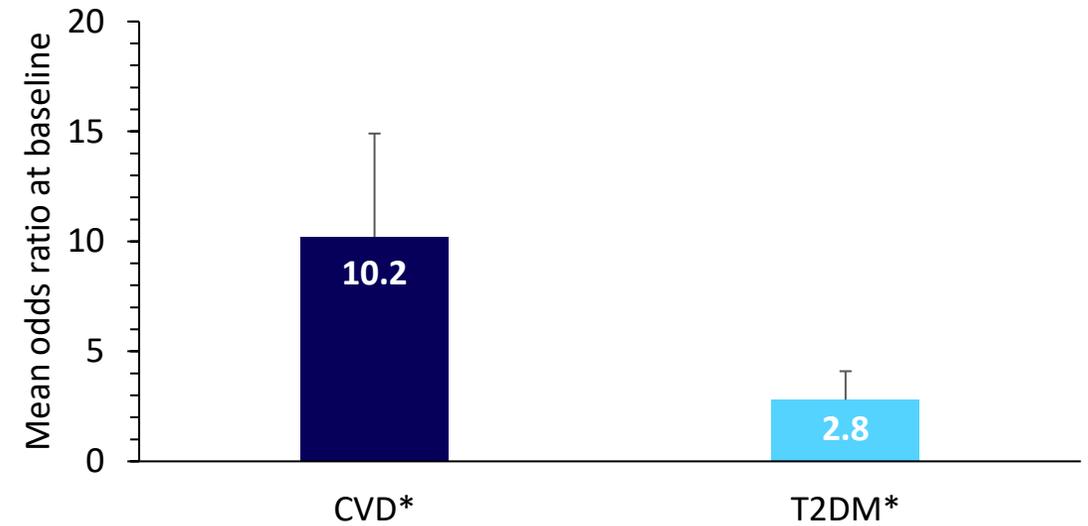
Risk at Baseline of Developing Future CVD or T2DM

Patient characteristics																						
Sex	F	M	F	F	F	M	M	F	M	M	F	F	F	F	M	F	F	M	M	F	M	F
Age at baseline	43	13	42	12	20	34	29	15	12	20	12	13	21	28	12	14	44	14	10	10	16	13
Gene	<i>BBS10</i>	<i>BBS1</i>	<i>BBS10</i>	<i>MKKS</i>	<i>BBS2</i>	<i>BBS1</i>	<i>BBS10</i>	<i>BBS10</i>	<i>BBS10</i>	<i>BBS1</i>	<i>BBS10</i>	<i>BBS1</i>	<i>BBS1</i>	<i>BBS1</i>	<i>BBS10</i>	<i>BBS10</i>	<i>BBS2</i>	<i>BBS10</i>	<i>BBS1</i>	<i>BBS1</i>	<i>BBS1</i>	<i>BBS1</i>
CVD odds ratio*	4.6	14.9	4.0	14.7	1.0	2.2	1.9	10.3	5.9	3.7	4.8	12.0	3.5	2.0	10.9	11.3	5.4	-0.5	12.3	11.1	16.9	7.4
T2DM odds ratio*	5.4	4.1	4.7	4.1	1.1	2.5	2.3	2.8	1.6	4.4	1.3	3.3	4.1	2.3	3.0	3.1	6.3	-0.1	3.4	3.1	4.7	2.0

Adults developing subsequent comorbidity



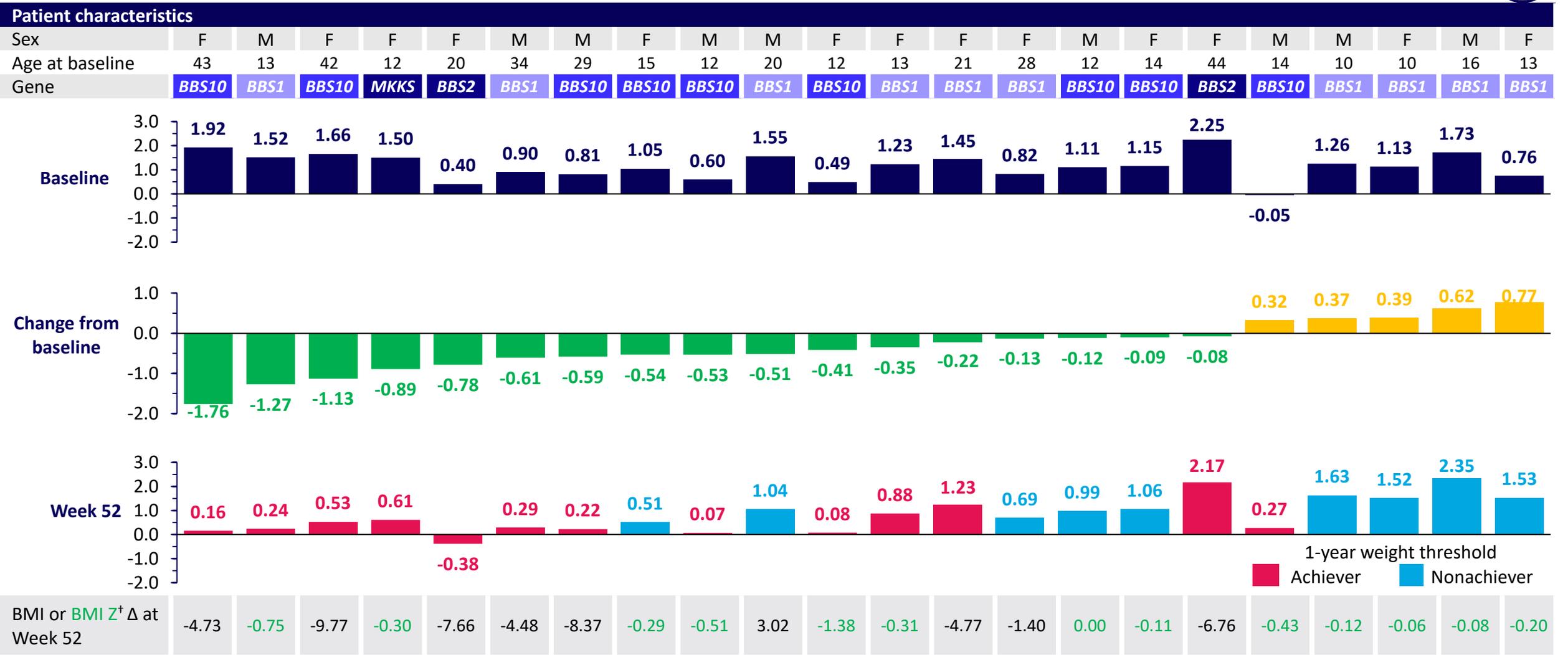
Children developing subsequent comorbidity



Error bars are the SD. *Each 1.0-point in MetS-Z-BMI score during childhood and adulthood increases the odds of future CVD by 9.8 and 2.4, respectively, and for T2DM by 2.7 and 2.8, by the ages of 38 and 50 respectively.^{1,2}
 1. DeBoer et al. *Diabetologia*. 2015;58:2745-2752. 2. DeBoer et al. *J Am Coll Cardiol*. 2015;66:755-757.



MetS-Z-BMI Score* at Baseline and Week 52



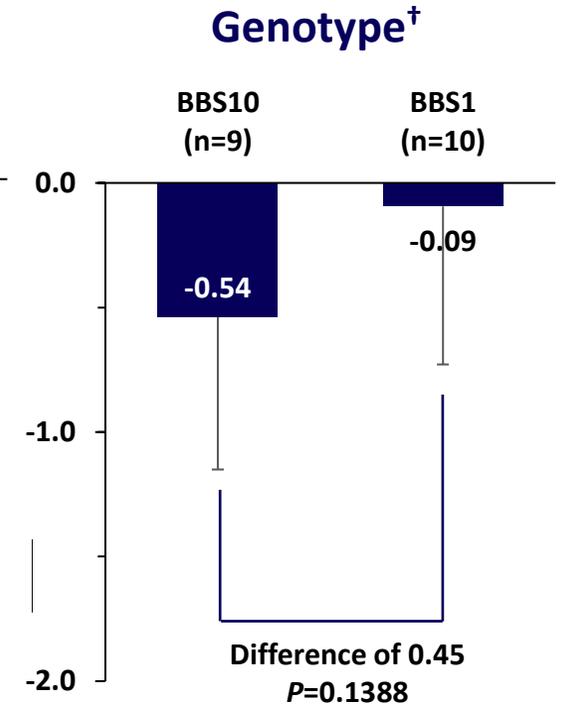
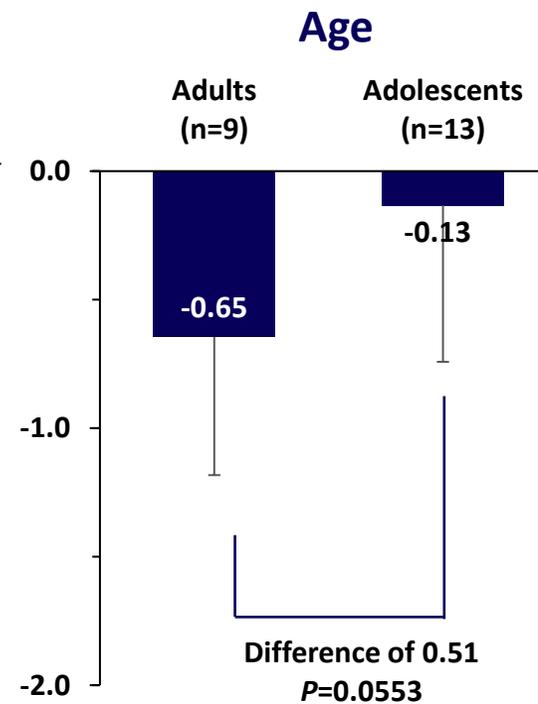
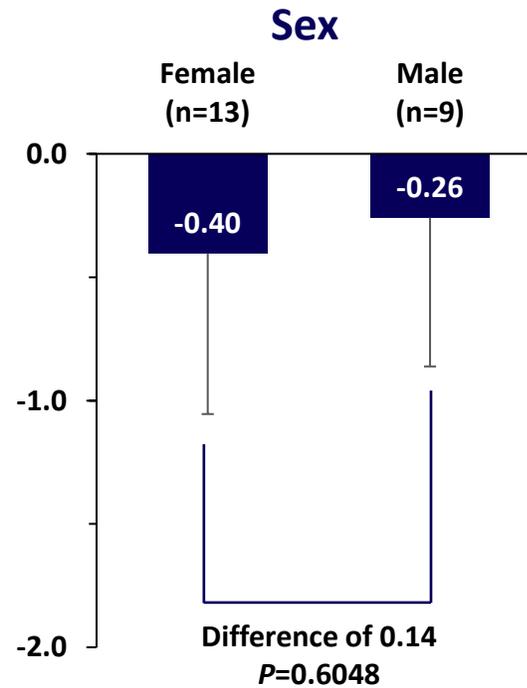
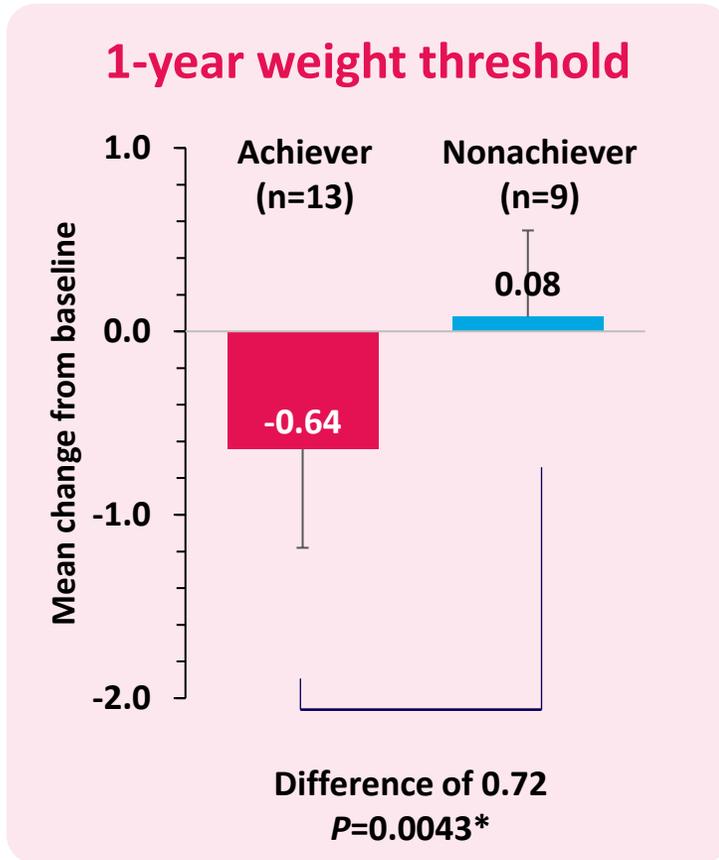
*MetS-Z-BMI score was calculated using confirmatory factor analysis.¹ BMI Z score was calculated according to the CDC 2022 method only in patients <18 years of age.
 1. Gurka et al. *Cardiovasc Diabetol.* 2012;11:128.



Mean MetS-Z-BMI Score Change From Baseline at Week 52: Subgroup Comparison

1-year weight threshold achievers had a significantly larger change in mean MetS-Z-BMI score compared with nonachievers after 52 weeks of setmelanotide

- No significant differences were observed at Week 52 for mean response by age, sex, or genotype



Error bars are the SD. *P-value was calculated using a 2-sided 2-sample t-test. [†]Analysis does not include BBS2 (n=2) and MKKS (n=1).



Summary and Conclusions

- One year of setmelanotide treatment was associated with reductions in MetS-Z-BMI scores in most patients with BBS, suggesting that MC4R pathway–targeted treatment in this patient population may reduce the risk of future MetS, CVD, and T2DM¹⁻³
- The mean decrease in MetS-Z-BMI score in patients achieving a predetermined weight threshold at 1 year 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
- Further work is being conducted to better understand the degree of improvements in MetS with setmelanotide observed in patients with monogenic and syndromic forms of obesity
- Limitations of this post hoc analysis include the lack of a control group and that the MetS calculation may lead to higher MetS scores in patients with metabolic parameters in the upper range of normal

These data suggest that 52 weeks of setmelanotide treatment in patients with BBS may result in MetS improvements beyond traditional weight-related measures

1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128. 2. Gurka et al. *Metabolism*. 2014;63:218-225. 3. Gurka et al. *Metabolism*. 2018;83:68-74.