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

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Melanocortin-4 Receptor Pathway–Related Obesity and Metabolic Syndrome

- Patients with rare monogenic obesity caused by biallelic variants of genes in the melanocortin-4 receptor (MC4R) pathway, such as *POMC* (including variants in *PCSK1*) or *LEPR*, experience hyperphagia (a pathologic, insatiable hunger) and early-onset, severe obesity[1,2]
  - Over time, obesity can lead to the development of related comorbidities, including metabolic syndrome (MetS), which is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM)[2-5]

Clinical features of metabolic syndrome[3,6]

Obesity

Reduced high-density lipoprotein (HDL) cholesterol

Increased triglycerides

Impaired glucose tolerance

Hypertension

- In Phase 3 trials, treatment with the MC4R agonist setmelanotide resulted in significant weight and hunger reductions in patients with proopiomelanocortin (POMC) or leptin receptor (LEPR) deficiency and demonstrated an effect on several parameters of MetS[1,*]

We hypothesized that patients responding to setmelanotide might also experience a decreased severity of MetS along with associated risks of CVD and T2DM

*Setmelanotide is indicated for chronic weight management in adult and pediatric patients ≥6 years of age with monogenic or syndromic obesity due to POMC, PCSK1, or LEPR deficiency as determined by an FDA-approved test or BBS.[7]

1. Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **2.** Wabitsch et al. *J Endocr Soc*. 2022;6:bvac057. **3.** Gurka et al. *Cardiovasc Diabetol*. 2012;11:128. **4.** Gurka et al. *Metabolism*. 2018;83:68-74. **5.** Wang et al. *Metab Syndr Relat Disord*. 2018;16:208-214. **6.** Gurka et al. *Metabolism*. 2014;63:218-225. **7.** IMCIVREE® (setmelanotide) [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc; 2022.

MetS Score Based on Body Mass Index

- The MetS score based on body mass index (BMI; MetS-Z-BMI) is a measurement that estimates risk and severity of MetS, which is associated with increased future risk of CVD and T2DM[1,2]
  - MetS-Z-BMI was created using 1999-2010 data from the US National Health and Nutrition Examination Survey (NHANES), resulting in a continuous MetS-Z-BMI risk score that is sex and race/ethnicity specific[1,2]
  - MetS-Z-BMI is calculated by multiplying age-, sex-, and race/ethnicity–specific factor coefficients by adiposity measures (ie, BMI or BMI Z score), HDL cholesterol, triglycerides, fasting glucose, and systolic blood pressure[1,2]

- Each 1.0-point increase 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[3,4]

	CVD Risk	T2DM Risk
Pediatric patients	↑ **9.8**	↑ **2.7**
Adults	↑ **2.4**	↑ **2.8**

1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128. **2.** Gurka et al. *Metabolism*. 2018;83:68-74. **3.** DeBoer et al. *Diabetologia*. 2015;58:2745-2752. **4.** DeBoer et al. *J Am Coll Cardiol*. 2015;66:755-757.

Objectives and Methods

Objective: to quantify the change in MetS risk as assessed through the MetS-Z-BMI Score[1] following 1 year of setmelanotide treatment

- Data were obtained from patients from 2 Phase 3 trials of patients with POMC (NCT02896192) or LEPR (NCT03287960) deficiency who had the necessary measurements at baseline and at ~1 year to calculate the MetS-Z-BMI score[2,*]

- 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 for correct use of specific MetS-Z-BMI confirmatory factor analysis[1]

- Patients were classified as 1-year weight threshold achievers or nonachievers on the basis of weight outcomes
  - Achievers were defined as achieving ≥10% weight reduction for adults or ≥0.3-point BMI Z score reduction for pediatric patients after 1 year of setmelanotide treatment[3-5]
  - 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

*Following the 12-week, open-label treatment phase, participants who reached a weight loss threshold of ≥5 kg reduction in weight (or ≥5% weight loss for participants weighing <100 kg at baseline) entered an 8-week double-blind, placebo-controlled withdrawal sequence.[2]

1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128. **2.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **3.** Knowler et al. *N Engl J Med*. 2002;346:393-403. **4.** Reinehr et al. *J Clin Endocrinol Metab*. 2016;101:3171-3179. **5.** US Preventative Services Task Force. *JAMA*. 2016;317:2417-2426.

Demographic and Baseline Characteristics of Patients With POMC or LEPR Deficiency

Baseline characteristics	Total (N=18)	POMC* (n=10)	LEPR (n=8)
Age, mean (standard deviation [SD]), y	20 (7.3)	22.0 (8.5)	18.4 (6.2)
Age range, n (%), y			
Adults ≥18	9 (50.0)	4 (40.0)	5 (62.5)
Children 10-18	9 (50.0)	6 (60.0)	3 (37.5)
Sex, n (%)			
Female	10 (55.6)	5 (50)	5 (62.5)
Male	8 (44.4)	5 (50)	3 (37.5)
Weight, mean (SD), kg	123.0 (32.8)	118.7 (37.5)	128.5 (27.4)
Waist circumference, mean (SD), cm	123.4 (18.9)	121.8 (19.0)	125.4 (19.8)

Characteristics used in MetS-Z-BMI score calculation	Total (N=18)	POMC* (n=10)	LEPR (n=8)
BMI, mean (SD), kg/m^2	42.8 (9.8)	40.4 (0.9)	45.78 (10.4)
BMI Z score, mean (SD)[†]	2.5 (0.3)	2.4 (0.3)	2.6 (0.2)
Systolic blood pressure, mean (SD), mm Hg	115.2 (9.1)	111.6 (7.8)	119.7 (8.9)
HDL cholesterol, mean (SD), mg/dL	40.8 (16.8)	40.4 (17.7)	41.4 (16.7)
Triglycerides, mean (SD), mg/dL	149.3 (124.9)	178.4 (158.3)	112.9 (54.4)
Fasting glucose, mean (SD), mg/dL	117.9 (84.3)	136.0 (107.8)	95.4 (35.9)
MetS-Z-BMI score, mean (SD)[‡]	1.5 (1.3)	1.6 (1.5)	1.3 (1.2)

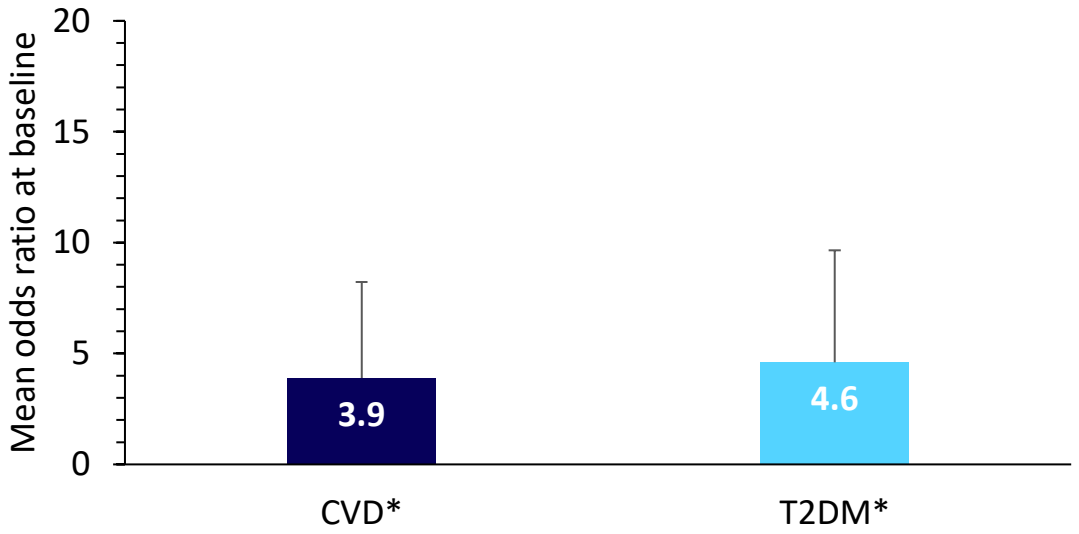
*Includes patients with biallelic variants in *POMC* (n=9) and *PCSK1* (n=1). [†]BMI Z score calculated for patients aged <18 years (n=9). BMI Z score calculated using the Centers for Disease Control and Prevention (CDC) 2022 methodology. [‡]MetS-Z-BMI was calculated using confirmatory factor analysis.[1]

1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128.

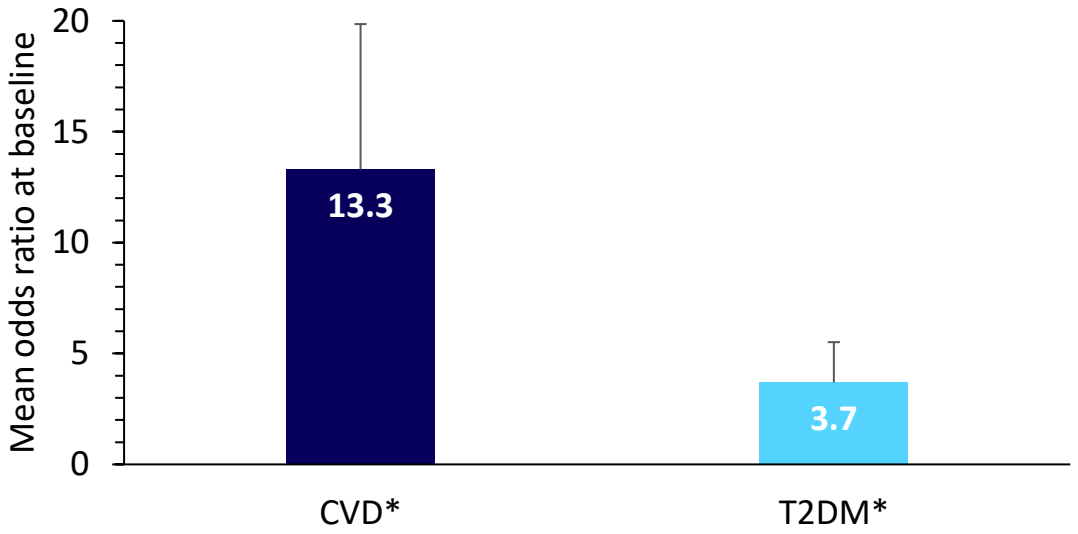
Risk at Baseline of Developing Future CVD or T2DM

Patient characteristics																		
Sex	M	M	F	M	F	F	F	F	M	M	F	M	M	M	F	F	F	F
Age at baseline	22	26	11	16	17	20	23	13	15	11	16	13	31	36	15	25	20	30
Gene	*POMC*	*POMC*	*POMC*	*POMC*	*POMC*	*POMC*	*LEPR*	*LEPR*	*POMC*	*PCSK1*	*POMC*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*POMC*
CVD odds ratio*	13.0	3.9	20.6	14.6	15.3	1.7	5.2	17.8	-0.9	13.6	14.9	17.2	-0.7	-0.1	6.6	8.0	2.6	1.5
T2DM odds ratio*	15.1	4.6	5.7	4.0	4.2	2.0	6.1	4.9	-0.3	3.8	4.1	4.7	-0.8	-0.1	1.8	9.4	3.1	1.8

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

Patient characteristics																		
Sex	M	M	F	M	F	F	F	F	M	M	F	M	M	M	F	F	F	F
Age at baseline	22	26	11	16	17	20	23	13	15	11	16	13	31	36	15	25	20	30
Gene	*POMC*	*POMC*	*POMC*	*POMC*	*POMC*	*POMC*	*LEPR*	*LEPR*	*POMC*	*PCSK1*	*POMC*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*POMC*
Baseline	5.4	1.6	2.1	1.5	1.6	0.7	2.2	1.8	-0.1	1.4	1.5	1.8	-0.3	0.0	0.7	3.3	1.1	0.6
Change from baseline	-2.9	-2.4	-2.4	-2.0	-1.4	-1.4	-1.4	-1.1	-1.0	-0.7	-0.5	-0.4	-0.4	-0.4	-0.3	-0.3	-0.2	0.1
Week 52	2.6	-0.8	-0.3	-0.5	0.2	-0.7	0.8	0.7	-1.1	0.7	1.0	1.4	-0.7	-0.4	0.3	3.0	0.9	0.8
BMI or BMI Z† Δ at Week 52	-9.1	-17.4	-1.2	-2.2	-0.7	-10.2	-9.0	-0.3	-1.3	-0.4	-0.4	-0.4	-7.8	-5.9	-0.1	-1.5	-1.7	-0.6

30-year-old discontinued treatment at day 100 because of an adverse event

1-year weight threshold

Achiever

Nonachiever

*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.

Individual Changes in MetS-Z-BMI Score* Factors at Week 52

Patient characteristics																		
Sex	M	M	F	M	F	F	F	F	M	M	F	M	M	M	F	F	F	F
Age at baseline	22	26	11	16	17	20	23	13	15	11	16	13	31	36	15	25	20	30
Gene	*POMC*	*POMC*	*POMC*	*POMC*	*POMC*	*POMC*	*LEPR*	*LEPR*	*POMC*	*PCSK1*	*POMC*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*LEPR*	*POMC*
BMI or BMI Z score† Δ at Week 52	-9.1	-17.4	-1.2	-2.2	-0.7	-10.2	-9.0	-0.3	-1.3	-0.4	-0.4	-0.4	-7.8	-5.9	-0.1	-1.5	-1.7	-0.6
Systolic blood pressure Δ at Week 52, mm Hg	3.6	-8.3	-1.4	-6.7	-1.7	-10.0	-23.0	-11.0	-4.0	2.4	0.0	-3.7	1.3	8.3	-6.4	-21.6	11.0	8.7
HDL cholesterol Δ at Week 52, mg/dL	20.0	18.0	23.6	32.0	18.0	-14.0	7.8	15.9	7.0	16.0	-1.0	0.0	11.6	6.9	7.0	2.7	8.5	4.7
Triglyceride Δ at Week 52, mg/dL	-468.0	-218.0	-16.8	-32.0	-34.0	-107.0	-79.7	-79.7	-32.0	-21.0	-148.0	-44.3	8.9	-1.8	-9.7	50.5	15.0	15.9
Fasting glucose Δ at Week 52, mg/dL	-67.0	-14.0	-91.9	-11.0	-68.0	-23.0	-7.0	-5.4	4.0	3.0	-3.0	2.0	8.0	0.0	5.4	-21.5	-5.4	1.8
MetS-Z-BMI score* Δ at Week 52	**-2.9**	**-2.4**	**-2.4**	**-2.0**	**-1.4**	**-1.4**	**-1.4**	**-1.1**	**-1.0**	**-0.7**	**-0.5**	**-0.4**	**-0.4**	**-0.4**	**-0.3**	**-0.3**	**-0.2**	**0.1**

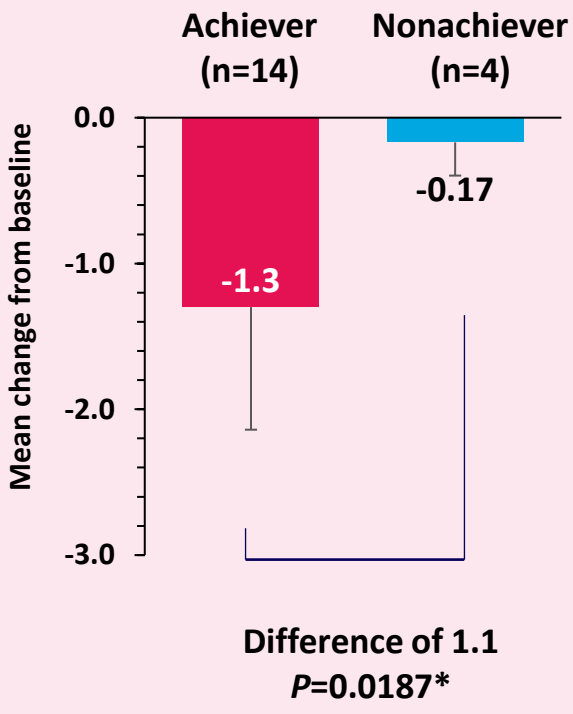
*MetS-Z-BMI score was calculated using confirmatory factor analysis.[1] †BMI Z score was calculated according to the CDC 2022 method only in patients <18 years of age.

1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128.

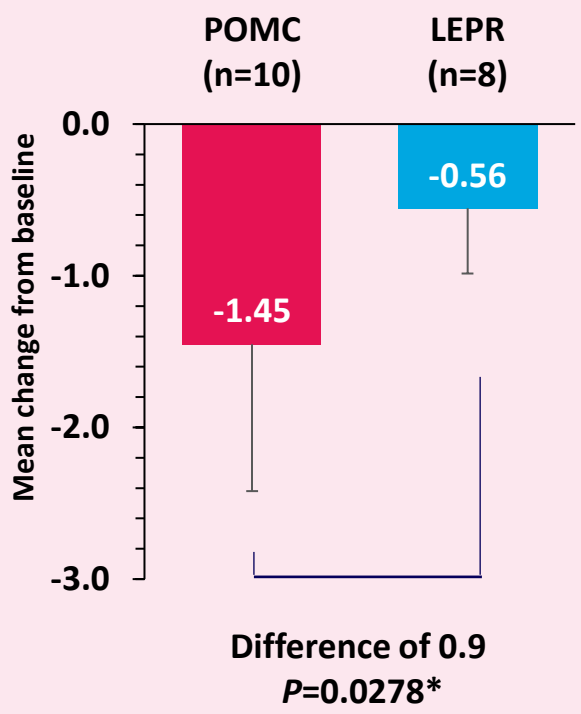
Mean MetS-Z-BMI Score Change From Baseline at Week 52: Subgroup Comparison

1-year weight threshold achievers and patients with POMC deficiency exhibited the most significant change in mean MetS-Z-BMI score after 52 weeks of setmelanotide

1-year weight threshold

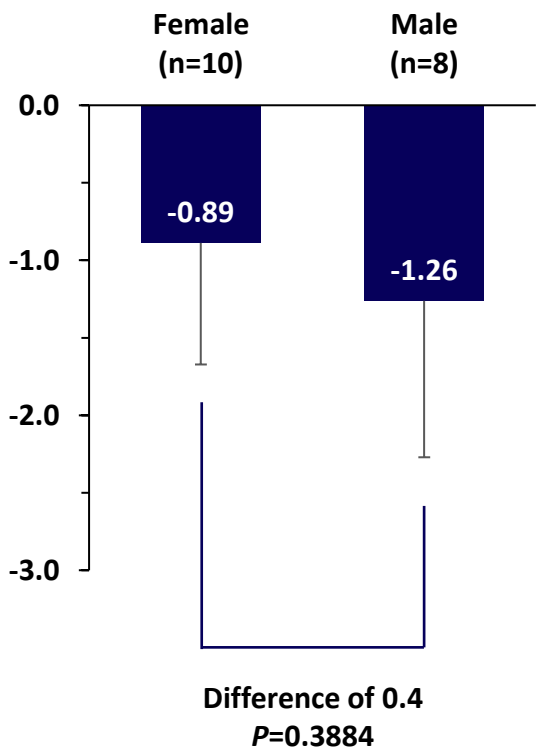


Genotype

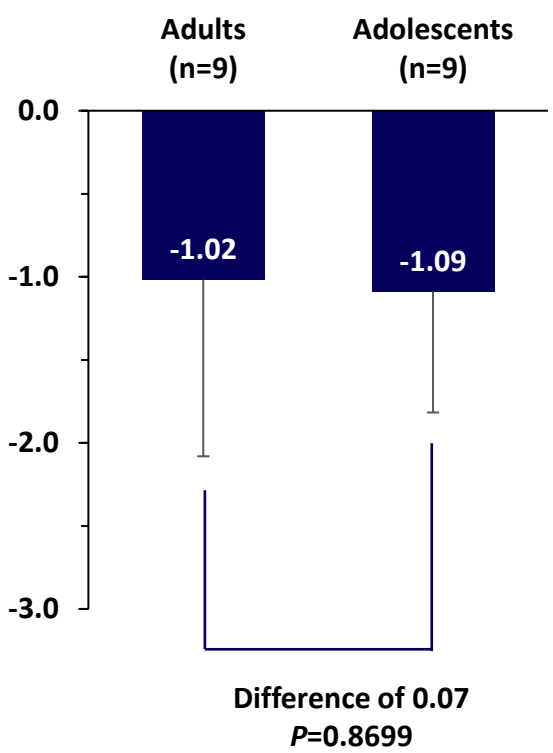


- No significant differences were observed at Week 52 for mean response by age or sex

Sex



Age



Error bars are the SD. **P*-value was calculated using a 2-sided 2-sample *t*-test.

Summary and Conclusions

- One year of treatment was associated with decreased MetS-Z-BMI scores in patients with POMC* and LEPR deficiency, suggesting intervention with setmelanotide may reduce the risk of future CVD and T2DM in those with rare genetic diseases of obesity, as observed with changes in MetS severity scores of other populations[1-3]

- All patients achieving a predetermined 52-week weight threshold (ie, ≥10% weight reduction in adults or ≥0.3-point BMI Z score reduction in pediatric patients) had reductions in MetS-Z-BMI score (range, −2.9 to −0.4). However, all patients had some decrease in their BMI or BMI Z score at Week 52

  - 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)

  - Despite not meeting weight-related thresholds, 3 of 4 nonachievers exhibited a reduction in MetS-Z-BMI score, indicating the potential impact of setmelanotide treatment beyond weight outcomes alone

- 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 POMC or LEPR deficiency may result in MetS improvements beyond traditional weight-related measures

*Includes patients with biallelic variants in *POMC* and *PCSK1*.

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.