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

Presentation FC8.5

Martin Wabitsch, MD, PhD, presenting

Martin Wabitsch,[1] Wendy K. Chung,[2] Peter Kühnen,[3] James Swain,[4] Jill C. Garrison,[5] Nicolas Touchot,[5] Jesús Argente,[6,7] Karine Clément[8,9]

[1]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, University of Ulm, Ulm, Germany; [2]Division of Molecular Genetics, Department of Pediatrics, Columbia University, New York, NY, USA; [3]Department of Pediatric Endocrinology, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin und Humboldt-Universität zu Berlin; [4]Honor Health Research Institute, Scottsdale, AZ, USA; [5]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [6]Department 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; [7]IMDEA Food Institute, Madrid, Spain; [8]Assistance Publique Hôpitaux de Paris, Nutrition Department, Pitié-Salpêtrière Hospital, Paris, France; [9]Sorbonne University, Inserm, Nutrition and Obesity, Systemic Approaches (NutriOmique) Research Group, Paris, France

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DISCLOSURE STATEMENT

Martin Wabitsch

☒ I have the following potential conflicts of interest to report:

- ☐ Research Contracts
- ☒ Consulting
- ☐ Employment in the Industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☒ Other(s) – speaking engagements for Rhythm Pharmaceuticals, Inc.

ESPE
European Society for Paediatric Endocrinology

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]

- 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 risk of MetS along with associated risks of CVD and T2DM

*Setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed BBS, loss-of-function biallelic POMC, including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency, or biallelic LEPR deficiency in adults and children ≥6 years of age.[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.** European Medicines Agency. https://www.ema.europa.eu/en/medicines/human/EPAR/imcivree#product-information-section. Accessed July 13, 2023.

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 future risk of CVD and T2DM in the US population[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), including HDL cholesterol, triglycerides, fasting glucose, and systolic blood pressure[1,2]

- Each 1.0-point increase in MetS-Z-BMI score during childhood increases the odds of future CVD by 9.8 and for T2DM by 2.7 by the ages of 38 and 50, respectively[3,4]

- Currently there is no validated continuous algorithm for calculating MetS-Z-BMI scores in European populations; patients of European origin were categorized as the closest matching US race and ethnicity

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.

Methods

Objective: to quantify the change in MetS risk as assessed through MetS-Z-BMI [1,2] following 1 year of setmelanotide treatment

- Data were obtained from pediatric patients (aged 6 to <18 years) with POMC or LEPR deficiency who completed 2 Phase 3 trials (NCT02896192, NCT03287960)[3,*]

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

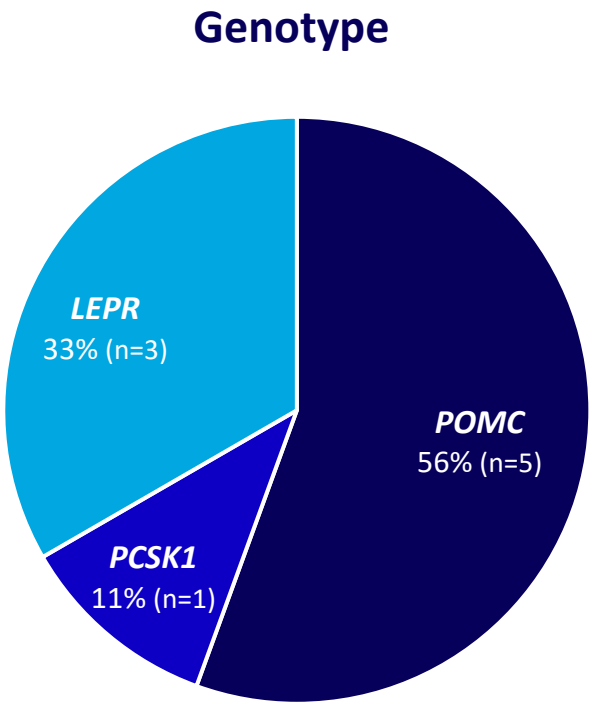
- Pediatric patients were classified as 1-year weight threshold achievers vs nonachievers on the basis of weight outcomes
  - Achievers were defined as achieving a ≥0.3-point BMI Z score reduction after 52 weeks of setmelanotide treatment[4-5]

*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. Patients missing height data at Week 52 were included using baseline value carried forward.

1. Gurka et al. *Cardiovasc Diabetol*. 2012;11:128. **2.** Gurka et al. *Metabolism*. 2018;83:68-74. **3.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **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 Pediatric Patients* With POMC† or LEPR Deficiency

Baseline characteristics	All pediatric patients* (N=9)	Pediatric patients with POMC† deficiency (n=6)	Pediatric patients with LEPR deficiency (n=3)
Age, mean (standard deviation [SD]; range), y	14.1 (2.2; 11-17)	14.3 (2.7; 11-17)	13.7 (1.2; 13-15)
Sex, n (%)			
Female	5 (55.6)	3 (50.0)	2 (66.7)
Male	4 (44.4)	3 (50.0)	1 (33.3)
Weight, mean (SD), kg	104.9 (27.4)	103.1 (32.9)	108.5 (16.7)
Waist circumference, mean (SD), cm	111.8 (12.8)	112.7 (15.8)	110.0 (5.3)
BMI, mean (SD), kg/m^2	38.8 (7.5)	38.1 (9.1)	40.1 (3.7)
BMI Z score, mean (SD)‡	2.5 (0.2)	2.4 (0.3)	2.6 (0.2)
Systolic blood pressure, mean (SD), mm Hg	112.8 (8.0)	109.5 (7.2)	119.3 (5.6)
HDL cholesterol, mean (SD), mg/dL	40.9 (20.1)	40.4 (17.7)	41.7 (28.6)
Triglycerides, mean (SD), mg/dL	121.9 (62.8)	112.3 (63.9)	141.1 (68.7)
Fasting glucose, mean (SD), mg/dL	105.2 (52.4)	116.7 (62.1)	82.1 (12.4)
MetS-Z-BMI score, mean (SD)§	1.4 (0.7)	1.3 (0.7)	1.4 (0.6)

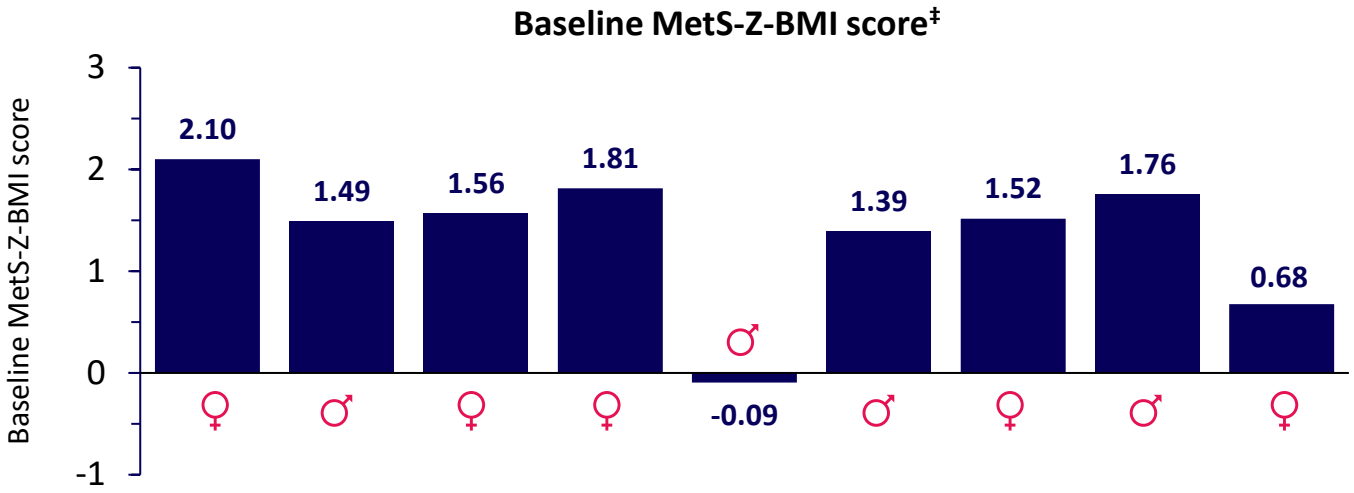


*Pediatric patients defined as aged <18 years. †Includes patients with biallelic variants in *POMC* (n=5) and *PCSK1* (n=1). ‡BMI Z score calculated with an established Centers for Disease Control and Prevention (CDC) program. §MetS calculations used confirmatory factor analysis.[1]

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

Baseline MetS-Z-BMI Score in Pediatric Patients* With POMC† or LEPR Deficiency

- Pediatric patients had a baseline mean (SD) **MetS-Z-BMI score**‡ of **1.36 (0.67)**
  - Baseline mean (SD) MetS-Z-BMI score was similar between variants of ***POMC***† **(1.41 [0.64])** and ***LEPR*** **(1.33 [0.74]; *P*=0.8652)**
- The mean (SD) odds ratio of children developing subsequent CVD or T2DM was **13.3 (6.6)** and **3.7 (1.8)**, respectively§



Distribution of baseline characteristics

Age	11	16	17	13	15	11	16	13	15
Gene	*POMC*	*POMC*	*POMC*	*LEPR*	*POMC*	*PCSK1*	*POMC*	*LEPR*	*LEPR*
BMI Z‖	2.15	2.58	2.46	2.64	2.57	2.07	2.69	2.77	2.30
CVD odds ratio§	20.6	14.6	15.3	17.8	-0.9	13.6	14.9	17.2	6.6
T2DM odds ratio	5.7	4.0	4.2	4.9	-0.3	3.8	4.1	4.7	1.8

Bar and columns align to represent data from the same individual patient
Patient order is aligned on the following slide

Female patients are indicated by ♀ and male patients are indicated by ♂. *Pediatric patients defined as aged <18 years. †Includes patients with biallelic variants in *POMC* (n=5) and *PCSK1* (n=1). ‡MetS calculations used confirmatory factor analysis.[1] §Each 1.0-point increase in MetS-Z-BMI score during childhood increases the odds of future CVD by 9.8 and the odds of future T2DM by 2.7 by the ages of 38 and 50, respectively.[2,3] ‖BMI Z score for MetS was calculated with an established CDC program.

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

Reductions in MetS-Z-BMI Score* Were Observed for All Pediatric Patients

Patient characteristics									
Age	11	16	17	13	15	11	16	13	15
Sex	F	M	F	F	M	M	F	M	F
Gene	*POMC*	*POMC*	*POMC*	*LEPR*	*POMC*	*PCSK1*	*POMC*	*LEPR*	*LEPR*

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

Change From Baseline in BMI Z Score and MetS-Z-BMI Score in Pediatric Patients* With POMC† or LEPR Deficiency

- Pediatric patients exhibited a mean (SD) change from baseline at Week 52 in
  - **MetS-Z-BMI score‡** of **–1.09 (0.73)**
  - **BMI Z score§** of **–0.77 (0.67)**
- No significant differences were observed in MetS-Z-BMI score at Week 52 for mean subgroups of sex or genotype, or when comparing these subgroups by clinical weight response

Distribution of change in characteristics at Week 52

Age	11	16	17	13	15	11	16	13	15
Sex	F	M	F	F	M	M	F	M	F
Gene	*POMC*	*POMC*	*POMC*	*LEPR*	*POMC*	*PCSK1*	*POMC*	*LEPR*	*LEPR*
BMI Z score Δ from baseline§	-1.20	-2.22	-0.71	-0.32	-1.26	-0.35	-0.37	-0.43	-0.10
Systolic blood pressure Δ from baseline, mm Hg	-1.4	-6.7	-1.7	-11.0	-4.0	2.4	0.0	-3.7	-6.4
HDL cholesterol Δ from baseline, mg/dL	23.6	32.0	18.0	15.9	7.0	16.0	-1.0	0.0	7.0
Triglyceride Δ from baseline, mg/dL	-16.8	-32.0	-34.0	-79.7	-32.0	-21.0	-148.0	-44.3	-9.7
Fasting glucose from baseline, mg/dL	-91.9	-11.0	-68.0	-5.4	4.0	3.0	-3.0	2.0	5.4
MetS-Z-BMI score change from baseline	-2.44	-1.96	-1.39	-1.09	-0.99	-0.70	-0.50	-0.40	-0.34

*Pediatric patients defined as aged <18 years. †Includes patients with biallelic variants in *POMC* (n=5) and *PCSK1* (n=1). ‡MetS calculations used confirmatory factor analysis.[1] §BMI Z score for MetS was calculated with an established CDC program.

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

Summary and Conclusions

- One year of setmelanotide treatment was associated with reduced scores in a comprehensive measure of metabolic parameters in pediatric patients with POMC* or LEPR deficiency, suggesting potential reduction in risk of future CVD and T2DM
  - The 1 patient not achieving the 1-year weight threshold demonstrated benefit from treatment with a reduction (ie, improvement) from baseline at Week 52 in MetS-Z-BMI score despite not having achieved a clinically meaningful change in weight, highlighting the utility of MetS-Z-BMI scores as a metric of treatment response

These data support the broad benefits of setmelanotide beyond weight loss and suggest clinical response to setmelanotide in children may lead to reduction in risk of comorbidities later in life

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