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

Presentation FC3.6

Jesús Argente, MD, PhD, presenting

Andrea Haqq,[1] Christine Poitou,[2,3] Wendy K. Chung,[4] Anoop Iqbal,[5] Elizabeth Forsythe,[6] Sonali Malhotra,[7-9] Nicolas Touchot,[7] Karine Clément,[2,3] Jesús Argente[10,11]

[1]Division of Pediatric Endocrinology, University of Alberta, Edmonton, AB, Canada; [2]Nutrition Department, Assistance Publique Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris, France; [3]Sorbonne University, Inserm, Nutrition and Obesity, Systemic Approaches (NutriOmique) Research Group, Paris, France; [4]Division of Molecular Genetics, Department of Pediatrics, Columbia University, New York, NY, USA; [5]Department of Clinical Research, Marshfield Clinic Research Institute, Marshfield, WI, USA; [6]Genetics and Genomic Medicine Programme, University College London Great Ormond Street Institute of Child Health, London, UK; [7]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [8]Massachusetts General Hospital, Boston, MA, USA; [9]Harvard Medical School, Boston, MA, USA; [10]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; [11]IMDEA Food Institute, Madrid, Spain

21-23 September
ESPE 2023
The Hague, Netherlands
The 61st Annual Meeting

DISCLOSURE STATEMENT

Jesús Argente

☒ 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 and advisory boards for Rhythm Pharmaceuticals, Inc.

ESPE
European Society for Paediatric Endocrinology

Bardet-Biedl Syndrome and Metabolic Syndrome

- Individuals with Bardet-Biedl syndrome (BBS) have variants in 1 of >20 genes that affect primary ciliary function[1-3]
- Impaired ciliary dysfunction impacts leptin receptor signaling and downstream activation of melanocortin-4 receptor (MC4R)–expressing neurons, resulting in hyperphagia (a pathologic, insatiable hunger) and early-onset, severe obesity[1-4]
  - Early-onset, severe obesity may confer heightened risk for developing obesity-related comorbidities and metabolic syndrome (MetS) later in life[5]

Clinical features of metabolic syndrome[6,7]

- Setmelanotide, an MC4R agonist, showed significant weight and hunger reductions and improved metabolic parameters in a Phase 3 trial of patients with BBS[8,*]

We hypothesized that patients with BBS responding to setmelanotide might also experience a decreased risk of MetS along with associated risks of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM)

*Setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed BBS, loss-of-function biallelic pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1, deficiency, or biallelic leptin receptor (LEPR) deficiency in adults and children ≥6 years of age.[9]

1. Seo et al. *Hum Mol Genet*. 2009;18:1323-1331. **2.** Guo et al. *PLoS Genet*. 2016;12:e1005890. **3.** Feuillan et al. *J Clin Endocrinol Metab*. 2011;96:e528-e535. **4.** da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **5.** Hampl et al. *Pediatrics*. 2023;151:e2022060640. **6.** Gurka et al. *Cardiovasc Diabetol*. 2012;11:128. **7.** Gurka et al. *Metabolism*. 2014;63:218-225. **8.** Haqq et al. *Lancet Diabetes Endocrinol*. 2022;10:859-868. **9.** 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, 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 and T2DM by 9.8 and 2.7, 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 52 weeks of setmelanotide treatment

- Data were obtained from pediatric 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
  - Identifiable age, sex, and race/ethnicity to determine appropriate MetS-Z-BMI coefficients

- Patients were classified 1-year weight threshold achievers or nonachievers on the basis of weight outcomes[†]
  - Achievers were defined as achieving ≥0.3-point BMI Z score reduction for pediatric patients after 52 weeks of setmelanotide treatment[4,5]

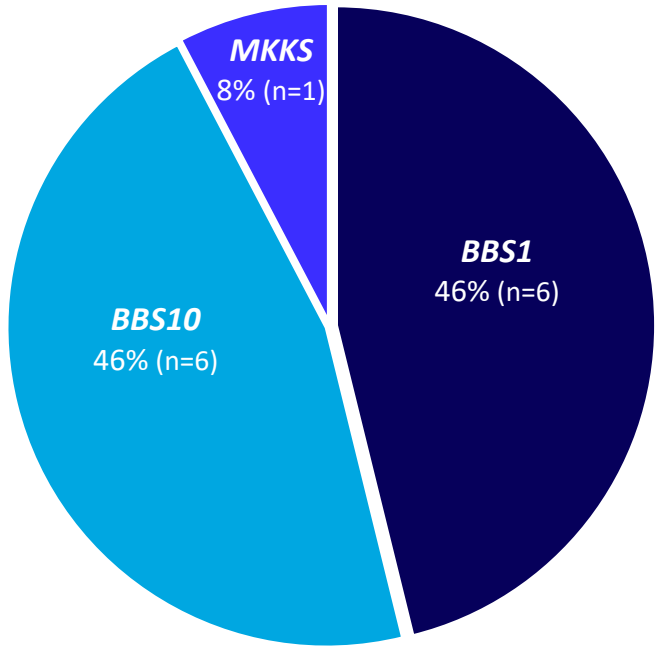
*Primary analysis data published previously. Patients missing height data at Week 52 were included using baseline value carried forward. [†]*P*-value for mean MetS-Z-BMI difference between 1-year weight threshold achievers vs nonachievers was calculated from a 2-sided 2-sample *t*-test and should be interpreted with caution.

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.** 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

Baseline characteristics	Total (N=13)	*BBS1* (n=6)	*BBS 10* (n=6)	*MKKS* (n=1)
Age, mean (standard deviation [SD]; range), y	12.8 (5.6; 10-16)	12.5 (2.3; 10-16)	13.2 (1.3; 12-15)	12.0
Sex, n (%) Female Male	 7 (53.8) 6 (46.1)	 3 (50) 3 (50)	 3 (50) 3 (50)	 1 (100) –
Weight, mean (SD), kg	101.9 (28.9)	97.6 (19.5)	111.0 (36.7)	73.4
Waist circumference, mean (SD), cm	110.5 (18.1)	112.3 (12.5)	110.6 (24.6)	99.5
BMI, mean (SD), kg/m^2	38.1 (10.0)	35.6 (7.0)	41.1 (13.2)	36.8
BMI Z score, mean (SD)*	2.4 (0.4)	2.4 (0.5)	2.5 (0.4)	2.6
Systolic blood pressure, mean (SD), mm Hg	113.3 (11.2)	115.7 (12.0)	110.7 (12.0)	115.0
HDL cholesterol, mean (SD), mg/dL	40.4 (6.4)	37.4 (4.0)	42.5 (7.7)	46.4
Triglycerides, mean (SD), mg/dL	123.1 (66.6)	137.7 (58.2)	84.1 (30.1)	269.3
Fasting glucose, mean (SD), mg/dL	79.8 (11.5)	79.9 (14.7)	78.7 (0.5)	86.5
Diabetes diagnosis, n (%) Prediabetes Diabetes mellitus	 4 (30.8) 0	 4 (66.7) 0	 0 0	 0 0
MetS-Z-BMI score, mean (SD)†	1.0 (0.5)	1.3 (0.3)	0.7 (0.5)	1.5

Genotype



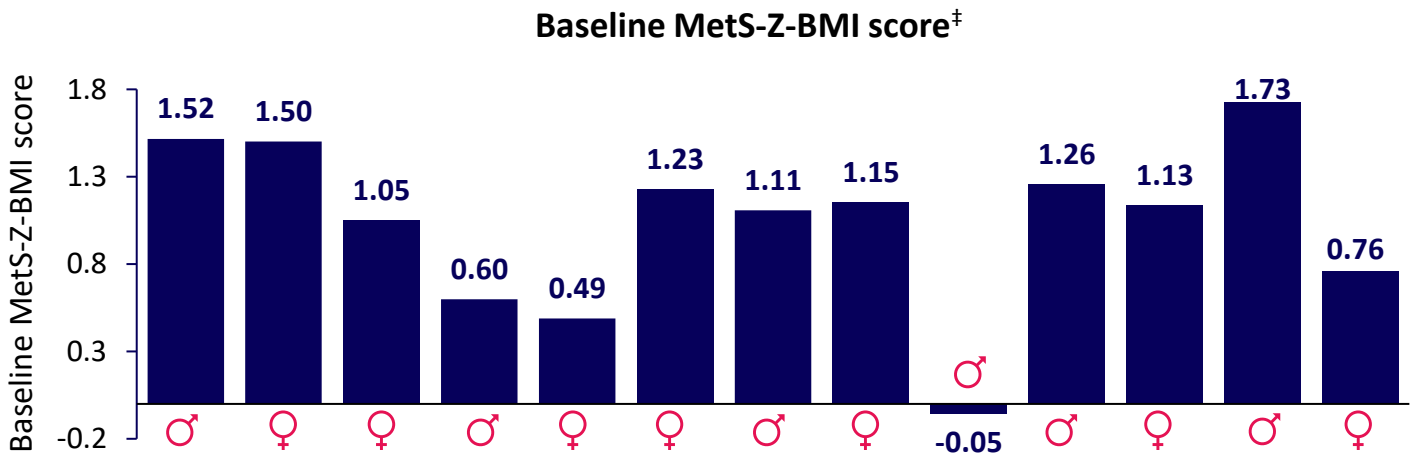
Concomitant medications for hypertension and dyslipidemia were reported for 2 patients (monopril: n=1; omega-3: n=1)

*BMI Z score calculated on the basis of the Centers for Disease Control and Prevention (CDC) 2022 method for pediatric patients (n=13). †MetS calculations used confirmatory factor analysis; BMI Z score for MetS was calculated with an established CDC program.[1]

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

Baseline MetS-Z-BMI Score Across Pediatric Patients* With BBS

- Pediatric patients had a baseline mean (SD) **MetS-Z-BMI score**† of **1.04 (0.48)**
  - A significant difference in baseline mean (SD) MetS-Z-BMI score was associated with variants of ***BBS1*** **(1.23 [0.3])** compared with variants of ***BBS10*** **(0.74 [0.47]; *P*=0.0429)**



Distribution of baseline characteristics													
Age	13	12	15	12	12	13	12	14	14	10	10	16	13
Gene	*BBS1*	*MKKS*	*BBS10*	*BBS10*	*BBS10*	*BBS1*	*BBS10*	*BBS10*	*BBS10*	*BBS1*	*BBS1*	*BBS1*	*BBS1*
BMI Z‡	1.5	2.6	2.7	2.1	1.9	2.6	3.0	2.8	2.5	2.8	2.9	2.5	2.1

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. †MetS calculations used confirmatory factor analysis. ‡BMI Z score for MetS was calculated with an established CDC program.[1]

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

Reductions in MetS-Z-BMI Score Observed Primarily in Clinical Responders

Distribution of baseline characteristics													
Age	13	12	15	12	12	13	12	14	14	10	10	16	13
Sex	M	F	F	M	F	F	M	F	M	M	F	M	F
Gene	*BBS1*	*MKKS*	*BBS10*	*BBS10*	*BBS10*	*BBS1*	*BBS10*	*BBS10*	*BBS10*	*BBS1*	*BBS1*	*BBS1*	*BBS1*

BMI Z score was calculated according to the CDC 2022 method only in patients <18 years of age.

Change From Baseline at Week 52 in Pediatric Patients* With BBS (n=13)

- At week 52, pediatric patients exhibited a mean (SD) change in
  - **MetS-Z-BMI score† of −0.13 (0.61)**
  - **BMI Z score‡ of −0.35 (0.37)**

Distribution of change in characteristics at Week 52

Age	14	13	16	13	13	14	13	15	15	11	11	17	14
Sex	M	F	F	M	F	F	M	F	M	M	F	M	F
Gene	*BBS1*	*MKKS*	*BBS10*	*BBS10*	*BBS10*	*BBS1*	*BBS10*	*BBS10*	*BBS10*	*BBS1*	*BBS1*	*BBS1*	*BBS1*
BMI Z score change from baseline‡	-0.75	-0.30	-0.29	-0.51	-1.38	-0.31	0.00	-0.11	-0.43	-0.12	-0.06	-0.08	-0.20
MetS-Z-BMI score change from baseline	-1.27	-0.89	-0.54	-0.53	-0.41	-0.35	-0.12	-0.09	0.32	0.37	0.39	0.62	0.77

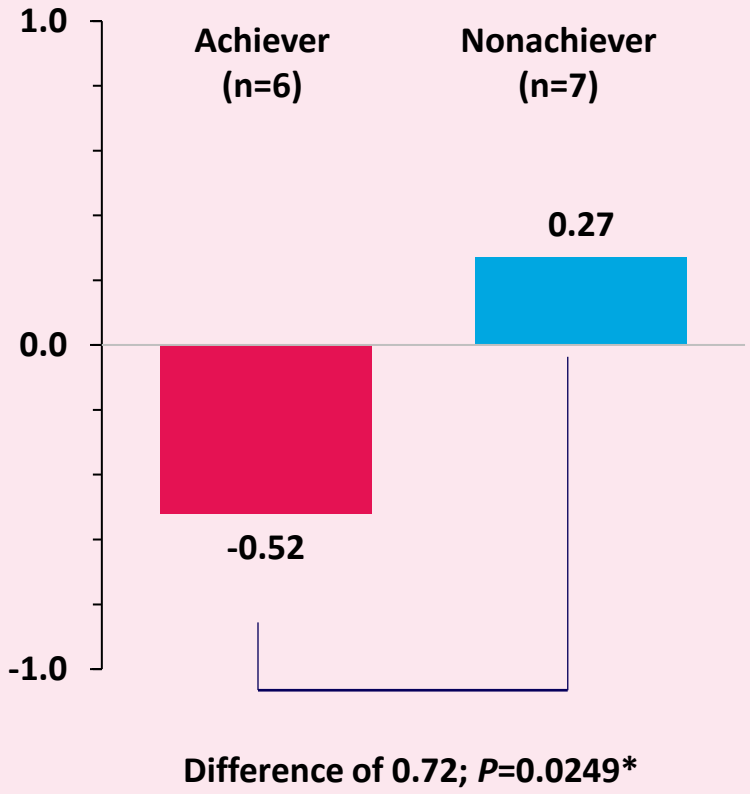
*Pediatric patients defined as aged <18 years. †MetS calculations used confirmatory factor analysis. ‡BMI Z score for MetS was calculated with an established CDC program.[1]

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

Mean Change From Baseline at Week 52: Subgroup Comparison

- Following 52 weeks of treatment, the change from baseline in mean (SD) MetS-Z-BMI scores was larger in 1-year weight threshold achievers versus nonachievers
  - **Achiever: −0.52 (0.54)**
  - **Nonachiever: 0.20 (0.47)**
- No significant differences were observed at Week 52 for mean response by sex or genotype or when comparing these subgroups by 1-year weight threshold

1-Year Weight Threshold



*MetS calculations used confirmatory factor analysis.[1]

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

Summary and Conclusions

- One year of setmelanotide treatment was associated with reductions in a comprehensive score capturing metabolic parameters, suggesting potential reduction of future risk of CVD and T2DM in pediatric patients with BBS
  - Following 1 year of setmelanotide treatment, patients achieving a predetermined weight threshold exhibited a significantly increased reduction in MetS-Z-BMI scores compared with patients who did not achieve the threshold, indicating the utility of MetS-Z-BMI scores as an additional metric of benefit with treatment
- A limitation of the MetS calculation is that patients with metabolic parameters in the upper range of normal may have higher MetS scores

These data support broad benefits of setmelanotide beyond weight loss and suggest that early initiation of treatment may lead to reduction in future risk of comorbidities later in life