Effects of Setmelanotide Treatment in Children and Adolescents With Proopiomelanocortin (POMC) Deficiency, Leptin Receptor (LEPR) Deficiency, and Bardet-Biedl Syndrome (BBS)

RFC4.2 **Session Date: Rapid Free Communications 4. Thursday 15 September 2022. Session Time: 14:25-14:55. Presentation time: 14:30-14:35. Order of presentation: 2 of 6.**

Jesús Argente,[1,2] Peter Kühnen,[3] Andrea M. Haqq,[4] Martin Wabitsch,[5] Wendy K. Chung,[6] Erica van den Akker,[7] Gabriel Á. Martos-Moreno,[1,2] Anoop Mohamed Iqbal,[8] Elizabeth Forsythe,[9] Béatrice Dubern,[10,11] Sonali Malhotra,[12-14] Guojun Yuan,[12] Nicolas Touchot,[12] Hélène Dollfus,[15] Sadaf Farooqi,[16] Karine Clément[11,17]

[1]Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [2]Universidad Autónoma de Madrid, Madrid, Spain; [3]Institute for Experimental Pediatric Endocrinology, Berlin, Germany; [4]University of Alberta, Edmonton, AB, Canada; [5]University of Ulm, Ulm, Germany; [6]Columbia University, New York, NY, USA; [7]Erasmus University Medical Center, Rotterdam, The Netherlands; [8]Marshfield Clinic Research Institute, Marshfield, WI, USA; [9]University College London Great Ormond Street Institute of Child Health, London, UK; [10]Hopital Trousseau, Paris, France; [11]Sorbonne Université, Paris, France; [12]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [13]Massachusetts General Hospital, Boston, MA, USA; [14]Harvard Medical School, Boston, MA, USA; [15]Hôpitaux Universitaires de Strasbourg and université de Strasbourg, Strasbourg, France; [16]University of Cambridge, Cambridge, UK; [17]Pitié-Salpêtrière Hospital, Paris, France

DISCLOSURE STATEMENT

Jesús Argente

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

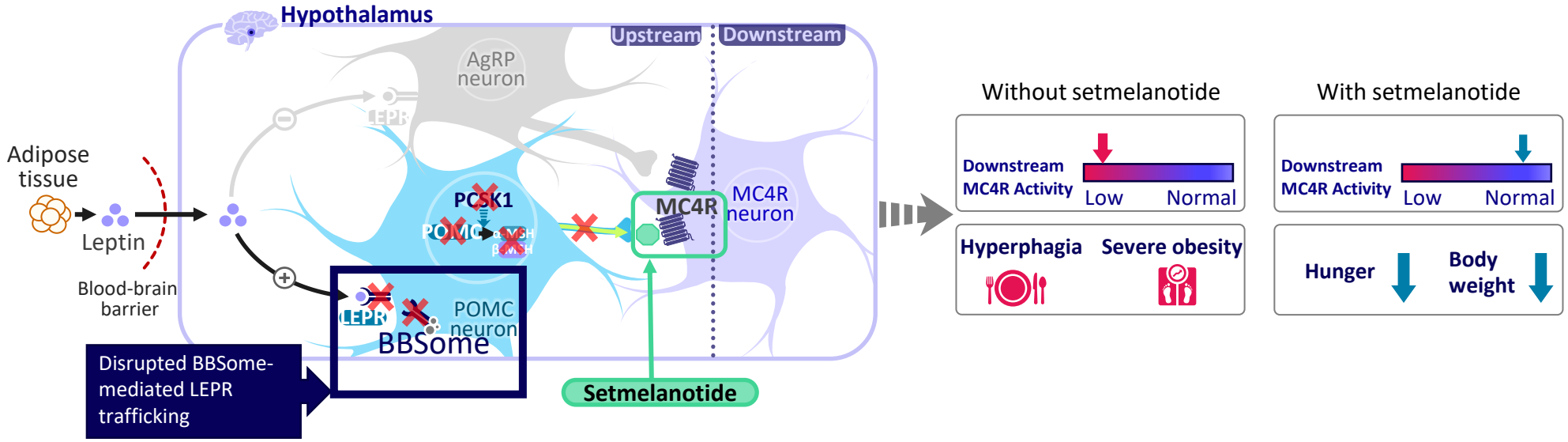
- ☐ Research Contracts
- ☐ Consulting
- ☐ Employment in the Industry
- ☐ Stockholder of a healthcare company
- ☐ Owner of a healthcare company
- ☒ Other(s) – Advisory board for Rhythm Pharmaceuticals, Inc.

No commercial logos or product names to be included please.

☐ I declare that I have no potential conflict of interest.

Variants in *POMC*, *PCSK1*, *LEPR*, and BBS Genes Are Associated With Hyperphagia and Early-Onset, Severe Obesity[1-6]

- Early intervention is critical for reducing disease burden, but consensus on optimally assessing the effects of antiobesity medications in pediatric patients is lacking[7]
- The MC4R agonist setmelanotide demonstrated significant reductions in body weight and hunger in patients with POMC (including PCSK1) deficiency, LEPR deficiency, and BBS[8-11]
  - Obesity in patients with BBS is related to altered BBS protein–mediated LEPR trafficking[12]



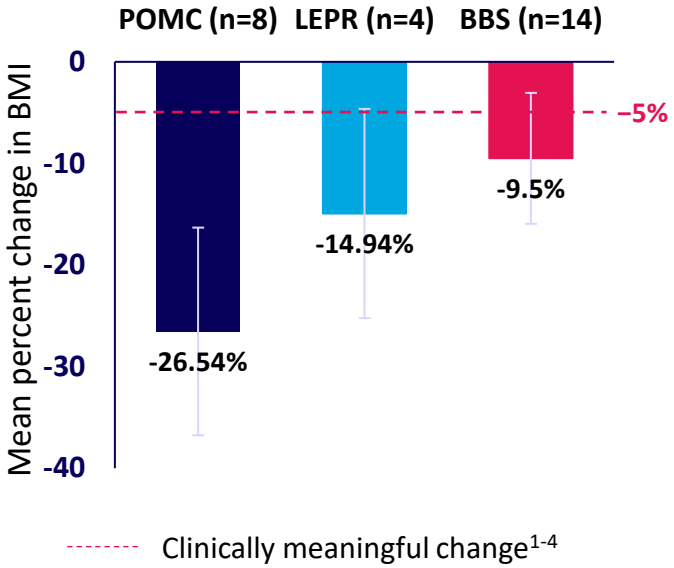
Objective: to assess the effects of ~1 year of setmelanotide from separate Phase 3 trials of patients aged 6 to 17 years with POMC deficiency (NCT02896192), LEPR deficiency (NCT03287960), and BBS (NCT03746522) using age-appropriate weight-related measures

AgRP, agouti-related peptide; BBS, Bardet-Biedl syndrome; BBSome, complex of 8 Bardet-Biedl syndrome proteins; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

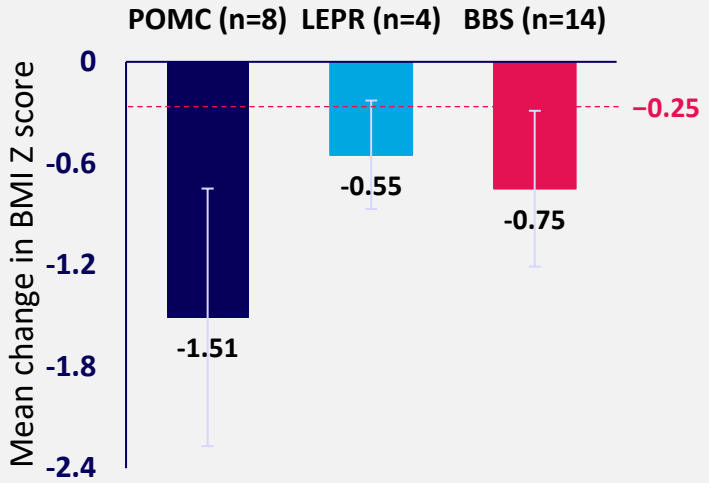
1. da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **2.** Farooqi, O'Rahilly. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **3.** Guo et al. *PLoS Genet*. 2016;12:e1005890. **4.** Vaisse et al. *Cold Spring Harb Perspect Biol*. 2017;9:a028217. **5.** Yazdi et al. *PeerJ*. 2015;3:e856. **6.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **7.** Pomeroy et al. *Pediatr Obes*. 2021;16:e12703. **8.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **9.** Clément et al. *Nat Med*. 2018;24:551-555. **10.** Haws et al. *Diabetes Obes Metab*. 2020;22:2133-2140. **11**. Kühnen et al. *N Engl J Med*. 2016;375:240-246. **12.** Seo et al. *Hum Mol Genet.* 2009;18:1323-1331.

Setmelanotide Was Associated With Reductions in All Weight-Related Measures in Pediatric Patients With POMC Deficiency, LEPR Deficiency, and BBS

BMI



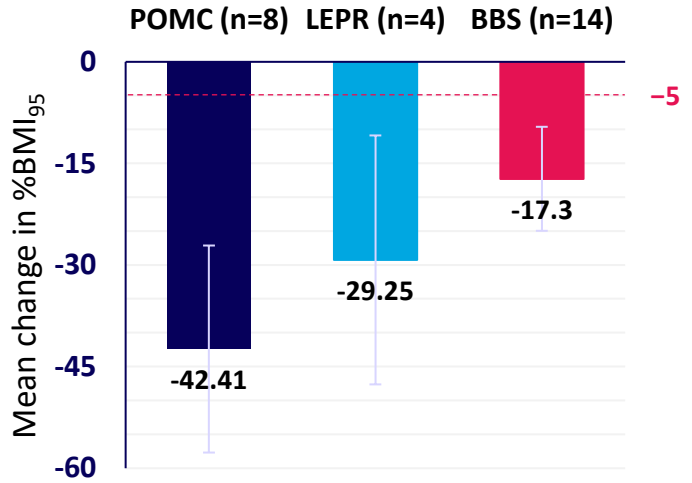
BMI Z Score



Patients achieving BMI Z score change criteria

Change in BMI Z Score	POMC deficiency, n/N (%)	LEPR deficiency, n/N (%)	BBS, n/N (%)
≥0.2	8/8 (100.0)	3/4 (75.0)	12/14 (85.7)
≥0.3	8/8 (100.0)	3/4 (75.0)	10/14 (71.4)

%BMI_{95}



BMI, body mass index; BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; POMC, proopiomelanocortin; %BMI_{95}, percent of the BMI 95th percentile. Error bars represent standard deviation.

1. Knowler et al. *N Engl J Med.* 2002;346:393-403. **2.** Reinehr et al. *J Clin Endocrinol Metab.* 2016;101:3171-3179. **3.** Kumar et al. *J Pediatr*. 2019;208:57-65.e4. **4.** US Preventive Services Task Force. *JAMA*. 2017;317:2417-2426.

Summary and Conclusions

- Setmelanotide was associated with improvements across all weight-related measures in pediatric patients with POMC (including PCSK1) deficiency, LEPR deficiency, and BBS
- The variability observed across weight parameters and populations highlights a need to identify optimal measures for assessing the efficacy of antiobesity medications in pediatric patients with rare MC4R pathway diseases
- These results demonstrate substantial clinical benefit of setmelanotide, supporting early intervention in pediatric populations with rare diseases involving the MC4R pathway

BBS, Bardet-Biedl syndrome; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.