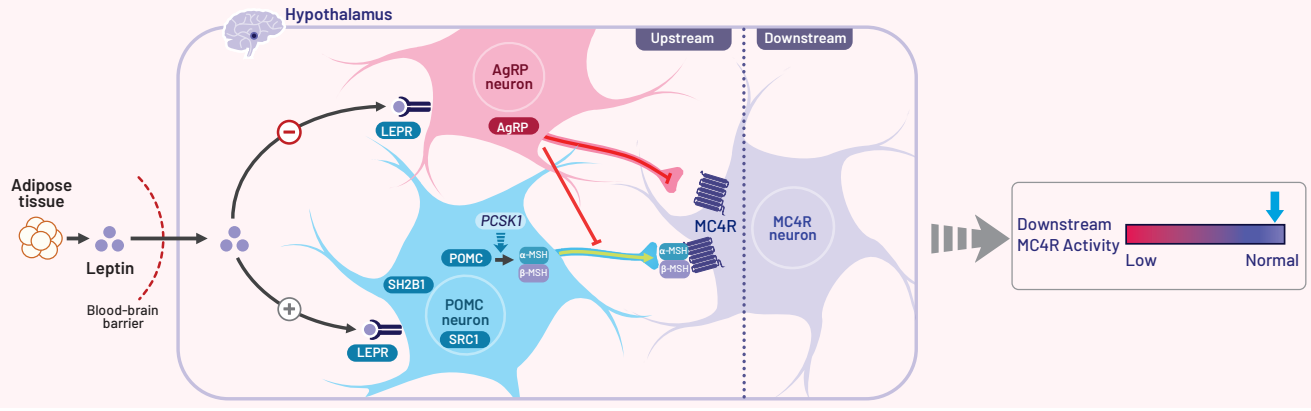
EMANATE Clinical Trial: NCT05093634

Rhythm PHARMACEUTICALS

The Melanocortin-4 Receptor (MC4R) Pathway Is a Key Regulator of Energy Balance[1-7]



An evidence-based framework found that *POMC*, *PCSK1*, *LEPR*, *NCOA1*, and *SH2B1* were strongly associated with the MC4R pathway, and rare variants in these genes can impair MC4R signaling[1,3,8-10]

Dysregulation of the MC4R pathway by genetic variants upstream of MC4R can lead to hyperphagia (pathological, insatiable hunger) and early-onset, severe obesity[2-4,11]

Recent evidence suggests *POMC*, *PCSK1*, and *LEPR* heterozygous variants are associated with hyperphagia and early-onset, severe obesity[12]

SH2B1 deficiency and SRC1 deficiency (caused by variants in *NCOA1*) are also associated with hyperphagia and early-onset, severe obesity[3,4]

EMANATE Study Design

EMANATE is a randomized, double-blind, placebo-controlled Phase 3 trial to assess the efficacy and safety of setmelanotide in patients with obesity and *POMC*, *PCSK1*, and *LEPR* heterozygous variants, or variants in *NCOA1* or *SH2B1*

[a]All patients will have their dose escalated over the course of 2 weeks to a final dose of up to 3 mg of setmelanotide.

The primary endpoint is mean change in body weight in patients treated with setmelanotide compared with placebo

Key secondary endpoints include changes to body weight, body mass index, waist circumference, and hunger scores, as well as evaluation of quality of life and safety and tolerability after 52 weeks of setmelanotide treatment

AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NCOA1, nuclear receptor coactivator 1; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, SH2B adaptor protein 1; SRC1, steroid receptor coactivator 1.

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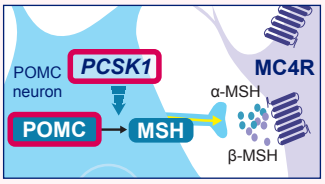
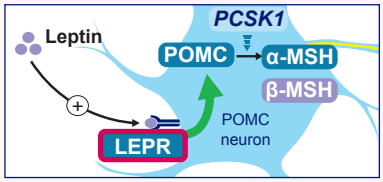
Location and Function Within the MC4R Pathway

POMC and *PCSK1* in the MC4R Pathway[2]



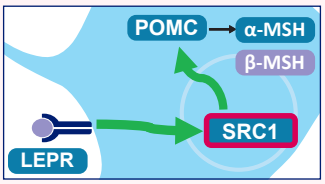
- *POMC* encodes for the **POMC protein**[2]
- POMC is processed by the serine endoprotease **PC1/3, encoded by *PCSK1***[13,14]
- POMC is **proteolytically cleaved to form α-MSH** and **β-MSH**, which activate MC4R downstream in the pathway[2,14,15]

LEPR in the MC4R Pathway[2]



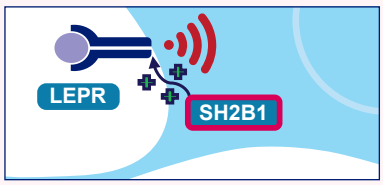
- *LEPR* encodes for the **LEPR protein**[2,16]
- *LEPR* variants cause **impaired** or **complete loss of LEPR signaling**[2,15,17]
- LEPR activation by leptin **triggers JAK/STAT signaling through SH2B1**[2]

NCOA1 in the MC4R Pathway[2,4]



- *NCOA1* encodes for the **transcriptional coactivator SRC1**[4,18]
- **SRC1** signaling is **required for proper leptin signaling**[4,18]
- **The SRC1 protein modulates the expression of POMC**[4]

SH2B1 in the MC4R Pathway[2]



- *SH2B1* encodes for the **adaptor protein SH2B1**[2,10,16]
- Deletion of *SH2B1* is associated with a **deletion in the 16p11.2 chromosomal region**[2,10]
- SH2B1 enhances activation of **LEPR downstream signaling pathways** through JAK2 activation[2,3]
- Impaired SH2B1 activity/expression leads to **insufficient LEPR activity**[19]

Variant Prevalence and Phenotype*

	Heterozygous POMC/PCSK1 insufficiency[12,16,20-24]	Heterozygous LEPR insufficiency[12,16,20,25,26]	SRC1 deficiency[4,16,18,27,†,‡]	SH2B1 deficiency[2,3,10,13,16,19,28,§,‖]
Prevalence[¶]	6,000 Individuals	4,000 Individuals	20,000 Individuals	23,000 Individuals
Early-onset obesity	✓	✓	✓	✓
Hyperphagia	✓	✓	✓	✓
Reduced adult height				✓
Hyperleptinemia/ Leptin resistance			✓	✓
Hyperinsulinemia/ Insulin resistance			✓	✓
Other observed characteristics	• Less severe symptoms than biallelic carriers • Hypertension	• Less severe symptoms than biallelic carriers • Dyslipidemia	• Fractures following minor injuries • Hepatic fibrosis	• Speech delay • Aggression • Developmental delay

*The EMANATE trial includes patients with heterozygous *POMC* and/or *PCSK1* and *LEPR* variants classified as pathogenic, likely pathogenic or variants of unknown significance and patients with homozygous, heterozygous, or compound heterozygous SRC1 and SH2B1 variants. †Hyperphagia and hyperleptinemia have been characterized in animal models. ‡Associated with variants in *NCOA1*. §Leptin resistance with SH2B1 has been characterized in animal models. ‖Associated with variants in *SH2B1*, including the 16p11.2 microdeletion encompassing *SH2B1*. ¶Estimated United States patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results, current estimated responder rates, and that 1.7% of the United States population presents with early-onset, severe obesity;[29,30] ~95% of individuals with early-onset, severe obesity remain obese into adulthood.[31]

JAK, Janus kinase; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; *NCOA1*, nuclear receptor coactivator 1; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, SH2B adaptor protein 1; SRC1, steroid receptor coactivator 1; STAT, signal transducer and activator of transcription.

References: 1. Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **2.** Yazdi et al. *PeerJ*. 2015;3:e856. **3.** Doche et al. *J Clin Invest*. 2012;122:4732-4736. **4.** Yang et al. *Nat Commun*. 2019;10:1718. **5.** Krashes et al. *Nat Neurosci*. 2016;19:206-219. **6.** Cone. *Endocr Rev*. 2006;27:736-749. **7.** Da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **8.** Kühnen et al. *N Engl J Med*. 2016;375:240-246. **9.** Farooqi et al. Poster presented at: European Society for Pediatric Endocrinology; September 22-26, 2021; Virtual. **10.** Bochukova et al. *Nature*. 2010;463:666-670. **11.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **12.** Courbage et al. *J Clin Endocrinol Metab*. 2021;106:2991-3006. **13.** Styne et al. *J Clin Endocrinol Metab*. 2017;102:709-757. **14.**Coll et al. *J Clin Endocrinol Metab*. 2004;89:2557-2562. **15.** Farooqi and O'Rahilly. *J Endocrinol*. 2014;223:T63-T70. **16.** Rhythm Pharmaceuticals. https://www.rhythmtx.com/our-focus. Accessed December 20, 2022. **17.** Farooqi et al. *N Engl J Med*. 2007;356:237-247. **18.** Lu et al. *J Mol Endocrinol*. 2019;62:37-46. **19.** Rui. *World J Diabetes*. 2014;5:511-526. **20.** Farooqi et al. *Diabetes*. 2006;55:2549-2553. **21.** Folon et al. *Lancet Diabetes Endocrinol*. 2023;11:182-190. **22.** Nordang et al. *Mol Genet Metab*. 2017;121:51-56. **23.** da Fonseca et al. *Eat Weight Disord*. 2021;26:1399-1408. **24.** Nalbantoğlu et al. *J Pediatr Endocrinol Metab*. 2022;35:1041-1050. **25.** Voigtmann et al. *Metabolism*. 2021;116:154438. **26.** Koerber-Rosso et al. *Mol Cell Pediatr*. 2021;8:10. **27.** Cacciottolo et al. *J Clin Endocrinol Metab*. 2022;107:e2532-e2544. **28.** Zorn et al. *Mol Cell Pediatr*. 2020;7:15. **29.** Hales et al. *JAMA*. 2018;319:1723-1725. **30.** United States Census Bureau. https://www.census.gov/newsroom/press-releases/2019/popest-nation.html. Accessed April 12, 2023. **31.** Ward et al. *N Engl J Med*. 2017;377:2145-2153.

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