Weight Category Improvement Following Setmelanotide in Pediatric Patients With Acquired Hypothalamic Obesity

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Disclosures

- Jennifer L. Miller has received funding from Harmony Biosciences, Rhythm Pharmaceuticals, Inc., Soleno Therapeutics, and TRYP Therapeutics.
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Introduction

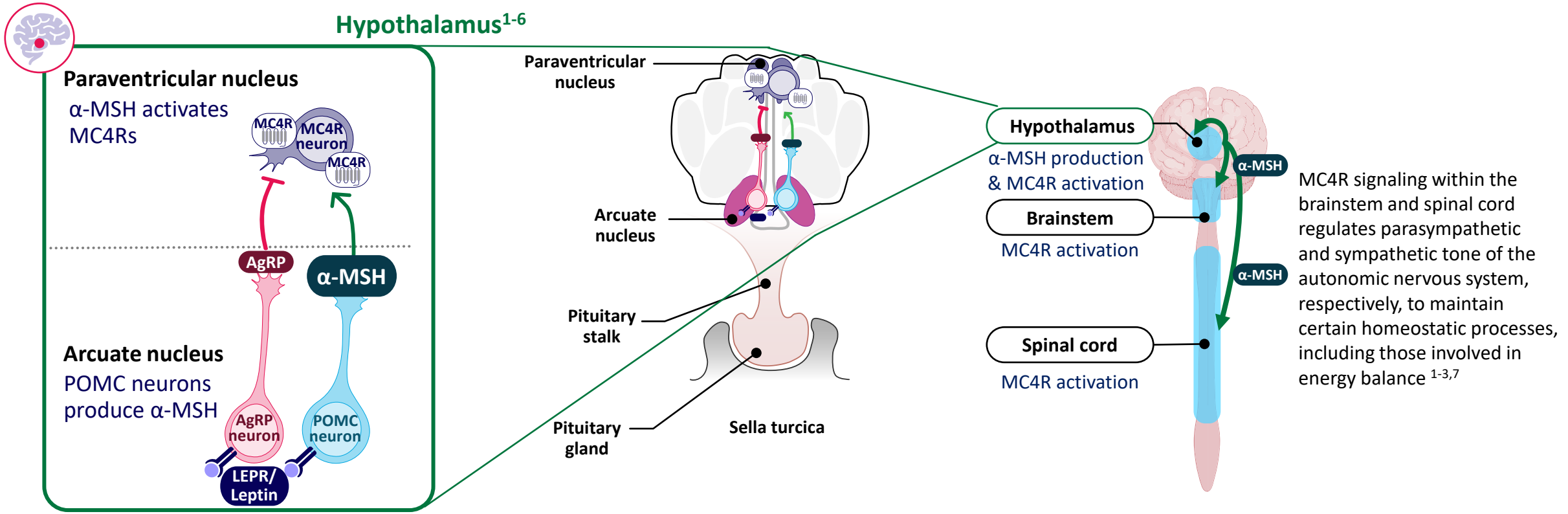
- Acquired hypothalamic obesity (aHO) is characterized by accelerated and sustained weight gain following injury to or structural abnormalities within the hypothalamus[1-3]
- In the Phase 3 TRANSCEND trial of the melanocortin-4 receptor (MC4R) agonist setmelanotide in aHO (NCT05774756), the primary endpoint of percent change in body mass index (BMI) at Week 52 was met[4]
- In the TRANSCEND trial, inclusion criteria allowed for the enrollment of patients as young as 4 years old[4]
- Improvements in weight category have previously been shown to be associated with improved quality of life and a reduced incidence of comorbidities[5-9]

Objective: To analyze the changes in weight category in the pediatric subpopulation of participants with aHO in the TRANSCEND trial after 1 year of setmelanotide treatment

aHO, acquired hypothalamic obesity; **BMI**, body mass index; **MC4R**, melanocortin-4 receptor.

1. Roth CL, McCormack SE. *Diabetes Obes Metab* 2024;26 Suppl 2:34-45. **2.** Rose SR, et al. *Obesity (Silver Spring)*. 2018;26(11):1727-1732. **3.** Kim JH, Choi JH. *Ann Pediatr Endocrinol Metab.* 2013;18(4):161-7. **4.** Phillips SA, et al. Presented at the Endocrine Society Annual Meeting; July 12-15, 2025; San Francisco, CA. **5.** Kroes, M, et al. *Curr Med Res Opin*. 2016;32(3):485–508. **6.** Haase CL, et al. *Int J Obes*. 2011;45:1249–1258. **7.** The Look AHEAD Research Group. *Lancet Diabetes Endocrinol*. 2016;4:913-921. **8.** Finucane FM, et al. *Front Endocrinol (Lausanne)*. 2023;14:1257061. **9.** le Roux CW, et al. *Lancet*. 2017;389(10077):1399-1409.

α-MSH Drives MC4R Pathway Signaling to Regulate Energy Balance and Body Weight[1-3]



α-MSH activation of MC4R regulates[1-3]:

- Hunger & food intake
- Energy expenditure

→ **Body weight**

α-MSH, α–melanocyte-stimulating hormone; **AgRP**, agouti-related peptide; **LEPR**, leptin receptor; **MC4R**, melanocortin-4 receptor; **POMC**, proopiomelanocortin.

1. Baldini et al. *J Endocrinol.* 2019;241:R1-R33. **2.** Dimitri. *Front Endocrinol.* 2022;13:846880. **3.** Hill et al. *Neuroendocrinol.* 2017;104:330-346. **4.** Hochberg et al. *Obes Rev*. 2010;11:709-721. **5.** Roth et al. *Obesity (Silver Spring).* 2011;19:36-42. **6.** Cone et al. *Nat Neurosci.* 2005;8(5):571-578. **7.** Sohn et al. *Cell.* 2013;152:612-619.

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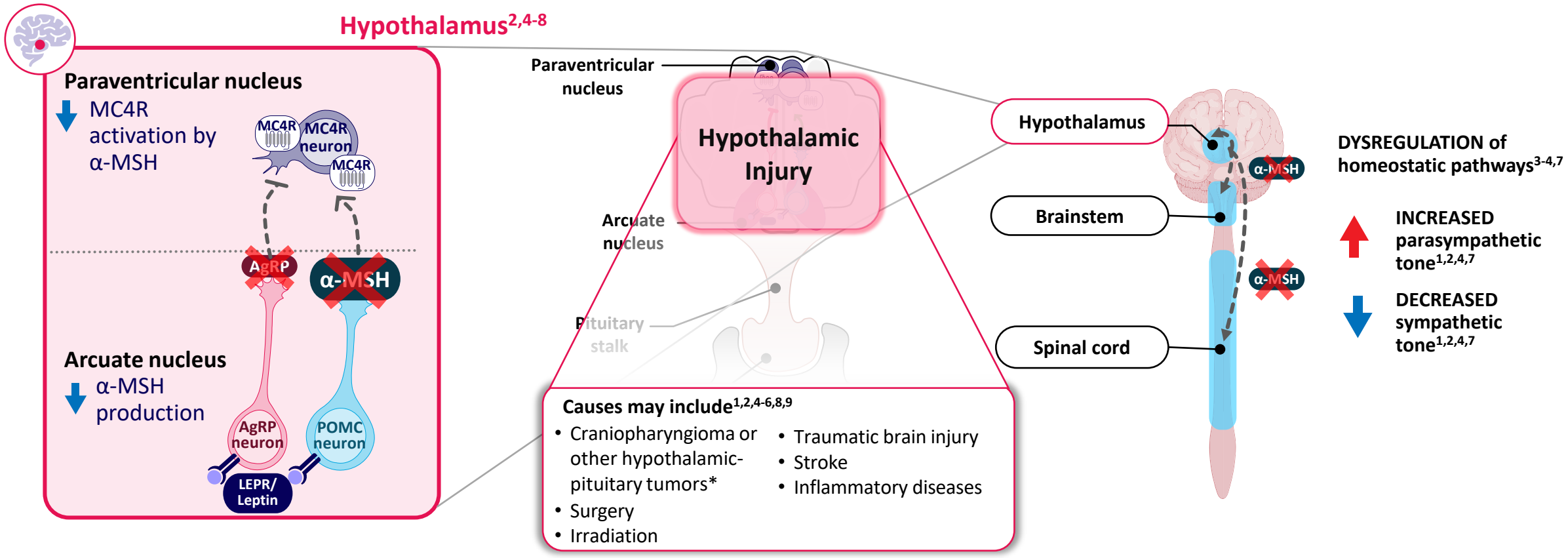
Loss of α-MSH Production Due to Hypothalamic Injury May Impair MC4R Pathway Signaling and Lead to Acquired Hypothalamic Obesity[1-3]



Decreased α-MSH activation of MC4R may result in[1-3,7]:

- Increased hunger/hyperphagia
- Reduced energy expenditure

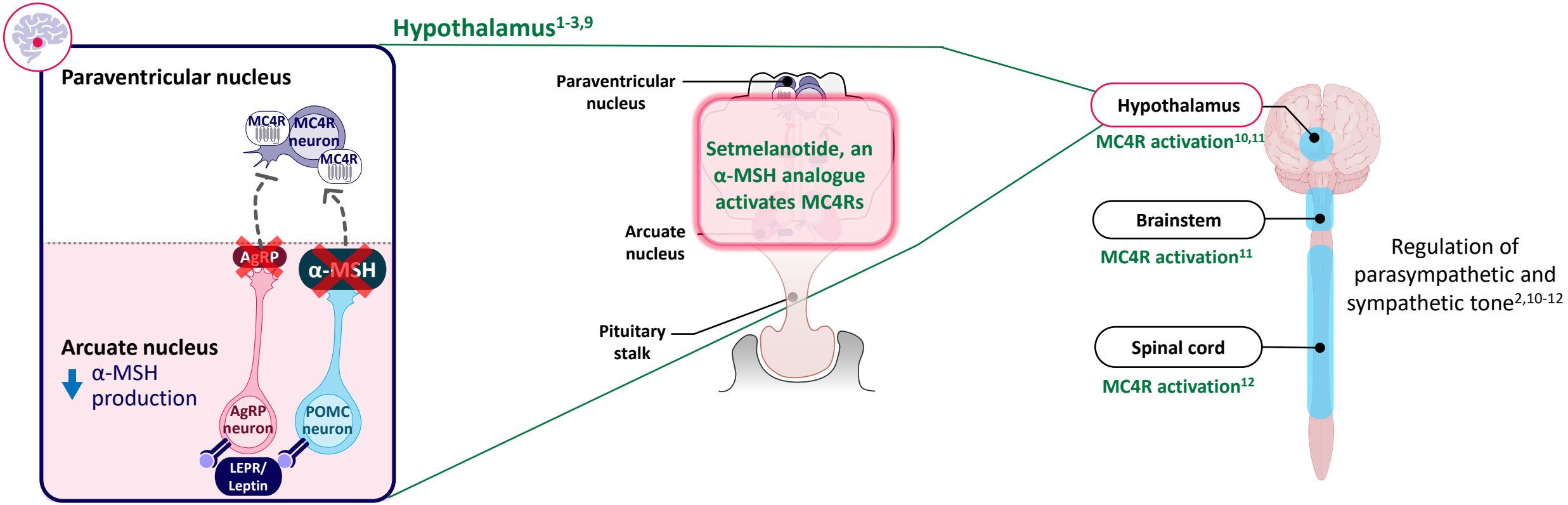
→ **Accelerated and sustained weight gain**

*Suprasellar tumors such as astrocytoma.[1,7]

α-MSH, α–melanocyte-stimulating hormone; **AgRP**, agouti-related peptide; **LEPR**, leptin receptor; **MC4R**, melanocortin-4 receptor; **POMC**, proopiomelanocortin.

1. Abuzzahab et al. *Horm Res Paediatr.* 2019;91:128-136. **2.** Roth. *Front Endocrinol (Lausanne).* 2011;2:49. **3.** Roth et al. *Metabolism.* 2010;59:186-194. **4.** Dimitri. *Front Endocrinol (Lusanne).* 2022;13:846880. **5.** Baldini et al. *J Endocrinol.* 2019;241:R1-R33. **6.** Hochberg et al. *Obes Rev.* 2010;11:709-721. **7.** Roth et al. *Obesity (Silver Spring).* 2011;19:36-42. **8.** Sohn et al. *Cell.* 2013;152:612-619. **9.** Gan et al. *Endocrine Reviews.* 2024;45:309–342.

Setmelanotide Targets the CNS and Replaces Deficient α-MSH, Restoring MC4R Pathway Signaling to Reduce Body Weight[1-8]



Setmelanotide has the potential to restore MC4R signaling, thereby improving energy balance[1-7,13]:

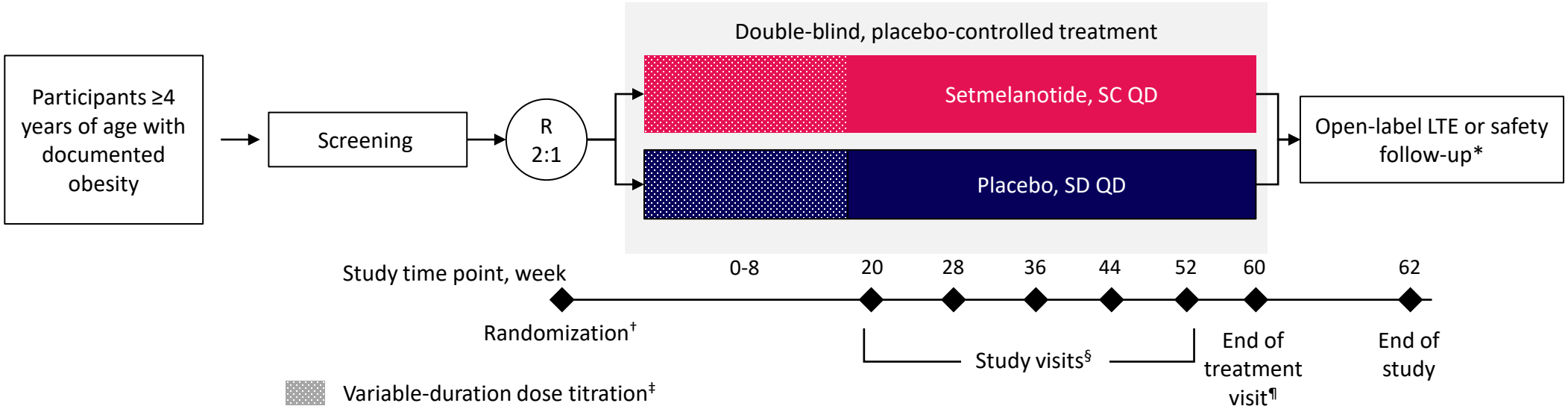
- Decreased hunger and improved satiety signaling
- Reduced symptoms of hyperphagia
- Increased energy expenditure

→ **Reduced body weight**

α-MSH, α–melanocyte-stimulating hormone; **AgRP**, agouti-related peptide; **CNS**, central nervous system; **LEPR**, leptin receptor; **MC4R**, melanocortin-4 receptor; **POMC**, proopiomelanocortin.

1. Dimitri. *Front Endocrinol (Lausanne).* 2022;13:846880. **2.** Roth et al. *Lancet Diabetes Endocrinol.* 2024;12(6):380-389. **3.** Roth and McCormack. *Diabetes Obes Metab.* 2024;26(suppl 2):34-45. **4.** Sohn et al. *Cell.* 2013;152(3):612-619. **5.** van Santen et al. *Front Endocrinol (Lausanne).* 2024;14:1307889. **6.** Müller. *Biomedicines.* 2025;13(5):1016. **7.** Dimitri. *Best Pract Res Clin Endocrinol Metab.* 2025;11:102018. **8.** IMCIVREE [package insert]. Boston, MA: Rhythm Pharmaceuticals Inc; 2026. **9.** Roth. *Front Endocrinol (Lausanne).* 2011;2:49. **10.** Sweeney et al. *Proc Natl Acad Sci USA.* 2021;118(14):e2011140118. **11.** Hansen et al. *Mol Metab.* 2021;47:101171. **12.** Ju et al. *Cell Rep.* 2022;41(5):111579. **13.** Chen et al. *J Clin Endocrinol Metab.* 2015;100(4):1639-1645.

Study Design



Primary efficacy endpoint

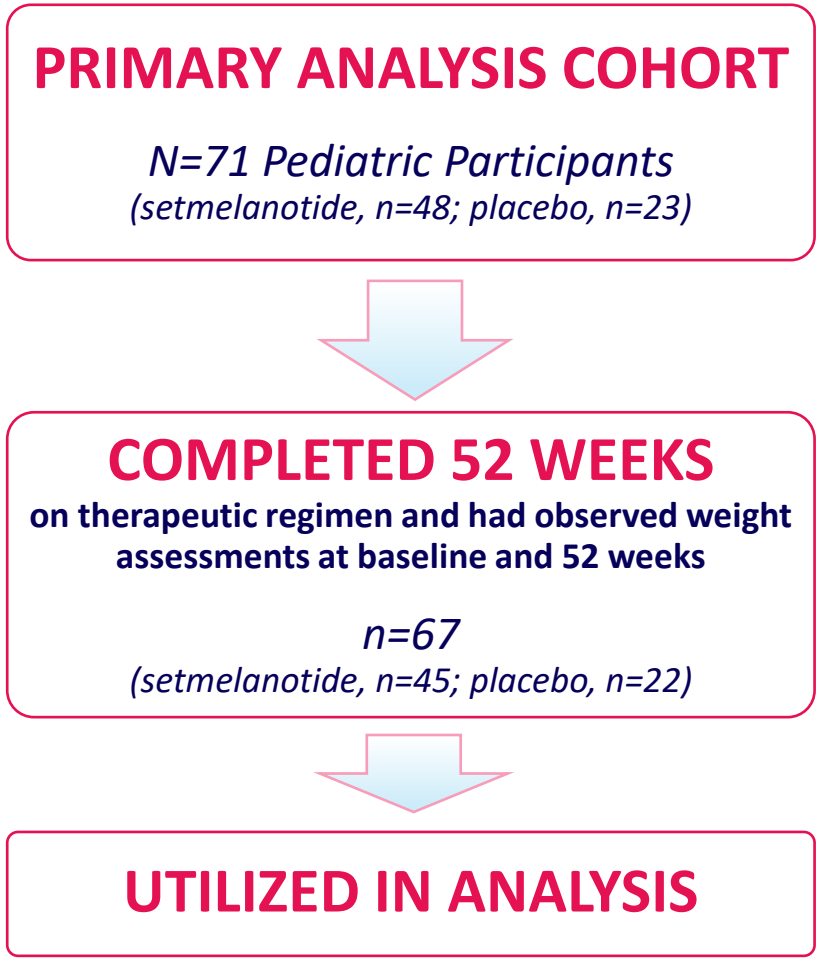
- Mean percent change in body mass index from baseline at 52 weeks on therapeutic regimen, setmelanotide vs placebo

Secondary and exploratory endpoints

- Other weight-related parameters, hunger, hyperphagia, quality of life, fatigue, sleep quality, physical activity, and body composition measures
- Safety and tolerability outcomes including adverse events

*Participants completing the trial may be eligible to participate in an open-label LTE trial; the safety follow-up visit is required only for participants prematurely discontinuing treatment or those completing the trial who do not enroll in the LTE.
†Baseline is defined as the last available measurement before randomization. Setmelanotide is administered once daily as a subcutaneous injection. ‡The initial dose of 0.5 mg to be escalated in increments of 0.5 to 1.0 mg until the patient reaches an individual therapeutic regimen based on age and weight. §Visits completed in clinic, at home, or via telehealth. ¶In-clinic visit.
LTE, long-term extension; **SC**, subcutaneous; **QD**, once daily; **R**, randomization.

Post-hoc Analysis Cohort



Baseline Patient Demographics

	Setmelanotide (n=48)	Placebo (n=23)
Age, mean ± SD (range), y	11.6 ±4.1 (4, 17)	11.3 ± 3.7 (4, 17)
Sex, n (%)		
Female	22 (45.8)	17 (73.9)
Male	26 (54.2)	6 (26.1)
Race, n (%)		
White	40 (83.3)	18 (78.3)
Black or African American	2 (4.2)	0
Asian	1 (2.1)	0
Other	5 (10.4)	5 (21.7)
Ethnicity, n (%)		
Not Hispanic or Latino	42 (87.5)	16 (69.6)
Hispanic or Latino	5 (10.4)	7 (30.4)
Unknown/Missing	1 (2.1)	0

Baseline Patient Demographics (cont)

	Setmelanotide (n=48)	Placebo (n=23)
Weight, mean (SD), kg	77.4 (33.8)	73.2 (27.4)
BMI, mean (SD), kg/m^2	32.7 (7.4)	32.1 (6.0)
BMI Z score (WHO), mean (SD)*	3.72 (1.81)	3.37 (1.29)
%BMI95 (CDC), mean (SD)†	132.3 (28.9)	128.6 (22.7)
Waist circumference, mean (SD), cm	99.7 (19.5)	100.2 (16.3)
Endocrine disorders in ≥20% of setmelanotide group, n (%)	48 (100)	22 (95.7)
Arginine vasopressin deficiency	43 (89.6)	16 (69.6)
Secondary adrenocortical insufficiency, adrenocorticotropic deficiency, or adrenal insufficiency	38 (79.2)	13 (56.5)
Growth hormone deficiency	34 (70.8)	14 (60.9)
Central hypothyroidism	31 (64.6)	15 (65.2)
Secondary hypogonadism	15 (31.3)	6 (26.1)
Hypothyroidism	11 (22.9)	1 (4.3)

*BMI Z score calculated according to the WHO 2007 method. †%BMI95 calculated according to the CDC 2022 method.
BMI, body mass index; **%BMI95**, percent of the body mass index 95th percentile; **CDC**, Centers for Disease Control and Prevention; **WHO**, World Health Organization.

Weight Category at Baseline in Pediatric Patients

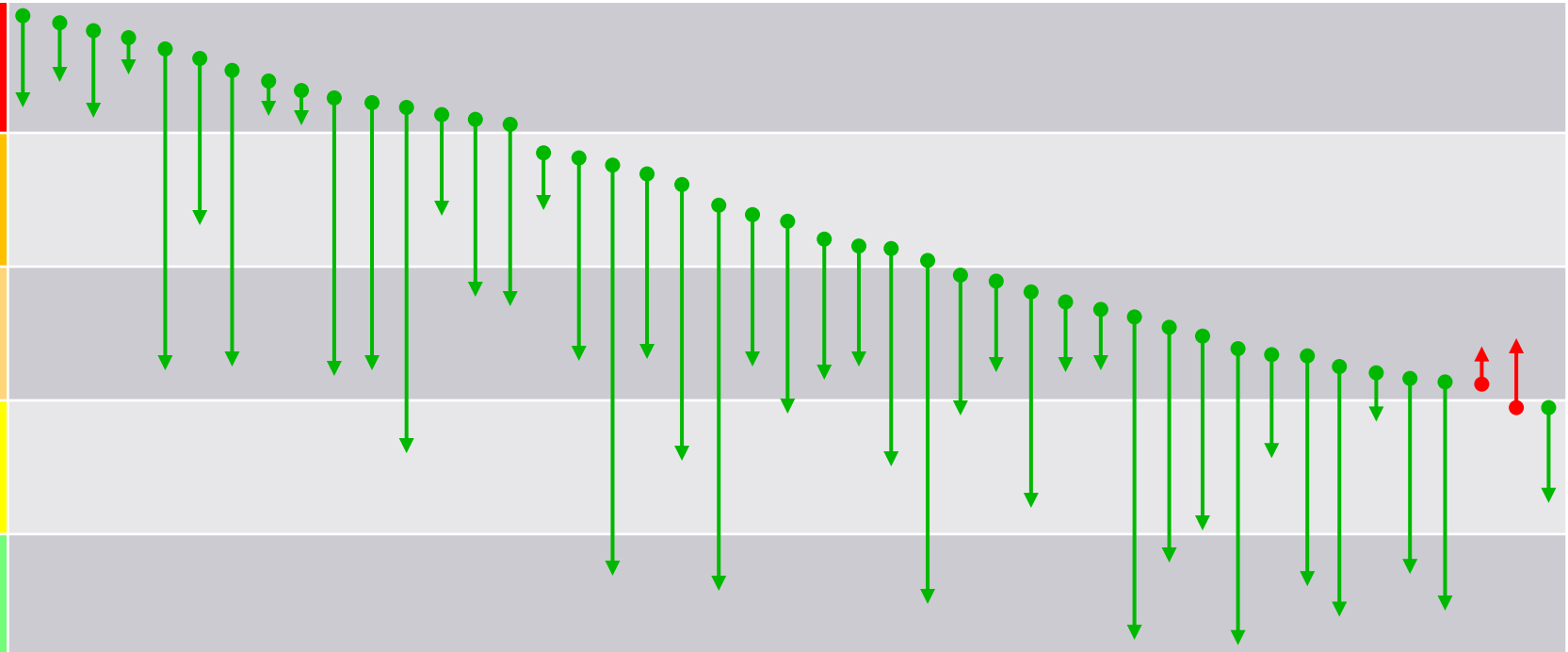
Weight Category	Setmelanotide N=45	Placebo N=22
Obesity III (%BMI95 ≥140%)	n=15	n=8
Obesity II (%BMI95 ≥120% to <140%)	n=12	n=5
Obesity I (≥95% to %BMI95 <120%)	n=16	n=7
Overweight (BMI ≥85th to <95th percentile)	n=2*	n=2†
Healthy (≥5th to <85th percentile)	n=0	n=0

- At baseline, 40 of 67 (59.7%) pediatric participants had class II or III obesity

Patients were allowed dietary and/or exercise regimens if the regimen/dose was stable 3 months before randomization, patients did not lose >2% BMI during the previous 3months, and the patient intended to keep the regimen/dose stable during the trial. All participants either met weight-related inclusion criteria at screening or were confirmed to have recently met weight-related inclusion criteria by the site investigator.
*2 patients in the setmelanotide group had a BMI <95th percentile at baseline (94.8%ile and 94.3%ile) †2 patients in the placebo group had a BMI <95th percentile at baseline (94.5%ile and 93.9%ile).
BMI, body mass index; **%BMI95**, percent of the body mass index 95th percentile.

Changes in Weight Category With Setmelanotide Treatment

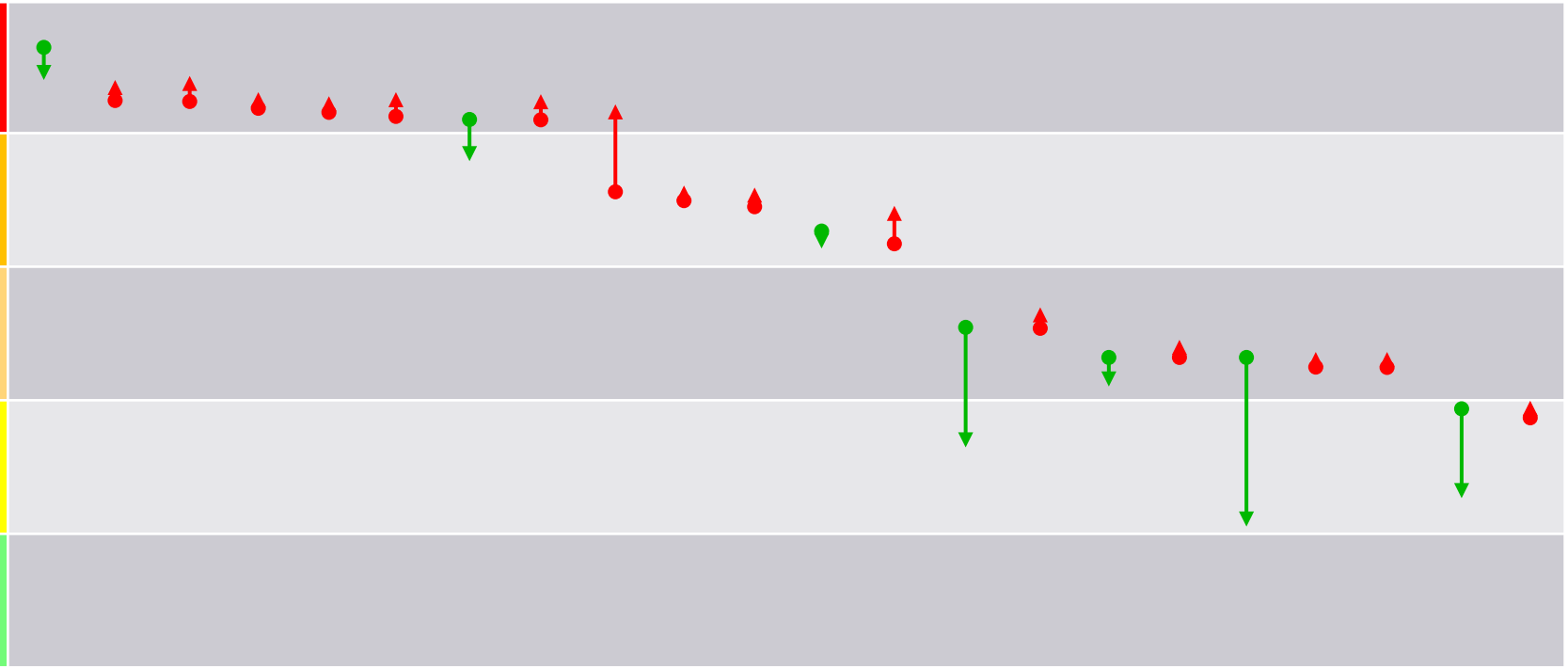
BMI percentile[1]		Weight Classification[1,2]	Setmelantoide (n=45)
≥95th percentile	≥140%*	Obesity class III (extreme)	
	≥120% to <140%*	Obesity class II (severe)	
	≥95% to <120%*	Obesity class I	
≥85th to <95th percentile[†]		Overweight	
≥5th to <85th percentile		Healthy Weight	



- After 1 year of treatment with setmelanotide:
  - 32 of 45 pediatric participants (**71.1%**) had improvements of **≥1 weight category**
  - 20 of 45 participants (**44.4%**) improved **≥2 weight categories**
  - 20 of 45 participants (**44.4%**) had **healthy weight** (n=10) or **overweight** (n=10)

*Percent of the 95th percentile. [†]Patients were allowed dietary and/or exercise regimens if the regimen/dose was stable 3 months before randomization, patients did not lose >2% BMI during the previous 3 months, and the patient intended to keep the regimen/dose stable during the trial. All participants either met weight-related inclusion criteria at screening or were confirmed to have recently met weight-related inclusion criteria by the site investigator.
BMI, body mass index; **%BMI95**, percent of the body mass index 95th percentile.
1. Centers for Disease Control and Prevention. (June, 2024). *Child and Teen BMI Categories*. https://www.cdc.gov/bmi/child-teen-calculator/bmi-categories.html 2. Hampl et al. *Pediatrics*. 2023;151:e2022060640.

Changes in Weight Category With Placebo Treatment

BMI percentile[1]		Weight Classification[1,2]	Placebo (n=22)
≥95th percentile	≥140%*	Obesity class III (extreme)	
	≥120% to <140%*	Obesity class II (severe)	
	≥95% to <120%*	Obesity class I	
≥85th to <95th percentile[†]		Overweight	
≥5th to <85th percentile		Healthy Weight	

- After 1 year of treatment with placebo:
  - 3 of 22 participants (**13.6%**) had improvements of **≥1 weight category**
  - **0** participants improved **≥2 weight categories**
  - 4 of 22 participants (**18.2%**) had **overweight** and **none** had **healthy weight**

*Percent of the 95th percentile. [†]Patients were allowed dietary and/or exercise regimens if the regimen/dose was stable 3 months before randomization, patients did not lose >2% BMI during the previous 3 months, and the patient intended to keep the regimen/dose stable during the trial. All participants either met weight-related inclusion criteria at screening or were confirmed to have recently met weight-related inclusion criteria by the site investigator.
BMI, body mass index; **%BMI95**, percent of the body mass index 95th percentile.
1. Centers for Disease Control and Prevention. (June, 2024). *Child and Teen BMI Categories*. https://www.cdc.gov/bmi/child-teen-calculator/bmi-categories.html 2. Hampl et al. *Pediatrics*. 2023;151:e2022060640.

Setmelanotide Was Generally Well Tolerated

	Setmelanotide (n=48)	Placebo (n=23)	Overall (n=71)
≥1 AE of any cause	48 (100.0)	21 (91.3)	69 (97.2)
≥1 Drug-related AE	43 (89.6)	17 (73.9)	60 (84.5)
≥1 Serious AE	17 (35.4)	2 (8.7)	19 (26.8)
≥1 Drug-related serious AE	1 (2.1)*	0	1 (1.4)
≥1 AE that resulted in death	1 (2.1)†	0	1 (1.4)
≥1 AE leading to study drug withdrawal	3 (6.3)	2 (8.7)	5 (7.0)
≥1 AE leading to study discontinuation	1 (2.1)	0	1 (1.4)
AE in ≥20% of participants in setmelanotide arm			
Skin hyperpigmentation	28 (58.3)	2 (8.7)	30 (42.3)
Nausea	25 (52.1)	9 (39.1)	34 (47.9)
Vomiting	21 (43.8)	6 (26.1)	27 (38.0)
Headache	18 (37.5)	9 (39.1)	27 (38.0)
Injection site reaction	16 (33.3)	8 (34.8)	24 (33.8)
Diarrhea	13 (27.1)	5 (21.7)	18 (25.4)
Upper respiratory tract infection	10 (20.8)	4 (17.4)	14 (19.7)

*In a participant with arginine vasopressin deficiency who was unable to ingest their oral desmopressin tablet because of drug-associated nausea and vomiting, which led to increased blood sodium concentrations and subsequent hospitalization.
†Due to seizure in a participant with a preexisting seizure disorder was considered unrelated to treatment.
AE, adverse event.

Conclusions

- One year of setmelanotide treatment was associated with improvements in weight category, including the reclassification of a substantial proportion of patients into the overweight or healthy weight categories
- The safety profile of setmelanotide was consistent with previous trials in patients with aHO and other rare MC4R pathway–associated diseases[1-4]
- The US FDA recently approved an expanded indication for setmelanotide to reduce excess body weight and maintain reduction long term in adult and pediatric patients aged ≥4 years old with aHO[5]
- As prolonged obesity that manifests in pediatric patients has been shown to be associated with an increased risk of morbidity and mortality later in life,[6-9] the data from these analyses underscore the importance of correcting the MC4R pathway impairment in aHO early to help restore pediatric weight to a healthy trajectory

aHO, acquired hypothalamic obesity; **FDA**, Food and Drug Administration; **MC4R**, melanocortin-4 receptor; **US**, United States.

1. Roth et al. *Lancet Diabetes Endocrinol.* 2024;12(6):380-389. **2.** Clément et al. *Lancet Diabetes Endocrinol.* 2020;8(12):960-970. **3.** Haqq et al. *Lancet Diabetes Endocrinol*. 2022;10(12):859-868. **4.** Collet et al. *Mol Metab*. 2017;6(10):1321-1329. **5.** IMCIVREE [package insert]. Boston, MA: Rhythm Pharmaceuticals Inc; 2026. **6.** Sun J, et al. *Obes Rev*. 2021;22(3):e13138. **7.** Kibret KT, et al. *Obes Rev*. 2024;25(4):e13695. **8.** Bjerregaard LG, et al. *N Engl J Med*. 2018;378(14):1302-1312. **9.** Aguiar BCC, et al. *Prev Med*. 2026;203:108492.

Thank you

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