

Two Year Phase 3 Trial Results of Setmelanotide in Patients With Acquired Hypothalamic Obesity

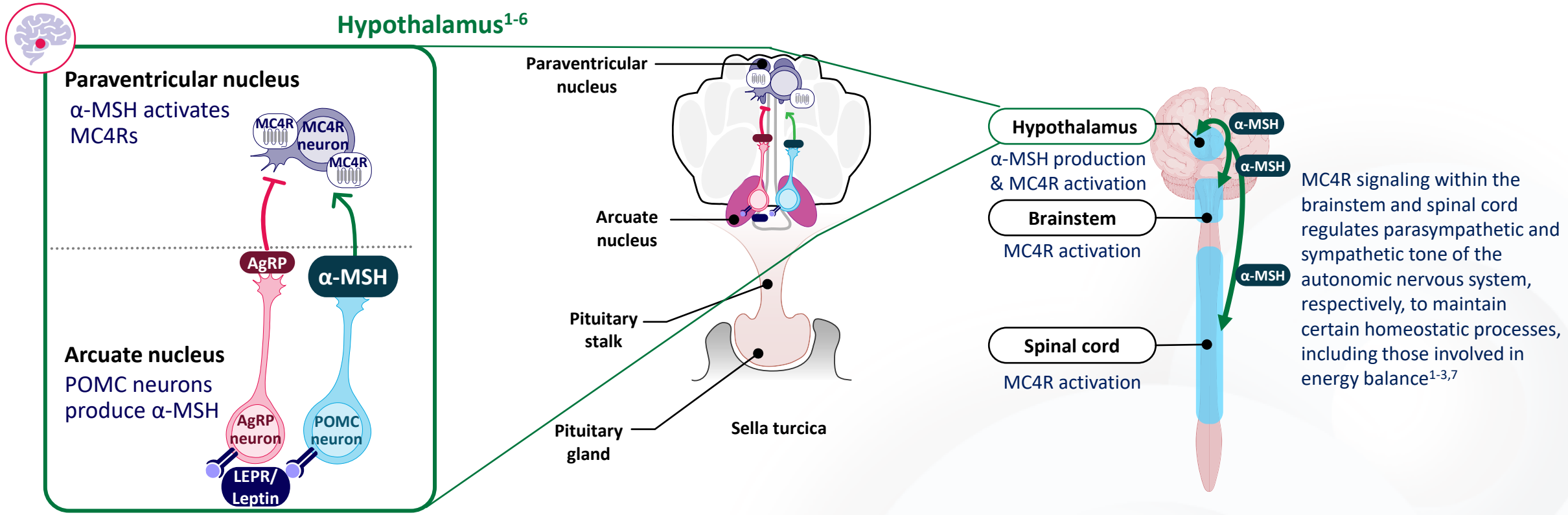
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Disclosures

- Susan A. Phillips received institutional funding for clinical trials and received payment for educational lectures from Rhythm Pharmaceuticals, Inc. and received consulting fees from Resolute Bio and Azurity Pharmaceuticals.
- This study was sponsored by Rhythm Pharmaceuticals, Inc.

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**

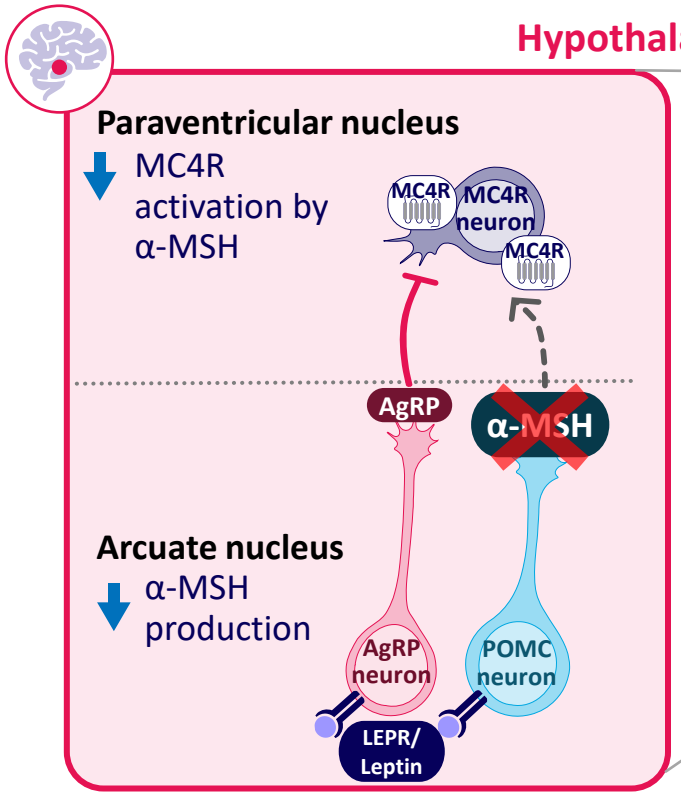
α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

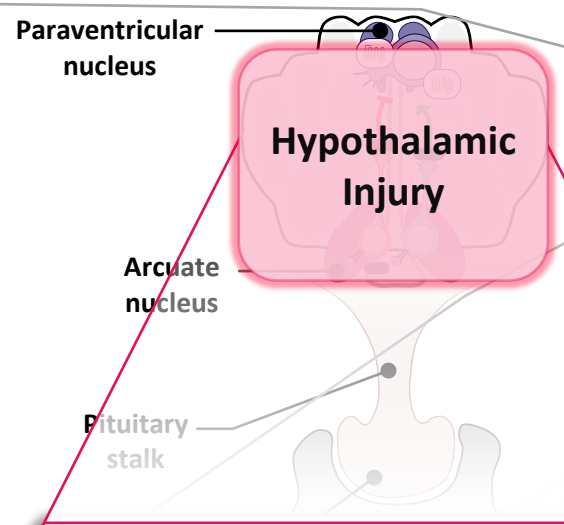
1. Baldini et al. *J Endocrinol.* 2019;241:R1-R33. **2.** Dimitri. *Front Endocrinol.* 2022;13:846880. **3.** Hill et al. *Neuroendocrinol.* 2017;104:330-346. **4.** Hochberg et al. *Obes Rev*. 2010;11:709-721. **5.** Roth et al. *Obesity (Silver Spring).* 2011;19:36-42. **6.** Cone et al. *Nat Neurosci.*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

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

obesityweek

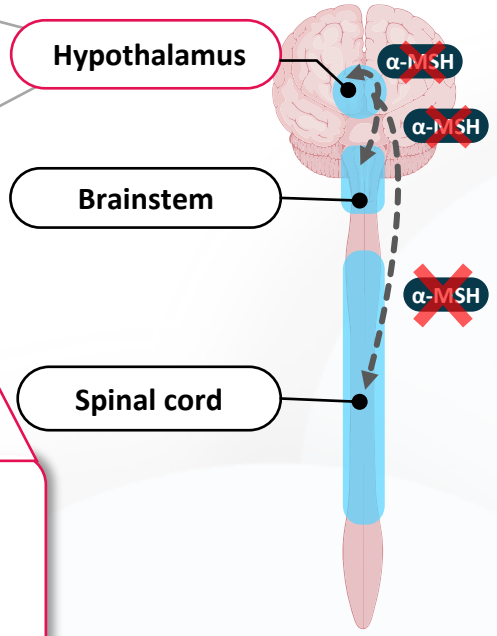
Hypothalamus[4-8]





Causes may include[1,2,4-6,8,9]

- Craniopharyngioma or other hypothalamic-pituitary tumors*
- Surgery
- Irradiation
- Traumatic brain injury
- Stroke
- Inflammatory diseases



DYSREGULATION of homeostatic pathways[3-4,7]

- **INCREASED parasympathetic tone**[1,2,4,7]
- **DECREASED sympathetic tone**[1,2,4,7]

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

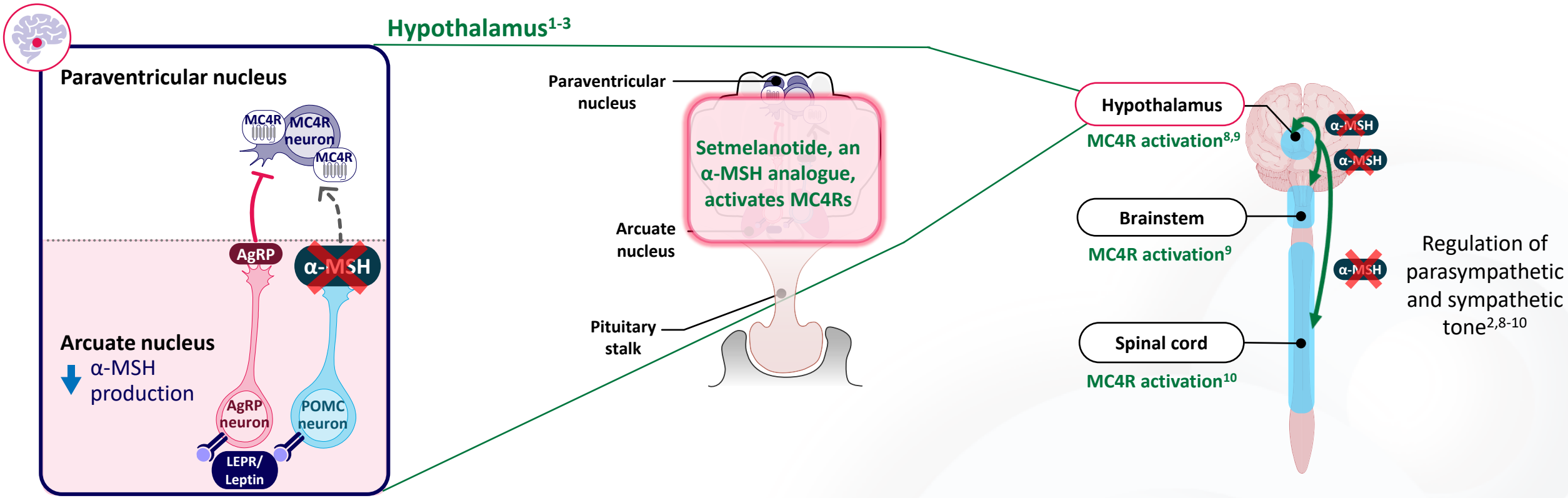
- Increased hunger/hyperphagia
- Reduced energy expenditure

→ **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 Replaces Deficient α-MSH, Restoring MC4R Pathway Signaling to Reduce Body Weight[1-7]



Setmelanotide has the potential to restore MC4R signaling, thereby improving energy balance[1-7,11]:

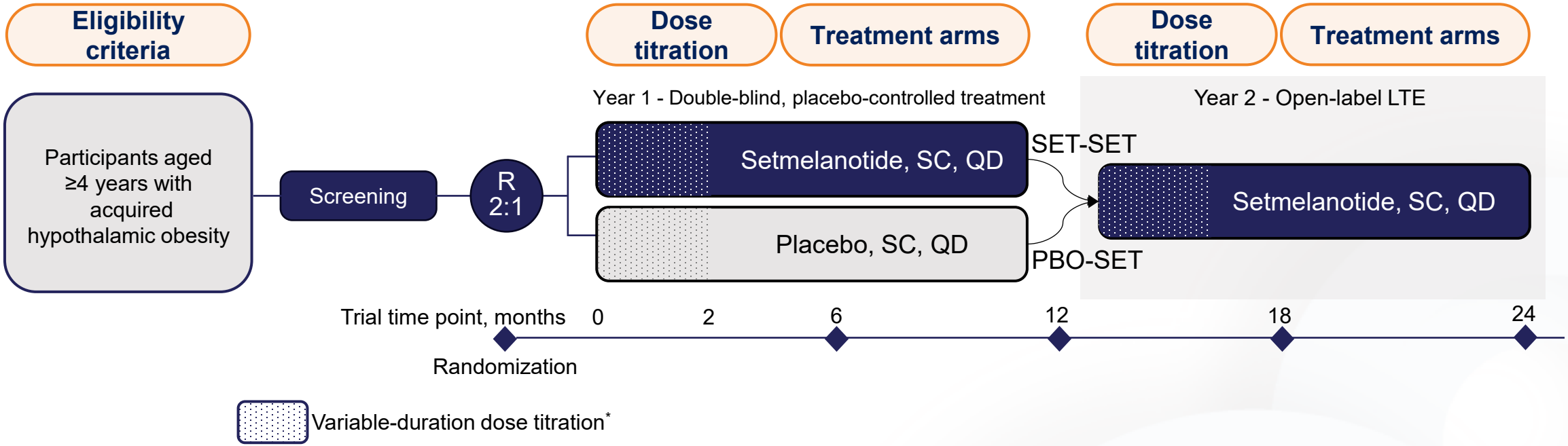
- Decreased hunger and improved satiety signaling
- Reduced symptoms of hyperphagia
- Increased energy expenditure

→ **Reduced body weight**

α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; 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.** Sweeney et al. *Proc Natl Acad Sci USA.* 2021;118(14):e2011140118. **9.** Hansen et al. *Mol Metab*. 2021;47:101171. **10.** Ju et al. *Cell Rep*. 2022;41(5):111579. **11.** Chen et al. *J Clin Endocrinol Metab*. 2015;100(4):1639-1645.

TRANSCEND Trial Design[1]



Primary efficacy endpoint

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

After 1 year, all participants received open-label setmelanotide

*The initial dose of 0.5 mg was escalated in increments of 0.5 to 1.0 mg until the participant reached an individual therapeutic regimen based on age and weight (1.5-3.0 mg QD).
LTE, long-term extension; QD, once daily; R, randomisation; SC, subcutaneous. SET-SET – continuous setmelanotide arm. PBO-SET, participants switched at year 2 from placebo to setmelanotide

1. Miller JL, et al. *NEJM*. 2026;395:138–150.

Introduction

- Results from the Phase 3 TRANSCEND trial (NCT05774756) in participants with acquired HO showed statistically significant and clinically meaningful weight and hunger reductions following treatment with the MC4R agonist setmelanotide after 1 year[1]

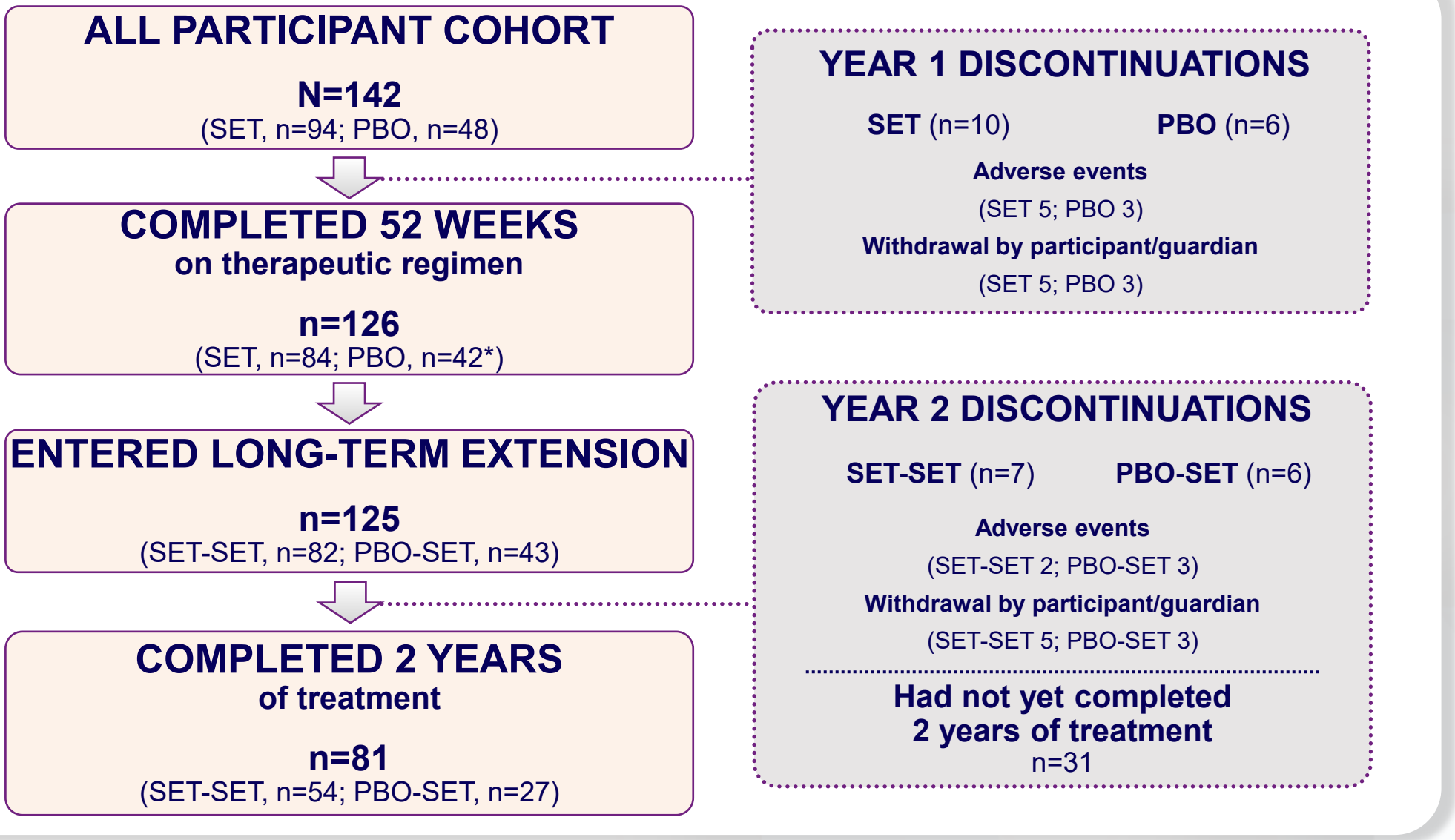


Objective: To summarize 2-year results from the long-term extension

HO, hypothalamic obesity; MC4R, melanocortin-4 receptor.

1. Miller JL, et al. *N Engl J Med*. 2026;395(2):138-150.

Disposition



*There were 3 retrieved trial dropouts in the placebo group that discontinued treatment but completed the trial.

SET, setmelanotide; PBO, placebo; SET-SET, continuous setmelanotide arm; PBO-SET, placebo participants switched to setmelanotide during long-term extension.

Baseline Participant Demographics

	Setmelanotide (n=94)	Placebo (n=48)
Age, mean ± SD (range), y	20.6 ± 13.4 (4-65)	22.9 ± 16.3 (4-66)
Sex, n (%)		
Female	54 (57.4)	31 (64.6)
Male	40 (42.6)	17 (35.4)
Race, n (%)		
White	71 (75.5)	36 (75.0)
Asian	11 (11.7)	5 (10.4)
Black or African American	6 (6.4)	1 (2.1)
Other	6 (6.4)	6 (12.5)
Ethnicity, n (%)		
Not Hispanic or Latino	85 (90.4)	40 (83.3)
Hispanic or Latino	8 (8.5)	8 (16.7)
Unknown/Missing	1 (1.1)	0

	Setmelanotide (n=94)	Placebo (n=48)
Weight, mean (SD), kg	94.2 (37.4)	93.5 (35.7)
BMI, mean (SD), kg/m^2	36.0 (9.2)	36.4 (8.8)
BMI z-score (<18 yrs, WHO), mean (SD, n)*	3.69 (1.81, 49)	3.41 (1.28, 27)
%BMI95 (<18 yrs, CDC), mean (SD, n)†	131.7 (28.9, 49)	129.9 (24.4, 27)
Waist circumference, mean (SD), cm	107.1 (20.9)	108.1 (17.6)

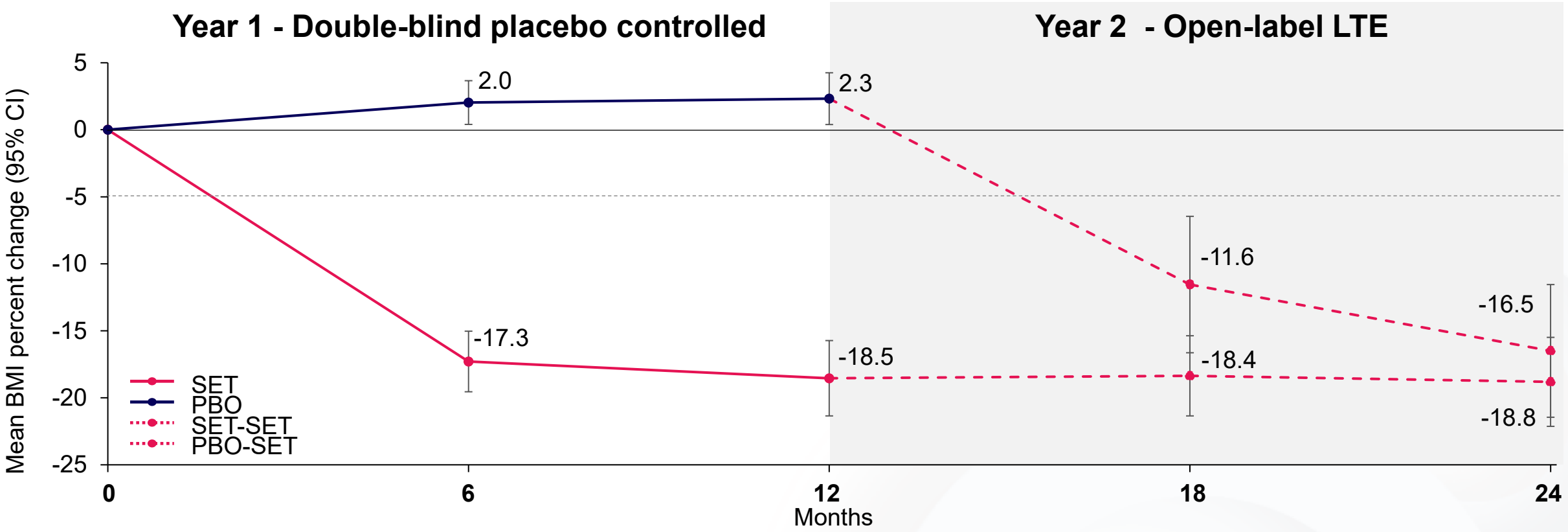
*BMI z-score calculated according to the WHO 2007 method. †%BMI95 calculated according to the CDC 2022 method.
SD, standard deviation; BMI, body mass index; %BMI95, percent of the body mass index 95th percentile; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization.

Baseline Participant Demographics (cont)

	Setmelanotide (n=94)	Placebo (n=48)
Tumor/damage type, n (%)		
Craniopharyngioma	73 (77.7)	37 (77.1)
Glioma	4 (4.3)	4 (8.3)
Astrocytoma	4 (4.3)	3 (6.3)
Germinoma	6 (6.4)	1 (2.1)
Hamartoma	1 (1.1)	2 (4.2)
Other	6 (6.4)	1 (2.1)
Tumor treatment, n (%)		
Hypothalamic surgery for lesion removal	85 (90.4)	43 (89.6)
Radiotherapy	46 (48.9)	26 (54.2)
Chemotherapy	21 (22.3)	9 (18.8)
Unknown/Missing	2 (2.1)	1 (2.1)
Hypothalamic involvement, n (%)		
Bilateral	61 (64.9)	31 (64.6)
Unilateral	8 (8.5)	4 (8.3)
Unknown/Missing	25 (26.6)	13 (27.1)

	Setmelanotide (n=94)	Placebo (n=48)
Endocrine disorders, n (%)	94 (100)	46 (95.8)
Arginine vasopressin deficiency	78 (83.0)	36 (75.0)
Adrenal insufficiency, secondary adrenocortical insufficiency, or adrenocorticotropic hormone deficiency	63 (67.0)	29 (60.4)
Central hypothyroidism	60 (63.8)	31 (64.6)
Growth hormone deficiency	62 (66.0)	28 (58.3)
Hypopituitarism	49 (52.1)	21 (43.8)
Secondary hypogonadism	38 (40.4)	17 (35.4)

Percent Change in BMI Over Time *(All Participants)*



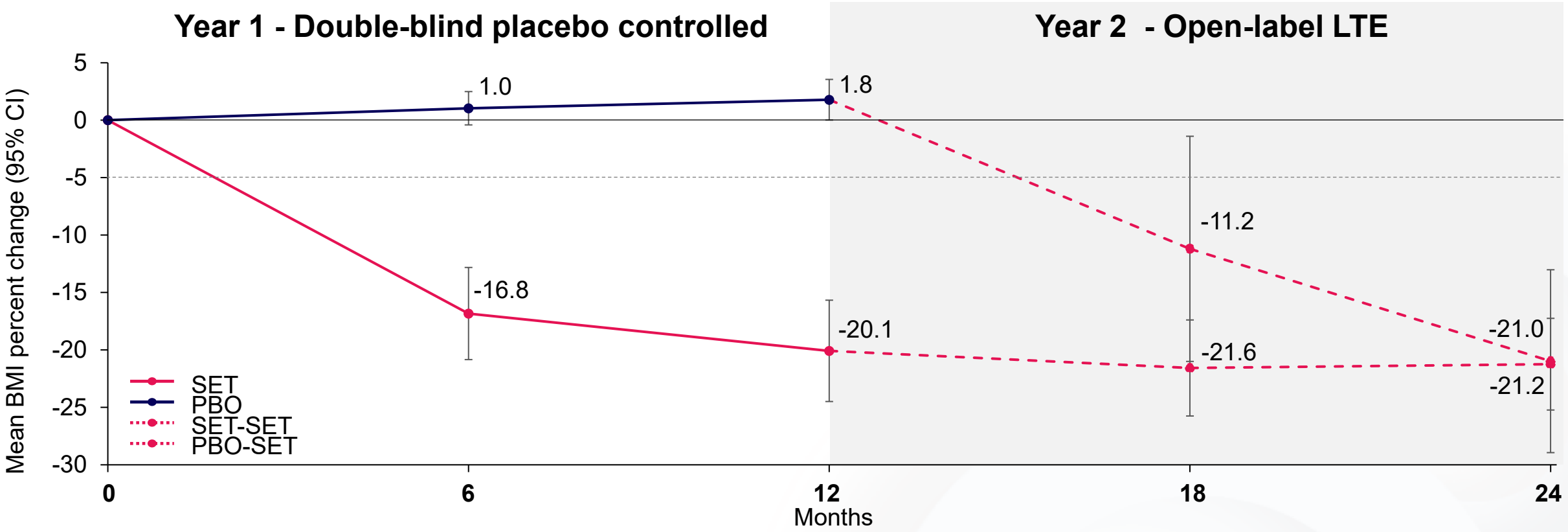
n=	94	84	85	69	54
n=	48	44	46	36	27

Placebo-adjusted mean BMI percent change in SET cohort	**-19.3%**	**-20.9%**

Values as observed. Dotted line indicates a clinically meaningful reduction in BMI of ≥5%.[1] BMI, body mass index; CI, confidence intervals; LTE, long term extension; PBO, placebo; PBO-SET, placebo participants switched to setmelanotide during LTE; SET, setmelanotide; SET-SET, continuous setmelanotide arm.

1. Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362.

Percent Change in BMI Over Time *(Adult Participants)*

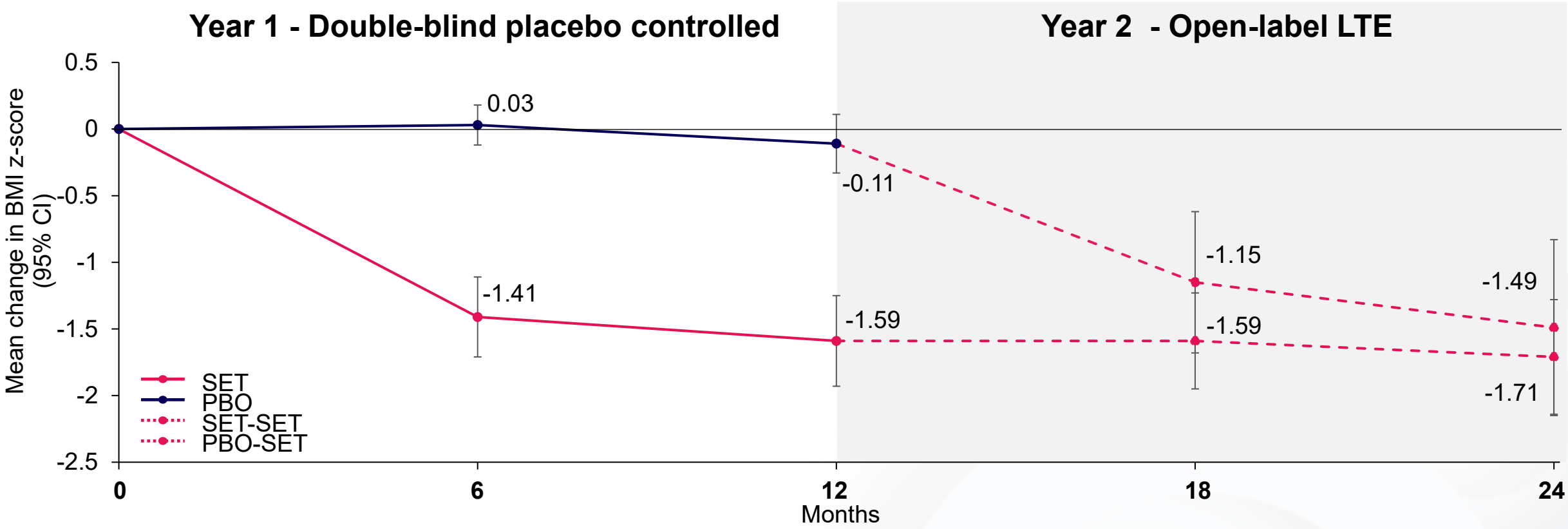


n=	45	40	39	29	23
n=	21	20	20	15	11
Placebo-adjusted mean BMI percent change in SET cohort		**-17.9%**	**-21.9%**		

Values as observed. Dotted line indicates a clinically meaningful reduction in BMI of ≥5%.[1] BMI, body mass index; CI, confidence intervals; LTE, long term extension; PBO, placebo; PBO-SET, placebo participants switched to setmelanotide during LTE; SET, setmelanotide; SET-SET, continuous setmelanotide arm.

1. Apovian CM, et al. *J Clin Endocrinol Metab*. 2015;100(2):342-362.

Change in BMI z-score Over Time *(Pediatric Participants)*



n=	49	44	44	35	27
n=	27	24	26	20	15
Placebo-adjusted mean BMI z-score change in SET cohort		**-1.44**	**-1.48**		

Values as observed. BMI, body mass index; CI, confidence intervals; LTE, long term extension; PBO, placebo; PBO-SET, placebo participants switched to setmelanotide during LTE; SET, setmelanotide; SET-SET, continuous setmelanotide arm.

Safety – Adverse Events

Adverse Events, n (%)	SET-SET		PBO-SET		Overall	
	Year 1 (n=94)	Year 2 (n=82)	Year 1 (n=48)	Year 2 (n=43)	Year 1 (N=142)	Year 2 (n=125)
Any	94 (100)	55 (67.1)	44 (91.7)	34 (79.1)	138 (97.2)	89 (71.2)
Serious	26 (27.7)	10 (12.2)	3 (6.3)	4 (9.3)	29 (20.4)	14 (11.2)
Treatment-related	83 (88.3)	22 (26.8)	33 (68.8)	30 (69.8)	52 (36.6)	52 (41.6)
Treatment-related serious	1 (1.1)*	0	0	0	1 (0.7)	0
Resulting in death	1 (1.1)†	1 (1.2)‡	0	0	1 (1.2)	1 (0.8)
Leading to trial drug withdrawal	5 (5.3)§	3 (3.7)‖	3 (6.3)**	3 (7.0)††	6 (4.2)	6 (4.8)
Leading to trial discontinuation	4 (4.3)	2 (2.4)	0	0	8 (5.6)	2 (1.6)
Any cause in ≥20% (Year 1) of participants						
Nausea	52 (55.3)	9 (11.0)	12 (25.0)	15 (34.9)	64 (45.1)	24 (19.2)
Skin hyperpigmentation	53 (56.4)	6 (7.3)	4 (8.3)	21 (48.8)	57 (40.1)	27 (21.6)
Headache	34 (36.2)	10 (12.2)	15 (31.3)	12 (27.9)	49 (34.5)	22 (17.6)
Vomiting	36 (38.3)	9 (11.0)	9 (18.8)	9 (20.9)	45 (31.7)	18 (14.4)
Injection site reaction	22 (23.4)	1 (1.2)	11 (22.9)	1 (2.3)	33 (23.2)	2 (1.6)
Diarrhea	20 (21.3)	7 (8.5)	10 (20.8)	10 (23.3)	30 (21.1)	17 (13.6)

Safety data are reported for all participants that received ≥1 dose of study treatment. *Hypernatremia (sodium levels 150-158 mmol/L [normal upper limit 145 mmol/L]) due to vomiting and an inability to tolerate desmopressin occurring in a participant with arginine vasopressin deficiency; after 2 days, setmelanotide was reinitiated upon discharge from the hospital. †Due to seizures in a patient with a history of seizure disorder, which was not considered related to the study drug. ‡Participant with a history of pilomyxoid astrocytoma, cranial radiation, arginine vasopressin deficiency, and dehydration died of ischemic stroke during year 2, deemed unrelated to treatment. §Due to injection site pruritus, muscle spasms, and rhinorrhea (same participant), nausea and vomiting (same participant), gastroesophageal reflux disease (n=1), and skin hyperpigmentation (n=2). ‖Due to ischemic stroke with coma, abdominal pain/headache/nausea (same participant), and increased sleepiness. **Due to injection site reaction, dyspnea, and hypersensitivity (n=1 each). ††Due to peripheral edema/pruritus/rash (same participant), cough, and sleepiness/skin hyperpigmentation (same participant). LTE, long-term extension; PBO-SET, placebo participants switched to setmelanotide during LTE; SET-SET, continuous setmelanotide arm.

Conclusions

- In this LTE of TRANSCEND, efficacy was maintained in the continuous setmelanotide group at 2 years, and those initially assigned PBO and switched to setmelanotide after year 1 achieved clinically meaningful improvements in BMI at year 2
- The safety profile of setmelanotide was generally consistent with previous trials in acquired HO[1-4]
- These robust data underscore the benefit of targeting (residual) MC4R signaling in acquired hypothalamic obesity
- Setmelanotide is approved to reduce excess body weight and maintain this reduction long-term in adults and pediatric patients aged 4 years and older with acquired HO in the US, the EU, the UK, Japan, and Canada, and is additionally indicated to control hunger in the EU and the UK[5-9]

EU, European Union; HO, hypothalamic obesity; LTE, long term extension; MC4R, melanocortin-4 receptor; UK, United Kingdom; 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® (setmelanotide) [US package insert]. Boston, MA: Rhythm Pharmaceuticals; 2026. **6.** IMCIVREE® (setmelanotide) [Canada product monograph]. Boston, MA: Rhythm Pharmaceuticals; 2026. **7.** IMCIVREE® (setmelanotide) [SmPC EMA]. Amsterdam, Netherlands: Rhythm Pharmaceuticals Netherlands B.V.; 2026. **8.** IMCIVREE® (setmelanotide) United Kingdom's MHRA. London: Rhythm Pharmaceutical UK Ltd; 2026. **9.** IMCIVREE® (setmelanotide) Japan MHLW. Rhythm Pharmaceuticals; 2026.



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