Oral presentation number: OC8.6

Efficacy and safety of setmelanotide in paediatric patients with acquired hypothalamic obesity: Final phase 3 trial results

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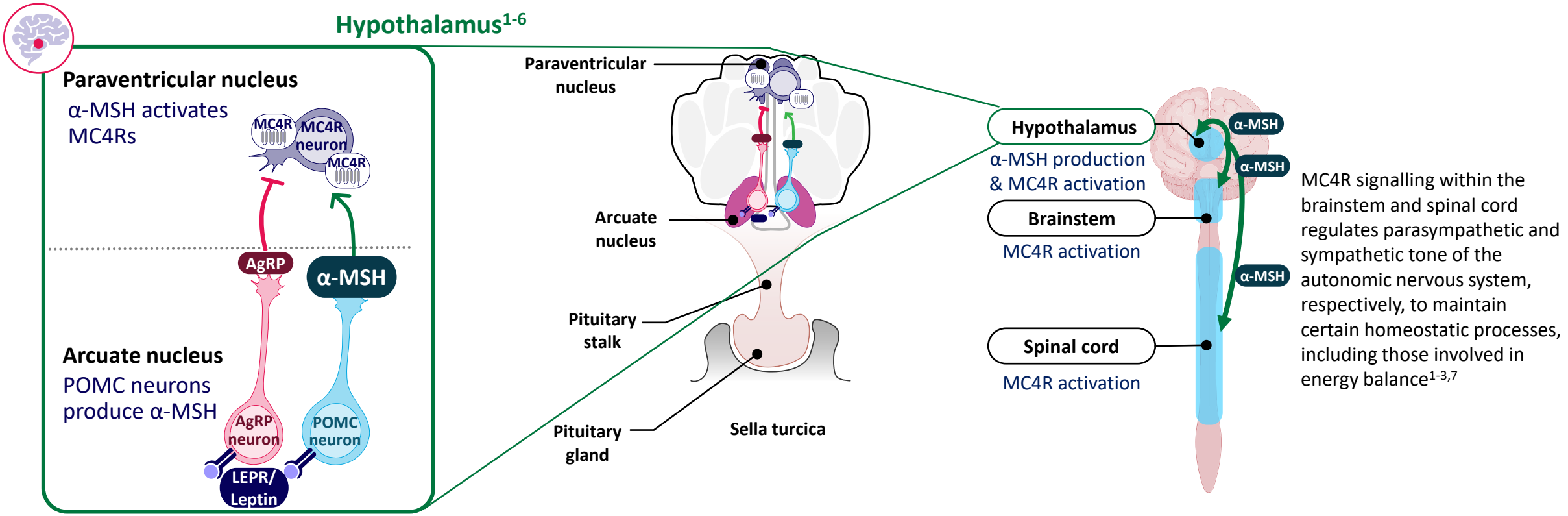
Christian L. Roth,[1] Jennifer L. Miller,[2] Susan A. Phillips,[3] Jill Hamilton,[4] Shana E. McCormack,[5] Megan M. Kelsey,[6] Ashley H. Shoemaker,[7] Cecilia Scimia,[7] Guojun Yuan,[7] Mehul Dattani,[8] Katie Larson Ode,[9] Zainaba Mohamed,[10] M. Jennifer Abuzzahab,[11] Martin Wabitsch,[12,13] Hanneke M. van Santen[14]

[1]Seattle Children's Research Institute, Norcliffe Foundation Center for Integrative Brain Research, University of Washington, Pediatrics, Seattle, WA, USA; [2]Pediatric Endocrinology, Department of Pediatrics, College of Medicine, University of Florida, Gainesville, FL, USA; [3]Pediatric Endocrinology, University of California San Diego/Rady Children's Hospital, San Diego, CA, USA; [4]Division of Endocrinology, Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, Canada; [5]Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA and Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [6]Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [7]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [8]University College London Great Ormond Street Institute of Child Health, Genetics and Genomic Medicine Programme, London, UK; [9]University of Iowa Stead Family Department of Pediatrics - Pediatric Endocrinology and Diabetes, Iowa City, IA, USA; [10]Department of Paediatric Endocrinology and Diabetes, Birmingham Women's and Children's Hospital NHS Trust, Birmingham, UK; [11]Children's Minnesota, St. Paul, MN, USA; [12]University Hospital Ulm, Department of Pediatrics and Adolescent Medicine, Division of Pediatric Endocrinology and Diabetes, Ulm; [13]Germany and German Center for Child and Adolescent Health (DZKJ), Partner Site, Ulm, Germany; [14]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands and the Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands

Presenting Author Disclosures

- **Christian L. Roth** is supported by grants from the National Institutes of Health (award numbers R21HD115119, R01DK135125, and R01DK135211; unrelated to this study) and was an advisory board member for Rhythm Pharmaceuticals, Inc.
- **Funding:** This study was funded by Rhythm Pharmaceuticals, Inc.
- **Acknowledgements:** Editorial assistance was provided under the direction of the authors by Rhythm Pharmaceuticals, Inc.

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



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

- Hunger & food intake
- Energy expenditure

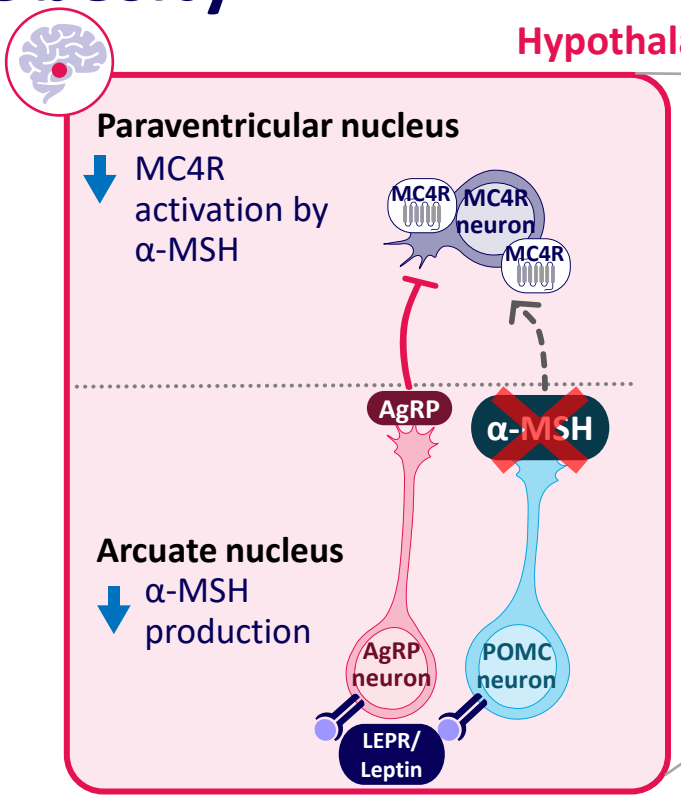
→ **Body weight**

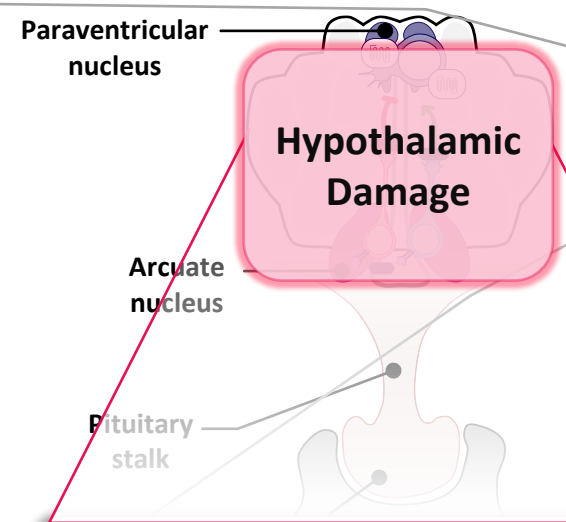
α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

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 Damage May Impair MC4R Pathway Signalling and Lead to Acquired Hypothalamic Obesity[1-3]

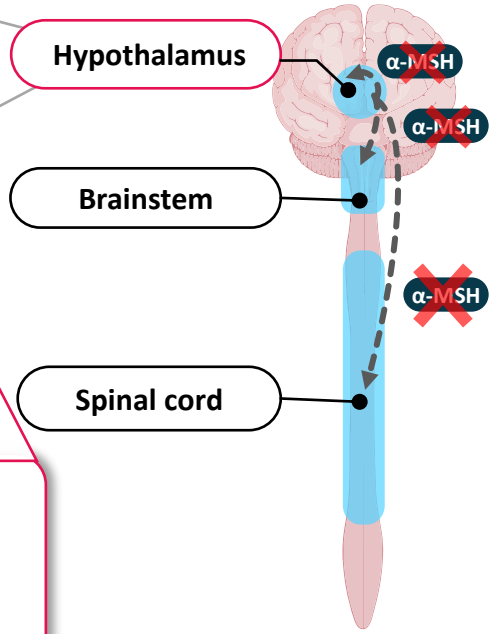
Hypothalamus[4-8]





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]**:**

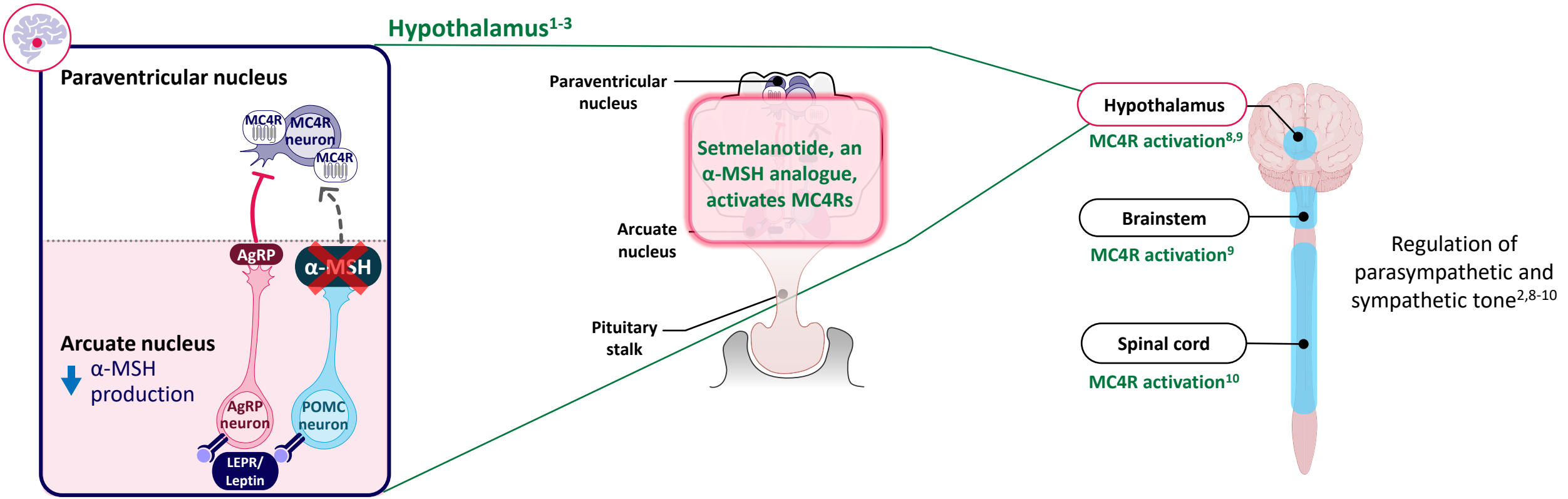
- Increased hunger/hyperphagia
- Reduced energy expenditure

→ **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 Signalling to Reduce Body Weight[1-7]



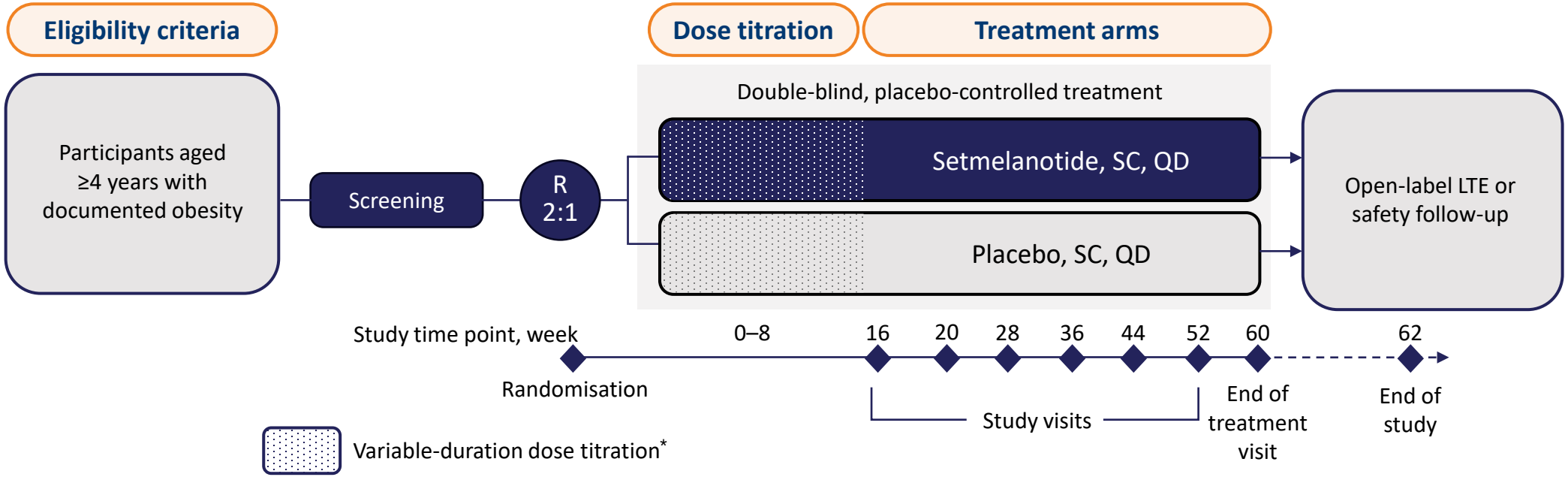
Setmelanotide has the potential to restore MC4R signalling, thereby improving energy balance[1-7,11]:

- Decreased hunger and improved satiety signalling
- 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. *Lancet DE.* 2024;12(6):380-389. **3.** Roth. *Diabetes Obes Metab*. 2024;26(suppl 2):34-45. **4.** Sohn. *Cell.* 2013;152(3):612-619. **5.** van Santen. *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. *PNAS USA.* 2021;118(14):e2011140118. **9.** Hansen. *Mol Metab*. 2021;47:101171. **10.** Ju. *Cell Rep*. 2022;41(5):111579. **11.** Chen. *JCEM*. 2015;100(4):1639-1645.

TRANSCEND study design[1]



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

- Hunger, hyperphagia, quality of life, fatigue, sleep quality, physical activity, and body composition measures
- Safety and tolerability outcomes including adverse events

*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.
LTE, long-term extension; QD, once daily; R, randomisation; SC, subcutaneous.

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

Introduction – Setmelanotide in aHO

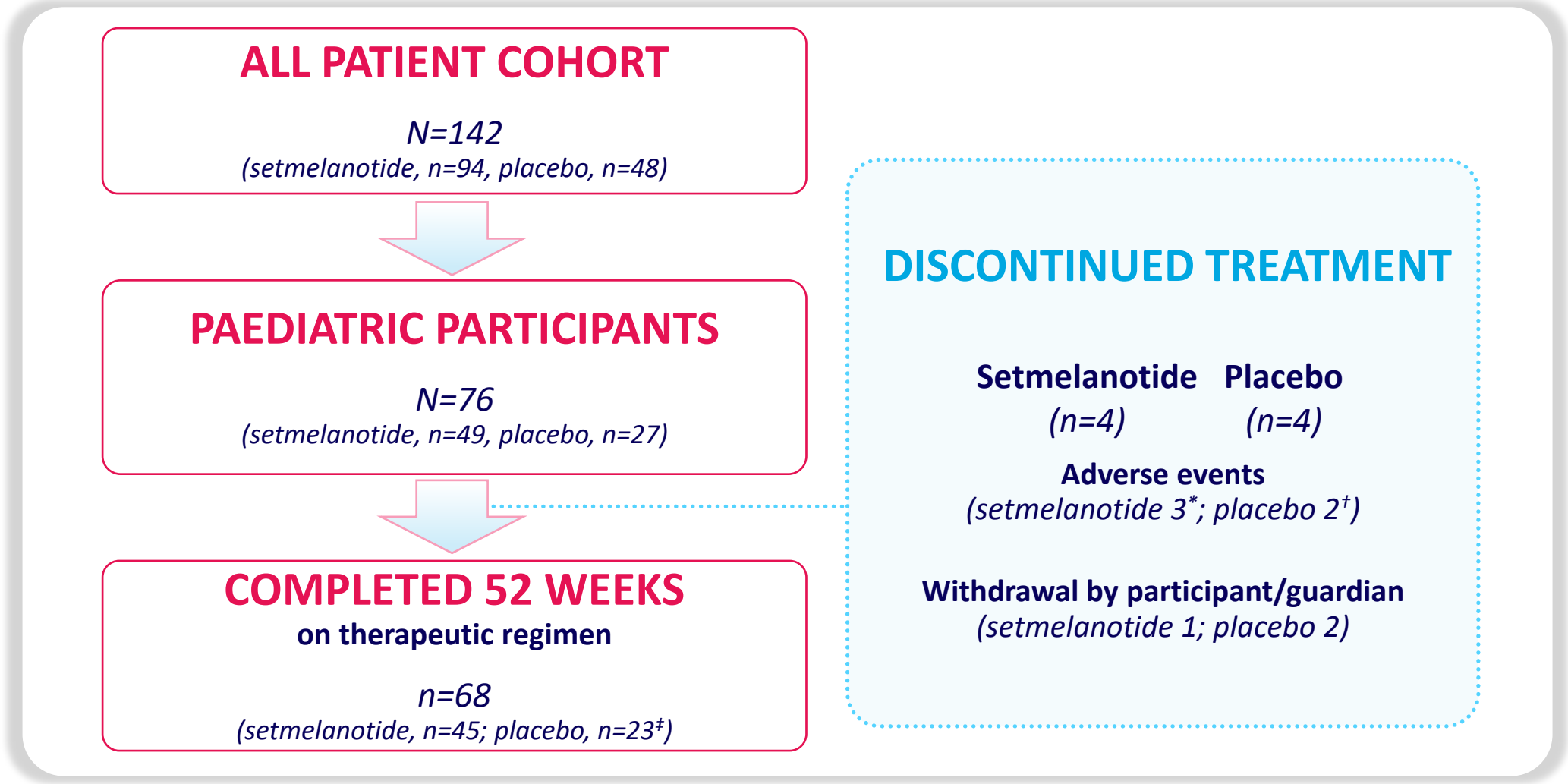
- Results from the pivotal cohort of 120 participants with aHO in the Phase 3 TRANSCEND trial (NCT05774756) showed statistically significant and clinically meaningful weight and hunger reductions following treatment with the MC4R agonist setmelanotide[1]
- Inclusion criteria in the TRANSCEND trial allowed for the enrollment of participants as young as 4 years old[1]
- The current presentation summarises the results from all 76 paediatric participants who received study drug, including 5 who were ongoing at the time the earlier primary analysis was performed.

Objective: To analyze changes in weight-related measures in the paediatric subpopulation of participants with aHO in the TRANSCEND trial

aHO, acquired hypothalamic obesity; MC4R, melanocortin-4 receptor.

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

Disposition



*Due to nausea and vomiting (same patient), skin hyperpigmentation and death (during the trial due to a seizure in a participant with a preexisting seizure disorder and considered to be unrelated to treatment), (n=1 each). † Due to hypersensitivity, and injection site reaction (n=1 each). ‡ There were 3 retrieved study dropouts in the placebo group that discontinued treatment but completed the study.

Baseline participant demographics

	Setmelanotide (n=49)	Placebo (n=27)
Age, mean ± SD (range), y	11.6 ±4.0 (4, 17)	11.7 ± 3.7 (4, 17)
Sex, n (%)		
Female	22 (44.9)	19 (70.4)
Male	27 (55.1)	8 (29.6)
Race, n (%)		
White	41 (83.7)	19 (70.4)
Black or African American	2 (4.1)	1 (3.7)
Asian	1 (2.0)	1 (3.7)
Other	5 (10.2)	6 (22.2)
Ethnicity, n (%)		
Not Hispanic or Latino	43 (87.8)	19 (70.4)
Hispanic or Latino	5 (10.2)	8 (29.6)
Unknown/Missing	1 (2.0)	0

	Setmelanotide (n=49)	Placebo (n=27)
Weight, mean (SD), kg	77.0 (33.5)	74.8 (26.9)
BMI, mean (SD), kg/m^2	32.6 (7.4)	32.8 (6.5)
BMI z-score (WHO), mean (SD)*	3.7 (1.8)	3.4 (1.3)
%BMI95 (CDC), mean (SD)†	131.7 (28.9)	129.9 (24.4)
Waist circumference, mean (SD), cm	99.6 (19.3)	101.0 (16.2)

*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.

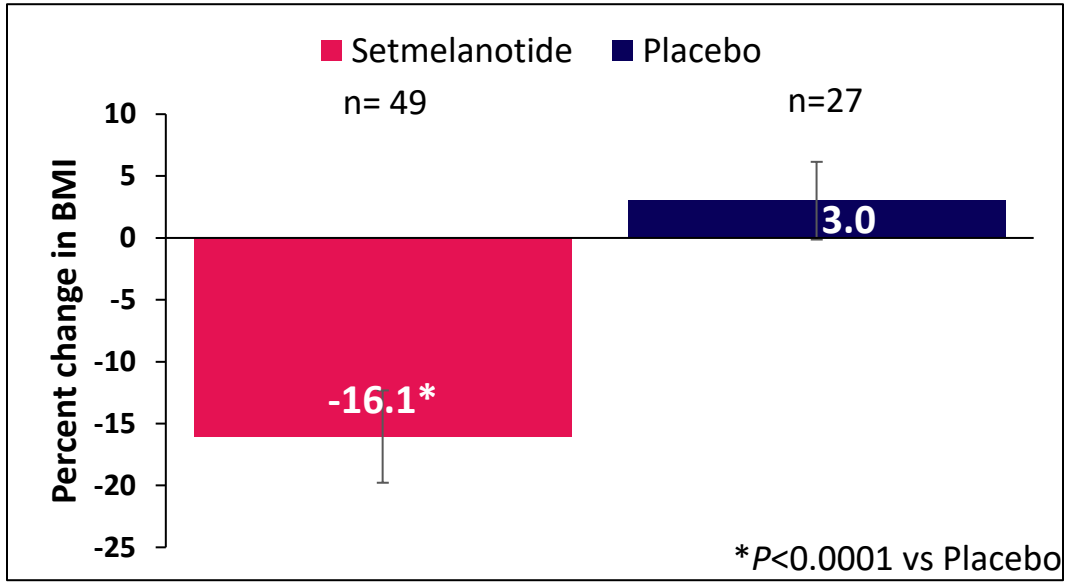
Baseline patient demographics (cont)

	Setmelanotide (n=49)	Placebo (n=27)
Tumor/damage type, n (%)		
Craniopharyngioma	37 (75.5)	17 (63.0)
Glioma	3 (6.1)	4 (14.8)
Astrocytoma	2 (4.1)	3 (11.1)
Germinoma	4 (8.2)	1 (3.7)
Hamartoma	1 (2.0)	2 (7.4)
Other	2 (4.1)	0
Tumor treatment, n (%)		
Hypothalamic surgery for lesion removal	44 (89.8)	23 (85.2)
Radiotherapy	26 (53.1)	12 (44.4)
Chemotherapy	16 (32.7)	8 (29.6)
Unknown/Missing	1 (2.0)	1 (3.7)
Hypothalamic involvement, n (%)		
Bilateral	35 (71.4)	19 (70.4)
Unilateral	2 (4.1)	2 (7.4)
Unknown/Missing	12 (24.5)	6 (22.2)

	Setmelanotide (n=49)	Placebo (n=27)
Endocrine disorders, n (%)	49 (100)	25 (92.6)
Arginine vasopressin deficiency	44 (89.8)	18 (66.7)
Central hypothyroidism or hypothyroidism	43 (87.8)	19 (70.4)
Adrenal insufficiency, secondary adrenocortical insufficiency, or adrenocorticotropic hormone deficiency	39 (79.6)	15 (55.6)
Growth hormone deficiency	36 (73.5)	16 (59.3)
Secondary hypogonadism	16 (32.7)	6 (22.2)
Precocious puberty	4 (8.2)	7 (25.9)

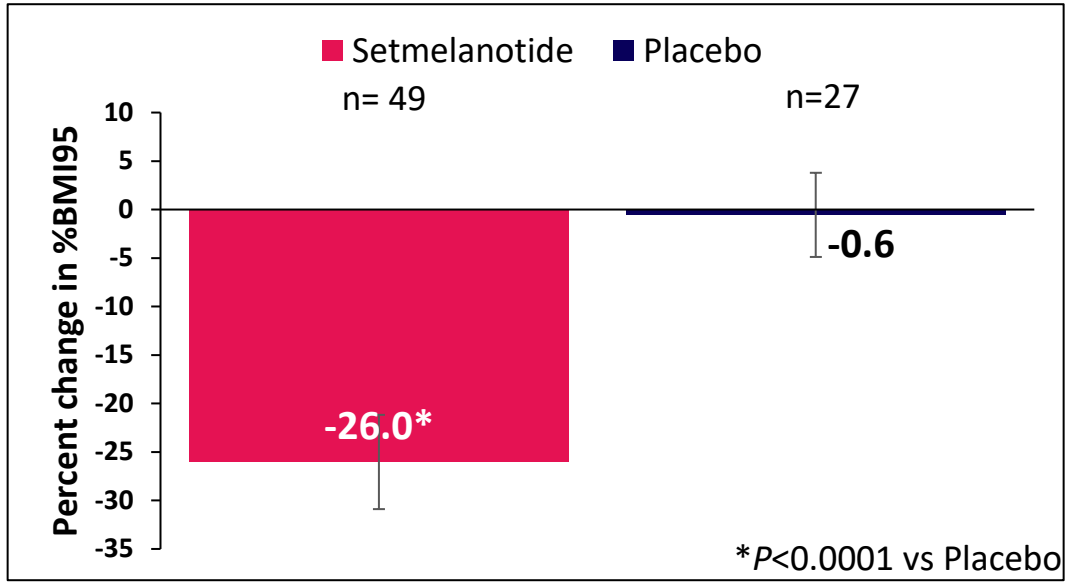
Significant reduction in BMI and BMI percent of the 95th percentile with setmelanotide at week 52 (participants aged <18 years)

52-Week Change in BMI



- At 52 weeks, the mean (SD) BMI percent change from baseline was −16.1 (1.9) for setmelanotide versus 3.0 (1.6) for placebo (*P*<0.0001).
- The placebo-adjusted difference is −19.1%.

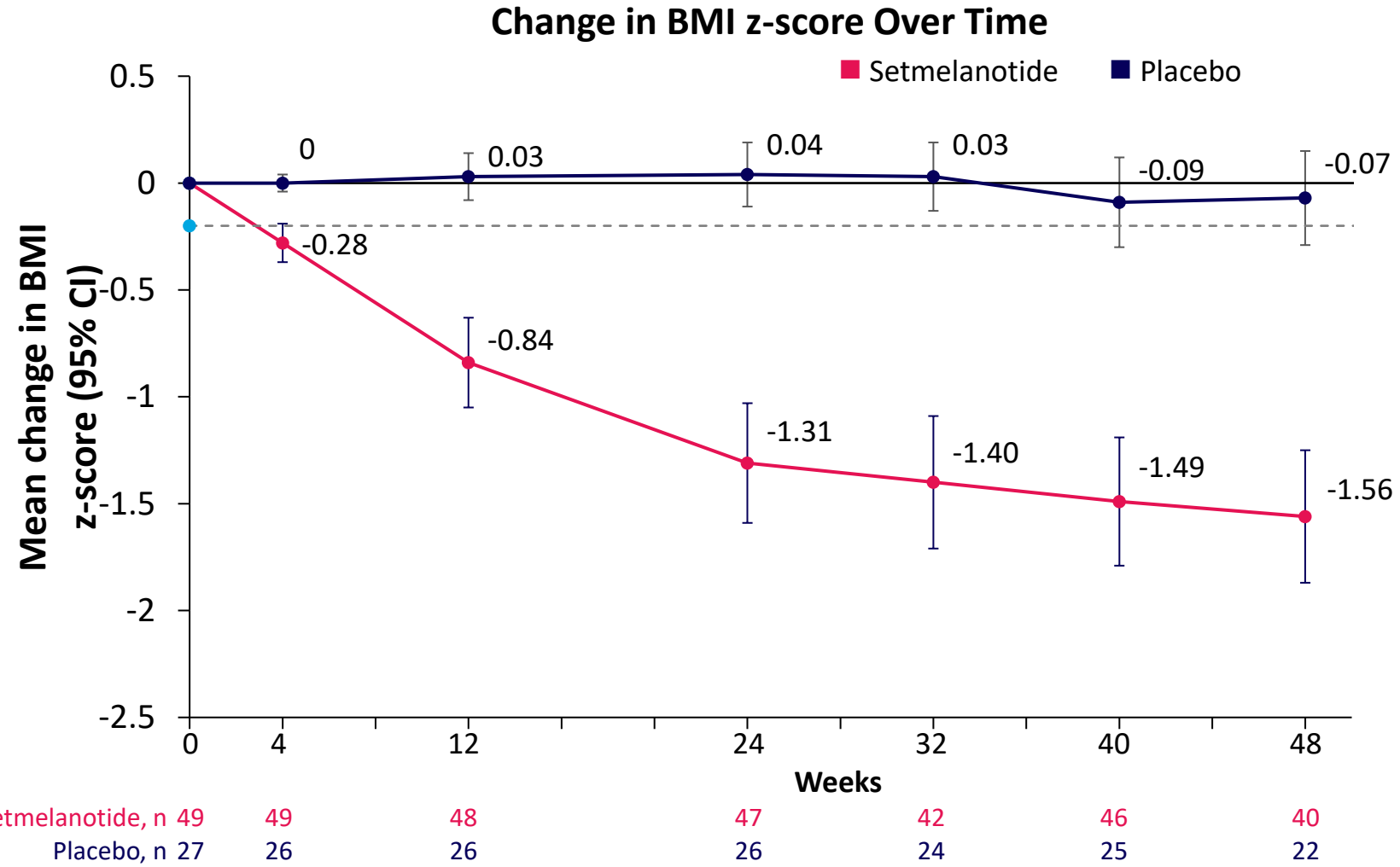
52-Week Change in BMI Percent of the 95th Percentile

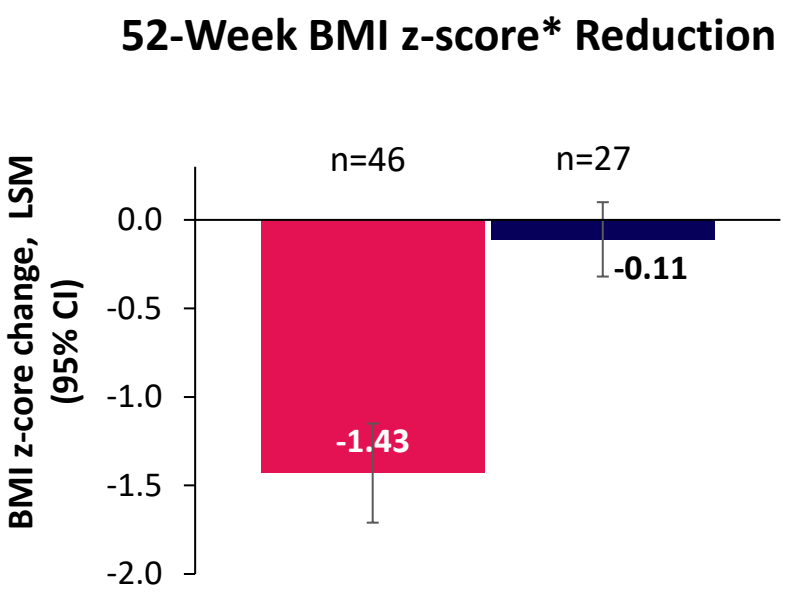


- At 52 weeks, the mean (SD) change in BMI percent of the 95th percentile was −26.0 (2.5) for setmelanotide versus –0.6 (2.2) for placebo (*P*<0.0001).
- The placebo-adjusted difference is −25.5.

Data are analysis of covariance LSM (95% confidence interval). %BMI95 calculated according to the CDC 2022 method.
BMI, body mass index; CI, confidence interval; %BMI95, percent of the BMI 95th percentile; CDC, Centers for Disease Control and Prevention; LSM, least square means.

Significant reduction in BMI z-score (WHO) with setmelanotide at week 52 (participants aged <18 years)



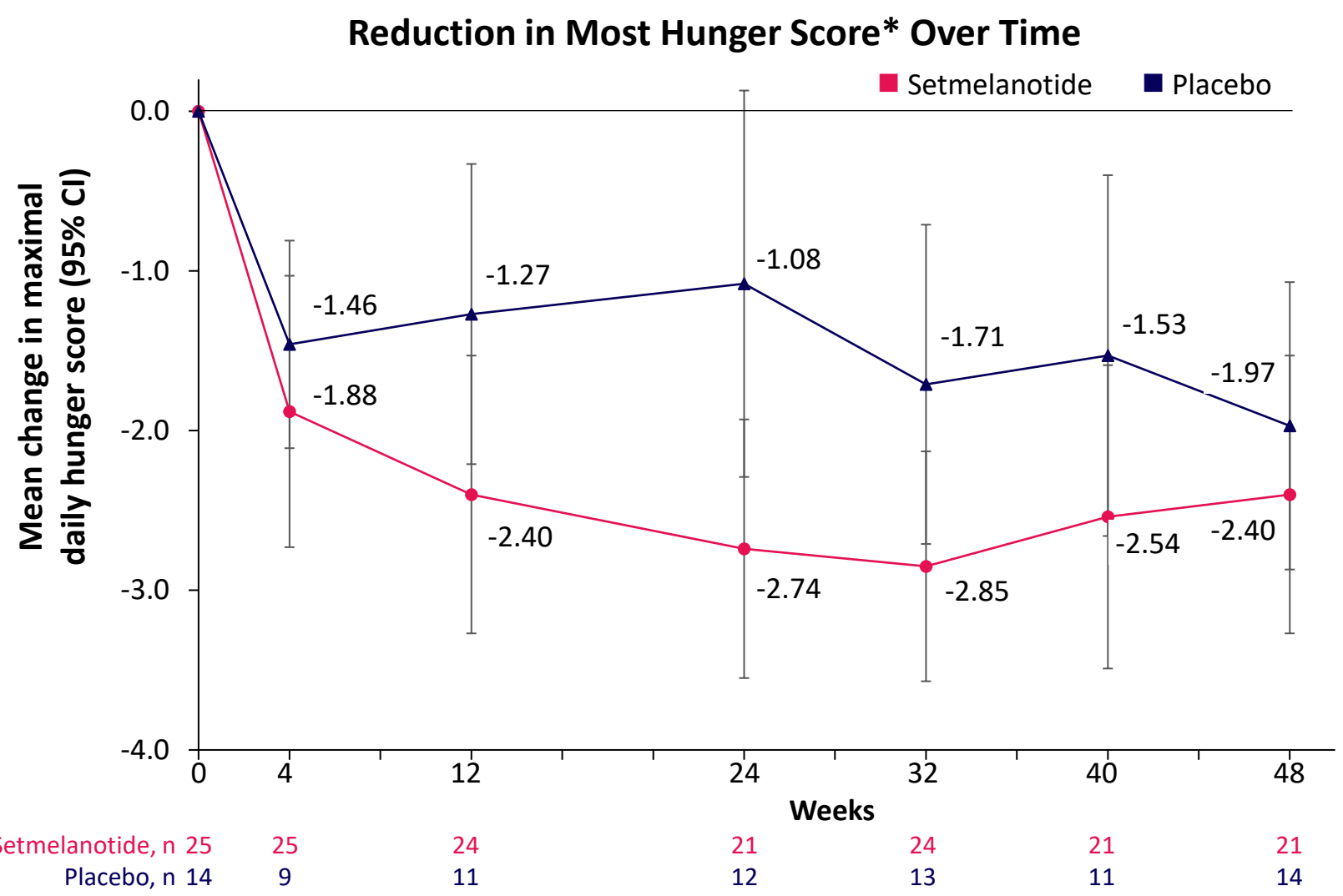


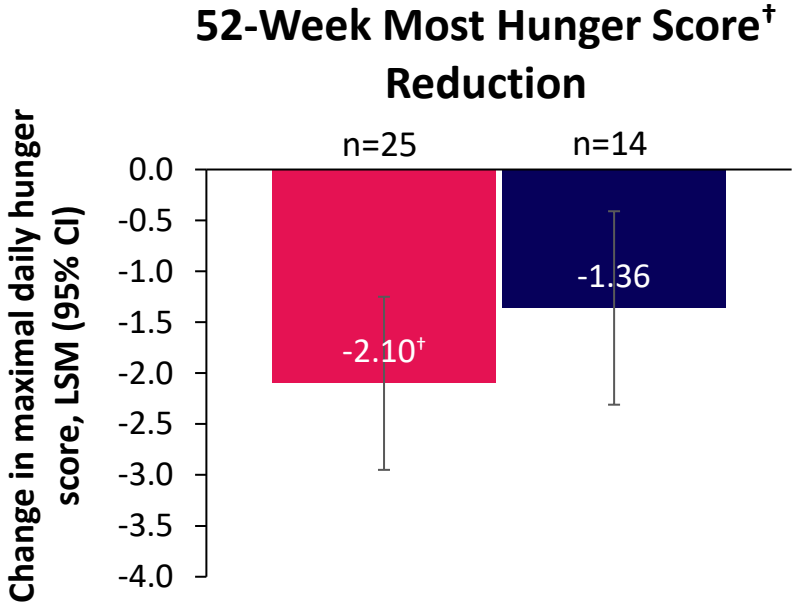
PBO-adjusted difference **–1.32**

***P*<0.0001 vs Placebo**

*Data are analysis of covariance LSM (95% confidence interval); the change in the z score could not be calculated for 3 participants who reached the age of 19 years during the trial.
BMI z-scores were calculated using the WHO 2007 method. Dashed line indicates a clinically relevant change of -0.2. CI, confidence interval; LSM, least squares mean.

Change in most hunger score with setmelanotide vs placebo (participants aged ≥12 to <18 years)





PBO-adjusted difference **-0.74**

***P*=0.2612 vs Placebo**

- The ability to detect a difference between the setmelanotide group and placebo group was limited by the low number of paediatric participants that were assessable for hunger.

*Weekly average of daily scores. participants ≥12 years of age who were able to self-report were administered the questionnaire. Participants were asked to rate their most hunger on an 11-point numerical rating scale from 0 to 10, where 0 = not hungry at all and 10 = hungriest possible via the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?"

†Data are analysis of covariance LSM (95% confidence interval). CI, confidence interval; LSM, least squares mean.

Safety

	Setmelanotide (n=49)	Placebo (n=27)	Overall (N=76)
AEs	49 (100.0)	25 (92.6)	74 (97.4)
AE leading to treatment or study discontinuation	2 (4.1)	2 (7.4)	4 (5.3)
Serious AEs	18 (36.7)	2 (7.4)	20 (26.3)
Serious AEs related to treatment	1 (2.0)*	0	1 (1.3)
AE resulting in death on study	1 (20)[†]	0	1 (1.3)
Most common AEs (≥30% in setmelanotide arm)			
Skin hyperpigmentation	29 (59.2)	2 (7.4)	31 (40.8)
Nausea	25 (51.0)	9 (33.3)	34 (44.7)
Vomiting	21 (42.9)	8 (29.6)	29 (38.2)
Headache	18 (36.7)	10 (37.0)	28 (36.8)
Injection site reaction	16 (32.7)	9 (33.3)	25 (32.9)

- One serious AE was considered related to setmelanotide: hypernatremia (sodium levels 150-158mmol/L [normal upper limit 145mmol/L]; resolved after 2 days with treatment
- There was one death due to seizures in a participant with a history of seizure disorder, which was not considered related to the study drug (setmelanotide)

*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 death (one participant), nausea and vomiting (same participant), and hyperpigmentation to arms, chest, and face (one participant). [§]Due to injection site reaction (one participant), and allergic reaction (one participant). AE, adverse event.

Conclusions

- In this paediatric dataset from the final results from the TRANSCEND trial in aHO, setmelanotide was associated with significant reductions in BMI measures
- The safety profile of setmelanotide was generally consistent with previous trials in participants with aHO and other rare MC4R pathway–associated diseases[1-4]
- These long-term data underscore the importance of correcting the MC4R pathway signalling disruption with targeted therapy
- Setmelanotide is approved for use in patients with aHO in the US, EU, UK, and Japan

aHO, acquired hypothalamic obesity; EU, European Union; 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.

THANK YOU

We would like to thank the participants and caregivers, without whom this trial could not have been completed

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