Long-Term Efficacy With Setmelanotide in Patients With Acquired Hypothalamic Obesity

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Disclosures

- M. Jennifer Abuzzahab receives institutional research support from Ascendis, Lumos, Medtronic, Rhythm Pharmaceuticals, Inc., and Soleno and received consulting/speaking fees from Ascendis, DayOne, Endo, Neurocrine, Novo Nordisk, Rezolute Bio, Rhythm Pharmaceuticals, Inc., and Soleno
- Christian L. Roth is supported by grants from the National Institutes of Health (award numbers R21HD115119, R01DK135125, and R01DK135211) and is on the advisory board of Rhythm Pharmaceuticals, Inc.
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- Guojun Yuan is an employee of and may hold stock options in Rhythm Pharmaceuticals, Inc.
- Cecilia Scimia is an employee of and may hold stock options in Rhythm Pharmaceuticals, Inc.
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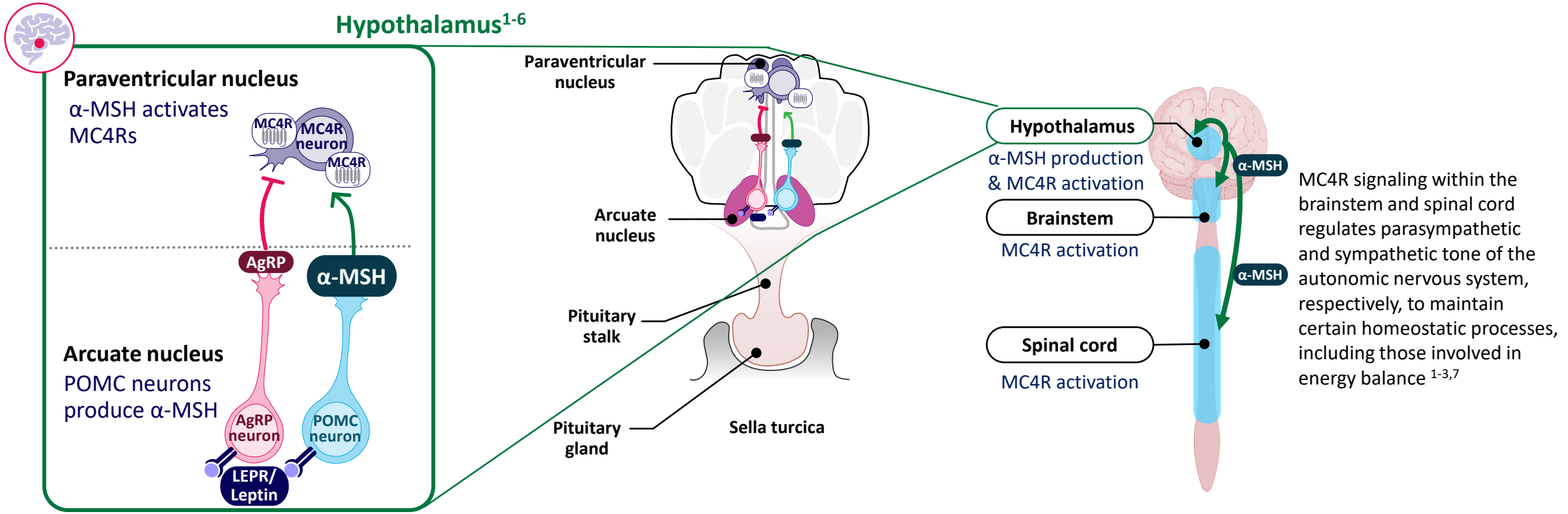
- This study was sponsored by Rhythm Pharmaceuticals, Inc.

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.

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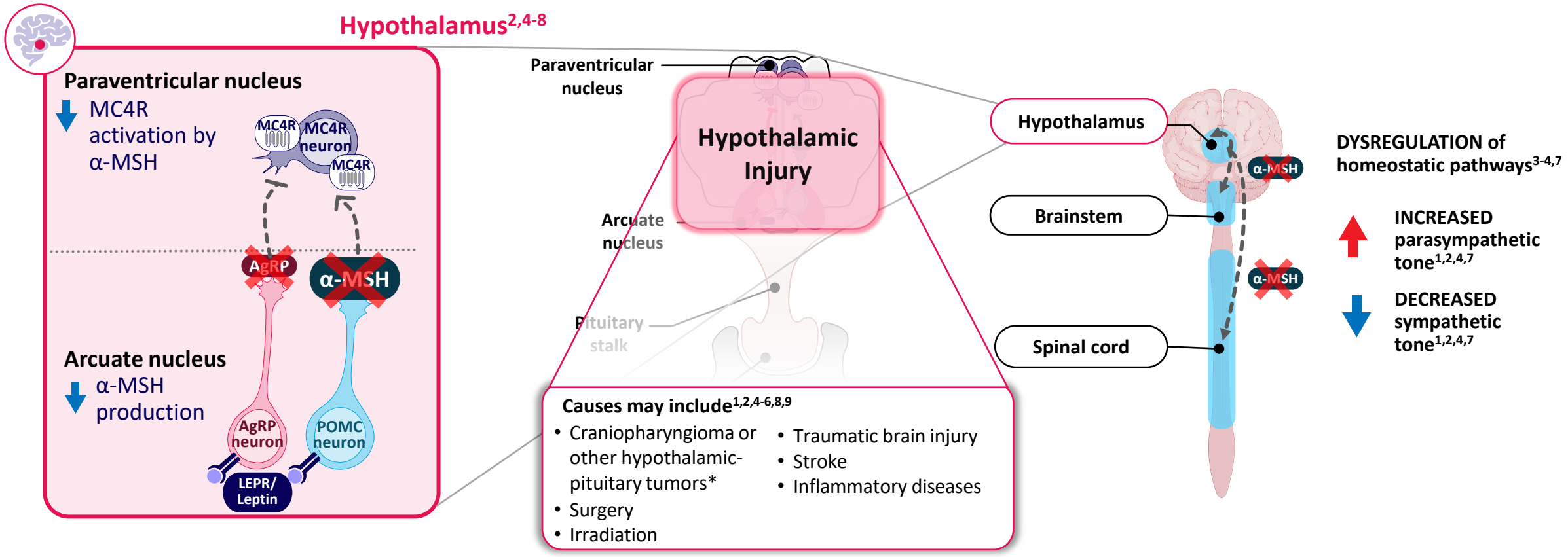
Loss of α-MSH Production Due to Hypothalamic Injury May Impair MC4R Pathway Signaling and Lead to Acquired Hypothalamic Obesity[1-3]



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

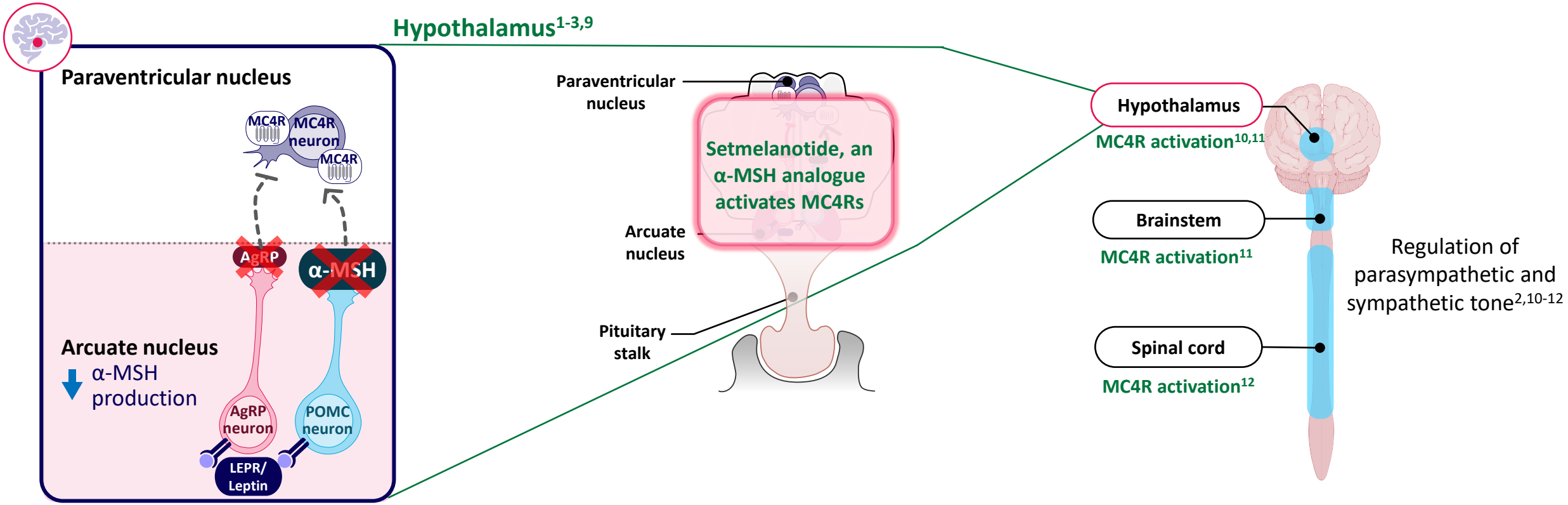
- Increased hunger/hyperphagia
- Reduced energy expenditure

→ **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]:

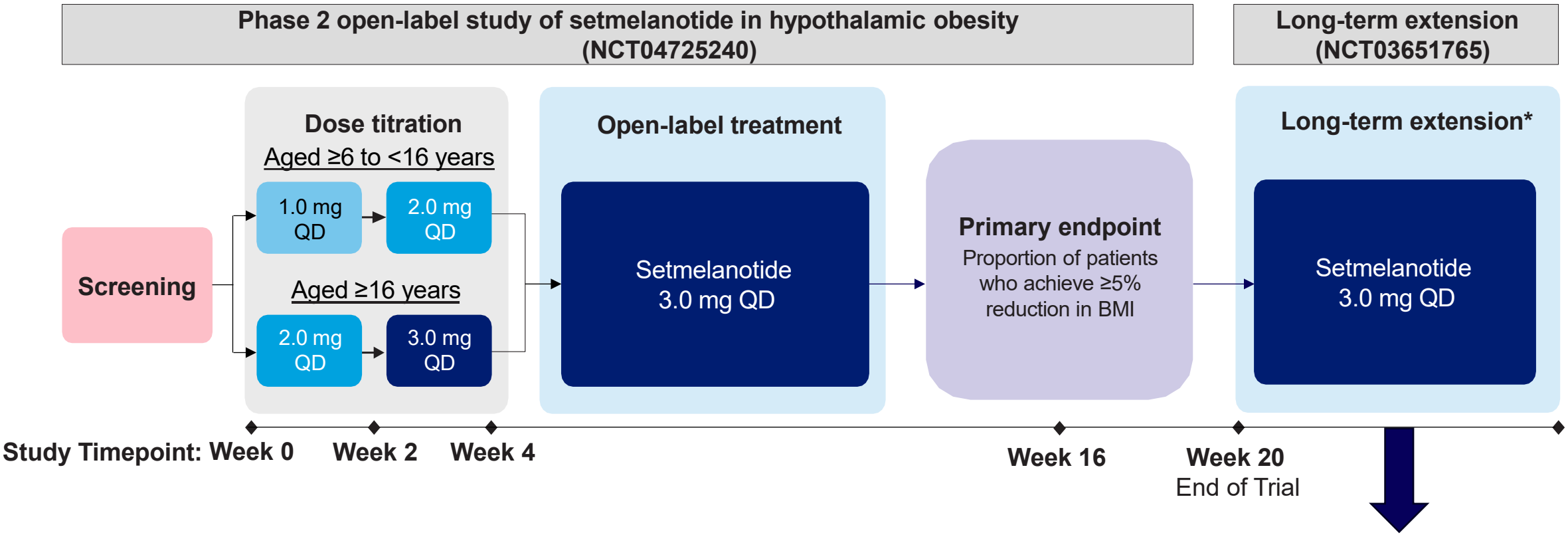
- Decreased hunger and improved satiety signaling
- Reduced symptoms of hyperphagia
- Increased energy expenditure

→ **Reduced body weight**

α-MSH, α–melanocyte-stimulating hormone; **AgRP**, agouti-related peptide; **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



Endpoints assessed in long-term extension:

- Change in BMI
- Change in BMI z-score
- Adverse events

*Participants who completed the 16-week Phase 2 index trial (NCT04725240), experienced a ≥5% reduction in BMI or had an investigator-determined clinically meaningful benefit, and exhibited adequate safety after 16 weeks of treatment were eligible to enroll in the Long-term extension (NCT03651765) study. **BMI**, body mass index; **QD**, once daily.

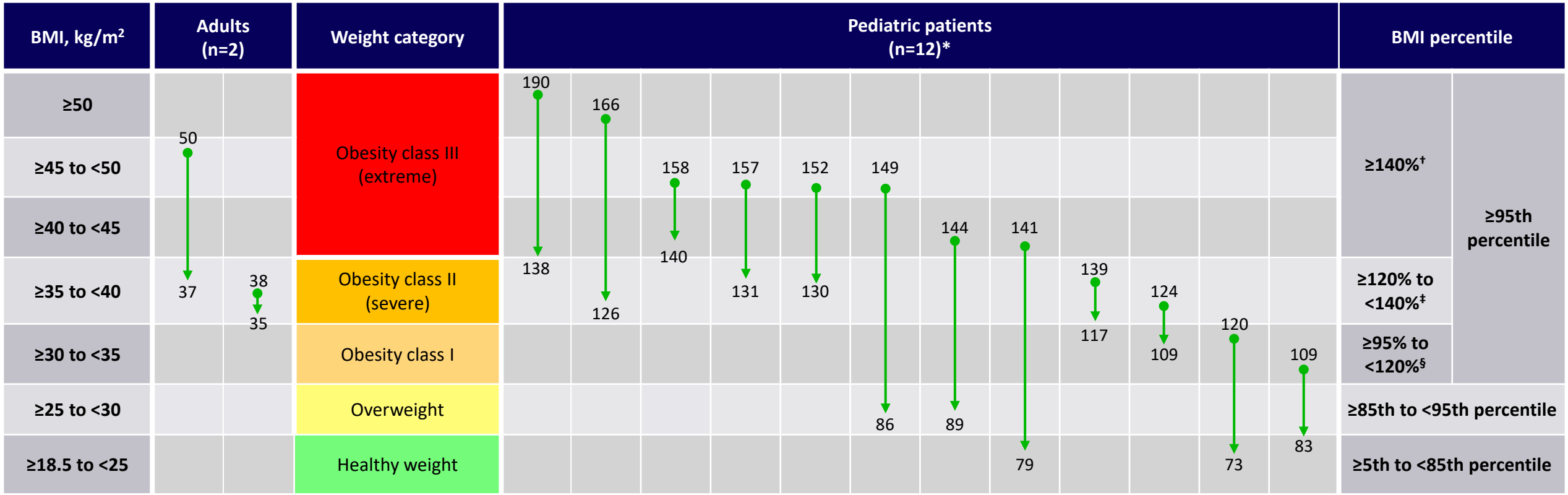
Introduction – Setmelanotide in aHO at 1 Year (Phase 2 Data)

- The primary endpoint (the proportion of patients that exhibited a ≥5% reduction in BMI from baseline at Week 16) was met:[1]
  - Achieved by 16 of 18 (89%) participants (90% CI, 69%–98%; *P*<0.001)
- Overall (n=14), at 12 months, the mean (SD) percent change from baseline in BMI was −22.0% (12.6%)
- For pediatric participants (n=12), the mean (SD) change from baseline in BMI z-score was −1.88 (1.15) at 12 months

aHO, acquired hypothalamic obesity; **BMI**, body mass index.

1. Roth CL, et al. *Lancet Diabetes Endocrinol*. 2024;12(6):380-389.

Introduction – Weight Class Change at 1 Year (Phase 2 Data)[1]



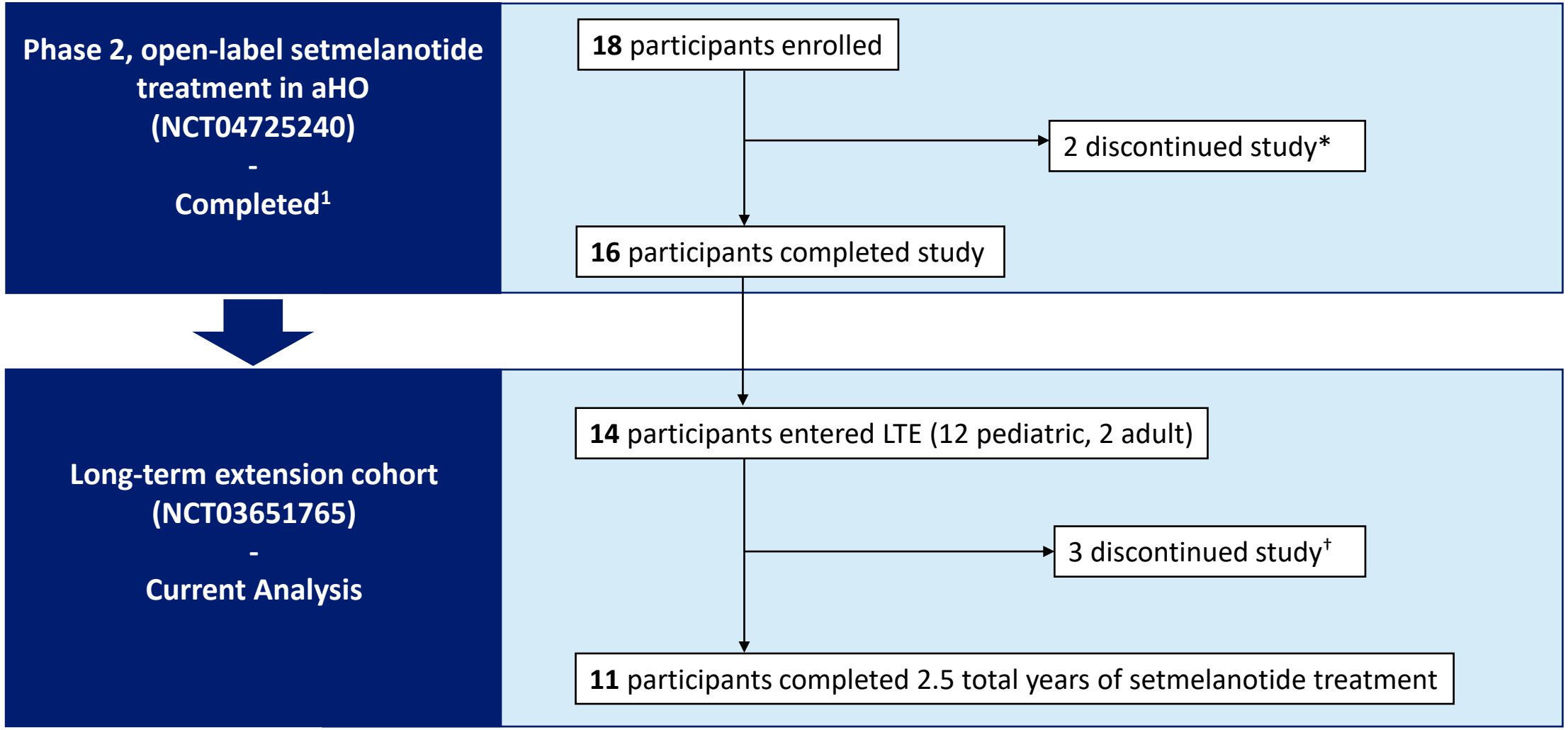
*Pediatric patients reported as %BMI95. †Or BMI ≥40 kg/m² (whichever is lower). ‡Or BMI ≥35 to <40 kg/m² (whichever is lower). §Or BMI ≥30 to <35 kg/m² (whichever is lower). **%BMI95**, percent of the 95th percentile for BMI; **BMI**, body mass index.

1. Roth CL, et al. Presented at the Obesity Society Annual Meeting; October 14-17, 2023, Dallas, Texas.

Objective

- To assess the continued efficacy and safety after 2.5 years of setmelanotide treatment

Study Disposition



*Discontinuations due to adverse events in one participant and non-adherence with study drug administration in the other participant. †Discontinuations due to non-compliance with study drug in two participants and study withdrawal by one participant. **aHO**, acquired hypothalamic obesity; **LTE**, long-term extension.

1. Roth CL, et al. *Lancet Diabetes Endocrinol*. 2024;12(6):380-389.

Baseline Demographics of Participants in LTE

	Setmelanotide (n=14)
Age, mean ± SD (range), y	13.6±5.0 (6.0–24.0)
Age Categories, n (%)	
6 to <18 years	12 (85.7)
≥18 years	2 (14.3)
Sex, n (%)	
Female	4 (28.6)
Male	10 (71.4)
Race, n (%)	
White	11 (78.6)
Black or African American	2 (14.3)
Native Hawaiian or Other Pacific Islander	1 (7.1)

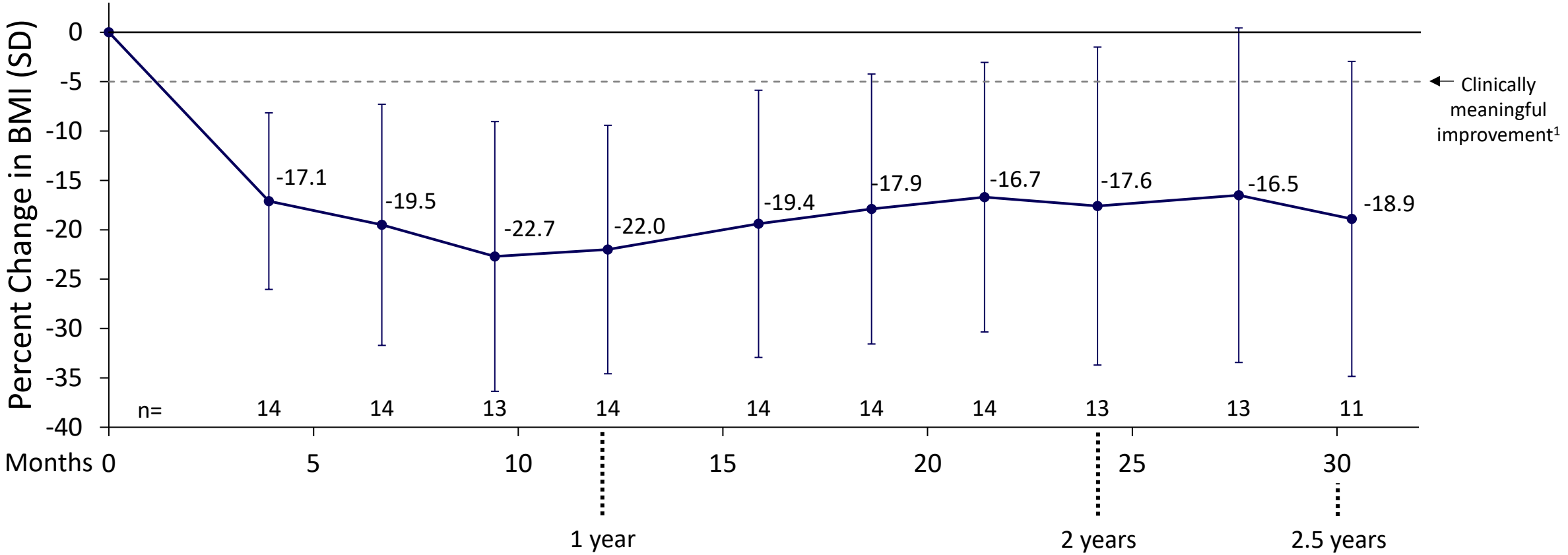
LTE, long-term extension; **SD**, standard deviation.

Baseline Demographics of Participants in LTE (cont)

	Setmelanotide (n=14)
Ethnicity, n (%)	
Hispanic or Latino	4 (28.6)
Not Hispanic or Latino	10 (71.4)
Weight, mean (SD), kg	99.1 (32.7)
BMI, mean (SD), kg/m^2	37.0 (7.1)
Percentage of the 95th percentile of BMI, mean (SD)*	
6 to <18 years [n=12]	145.8 (21.9)
Waist circumference, mean (SD), cm	112.0 (17.9)

*Percentage of the 95th percentile of BMI calculated according to the Centers for Disease Control and Prevention 2022 method.
BMI, body mass index; **LTE**, long-term extension; **SD**, standard deviation.

Mean Percent Change in BMI from Baseline to 2.5 years
In All Participants

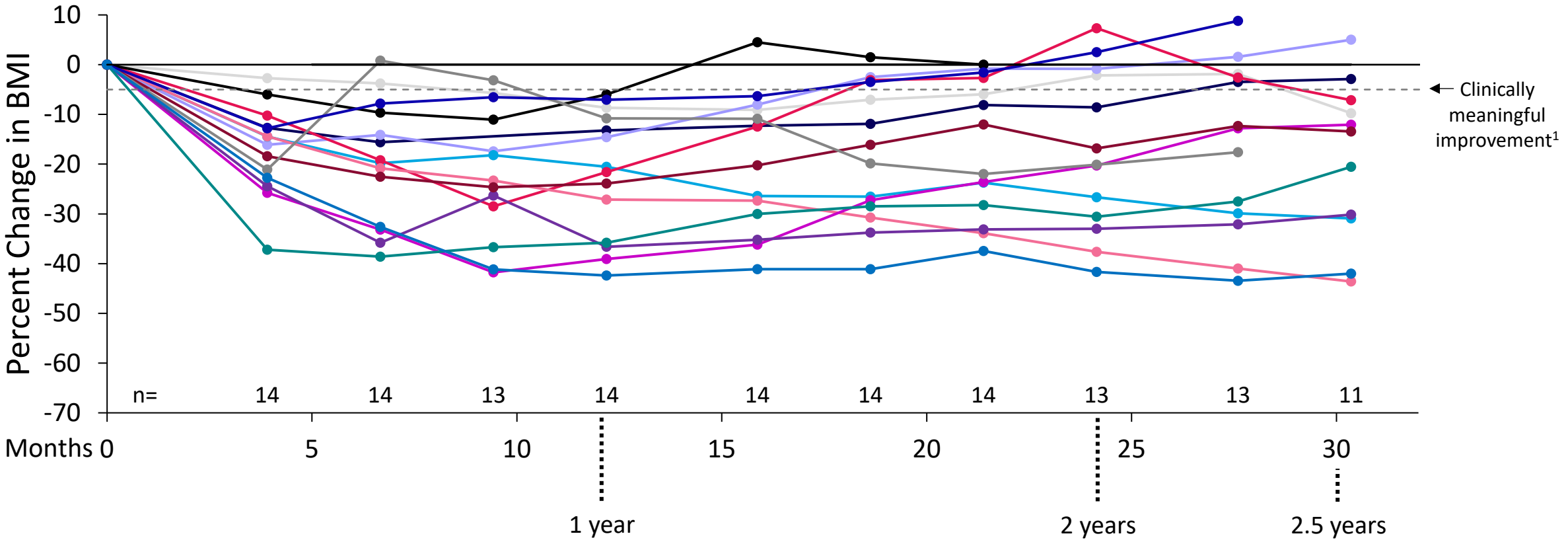


- After 2.5 years, the mean (SD) BMI percent change from baseline was −18.9% (16.0).

Error bars are SD. **BMI**, body mass index; **SD**, standard deviation.

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

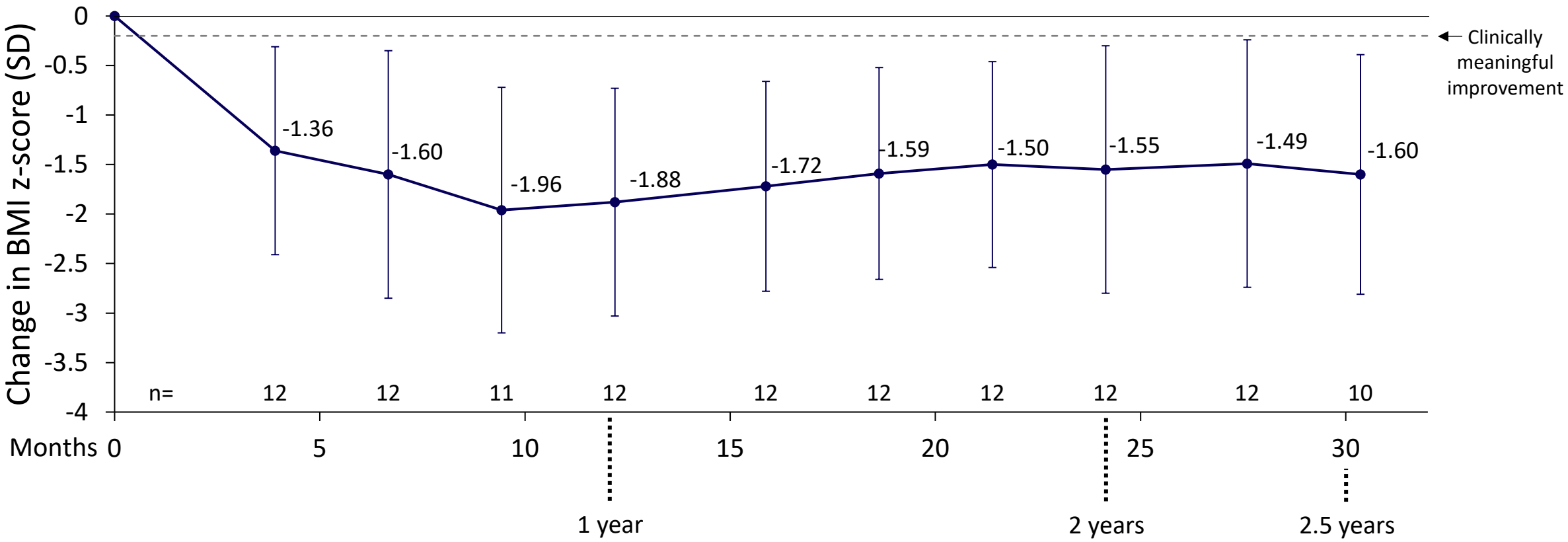
Individual Percent Change in BMI from Baseline to 2.5 years
In All Participants



BMI, body mass index.

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

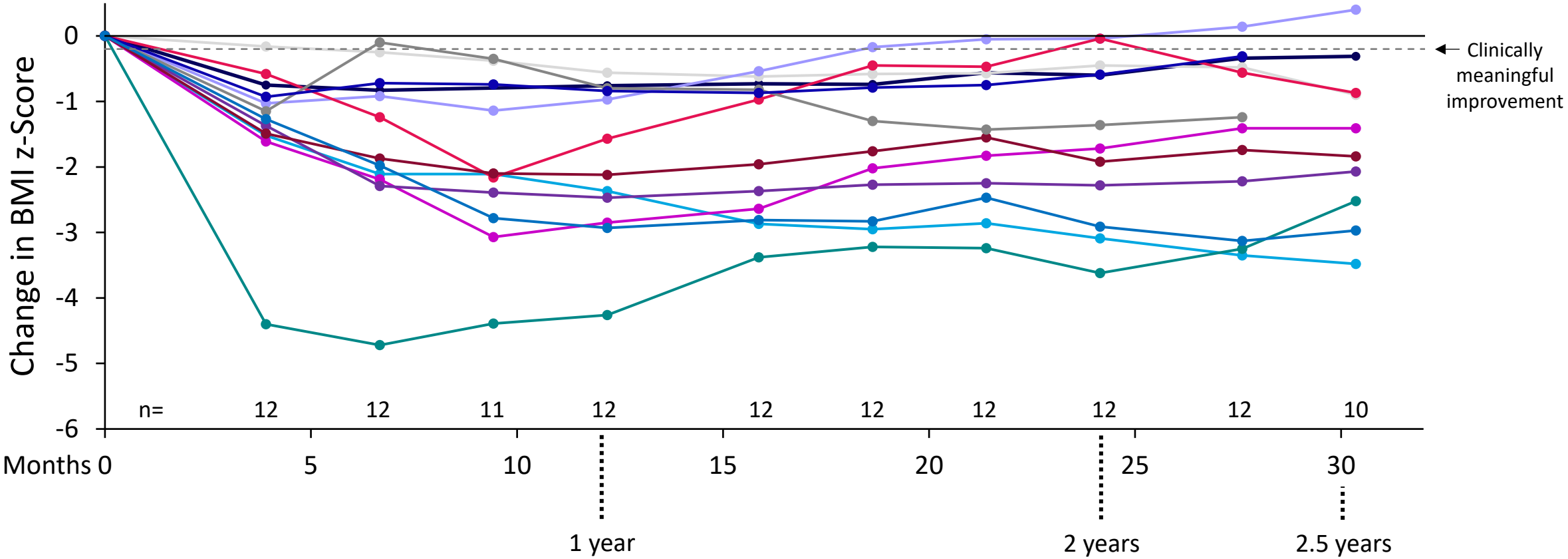
Mean Change in BMI z-Score from Baseline to 2.5 Years
In Pediatric Participants



- After 2.5 years, the mean (SD) change from baseline in BMI z-score was –1.60 (1.21).

Error bars are SD.
BMI, body mass index; **SD**, standard deviation.

Individual Change in BMI z-score from Baseline to 2.5 years
In Pediatric Participants



BMI, body mass index.

Setmelanotide was Generally Well Tolerated

n (%)	Setmelanotide (n=14)
AEs	14 (100)
AE leading to treatment or study discontinuation	0
Serious AEs	4 (28.6)
AE resulting in death on study	0
AE in ≥20% of participants	
Nausea	8 (57.1)
Skin hyperpigmentation	7 (50.0)
Upper respiratory tract infection	6 (42.9)
Vomiting	6 (42.9)
Headache	5 (35.7)
COVID-19	4 (28.6)
Increased erection	4 (28.6)
Injection site induration	4 (28.6)
Abdominal pain	3 (21.4)
Back pain	3 (21.4)
Injection site pain	3 (21.4)

AE, adverse event; **COVID-19**; coronavirus disease 2019.

Conclusions

- Two and a half years of setmelanotide treatment was associated with robust, sustained, and clinically significant BMI and BMI z-score reductions in patients with aHO
- The safety profile was generally consistent with that observed in previous clinical trials of setmelanotide[1-4]
- These long-term data underscore the importance of targeting the deficiency in MC4R signaling to prevent the accelerated, sustained weight gain typical in this population

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

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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