Efficacy and Safety of Setmelanotide in Acquired Hypothalamic Obesity: Results From the Double-Blind, Multicenter, Placebo-Controlled, Randomized Phase 3 TRANSCEND Trial

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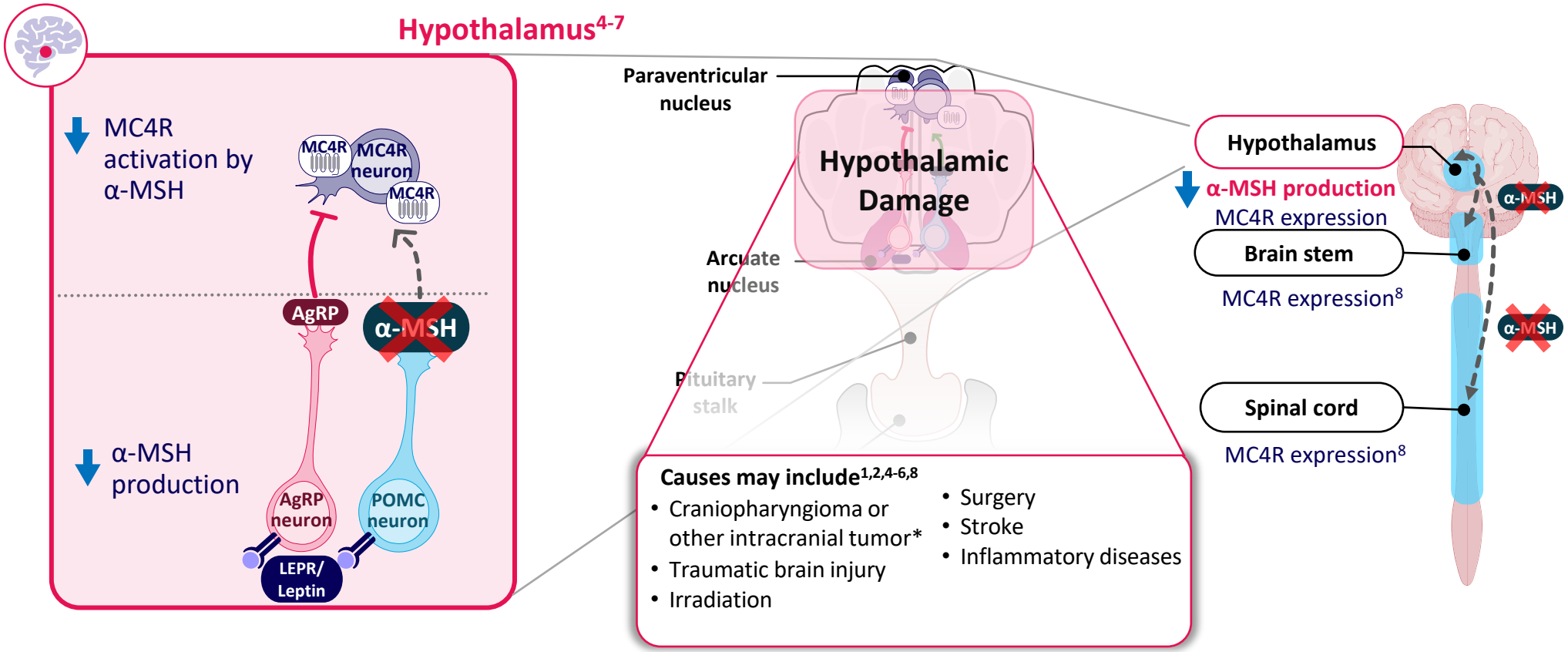
Setmelanotide Is Under Investigation for the Treatment of Acquired Hypothalamic Obesity and is not Approved by the FDA for Treatment of Acquired Hypothalamic Obesity

The views expressed in this educational program are those of the faculty and do not necessarily represent the views of the Endocrine Society.

*Co-senior authors.

Note: This version incorporates post-presentation updates following receipt and analysis of final dataset and minor edits for clarity

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



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

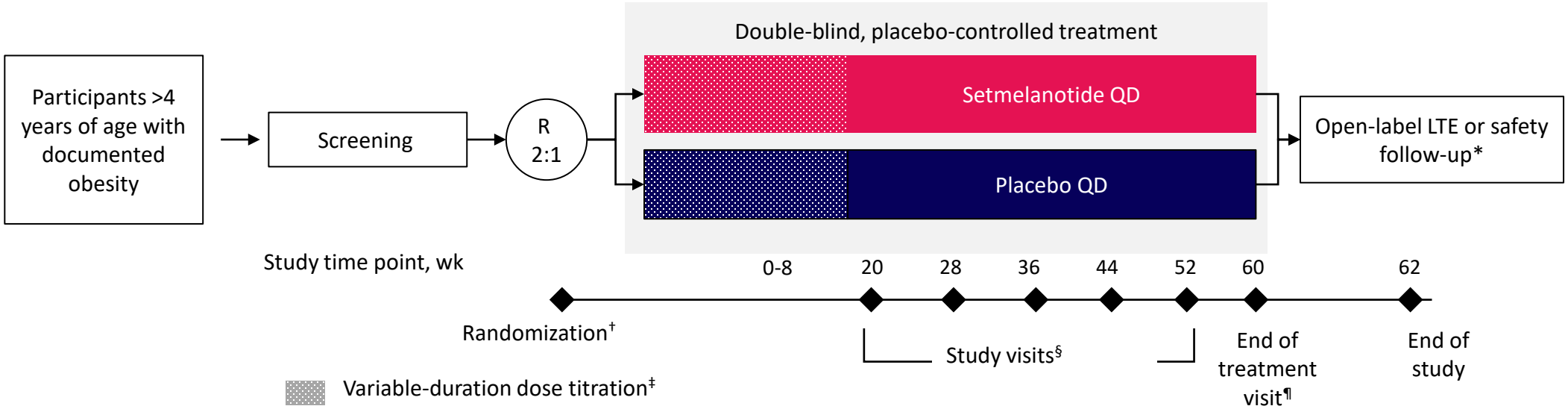
- Hyperphagia
- Reduced energy expenditure

→ **Accelerated and sustained weight gain**

*Suprasellar tumors such as astrocytoma.[1,7] α-MSH, α–melanocyte-stimulating hormone; aHO, acquired hypothalamic obesity; 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.

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 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. ‡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; QD, once daily; R, randomization.

Baseline Patient Demographics

	Setmelanotide (n=81)	Placebo (n=39)
Age, mean ± SD (range), y	**19.2 ± 13.0 (4-65)**	**21.4 ± 13.8 (4-66)**
Age <18 y, n (%)	48 (59.3)	23 (59.0)
Age ≥18 y, n (%)	33 (40.7)	16 (41.0)
Sex, n (%)		
Female	45 (55.6)	27 (69.2)
Male	36 (44.4)	12 (30.8)
Weight, mean (95% CI), kg	**92.9 (84.4-101.4)**	**94.1 (81.5-106.7)**
In those ≥18 y	115.6 (103.6-127.6)	124.2 (106.7-141.7)
BMI, mean (95% CI), kg/m^2	**35.7 (33.7-37.8)**	**36.8 (33.8-39.8)**
Participants ≥18 years, kg/m^2	40.1 (36.7-43.6)	43.5 (38.5-48.4)
BMI Z score (WHO), 4 to <18 y, mean (95% CI)*	**3.72 (3.19-4.25)**	**3.37 (2.81-3.93)**
%BMI95 (CDC), 4 to <18 y, mean (95% CI)†	**132.3 (124.0-140.7)**	**128.6 (118.8-138.5)**
Waist circumference (95% CI), cm	**106.6 (101.8-111.4)**	**108.6 (102.6-114.7)**
Maximal daily hunger score, mean (n; 95% CI)‡	**6.77 (57; 6.15-7.38)**	**7.23 (24; 6.34-8.13)**
Prior GLP-1 therapy, n (%)	**10 (12.3)**	**6 (15.4)**
Prior and concomitant GLP-1 therapy	9 (11.1)	6 (15.4)

*BMI Z score calculated according to the WHO 2007 method. †%BMI95 calculated according to the CDC 2022 method. ‡Weekly average of daily scores.
%BMI95, percent of the body mass index 95th percentile; CDC, Centers for Disease Control and Prevention; CI, confidence interval; GLP-1, glucagon-like peptide-1; WHO, World Health Organization.

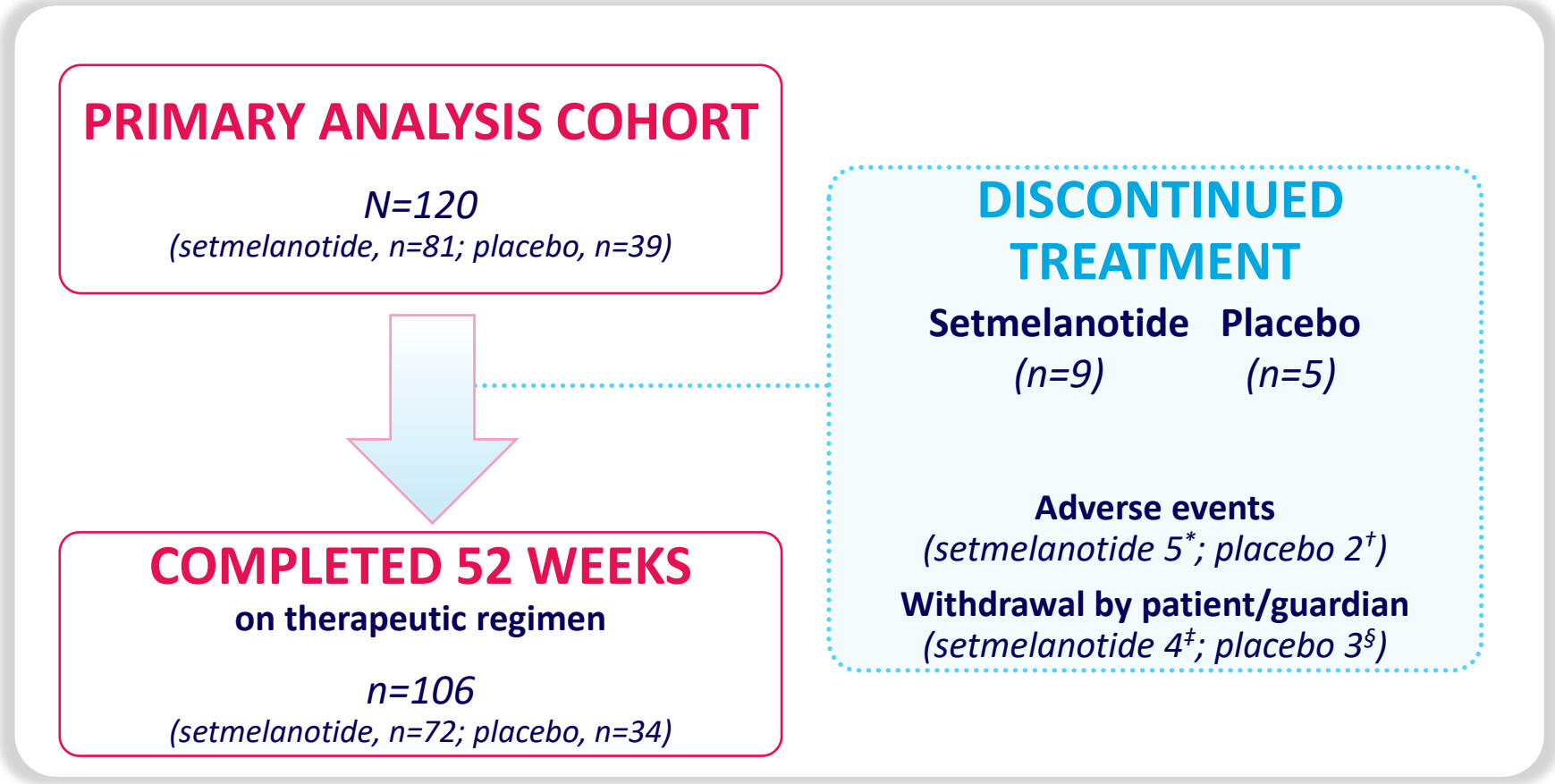
Baseline Patient Demographics (Cont)

	Setmelanotide (n=81)	Placebo (n=39)
Tumor/damage type, n (%)		
Craniopharyngioma	63 (77.8)	30 (76.9)
Glioma	4 (4.9)	3 (7.7)
Astrocytoma	3 (3.7)	3 (7.7)
Germinoma	5 (6.2)	1 (2.6)
Hamartoma	1 (1.2)	1 (2.6)
Other and non–tumor-related	5 (6.2)*	1 (2.6)†
Tumor treatment, n (%)		
Hypothalamic surgery for lesion removal	73 (90.1)	35 (89.7)
Radiotherapy	39 (48.1)	21 (53.8)
Chemotherapy	18 (22.2)	8 (20.5)
Hypothalamic involvement, n (%)		
Bilateral	53 (65.4)	26 (66.7)
Unilateral	7 (8.6)	2 (5.1)
Unknown	21 (25.9)	10 (25.6)
Missing	0	1 (2.6)

	Setmelanotide (n=81)	Placebo (n=39)
Endocrine disorders, n (%)	**81 (100.0)**	**38 (97.4)**
Central hypothyroidism or hypothyroidism	68 (84.0)	30 (76.9)
Arginine vasopressin deficiency	67 (82.7)	30 (76.9)
Adrenal insufficiency, secondary adrenocortical insufficiency, or adrenocorticotropic hormone deficiency	56 (69.1)	23 (59.0)
Growth hormone deficiency	55 (67.9)	22 (56.4)
Secondary hypogonadism	32 (39.5)	13 (33.3)
Precocious puberty	5 (6.2)	6 (15.4)

*Arachnoid cyst, heterogeneous mass in the suprasellar region involving the hypothalamus and optic chiasm, mature teratoma, cavernous haemangioma, and either craniopharyngioma or astrocytoma (n=1 each). †Hypothalamic glioma pilocytic astrocytoma.

Disposition



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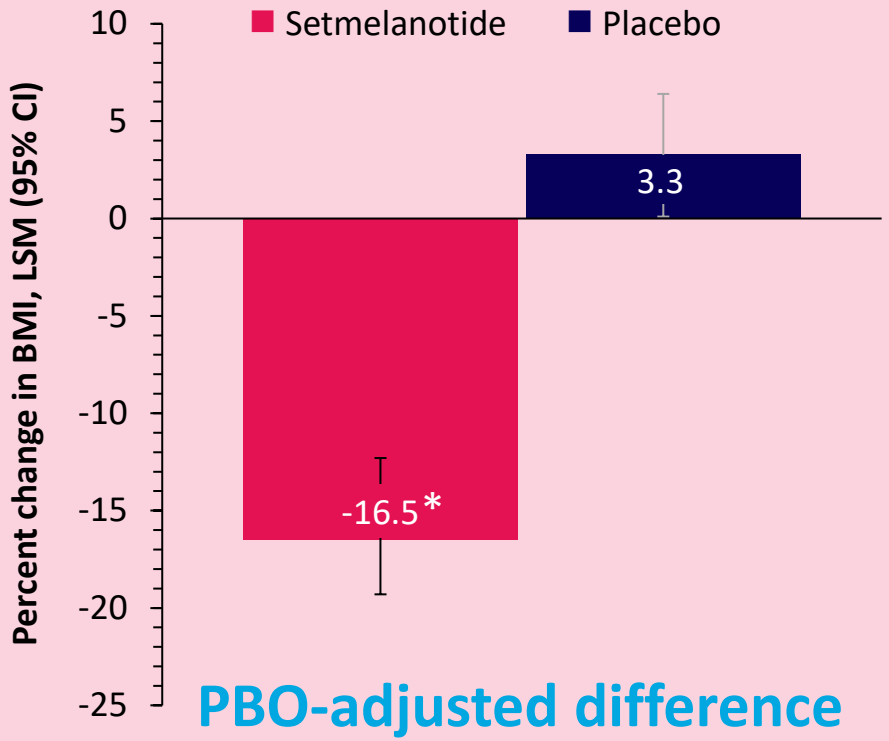
ENROLLED IN OPEN-LABEL EXTENSION

As of data cutoff, April 3, 2025

*Due to injection site pruritus, muscle spasms, and rhinorrhea (same patient), nausea and vomiting (same patient), and gastroesophageal reflux disease, seizure, and skin hyperpigmentation (n=1 each). †Due to hypersensitivity and injection site reaction (n=1 each). ‡Two patients characterized as "withdrawal by patient/guardian" also experienced an adverse event that led to study discontinuation (1 of whom also experienced an adverse event that led to study treatment discontinuation). §One patient characterized as "withdrawal by patient/guardian" also experienced an adverse event leading to study treatment discontinuation.

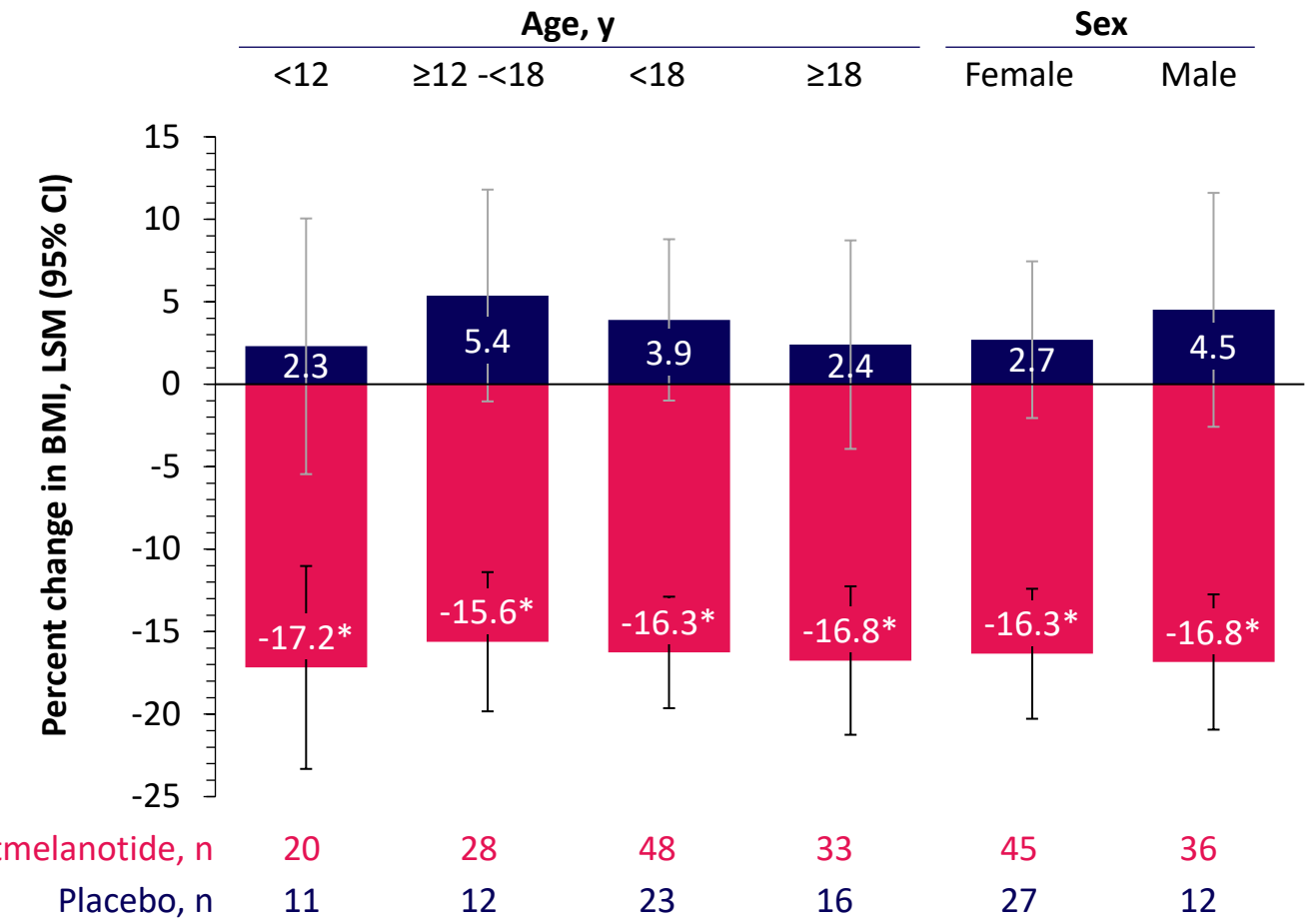
Significant Reduction in BMI With Setmelanotide at Week 52, and Consistent Response Across Subgroups

Primary Endpoint



PBO-adjusted difference

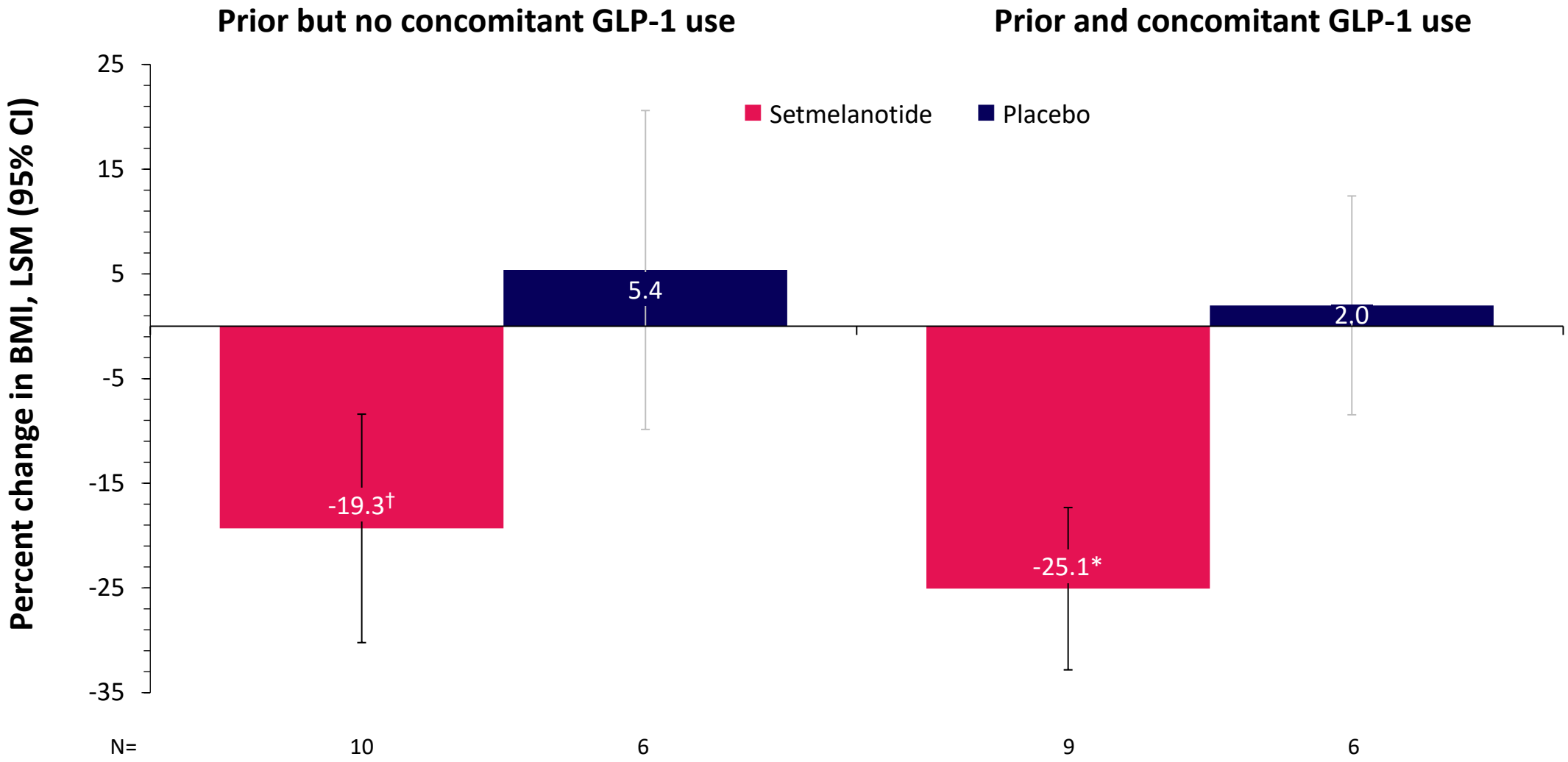
-19.8%



**P*<0.0001 vs placebo.

LSM difference in mean percent change from baseline in BMI at Week 52, obtained from an analysis of covariance model. Rubin's Rule was used to provide the overall estimates of differences in LSMs and *P*-value. BMI, body mass index; CI, confidence interval; LSM, least squares mean; PBO, placebo.

Significant BMI Reductions Observed in Participants With Prior or Prior and Concomitant Use of GLP-1RA

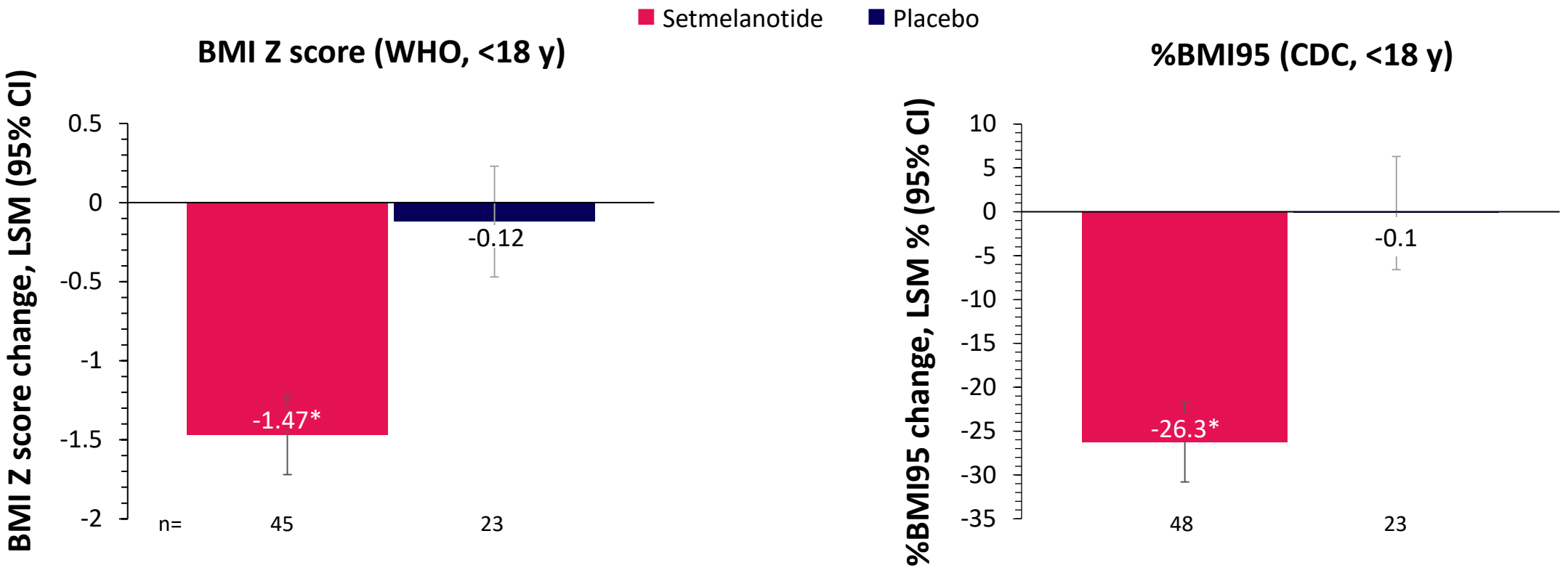


Note: Footnote markers have been updated post presentation to align to the corresponding p-value

†*P*=0.0046 and **P*<0.0001 vs placebo.

BMI, body mass index; CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; LSM, least squares mean.

Statistically Significant Reduction in Weight-Related Measures in Participants Aged <18 Years With Setmelanotide vs Placebo at Week 52



-1.35

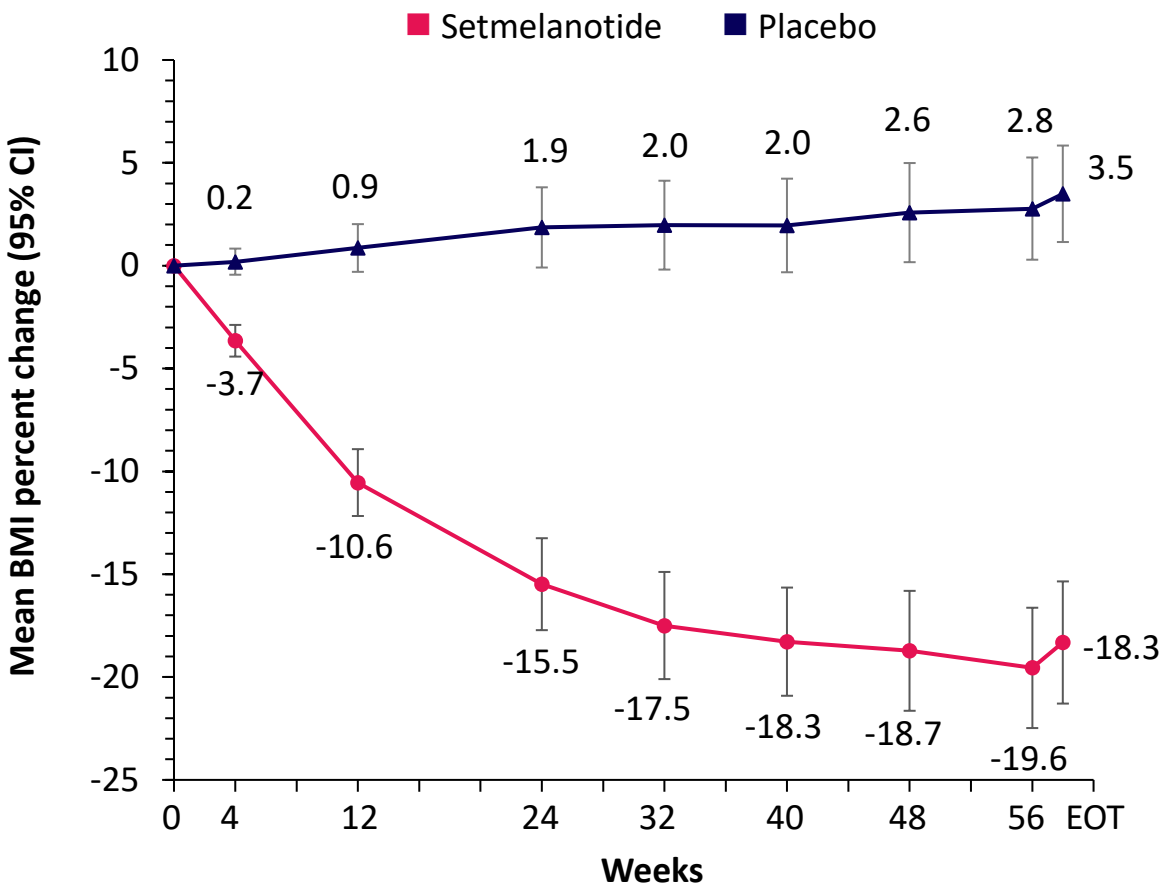
-26.2%

PBO-adjusted difference

*P<0.0001 vs placebo.

Data are analysis of covariance LSM (95% confidence interval) unless otherwise indicated.
%BMI95, percent of the body mass index 95th percentile; CDC, Centers for Disease Control and Prevention; PBO, placebo; WHO, World Health Organization.

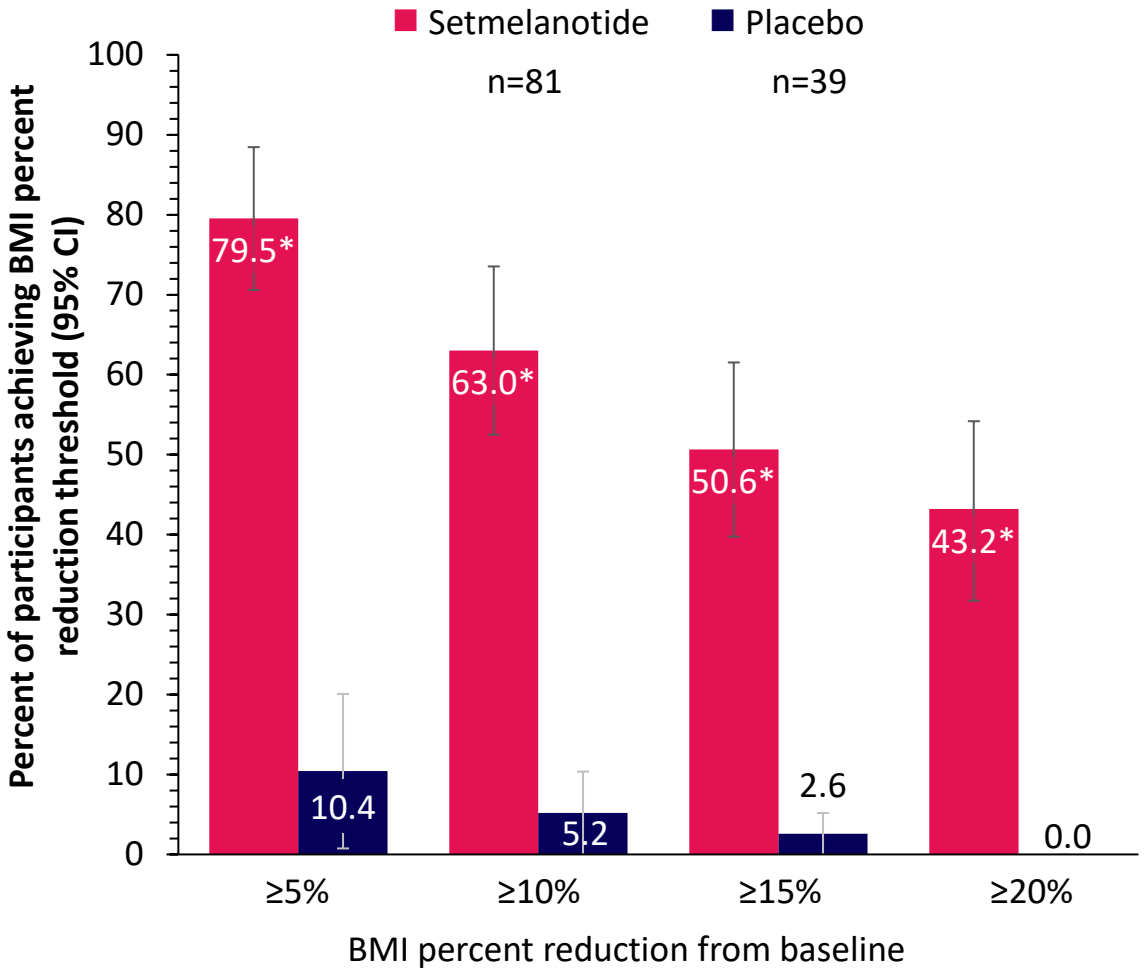
Rapid and Significant BMI Percent Reduction Starting at Week 4



Setmelanotide, n	81	81	77	75	68	73	68	69	71
Placebo, n	39	38	37	38	34	36	33	35	37

Note: Graph axis labels reflect post-presentation edits for accuracy and clarity

A Higher Proportion Achieved Percent BMI Reductions for All BMI Thresholds

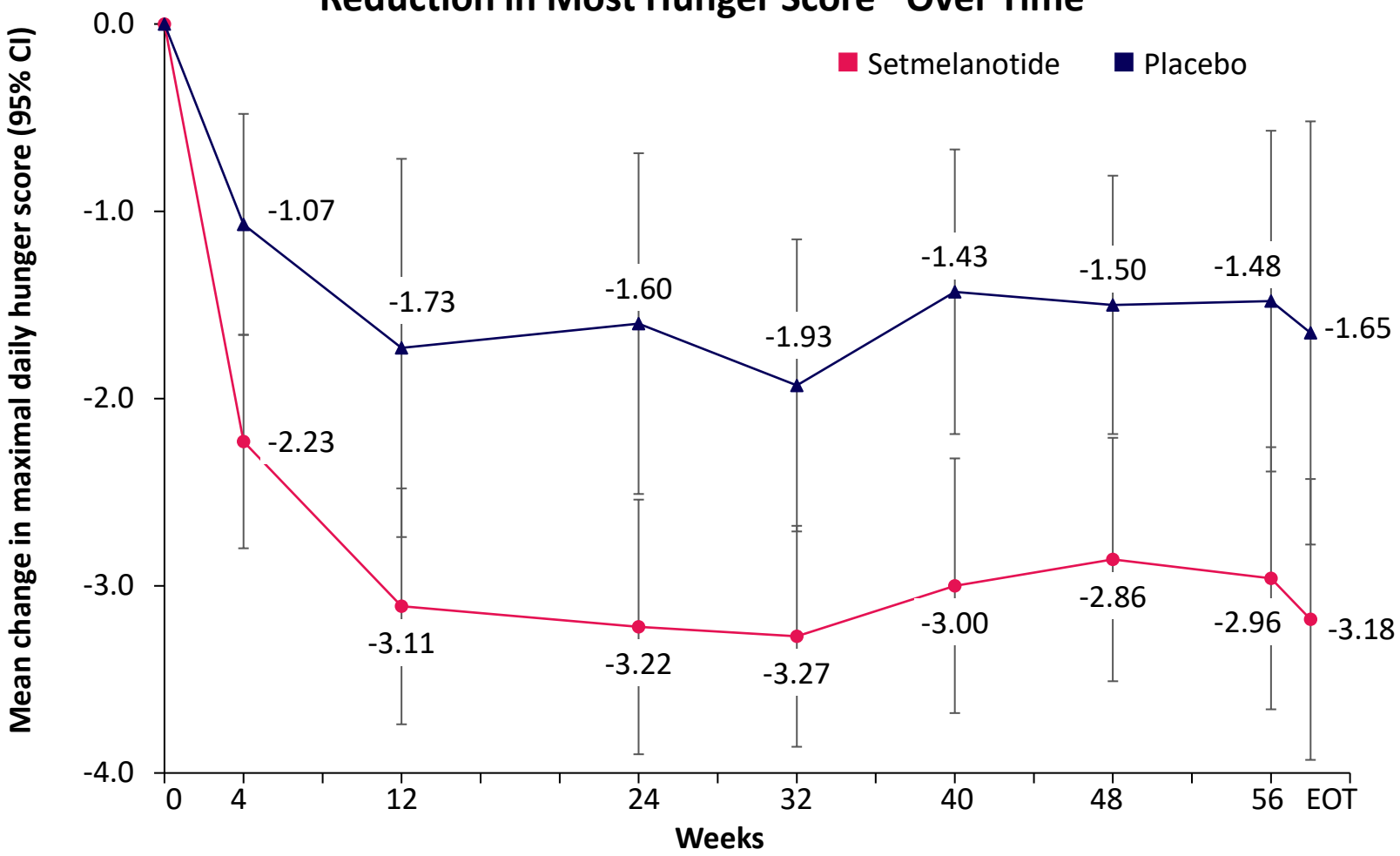


*P<0.0001 vs placebo.

BMI, body mass index; CI, confidence interval.

Rapid and Statistically Significant Reduction in Most Hunger Score With Setmelanotide vs Placebo (Participants Aged ≥12 Years)

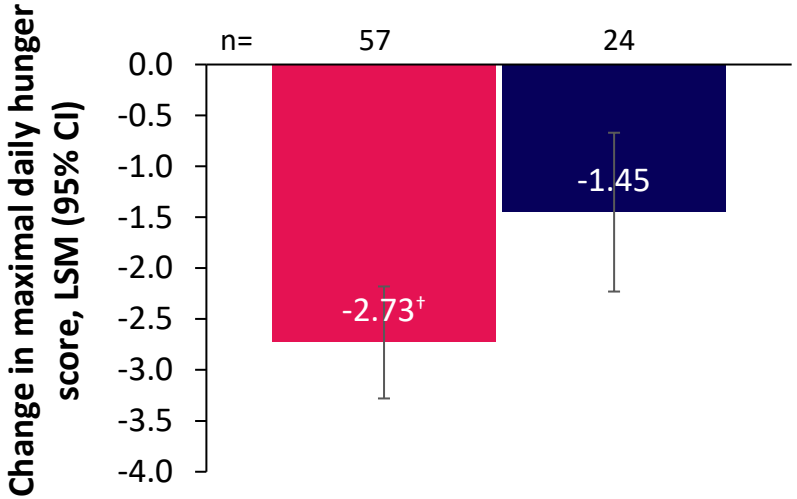
Reduction in Most Hunger Score* Over Time



Setmelanotide, n 57	52	53	44	50	46	44	44	39
Placebo, n 24	18	19	23	22	19	18	17	15

Note: Slide reflects post-presentation updates following receipt and analysis of final data

52-Week Most Hunger Score* Reduction



PBO-adjusted difference **-1.28**

†*P*=0.0086 vs placebo.

*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?" CI, confidence interval; LSM, least squares mean.

Setmelanotide Was Generally Well Tolerated With No New AE Signals

	Setmelanotide (n=81)	Placebo (n=39)	Overall (n=120)
≥1 AE of any cause	81 (100.0)	35 (89.7)	116 (96.7)
≥1 Drug-related AE	71 (87.7)	26 (66.7)	97 (80.8)
≥1 Serious AE	23 (28.4)	3 (7.7)	26 (21.7)
≥1 Drug-related serious AE	1 (1.2)*	0	1 (0.8)
≥1 AE that resulted in death	1 (1.2)	0	1 (0.8)
≥1 AE leading to study drug withdrawal	6 (7.4)	3 (7.7)	9 (7.5)
≥1 AE leading to study discontinuation	4 (4.9)	0	4 (3.3)
Most common (≥20% in setmelanotide arm)			
Skin hyperpigmentation	45 (55.6)	3 (7.7)	48 (40.0)
Nausea	41 (50.6)	12 (30.8)	53 (44.2)
Headache	31 (38.3)	12 (30.8)	43 (35.8)
Vomiting	32 (39.5)	7 (17.9)	39 (32.5)
Diarrhea	19 (23.5)	8 (20.5)	27 (22.5)
Injection site reaction	19 (23.5)	9 (23.1)	28 (23.3)

- One serious AE was considered related to the study drug (setmelanotide): hypernatremia (sodium levels 150-158 mmol/L [normal upper limit 145 mmol/L]; resolved after 2 days with treatment
- There was 1 death due to seizures in a patient with a history of seizure disorder, which was not considered related to the study drug
- Safety was generally consistent with previously reported AEs in other clinical trials

Note: Slide reflects post-presentation updates following receipt and analysis of final data

*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. AE, adverse event.

Conclusions

- aHO is a devastating disease that has had no reliable approved treatment options to date
- TRANSCEND is the largest and longest placebo-controlled trial in participants with aHO 4-66 years of age
- Setmelanotide, an analogue of the endogenous hormone α-MSH, demonstrated robust and clinically significant results on the primary and all key secondary endpoints regardless of age or sex
  - The primary endpoint was met with setmelanotide-treated participants achieving a −19.8% placebo-adjusted difference in percent BMI reduction from baseline ($P<0.0001$)
  - All key secondary weight-related endpoints and the most hunger score showed larger improvements with setmelanotide relative to placebo
  - Participants previously treated unsuccessfully with a GLP-1 for obesity or concomitantly during the trial with setmelanotide also achieved robust and clinically significant reductions in percent BMI reductions
- AEs were consistent with those reported in other clinical trials
  - AEs occurring more frequently in the setmelanotide arm included skin hyperpigmentation, nausea, headache, and vomiting
- These results suggest that setmelanotide may be a promising potential treatment option for patients with evidence of damage to the MC4R pathway

Additional participants outside the primary analysis cohort who remain blinded to treatment and are ongoing will complete the trial 1H 2026. A long-term extension of the trial is also ongoing. α-MSH, α–melanocyte-stimulating hormone; AE, adverse event; aHO, acquired hypothalamic obesity; BMI, body mass index; GLP-1, glucagon-like peptide-1; MC4R, melanocortin-4 receptor.

Thank You

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

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