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Impact of setmelanotide on metabolic index scores in paediatric participants with acquired hypothalamic obesity – A phase 3 trial post hoc analysis

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Disclosures

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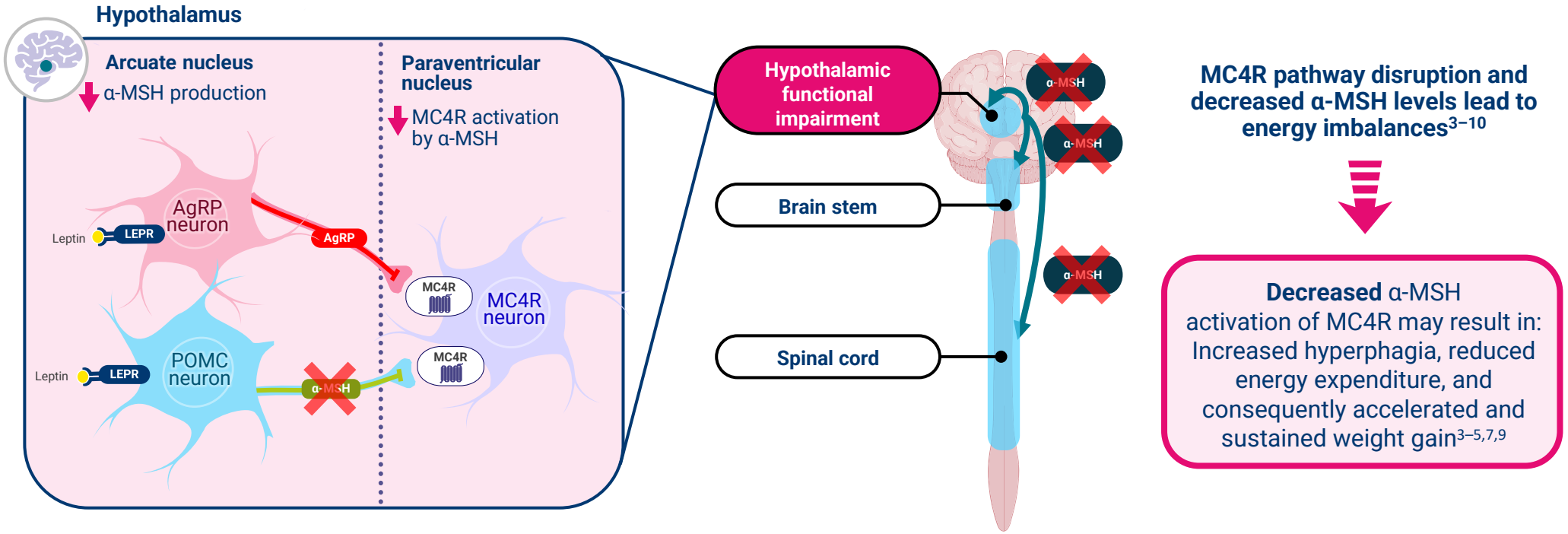
Acquired hypothalamic obesity (aHO) is a rare complex disease resulting from physical injury or structural abnormality of the hypothalamus[1,2]

- A key feature of aHO is disrupted melanocortin-4 receptor (MC4R) pathway signalling which can lead to hyperphagia (pathological, insatiable hunger), decreased energy expenditure, and accelerated and sustained weight gain[1–5]

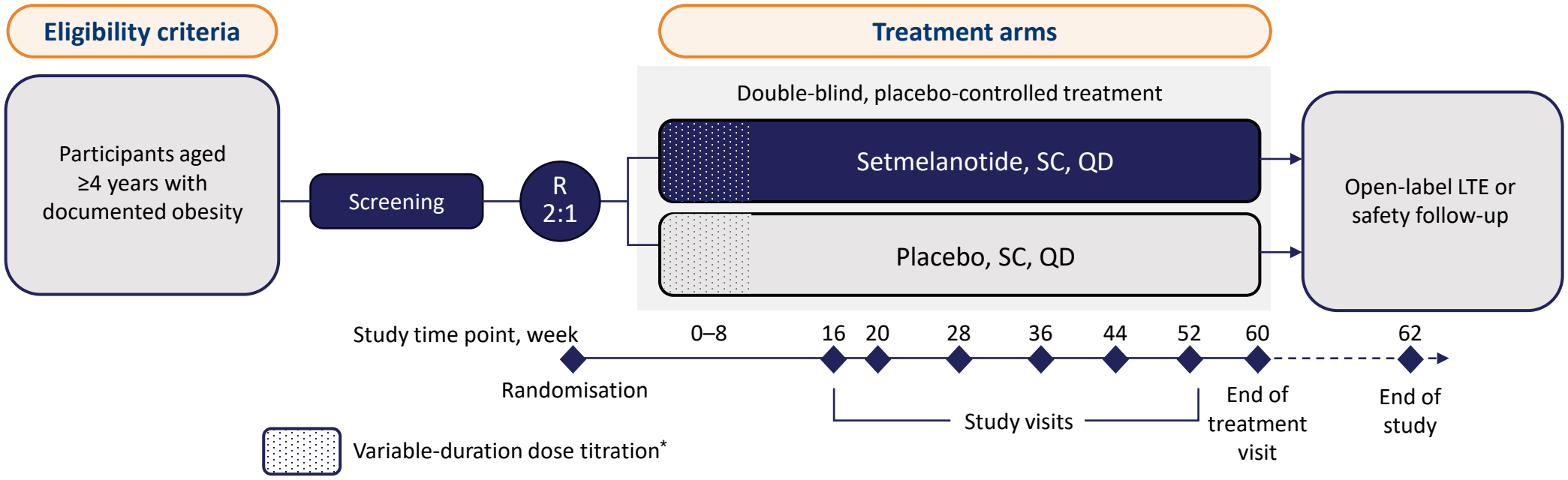


aHO, acquired hypothalamic obesity; AgRP, agouti-related peptide; α-MSH, alpha–melanocyte-stimulating hormone; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

1. Roth CL, McCormack SE. *Diabetes Obes Metab*. 2024;26 Suppl 2:34–45; **2.** Müller HL, et al. *Nat Rev Dis Primers*. 2019;5(1):75; **3.** Abuzzahab MJ, et al. *Horm Res Paediatr.* 2019;91(2):128–136; **4**. Roth CL. *Front Endocrinol (Lausanne).* 2011;2:49; **5.** Roth CL, et al. *Metabolism*. 2010;59(2):186–194; **6.** Hochberg I, Hochberg Z. *Obes Rev.* 2010;11(10):709–721; **7.** Dimitri P. *Front Endocrinol (Lausanne).* 2022;13:846880; **8.** Sohn JW, et al. *Cell.* 2013;152(3):612–619; **9.** Roth CL, et al. *Obesity (Silver Spring).* 2015;23(6):1226–1233; **10.** Roth CL, et al. *Pediatr Res.* 2007;61(4):496–501.

Background

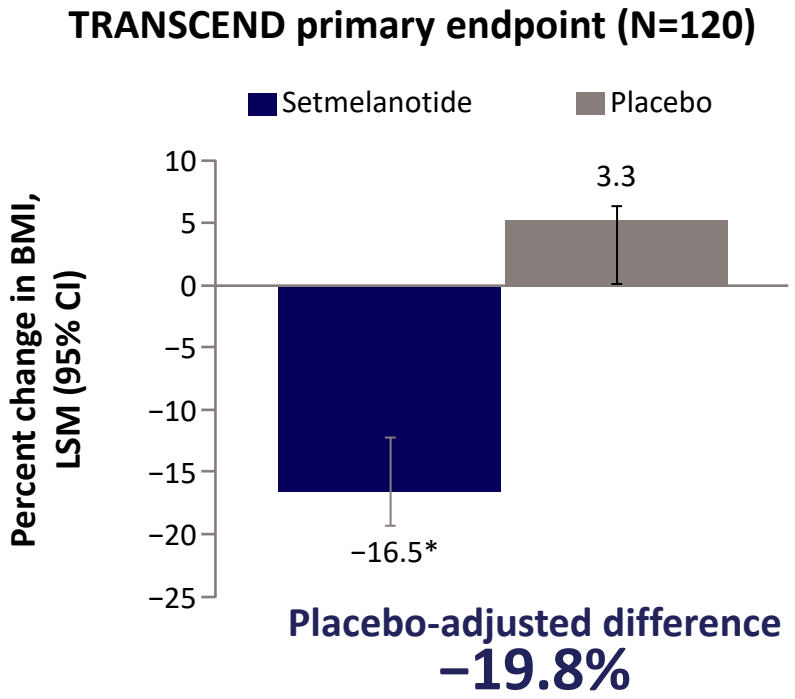
- Setmelanotide, an MC4R agonist, is a precision medicine designed to restore disrupted MC4R pathway signalling
- In the Phase 3, double-blind TRANSCEND trial patients with aHO (N=120) aged 4–66 years were randomised 2:1 to receive setmelanotide (0.5 mg subcutaneously [SC] once daily [QD], titrated up to 1.5–3.0 mg QD) or placebo for up to 60 weeks[1]



*The initial dose of 0.5 mg was escalated in increments of 0.5–1.0 mg until the participant reached an individual therapeutic regimen based on age and weight.
aHO, acquired hypothalamic obesity; LTE, long-term extension; MC4R, melanocortin-4 receptor; QD, once daily; R, randomisation; SC, subcutaneously.
1. Miller JL, et al. *N Engl J Med*. 2026;395(2):138–150.

Background and objective

- aHO is associated with metabolic complications, including insulin resistance, dyslipidaemia, and hepatic steatosis[1,2]
- In the global Phase 3 TRANSCEND trial (NCT05774756), setmelanotide **met the primary endpoint** at Week 52, with a placebo-adjusted **BMI reduction of 19.8%** (*p*<0.0001), and a placebo-adjusted **reduction in most hunger scores of 1.28 points (*p*=0.009)**[3]



Objective: This post hoc analysis aimed to assess the impact of setmelanotide on composite metabolic index scores in paediatric patients (aged ≥4 to <18 years) with aHO in the Phase 3 TRANSCEND trial, reflecting cardiometabolic risk beyond BMI reduction

*p<0.0001 versus placebo.
aHO, acquired hypothalamic obesity; BMI, body mass index; CI, confidence interval; LSM, least squares mean.
1. Roth CL, McCormack SE. *Diabetes Obes Metab*. 2024;26 Suppl 2:34–45; **2.** Dimitri P. *J Obes Metab Syndr.* 2019;28(1):4–17; **3.** Miller JL, et al. *N Engl J Med*. 2026;395(2):138–150.

Methods

Routinely available clinical measurements of well-established composite metabolic indices were used

Metabolic index	Metabolic index component							Lower score reflects
	BMI / BMI z-score	Waist circumference	Triglycerides	High-density lipoprotein (HDL)	Fasting glucose	Systolic blood pressure (SBP)	Gamma-glutamyl transferase (GGT)	
Metabolic syndrome severity Z BMI (MetS-Z-BMI)[1]	✓		✓	✓	✓	✓		Lower overall metabolic syndrome severity, T2D, and CVD risk
Lipid accumulation product (LAP)[2]		✓	✓					Lower metabolic syndrome, T2D, and CVD risk
Triglyceride–waist circumference index (TYG-WC)[3]		✓	✓		✓			Lower all-cause and cardiovascular mortality risk
Visceral adiposity index (VAI)[4]	✓	✓	✓	✓				Lower visceral adiposity dysfunction and cardiometabolic risk
Fatty liver index (FLI)[5]	✓	✓	✓				✓	Lower risk of hepatic steatosis and CVD

BMI, body mass index; CVD, cardiovascular disease; FLI, fatty liver index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; LAP, lipid accumulation product; MetS, metabolic syndrome; SBP, systolic blood pressure; TYG-WC, triglyceride–waist circumference index; T2D, type 2 diabetes; VAI, visceral adiposity index.

1. Hsu PW-C, et al. *J Diabetes Investig.* 2025;16(5):907–916; **2.** Chen Z-Y, et al. *Front Endocrinol (Lausanne).* 2023;14:1179990; **3.** Zou Y, et al. *BMC Gastroenterol.* 2025;25(1):325; **4.** Ejtahed H-S, et al. *J Cardiovasc Thorac Res.* 2019;11(4):280–286; **5.** Song K, et al. *Clin Gastroenterol Hepatol.* 2025~~6~~;24(2):421–431.e6.

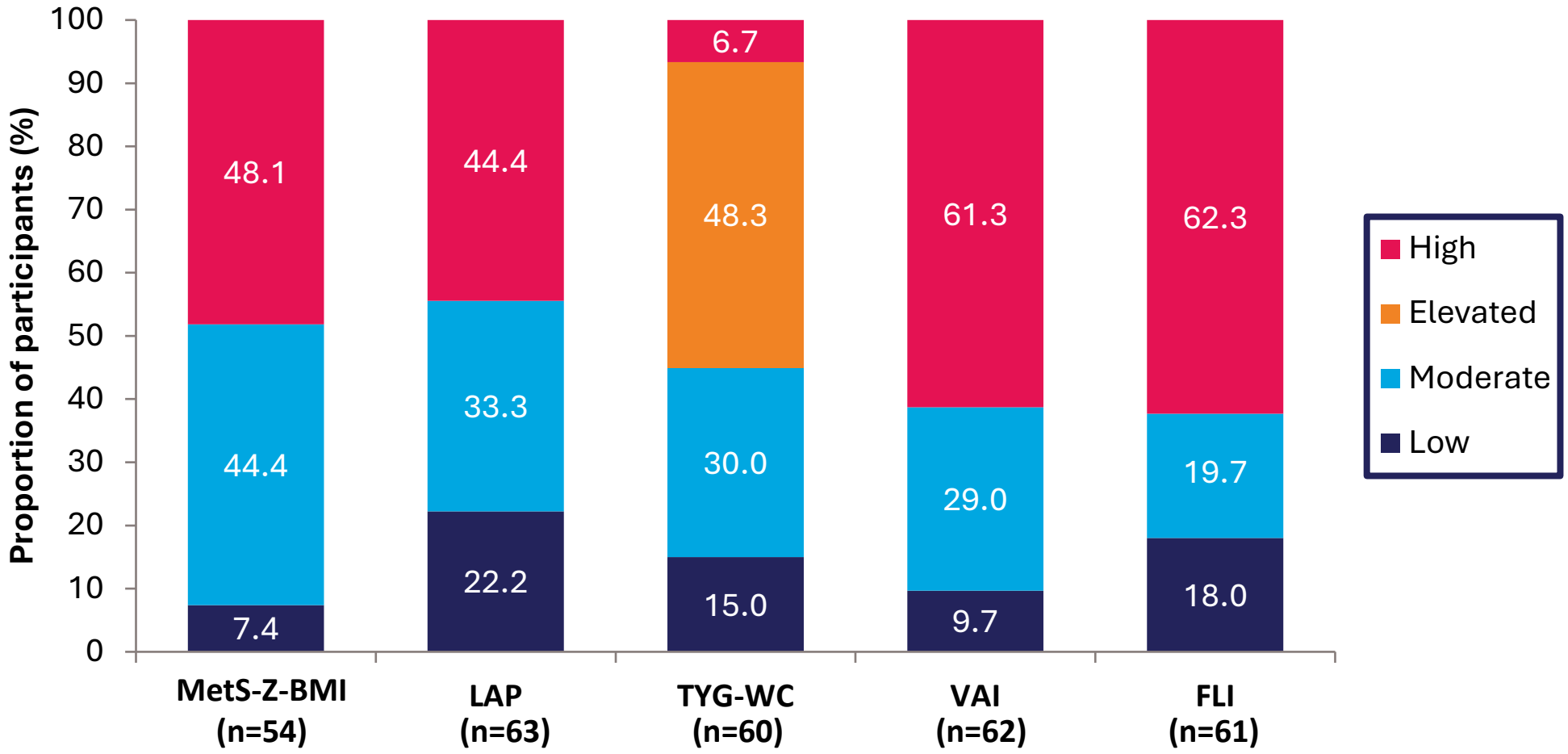
Results

Baseline demographics (N=71)

	Setmelanotide (n=48)	Placebo (n=23)
Age, mean ± SD (range), y	11.6 ± 4.1 (4, 17)	11.3 ± 3.7 (4, 17)
Sex, male, n (%)	26 (54.2)	6 (26.1)
Race, n (%)		
White	40 (83.3)	18 (78.3)
Black/African American	2 (4.2)	0
Asian	1 (2.1)	0
Other	5 (10.4)	5 (21.7)
Weight, mean (SD), kg	77.4 (33.8)	73.2 (27.4)
BMI, mean (SD), kg/m²	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)

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

Metabolic burden in paediatric patients with aHO was high at baseline



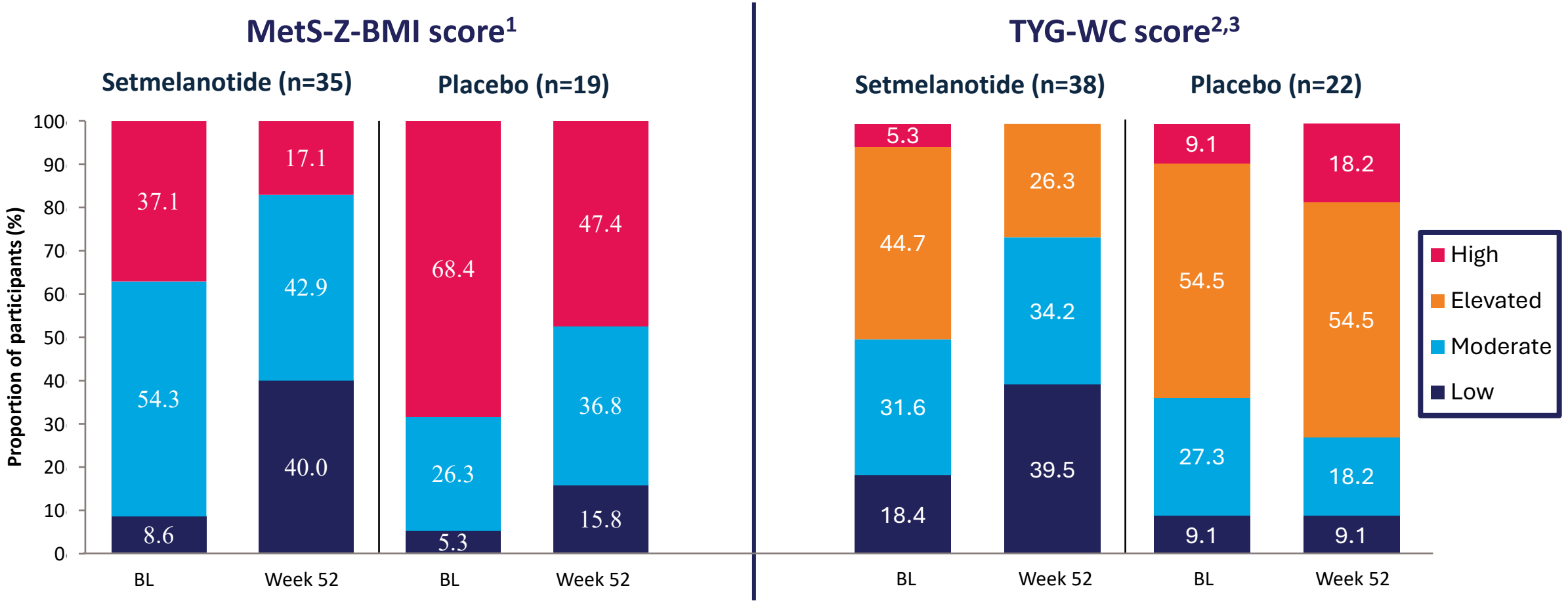
TYG-WC score ranges: low, moderate, elevated, high; MetS-Z-BMI, LAP, VAI and FLI score ranges: low, moderate, high.
The analyses are based on the population with both baseline and 52-week values available for each parameter; missing data were due to limited dual-energy X-ray absorptiometry data in this study. Totals may not sum to 100% due to rounding.
aHO, acquired hypothalamic obesity; BMI, body mass index; FLI, fatty liver index; LAP, lipid accumulation product; MetS, metabolic syndrome; SD, standard deviation; TYG-WC, triglyceride–waist circumference index; VAI, visceral adiposity index.

Improvements across all metabolic index scores with setmelanotide

Metabolic index	Setmelanotide change from baseline, mean (SD)	n=48	Placebo change from baseline, mean (SD)	n=23	Placebo-adjusted treatment difference	*p* value
MetS-Z-BMI[1]	−0.8 (0.9)	35	−0.2 (0.5)	19	−0.6	0.006
LAP[2]	−25.6 (41.0)	41	+3.6 (36.8)	22	−29.2	<0.0001
TYG-WC[3]	−116.8 (137.5)	38	+34.0 (74.7)	22	−150.8	<0.0001
VAI[4]	−1.3 (2.2)	40	−0.4 (2.0)	22	−0.9	0.004
FLI[5]	−20.6 (26.1)	39	+6.1 (12.5)	22	−26.7	<0.0001

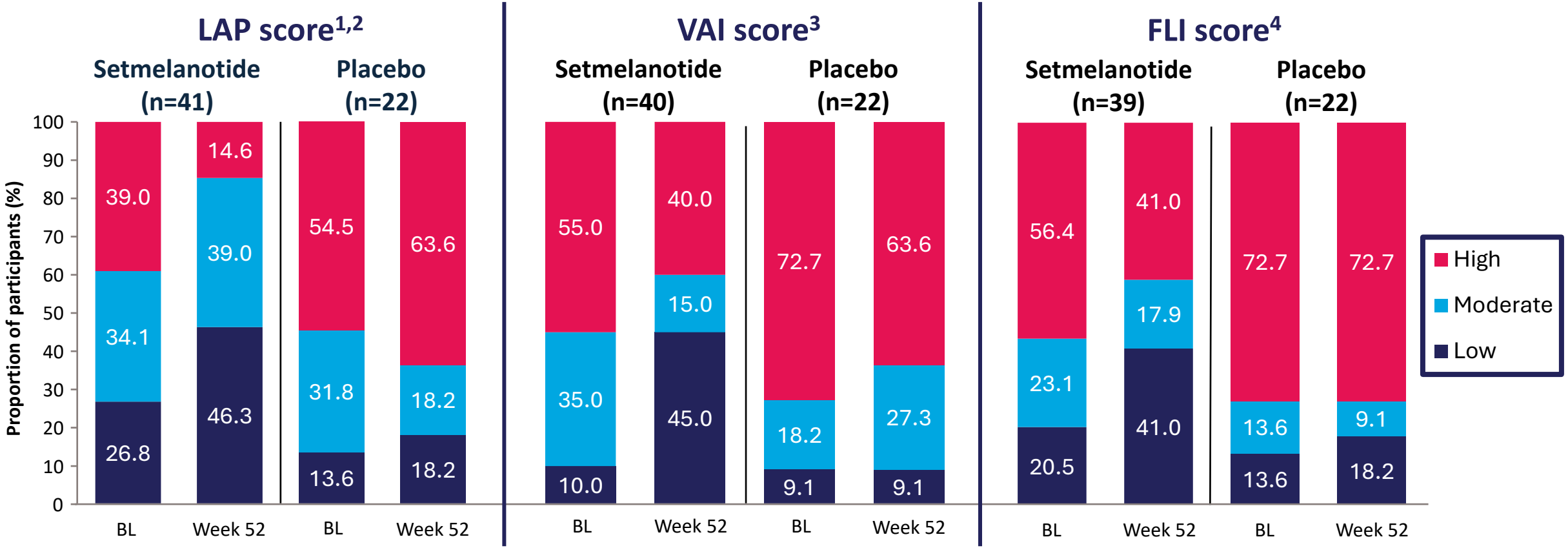
The analyses are based on the population with both baseline and 52-week values available for each parameter; missing data were due to limited dual-energy X-ray absorptiometry data in this study. Totals may not sum to 100% due to rounding.
BMI, body mass index; FLI, fatty liver index; LAP, lipid accumulation product; MetS, metabolic syndrome; SD, standard deviation; TYG-WC, triglyceride–waist circumference index; VAI, visceral adiposity index.
1. Hsu PW-C, et al. *J Diabetes Investig.* 2025;16(5):907–916; **2.** Chen Z-Y, et al. *Front Endocrinol (Lausanne).* 2023;14:1179990; **3.** Zou Y, et al. *BMC Gastroenterol.* 2025;25(1):325; **4.** Ejtahed H-S, et al. *J Cardiovasc Thorac Res.* 2019;11(4):280–286; **5.** Song K, et al. *Clin Gastroenterol Hepatol.* 2026;24(2):421–431.e6.

Higher proportion of participants in lower MetS-Z-BMI and TYG-WC risk categories with setmelanotide versus placebo



MetS-Z-BMI score ranges: <0 = low, 0–1 = moderate; >1–2 = high; Lower scores indicate decreased metabolic syndrome severity, T2D, and CVD risk. MetS-Z-BMI score ranges applied in this analysis previously validated in individuals aged ≥12 years.
TYG-WC score ranges: <650 = low, 650–850 = moderate, 851–1100 = elevated, >1100 = high; Lower TYG-WC values are associated with decreased risk of all-cause and cardiovascular mortality. TYG-WC score ranges applied in this analysis were previously validated in individuals aged ≥18 years.
BL, baseline; BMI, body mass index; CVD, cardiovascular disease; MetS, metabolic syndrome; T2D, type 2 diabetes; TYG-WC, triglyceride–waist circumference index.
1. Hsu PW-C, et al., *J Diabetes Investig*. 2025;16:(5)907–916; **2.** Wei X, et al. *Cardiovasc Diabetol*. 2024;23(1):134; **3.** Zou Y, et al. *BMC Gastroenterol*. 2025;1;25:325.

Higher proportion of participants in lower LAP, VAI and FLI risk categories with setmelanotide versus placebo



LAP score ranges: Men: <30 (low), 30–75 (moderate), >75 (high); Women: <25 (low), 25–60 (moderate), >60 (high); Lower LAP values are associated with decreased risk of metabolic syndrome, CVD, and T2D. LAP score ranges applied in this analysis were previously validated in individuals aged ≥18 years.. VAI score ranges: Boys ≥1.30 (high), 0.63–1.29 (moderate), ≤0.62 (low – no risk); Girls ≥1.78 (high), 1.00–1.77 (moderate), ≤0.99 (low – no risk); Lower VAI values are associated with decreased risk of visceral adiposity dysfunction and cardiometabolic risk. VAI score ranges applied in this analysis were previously validated in individuals aged ≥7 years. FLI score ranges: <20 (low), 20–50 (moderate), >50 (high); Lower FLI values are associated with decreased risk of hepatic steatosis and CVD risk. FLI score ranges applied in this analysis were previously validated in individuals aged ≥6 years. Totals may not sum to 100% due to rounding

BL, baseline; CVD, cardiovascular disease; FLI, fatty liver index; LAP, lipid accumulation product; T2D, type 2 diabetes; VAI, visceral adiposity index.

1. Chen S, et al. *Nutr Metab Cardiovasc Dis*. 2023;34:1467–1476; **2.** Chen Z-Y, et al. *Front Endocrinol (Lausanne).* 2023;14:1179990; **3.** Ejtahed H-S, et al. *J Cardiovasc Thorac Res.* 2019;Oct 24;11(4):280–286; **4.** Song K, et al. *Clin Gastroenterol Hepatol.* 2025;24(2):421–431.e6.

Conclusions

Setmelanotide treatment in paediatric patients with aHO was associated with **significant improvements** in **several metabolic indices** versus placebo, suggesting treatment-related reductions in **metabolic syndrome severity**, **visceral adiposity**, **hepatic steatosis**, **T2D,** and **overall cardiometabolic risk**

Early treatment with setmelanotide may provide **metabolic benefits** beyond reductions in hyperphagia and body weight in this population, supporting its potential as a therapeutic option for **paediatric patients with aHO**

A limitation is that many of these metabolic risk scores have not yet been validated for predicting future cardiovascular events in paediatric populations.
aHO, acquired hypothalamic obesity; T2D, type 2 diabetes.

THANK YOU

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

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