Oral presentation number: FC10.4

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

Scan here for a copy of this presentation, a plain language summary and supplementary materials

Hanneke M. van Santen[1,2], Susan A. Phillips[3], Jill Hamilton[4], Shana E. McCormack[5,6], Christian L. Roth[7], Nicolas Touchot[8], Cecilia Scimia[8], Shuang Hu[8], Mehul T. Dattani[9], Megan M. Kelsey[10], Zainaba Mohamed[11], Katie Larson Ode[12], Ashley H. Shoemaker[13], Martin Wabitsch[14,15], Jennifer L. Miller[16] on behalf of the TRANSCEND Trial Group

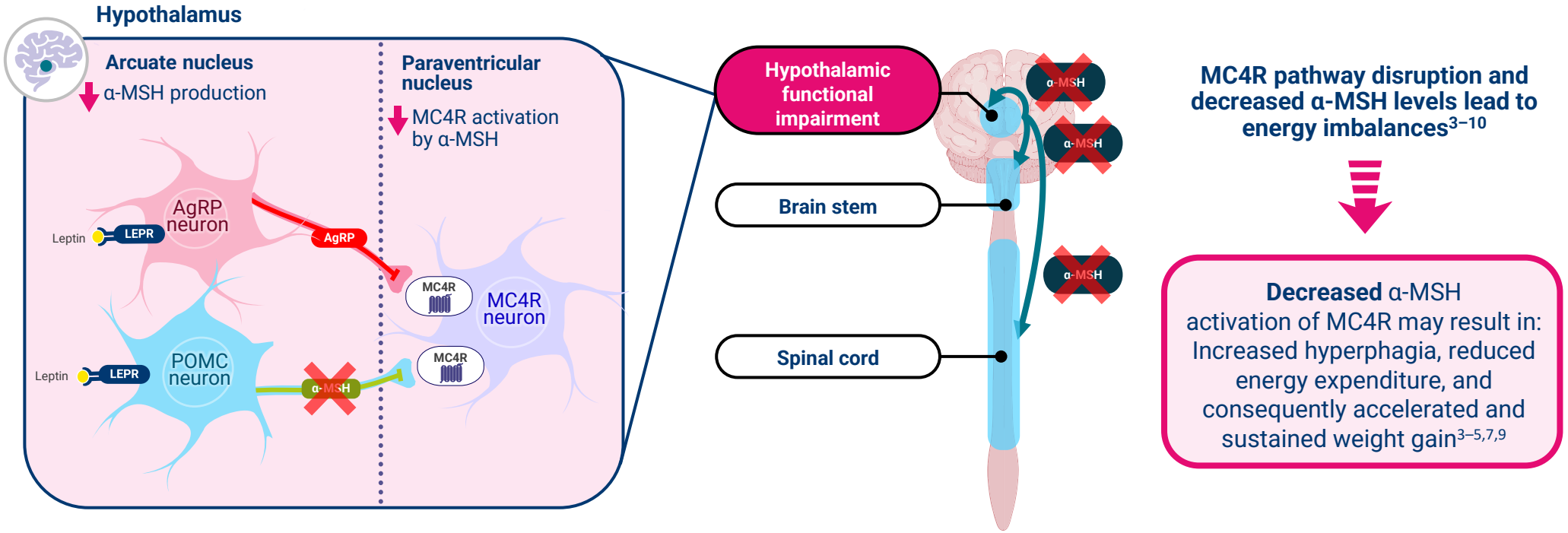
[1]Princess Máxima Center for Pediatric Oncology, Utrecht, The Netherlands;-[2]Department of Pediatric Endocrinology, Wilhelmina Children's Hospital, University Medical Center Utrecht, Utrecht, The Netherlands; [3]Pediatric Endocrinology, Rady Children's Hospital/University of California San Diego, San Diego, CA, USA; [4]Division of Endocrinology, Hospital for Sick Children, Department of Pediatrics, University of Toronto, Toronto, ON, Canada; [5]Division of Endocrinology and Diabetes, Children's Hospital of Philadelphia, Philadelphia, PA, USA; [6]Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA; [7]Seattle Children's Hospital, University of Washington, Seattle, WA, USA; [8]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [9]University College London Great Ormond Street Institute of Child Health, Genetics and Genomic Medicine Programme, London, UK; [10]Department of Pediatrics, University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [11]Birmingham Women's and Children's Hospital NHS Trust, Birmingham, UK; [12]University of Iowa Stead Family Department of Pediatrics – Pediatric Endocrinology and Diabetes, Iowa City, IA, USA; [13]Vanderbilt University Medical Center, Nashville, TN, USA; [14]Department of Pediatrics and Adolescent Medicine, Division of Pediatric Endocrinology and Diabetes, University Hospital Ulm, Ulm, Germany; [15]German Center for Child and Adolescent Health (DZKJ), Partner Site, Ulm, Germany; [16]Pediatric Endocrinology, Department of Pediatrics, College of Medicine, University of Florida, Gainesville, FL, USA

Disclosures

- **HMvS** is a local primary investigator of clinical trials funded by Rhythm Pharmaceuticals, Inc.; has received funding from Novo Nordisk, Pfizer, and Rhythm Pharmaceuticals, Inc. for the organisation of the ESPE Science Symposium and 6th Craniopharyngioma Post-graduate Course; has received reimbursement for travel expenses for scientific meetings from Rhythm Pharmaceuticals, Inc., and has received funding for research projects from Pfizer and Rhythm Pharmaceuticals, Inc.
- **Acknowledgements:** This study was sponsored by Rhythm Pharmaceuticals, Inc. Editorial assistance was provided by Spectrum Science, and funded by Rhythm Pharmaceuticals, Inc. under the direction of the authors.

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]

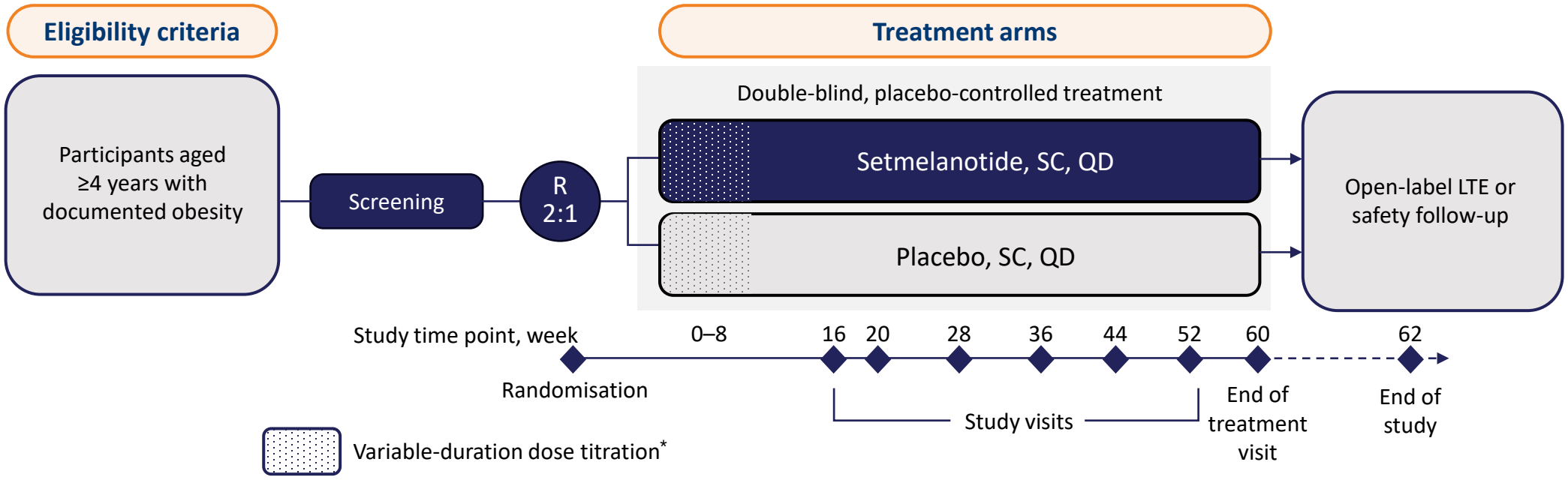


aHO, acquired hypothalamic obesity; AgRP, agouti-related peptide; α-MSH, alpha–melanocyte-stimulating hormone; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

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

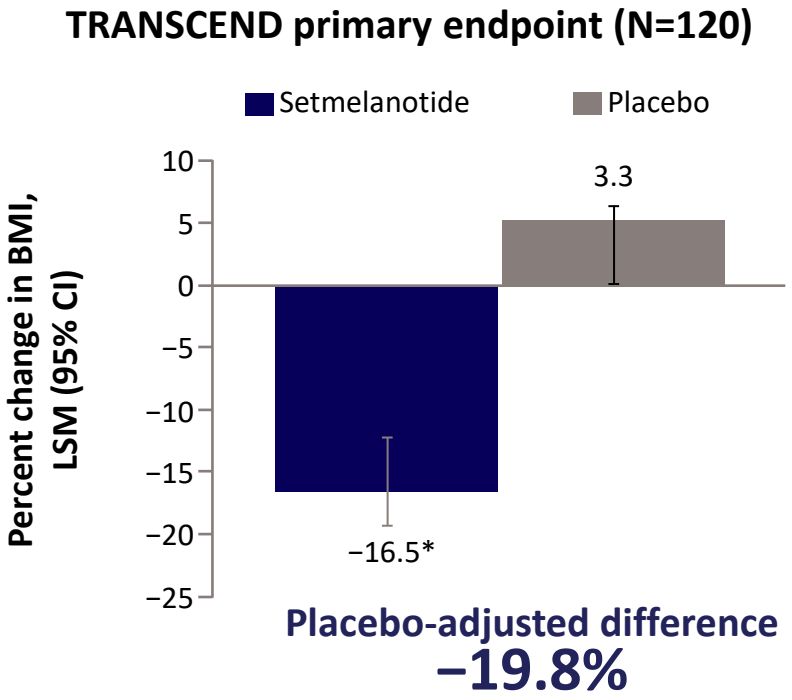
- Setmelanotide, an MC4R agonist, is a precision medicine designed to restore disrupted MC4R pathway signalling
- In the Phase 3, double-blind TRANSCEND trial patients with aHO (N=120) aged 4–66 years were randomised 2:1 to receive setmelanotide (0.5 mg subcutaneously [SC] once daily [QD], titrated up 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 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;24(2):421–431.e6.

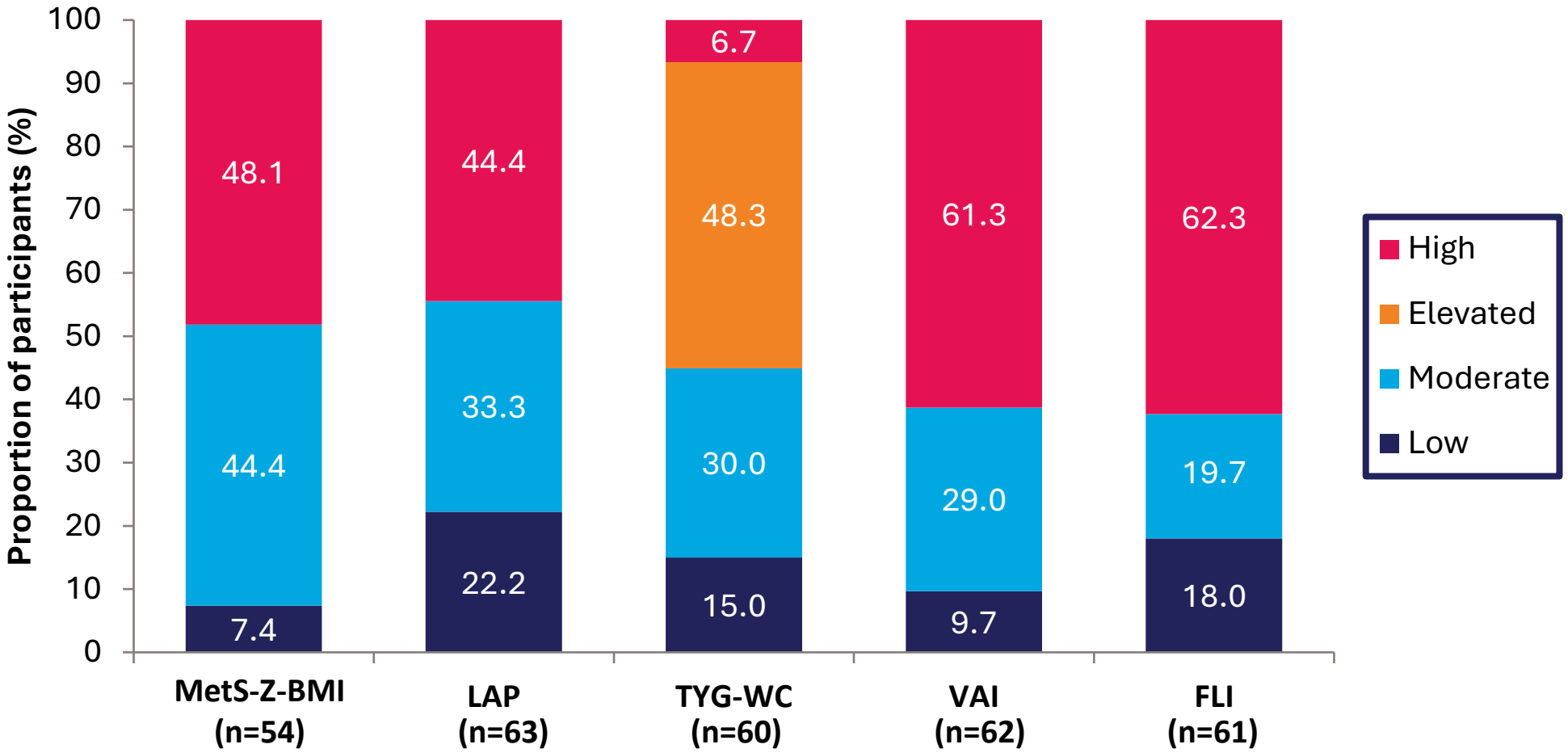
Results

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



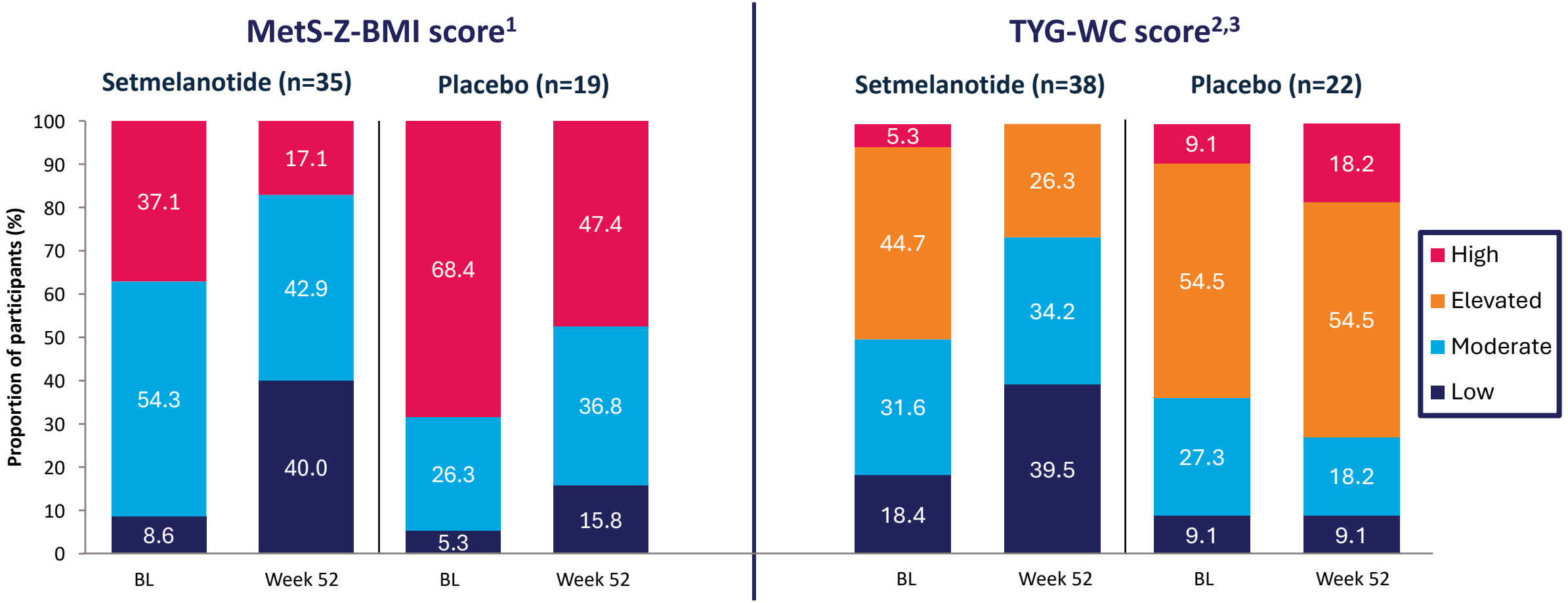
TYG-WC score ranges: low, moderate, elevated, high; MetS-Z-BMI, LAP, VAI and FLI score ranges: low, moderate, high.
The analyses are based on the population with both baseline and 52-week values available for each parameter; missing data were due to limited dual-energy X-ray absorptiometry data in this 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

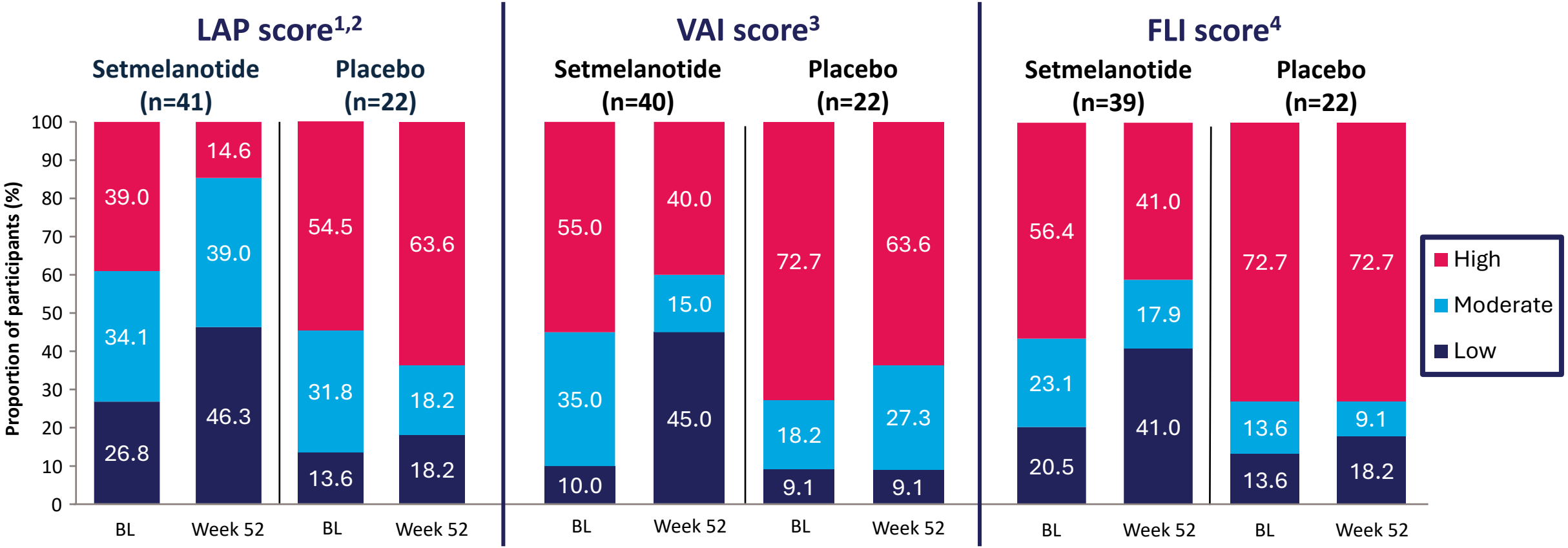
The analyses are based on the population with both baseline and 52-week values available for each parameter; missing data were due to limited dual-energy X-ray absorptiometry data in this study. Totals may not sum to 100% due to rounding.
BMI, body mass index; FLI, fatty liver index; LAP, lipid accumulation 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

Scan here for a copy of this presentation, a plain language summary and supplementary materials