

Impact of setmelanotide on metabolic index scores in phase 3 trial participants with acquired hypothalamic obesity

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Introduction

- Acquired hypothalamic obesity (aHO) is a rare complex disease, resulting from physical injury to 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 gain¹
- Commonly associated with pituitary hormone deficiencies, fatigue, or sleep disturbances, aHO puts patients at high risk for metabolic complications like type 2 diabetes, insulin resistance, dyslipidaemia, and hepatic steatosis^{1,4}
- A set of well-established composite metabolic index scores are available that use routinely available clinical measurements, to provide non-invasive, comprehensive estimates of cardiometabolic risk
- In the global phase 3 TRANSCEND trial, the primary endpoint was met: there was a -19.8% placebo-adjusted reduction in body mass index (BMI) after 52 weeks (at therapeutic dose) of setmelanotide treatment ($P < 0.0001$)³

Objectives

- These post hoc analyses of the international phase 3 TRANSCEND trial (NCT05774756) assess the impact of setmelanotide on metabolic index scores

Methods

- Patients with aHO aged ≥ 4 years in the phase 3, double-blind TRANSCEND trial were randomised 2:1 to receive setmelanotide (0.5 mg subcutaneously once daily [QD], titrated up to 1.5–3.0 mg QD) or placebo for up to 60 weeks
- Changes in metabolic syndrome Z-BMI (MetS-Z-BMI)⁵, lipid accumulation product (LAP)⁶, triglyceride-glucose waist circumference index (TYG-WC)⁷, visceral adiposity index (VAI)⁸, and fatty liver index (FLI)⁹ were calculated and analysed after 52 weeks of therapeutic dose (see references for calculations and ranges used in these analyses)

Results

- Overall, 120 participants were included (81 setmelanotide, 39 placebo), with a mean (SD) age of 19.9 years (13.8; range: 4–66 years), a mean BMI in participants ≥ 18 years of 41.2 (9.7) kg/m², and a mean BMI z-score in participants < 18 years of 3.61 (1.66)
- The mean (SD) change from baseline to Week 52 in the setmelanotide-treated group vs placebo was greater across all indices (Table 1)

Table 1: Metabolic index scores mean change from baseline - mITT (n=120)

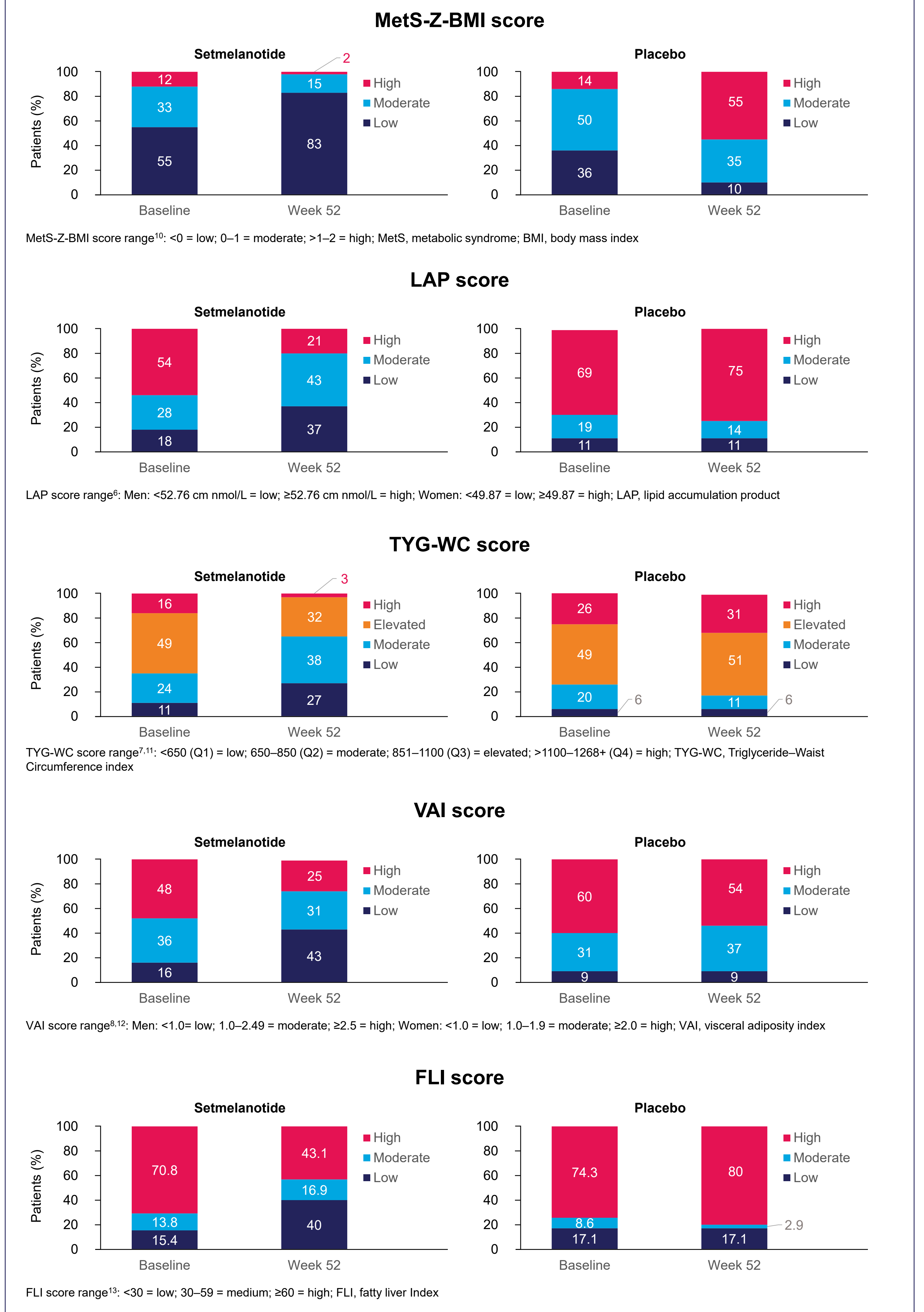
Change from baseline, mean (SD)	Setmelanotide	n=81	Placebo	n=39	p value
MetS-Z-BMI*	-0.9 (1.0)	53	-0.2 (0.4)	31	<0.0001
LAP	-36.4 (58.8)	68	-2.6 (37.0)	36	<0.0001
TYG-WC	-138.3 (140.1)	63	+21.2 (73.2)	35	<0.0001
VAI	-1.5 (2.8)	67	-0.4 (1.7)	35	0.001
FLI	-24.2 (26.7)	65	+4.4 (11.1)	35	<0.0001

*The analyses are based on the population with both baseline and 52-week values available for each parameter, missing data was due to low DXA data in this study
 *For paediatric patients, BMI z-score served as the weight-based measure in this analysis
 mITT, modified intent-to-treat; MetS, metabolic syndrome; LAP, lipid accumulation product; TYG-WC, Triglyceride–Waist Circumference index; VAI, visceral adiposity index; FLI, fatty liver index; BMI, body mass index; SD, standard deviation

Results (continued)

- In general, a shift from high-risk categories toward low/moderate was observed in the setmelanotide arm, while in the placebo arm this remained stable or further increased (Figure 1)

Figure 1: Change in metabolic index risk categories



Conclusions

- Setmelanotide treatment in patients with aHO led to relevant changes in multiple metabolic index scores and a shift to a state with lower metabolic risk versus placebo
- These data suggest reductions in visceral fat burden, hepatic steatosis, and overall cardiometabolic risk, however a limitation is that the efficacy of many of these metabolic risk scores in predicting future cardiovascular events in children has not been validated
- The findings highlight the broad metabolic benefits and strong clinically meaningful efficacy of setmelanotide in this population, supporting its potential as a therapeutic option for patients with aHO

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