Cardiometabolic Results From a Phase 3 Trial of Setmelanotide in Acquired Hypothalamic Obesity

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Introduction

- Melanocortin-4 receptor (MC4R) pathway signaling in the hypothalamus plays a critical role in the regulation of energy balance and body weight[1-3]
- Injury to the hypothalamus (eg, tumor growth, surgical injury, radiation injury, inflammation due to infection, traumatic brain injury, hemorrhage) can impair MC4R pathway signaling and lead to acquired hypothalamic obesity (HO)[2,4-8]
- Acquired HO is characterized by accelerated and sustained weight gain, often accompanied by hyperphagia (a chronic pathologic condition characterized by insatiable hunger, impaired satiety, and persistent abnormal food-seeking behaviors), energy imbalance, and obesity[2,9,10]
- Sustained obesity in this patient population can lead to a significantly increased risk of developing cardiometabolic disease[11-13]
- In the global Phase 3 TRANSCEND trial, treatment with setmelanotide, an MC4R agonist, led to statistically significant improvements across weight- and hunger-related parameters[14]
  - The primary endpoint was met: there was a −19.8% placebo-adjusted reduction in body mass index after 52 weeks (at therapeutic dose) of setmelanotide treatment (P<0.0001)[14]

Objectives

- To assess the cardiometabolic outcomes from baseline to Week 52 in the pivotal Phase 3 TRANSCEND trial (NCT05774756)

Methods

- Participants aged ≥4 years with body mass index ≥95th percentile (in those aged 4 to <18 years) or ≥30 kg/m^2 (in those aged ≥18 years) with acquired HO following hypothalamic tumor, lesion, or injury were included
- Participants were randomized 2:1 to setmelanotide (0.5 mg subcutaneously once daily, titrated up to 1.5-3.0 mg once daily based on age, weight, and tolerability) or placebo for up to 60 weeks
- Cardiometabolic parameters after 52 weeks on therapeutic dose (a secondary endpoint) were assessed via vital signs (blood pressure) and clinical laboratory tests of serum and urine at a central laboratory
  - Serum proteomic analyses at 52 weeks (an exploratory endpoint) were also assessed at a central laboratory; subgroup and percentile analyses were post hoc

Table 1. Baseline Demographics

	Setmelanotide (n=81)	Placebo (n=39)
Age, y		
Mean ± SD (range), y	19.2 ± 13.0 (4-65)	21.4 ± 15.5 (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)
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)†
Weight, mean (95% CI), kg	92.9 (84.4-101.4)	94.1 (81.5-106.7)
In participants aged ≥18 y, kg	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)
In participants aged ≥18 y, kg/m^2	40.1 (36.7-43.6)	43.5 (38.5-48.4)
BMI Z score in participants aged 4 to <18 y, mean (95% CI)‡	3.72 (3.19-4.25)	3.37 (2.81-3.93)
Percentage of the 95th percentile of BMI in participants 4 to <18 y, mean (SD)§	132.3 (124.0-140.7)	128.6 (118.8-138.5)

*Arachnoid cyst, heterogeneous mass in the suprasellar region involving the hypothalamus and optic chiasm, mature teratoma (not classified as tumor by the investigators given the benign course and the differentiated cell type), cavernous hemangioma (not classified as tumor by the investigators given it was considered a vascular malformation), and either craniopharyngioma or astrocytoma (not classified as tumor by the investigators given uncertainty of diagnosis). †Hypothalamic glioma pilocytic astrocytoma (not classified as tumor by the investigators given the differentiated cell type). ‡BMI Z score calculated according to the World Health Organization 2007 method. §Percentage of the 95th percentile of BMI calculated according to the Centers for Disease Control and Prevention 2022 method. BMI, body mass index; CI, confidence interval; SD, standard deviation.

Results

- Baseline demographics were generally comparable between the treatment groups (Table 1)

Efficacy outcomes

- Setmelanotide treatment was associated with significant improvement across most cardiometabolic parameters and proteomic biomarkers, relative to placebo, after 52 weeks (Table 2)

Table 2. Change in Cardiometabolic Parameters at Week 52*

	Setmelanotide (n=81)		Placebo (n=39)		
	Baseline, mean (95% CI)	LSM change at week 52 (95% CI)	Baseline, mean (95% CI)	LSM change at week 52 (95% CI)	*P* value†
Nonambulatory blood pressure					
Systolic blood pressure, mm Hg	112.4 (109.4, 115.4)	-2.8 (-5.2, -0.3; n=73)	114.9 (110.1, 119.8)	3.0 (-0.5, 6.4; n=37)	0.0081
Diastolic blood pressure, mm Hg	72.0 (69.5, 74.5)	-1.3 (-2.9, 0.4; n=73)	73.4 (69.8, 77.0)	2.8 (0.5, 5.1; n=37)	0.0056
Lipid Levels					
Total cholesterol, mmol/L	4.7 (4.4, 4.9)	-0.2 (-0.4, 0.0; n=67)	4.7 (4.4, 5.1)	0.2 (-0.1, 0.5; n=36)	0.0176
Low-density lipoprotein cholesterol, mmol/L	2.7 (2.5, 2.9)	-0.3 (-0.5, -0.1; n=66)	2.7 (2.4, 3.0)	0.1 (-0.1, 0.3; n=34)	0.0077
High-density lipoprotein cholesterol, mmol/L	1.2 (1.1, 1.2)	0.4 (0.3, 0.5; n=66)	1.1 (1.0, 1.2)	0.1 (0.0, 0.2; n=35)	0.0001
Triglycerides, mmol/L	1.7 (1.5, 1.9)	-0.6 (-0.8, -0.4; n=67)	2.1 (1.6, 2.6)	0.0 (-0.3, 0.2; n=36)	0.0003
Hematologic and chemistry parameters					
HbA1c, %	5.5 (5.3, 5.7)	-0.3 (-0.3, -0.2; n=67)	5.4 (5.2, 5.6)	0.0 (-0.1, 0.1; n=35)	<0.0001
Aspartate aminotransferase, U/L	25.3 (22.5, 28.1)	-6.4 (-9.8, -3.0; n=66)	26.8 (19.9, 33.7)	1.1 (-3.5, 5.7; n=35)	0.0107
Alanine aminotransferase, U/L	31.3 (25.3, 37.2)	-13.9 (-20.1, -7.8; n=65)	30.8 (20.8, 40.8)	0.9 (-7.4, 9.3; n=35)	0.0051
Bilirubin, µmol/L	7.1 (6.3, 7.8)	1.5 (0.4, 2.6; n=66)	9.5 (6.5, 12.4)	0.1 (-1.5, 1.6; n=35)	0.1410
C-reactive protein, mg/L	7.8 (5.7, 9.9)	-2.5 (-4.3, -0.7; n=60)	7.9 (4.1, 11.8)	0.5 (-2.1, 3.1; n=29)	0.0631
Exploratory proteomic analyses					
C-peptide, ng/mL	4.3 (2.6, 6.0)	-2.3 (-2.8, -1.8; n=56)	4.0 (2.8, 5.2)	-0.4 (-1.0, 0.3; n=31)	<0.0001
Leptin, ng/mL	46.6 (37.3, 55.9)	-24.1 (-29.8, -18.3; n=56)	46.0 (34.6, 57.4)	-2.2 (-10.0, 5.6; n=30)	<0.0001
Insulin, µIU/mL	43.0 (32.8, 53.2)	-28.3 (-35.6, -21.1; n=55)	48.6 (27.8, 69.3)	-6.0 (-15.8, 3.9; n=30)	0.0005

*52 weeks at therapeutic dose. †Comparison of the changes from baseline, setmelanotide versus placebo. HbA1c, hemoglobin A1c; LSM, least squares mean.

- Fifty-two weeks of treatment was generally associated with small reductions in blood pressure with setmelanotide compared with increases in blood pressure with placebo across pediatric, adult, male, and female participants (Table 3)

Table 3. Change in Blood Pressure at Week 52* Across Age and Sex Subgroups

Least squares mean change from baseline at week 52: systolic blood pressure, mm Hg												
<12 y		≥12 to <18 y		<18 y		≥18 y		Female		Male	
SET (n=20)	PBO (n=10)	SET (n=25)	PBO (n=12)	SET (n=45)	PBO (n=22)	SET (n=28)	PBO (n=15)	SET (n=41)	PBO (n=25)	SET (n=32)	PBO (n=12)
+1.56	+0.21	-4.96	+4.49	-2.22	+2.45	-2.84	+4.27	-3.06	+4.85	-3.15	+0.34
Least squares mean change from baseline at week 52: diastolic blood pressure, mm Hg											
<12 y		≥12 to <18 y		<18 y		≥18 y		Female		Male	
SET (n=20)	PBO (n=10)	SET (n=25)	PBO (n=12)	SET (n=45)	PBO (n=22)	SET (n=28)	PBO (n=15)	SET (n=41)	PBO (n=25)	SET (n=32)	PBO (n=12)
-0.27	+3.57	-1.44	+2.42	-1.01	+2.89	-1.25	+3.18	-1.74	+3.75	+0.11	+0.74

*52 weeks at therapeutic dose. PBO, placebo; SET, setmelanotide.

- When evaluated using age-based percentiles for pediatric patients, setmelanotide was associated with decreases in blood pressure across age groups, consistent with the overall findings (Table 4)

Table 4. Change in Blood Pressure Percentiles at Week 52*

Least squares mean change from baseline at week 52: systolic blood pressure			
<18 y, percentile		≥18 y, mm Hg	
SET (n=38)	PBO (n=20)	SET (n=35)	PBO (n=17)
-6.70	+0.50	-5.08	+2.13
Least squares mean change from baseline at week 52: diastolic blood pressure			
<18 y, percentile		≥18 y, mm Hg	
SET (n=38)	PBO (n=20)	SET (n=35)	PBO (n=17)
-2.30	+2.88	-2.06	+2.78

Participants who changed from age <18 y at baseline to age ≥18 y at the primary time point were included in the adult group because a percentile could not be calculated for their primary time point value. *52 weeks at the therapeutic dose. PBO, placebo; SET, setmelanotide.

Safety outcomes

- Setmelanotide was generally well tolerated
- The most frequent adverse events (≥20% in the setmelanotide arm) were skin hyperpigmentation, nausea, headache, vomiting, diarrhea, and injection site reactions
- Adverse events of blood pressure increase were observed in 1 participant (1.2%) who received setmelanotide and in 1 participant (2.6%) who received placebo
- Adverse events of hypertension were observed in 2 participants (2.5%) who received setmelanotide and in 2 participants (5.1%) who received placebo
- One serious adverse event was considered related to setmelanotide: hypernatremia (sodium levels 150-158 mmol/L [normal upper limit 145 mmol/L]), which resolved after 2 days with treatment
- There was 1 death due to seizures in a participant with a history of seizure disorder, which was not considered related to the study drug

Conclusions

- In the Phase 3 TRANSCEND trial in participants with acquired HO, statistically significant and clinically meaningful changes were observed in almost all cardiometabolic parameters
  - Changes were observed across age groups, suggesting early intervention may confer long-term benefit on cardiometabolic health
- These results underscore the broader impact setmelanotide treatment may have beyond weight loss alone in patients with acquired HO

Future Directions

- A supplemental new drug application and marketing authorization application for setmelanotide in acquired HO have been submitted to the US Food and Drug Administration and the European Medicines Agency, respectively

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