Setmelanotide, a Melanocortin-4 Receptor Agonist, in Prader-Willi Syndrome: Initial Phase 2 Results

#SAT-713

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Background

- Patients with Prader-Willi syndrome (PWS) often lack expression of genes involved with the development and function of the hypothalamic melanocortin-4 receptor (MC4R) pathway[1,2]
- This may result in decreased alpha-melanocyte-stimulating hormone (α-MSH) levels and disrupted pathway signaling,[3] leading to hyperphagia (insatiable hunger and abnormal food-seeking behaviors) and obesity[4,5]
- There are no approved treatments for weight reduction in PWS; diazoxide choline extended-release was recently approved by the FDA for hyperphagia in PWS[6]
- Setmelanotide, an MC4R agonist, has been associated with weight reduction in several other MC4R pathway diseases,[7-10] and was previously evaluated in a Phase 2 PWS trial with doses up to 2.5 mg and a primary endpoint at 4 weeks (NCT02311673)

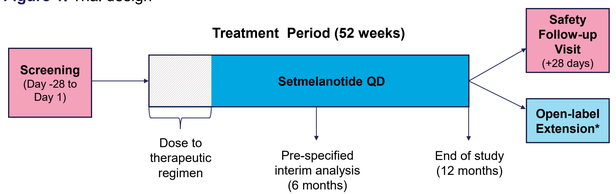
Objective

- To assess the efficacy and safety of setmelanotide in an ongoing Phase 2 trial in PWS (NCT06772597), with higher doses and an extended duration of treatment compared with the previous trial

Methods

- Participants with PWS and obesity (BMI ≥30 kg/m^2 [≥18 years] or BMI ≥95th percentile [<18 years]), aged ≥6 to ≤65 years old, were included
- All participants received open-label setmelanotide once-daily (QD) titrated to up to 5 mg/day, as tolerated
- The primary endpoint was the frequency and severity of adverse events (AEs) over 52 weeks
- Secondary endpoints included BMI, BMI z-score, body composition via dual-energy X-ray absorptiometry (DEXA), Hyperphagia Questionnaire for Clinical Trials (HQ-CT; scored from 0-36), and Prader-Willi Syndrome Anxiousness and Distress Behaviors Questionnaire (PADQ; scored from 0-56)
  - An HQ-CT score of ≥13 at baseline was considered moderate-to-severe hyperphagia,[11] and an improvement of ≥7 was considered clinically meaningful[12,13]
  - For PADQ, an improvement of ≥11 was considered clinically meaningful[14]

Figure 1. Trial design



*Open-label extension continues for up to 4 years (or until commercial product is available, or the sponsor closes the study). QD, once daily.

Results

- Of 18 participants that enrolled, 11 were adult and 7 were pediatric participants
  - One participant discontinued study (due to withdrawal by parent/guardian), and 17 participants received ≥6 months of setmelanotide treatment
- At baseline, the mean age was 17.1 years (Table 1), and 9 participants received concomitant diazoxide choline extended-release during the trial
- Across all 17 participants who completed 6 months on study, the mean (SD) BMI percent change from baseline at Month 6 was −3.06% (3.21)
- In 10 adult participants, the mean (SD) BMI percent change from baseline at Month 6 was −3.11% (3.74; Figure 2A), and in 7 pediatric participants, was −3.00% (2.53; Figure 2B)
- The mean (SD) BMI z-score change from baseline at Month 6 was −0.35 (0.26) in the pediatric participants
- In 16 participants with available DEXA data, there was a mean (SD) percent change from baseline at Month 6 in fat mass of −4.19% (6.78) and a mean (SD) percent change in lean mass of +0.74% (2.87)
- Of 10 participants with an HQ-CT score of ≥13 at baseline (moderate-to-severe hyperphagia), 8 had a clinically meaningful improvement of ≥7 points at Month 6
- Of 15 participants with a PADQ score of ≥11 at baseline (i.e., those able to experience a meaningful change), 10 exhibited a clinically meaningful improvement of ≥11 points at Month 6

Table 1. Baseline characteristics

	SET (n=18)
Age, mean ± SD (range), y	17.1 (5.6; 6-23)
Age categories, n (%)	
<12 years	3 (16.7)
≥12 to <18 years	4 (22.2)
≥18 years	11 (61.1)
Sex, female, n (%)	8 (44.4)
Race, n (%)	
White	15 (83.3)
Multiple	2 (11.1)
Asian	1 (5.6)
BMI, mean (SD), kg/m^2	39.0 (9.3)
In participants aged ≥18 y, kg/m^2	41.1 (9.6)
BMI z-score in participants aged 4 to <18 y, mean (SD)*	4.15 (1.87)
HQ-CT, mean (SD)	12.83 (8.05)
PADQ, mean (SD)	29.94 (15.12)

BMI, body mass index; HQ-CT, Hyperphagia Questionnaire for Clinical Trials; PADQ, Prader-Willi Syndrome Anxiousness and Distress Behaviors Questionnaire; SD, standard deviation; SET, setmelanotide.
*BMI z-score calculated according to the World Health Organization 2007 method.[15]

Figure 2A. Efficacy in adult participants at 6 months

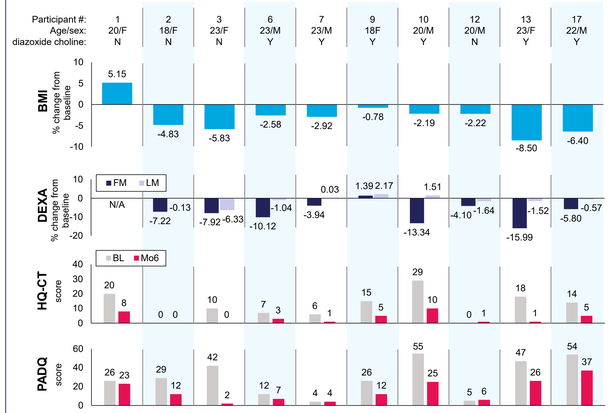
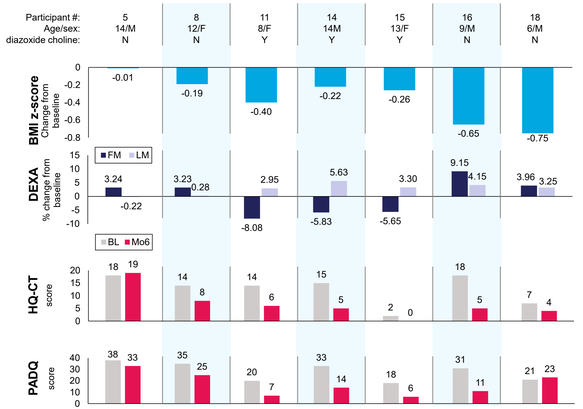


Figure 2B. Efficacy in pediatric participants at 6 months



Higher scores for HQ-CT and PADQ indicate greater severity. BMI, body mass index; BL, baseline; DEXA, dual-energy X-ray absorptiometry; FM, fat mass; HQ-CT, Hyperphagia Questionnaire for Clinical Trials; N/A, not available; LM, lean mass; Mo6, Month 6; PADQ, Prader-Willi Syndrome Anxiousness and Distress Behaviors Questionnaire.

- The two most common AEs were injection site reactions and skin hyperpigmentation
- There were no AEs leading to treatment discontinuation, serious AEs, or deaths reported during the trial

Table 2. Safety

n (%)	SET (n=18)
Any AE	18 (100)
AE considered related to treatment by investigator	18 (100)
AE leading to treatment discontinuation	0
AE leading to study discontinuation	0
Serious AE	0
AE resulting in death	0
AEs in ≥2 participants	
Injection site reaction	11 (61.1)
Skin hyperpigmentation	10 (55.6)
Fatigue	6 (33.3)
Norovirus infection	2 (11.1)
Hypothyroidism	2 (11.1)
Diabetes mellitus	2 (11.1)

AE, adverse event.

Conclusions

- Improvements in BMI, BMI z-score, fat mass, hyperphagia scores, and anxiousness scores were observed following 6 months of setmelanotide treatment
- Fat mass decreases tended to exceed BMI/BMI z-score decreases, with relative preservation of lean mass
- HQ-CT and PADQ scores decreased in nearly all participants
- Due to the small sample size, the potential impact of concomitant diazoxide choline extended-release requires further investigation
- These Phase 2 data in participants with PWS support planned Phase 3 trials

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