Setmelanotide Treatment in Patients With Acquired Hypothalamic Obesity and Previous Weight Loss Surgery

#SAT-712

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Background

- Acquired hypothalamic obesity (aHO) is characterized by accelerated and sustained weight gain following injury to the hypothalamus[1-4]
- Hypothalamic damage can impair the melanocortin-4 receptor (MC4R) pathway, which regulates hunger, satiety, and energy expenditure, and lead to aHO[4,6-7]
- Traditional obesity management strategies, including bariatric surgery, are a less viable option in most individuals with aHO[5]
- In an international, placebo-controlled, Phase 3 trial of the MC4R agonist setmelanotide in participants with aHO (NCT05774756), the primary endpoint of percent change in body mass index (BMI) at Week 52 was met with a placebo-adjusted difference of −19.8%[8]

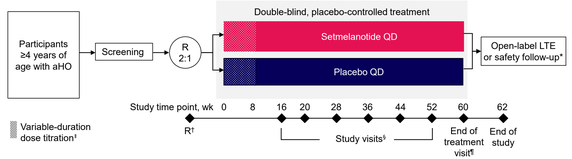
Objective

- To report on a case series of participants from this Phase 3 trial who had a pre-trial history of bariatric surgery

Methods

- Participants aged ≥4 years with BMI ≥95th percentile (4 to <18 years) or BMI ≥30 kg/m^2 (≥18 years) with aHO following hypothalamic tumor, lesion, or injury were included
  - Participants with a history of bariatric surgery were eligible for the trial if the procedure had occurred >2 years prior to enrollment
  - Participants were excluded if they experienced a weight loss >2% (≥18 years old) or a BMI reduction of >2% (4 to <18 years old) within 3 months before screening
- Participants were randomized 2:1 to setmelanotide or placebo for up to 60 weeks (Figure 1)

Figure 1. Study design



LTE, long-term extension; QD, once daily; R, randomization; wk, week.
*Participants completing the trial were eligible for an open-label LTE trial; the safety follow-up visit was for participants prematurely discontinuing treatment or those completing the trial who do not enroll in the LTE. †Baseline was defined as the last available measurement before randomization. ‡Initial dose of 0.5 mg subcutaneously once daily, titrated up to 1.5-3.0 mg based on age, weight, and tolerability. §Visits completed in clinic, at home, or via telehealth. ¶In-clinic visit.

Results

Participant Disposition and Baseline Demographics

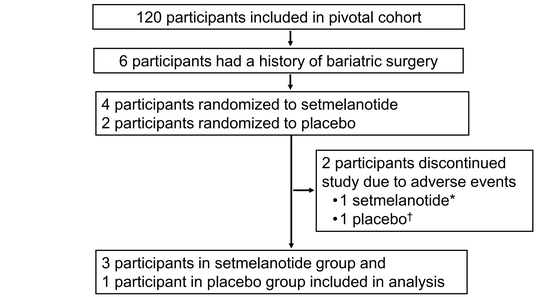
- Of the total 120 participants included in the pivotal cohort of this trial, six adult participants (age range 21-49 years, 5/6 were female) had bariatric surgery, which had occurred at varying intervals prior to the trial (all ≥3 years prior) (Table 1 and Figure 2)
  - Procedure types included gastric sleeve (n=4), gastric bypass (n=3), gastrojejunostomy end-to-side (n=1), and gastric band with subsequent reversal (n=1)
  - Three participants received two different procedures

Table 1. Baseline demographics

Participant	Age	Sex	Surgery Type	Baseline BMI (kg/m^2)	Treatment
1	21	F	• Gastric sleeve • Gastric bypass	46.8	Setmelanotide
2	33	F	• Gastric sleeve • Gastrojejunostomy end-to-side	50.0	Setmelanotide
3	43	F	• Gastric bypass	43.6	Setmelanotide
4	49	F	• Gastric bypass	29.8*	Setmelanotide
5	28	M	• Gastric sleeve	38.2	Placebo
6	43	F	• Gastric band with subsequent removal • Gastric sleeve	46.0	Placebo

*Participant had a BMI of 30.2 kg/m^2 at screening.
F, female; M, male.

Figure 2. Participant disposition

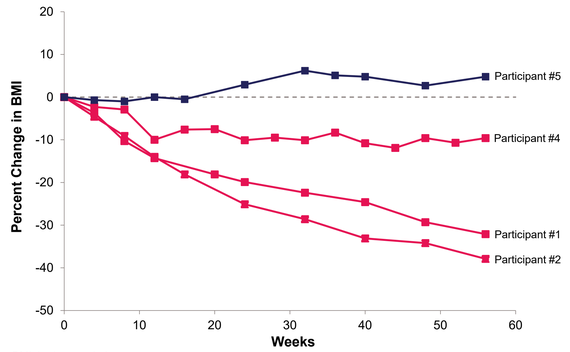


*Participant who received setmelanotide discontinued due to rhinorrhea, itching at injection site, and muscle spasms in legs, all considered unrelated to treatment.
†Participant who received placebo discontinued due to breathing difficulties, considered unrelated to treatment.

Efficacy

- All three setmelanotide participants who completed the study had BMI reductions from baseline after 52 weeks (Figure 3)
  - Individual changes from baseline: -32.1% from 46.8 kg/m^2 baseline BMI; -37.9% from 50.0 kg/m^2; and -9.6% from 29.8 kg/m^2
- By contrast, the placebo participant who completed the study had an increase in BMI from baseline after 52 weeks:
  - Individual change from baseline: 4.8% increase from 38.2 kg/m^2

Figure 3. Percent change in BMI in individual participants



BMI, body mass index.

Safety

- Amongst the 4 participants with a pre-trial history of bariatric surgery that completed the trial, setmelanotide was generally well tolerated (Table 2)
- Treatment-related adverse events were reported in one participant who received setmelanotide (upper abdominal pain, constipation, nausea, and headache) and in one participant who received placebo (increased blood uric acid, peripheral swelling, and photosensitivity)
- Treatment regimens of pituitary hormone replacement, and micronutrient supplements including vitamin D, iron, calcium, B12, and folic acid, remained generally consistent throughout the trial in these participants

Table 2. Safety

Participant	Treatment	Treatment-related	Treatment-unrelated
1	Setmelanotide	Upper abdominal pain, constipation, nausea, headache	Pyelonephritis, vitamin D deficiency, abnormal liver function test, vomiting, urinary tract infection
2	Setmelanotide	-	Oropharyngeal pain
4	Setmelanotide	-	Influenza
5	Placebo	Increased blood uric acid, peripheral swelling, photosensitivity	Influenza, vitamin D deficiency, dry eye, nausea, headache, carotid artery aneurysm, sinusitis, flushing, rash, pain in extremity, increased blood creatine phosphokinase, toothache, groin infection

Conclusions

- The persistence of obesity that conferred trial eligibility in participants with aHO and a history of bariatric surgery highlights the unmet treatment needs for this population
- The response to setmelanotide observed in these participants underscores the importance of targeting the deficiency in MC4R signaling in patients with aHO

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