Effects of Setmelanotide on Obesity, Hunger, and Safety in SH2B1 Deficiency: a Phase 2 Trial

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Summary

- **3 months of setmelanotide treatment may identify individuals with obesity due to functional genetic disturbance of *SH2B1* who respond to setmelanotide, and long-term benefits should be evaluated in these individuals**

Introduction

- Hyperphagia and early-onset, severe obesity may signify a genetic cause, such as impaired signaling through the melanocortin-4 receptor (MC4R) pathway[1]
- SH2B adaptor protein 1 promotes leptin signaling in the MC4R pathway[2,3]
- *SH2B1* variants or a 220–kilobase pair distal deletion of chromosome 16p11.2, including *SH2B1*, are associated with hyperphagia and early-onset, severe obesity[4,5]
- The specific MC4R agonist setmelanotide reduces hunger and body weight in certain individuals with rare genetic diseases of obesity caused by impairment of the MC4R pathway[6,7]

Objective

- To investigate if setmelanotide can safely reduce body weight and hunger in individuals with *SH2B1* heterozygous variants or 16p11.2 deletion

Methods

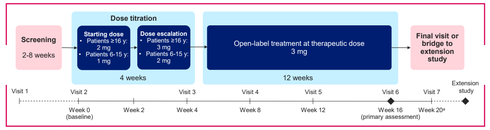
Study Design

- This ongoing Phase 2 uncontrolled study (NCT03013543) investigated setmelanotide treatment in individuals aged ≥6 years with *SH2B1* heterozygous variants or 16p11.2 deletion and obesity
  - Obesity was defined as body mass index (BMI) ≥95th percentile for those aged 6–15 years or BMI ≥30 kg/m^2 for those aged ≥16 years
  - Relevant exclusion criteria included >2% weight loss from diet or exercise within 2 months, >10% durable weight loss from prior gastric bypass surgery, gastric bypass surgery within 6 months, and any use of obesity drugs within 3 months
- Following dose titration, participants received open-label setmelanotide until Month 3 (Figure 1)

Endpoints and Assessments

- The primary endpoint was the proportion of patients who achieve ≥5% body weight reduction from baseline at Month 3 of treatment with setmelanotide
- The proportion of patients who achieved ≥0.15 reduction in BMI Z score (for those aged <18 years) or ≥5% weight loss (for those aged ≥18 years) was also assessed as an exploratory endpoint at Month 3
- As a secondary endpoint, patients ≥12 years old reported their own hunger daily through questionnaires
  - Hunger scores were reported on a numerical scale ranging from 0 to 10, with 0 being not hungry at all and 10 being the hungriest possible
- Unless otherwise stated, efficacy data are from the full analysis set, defined as all patients who received ≥1 dose of study drug and had baseline data
  - The safety analysis set was defined as all patients who received ≥1 dose of study drug
  - The completers' set was defined as all patients in the full analysis set who had weight data collected ≥1 time between Day 60 and 120

Figure 1. Study design.



*Final visit at Week 20 for patients not enrolling in a separate extension study.

Results

Patient Disposition and Demographics

- 22 patients with *SH2B1* heterozygous variants and 13 patients with 16p11.2 deletion were enrolled beginning in August 2019 and received setmelanotide (Table 1)
- 10 patients discontinued treatment
  - 9 discontinued because of adverse events (AEs) and 1 withdrew because of skin pigmentation

Table 1. Patient Demographics

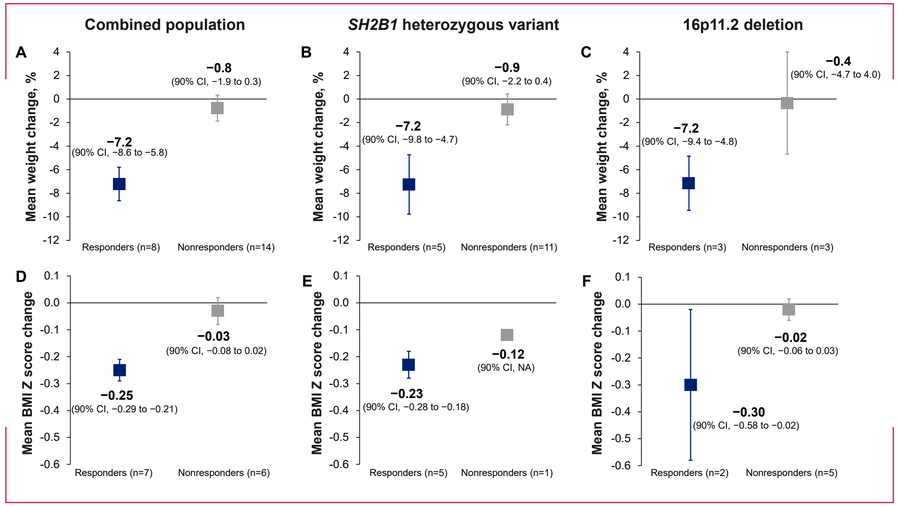
	Full analysis set (N=35)
Age, mean (SD) [range], years	31.1 (17.3) [8–67]
Female, n (%)	24 (68.6)
Race, n (%)	
White	23 (65.7)
Black or African American	6 (17.1)
American Indian or Alaska Native	1 (2.9)
Asian	1 (2.9)
Other	4 (11.4)
Ethnicity, n (%)	
Hispanic or Latino	4 (11.4)
Not Hispanic or Latino	27 (77.1)
Not reported	2 (5.7)
Unknown	2 (5.7)
Genetic type	
SH2B1 heterozygous variant	22 (62.9)
16p11.2 deletion	13 (37.1)
ACMG classification	
Variant of uncertain significance	34 (97.1)
Not available	1 (2.9)
Body weight, mean (SD), kg	127.4 (38.8)
Body weight in those ≥18 years old, mean (SD) [n], kg	139.7 (35.4) [22]
BMI, mean (SD), kg/m^2	47.2 (12.8)
BMI Z score in those <18 years old, mean (SD) [n]	3.6 (0.6) [13]
"Most" hunger score in those ≥12 years old, mean (SD) [n]	7.3 (2.0) [32]

ACMG, American College of Medical Genetics; BMI, body mass index; SD, standard deviation.

Efficacy at Month 3

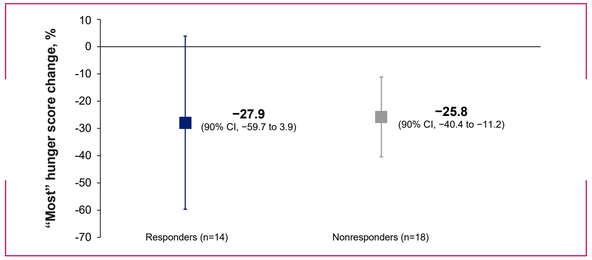
- 13 of the 35 patients (37.1%) achieved the primary endpoint of ≥5% body weight reduction from baseline at Month 3
- 15 of the 35 patients (42.9%; 10 had *SH2B1* variants and 5 had 16p11.2 deletion) achieved ≥0.15 reduction in BMI Z score in those <18 years old or ≥5% weight loss in those ≥18 years old and were classified as responders
  - 7 of 13 patients <18 years old were responders (53.8%; 5 had *SH2B1* variants and 2 had 16p11.2 deletion)
  - 8 of 22 patients ≥18 years old were responders (36.4%; 5 had *SH2B1* variants and 3 had 16p11.2 deletion)
  - In the completers' set, 59.1% of patients (13/22) were considered responders, including 53.8% of patients (7/13) ≥18 years old and 66.6% of patients (6/9) <18 years old
- Mean (90% confidence interval [CI]) change in BMI Z score in patients <18 years old was −0.25 (−0.29 to −0.21; n=7) for responders versus −0.03 (−0.08 to 0.02; n=6) for nonresponders (Figure 2)
  - In the completers' set, mean (90% CI) BMI Z score change was −0.25 (−0.30 to −0.19; n=6) for responders and 0.05 (−0.16 to 0.07; n=3) for nonresponders
- Mean (90% CI) percent weight change in patients ≥18 years old was −7.2% (−8.6% to −5.8%; n=8) for responders versus −0.8% (−1.9% to 0.3%; n=14) for nonresponders
  - In the completers' set, mean (90% CI) percent weight change was −7.3% (−9.0% to −5.7%; n=7) for responders and was −0.2% (−2.8% to 2.4%; n=6) for nonresponders
- Mean (90% CI) percent reduction in "most" hunger score in participants ≥12 years old was −27.9% (−59.7% to 3.9%; n=14) for responders versus −25.8% (−40.4% to −11.2%; n=18) for nonresponders (Figure 3)

Figure 2. (**A–C**) Percent change in body weight (in those ≥18 years old) and (**D–F**) absolute change in BMI Z score (in those <18 years old) at Month 3.



Full analysis set reported. A responder was defined as having ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% confidence interval. BMI, body mass index; NA, not applicable.

Figure 3. Percent change in "most" hunger score (in those ≥12 years old) at Month 3.



Full analysis set reported. A responder was defined as having ≥5% weight loss in those ≥18 years old or ≥0.15 reduction in BMI Z score in those <18 years old. Error bars represent the 90% confidence interval.

Safety at Month 3

- The most common AEs were skin hyperpigmentation (71.4%) and nausea (48.6%) (Table 2)
  - 94.3% of patients reported ≥1 AE
- One serious AE of melanocytic nevus occurred in an adult, for which melanoma was excluded, and which was considered neither melanoma nor treatment related

Table 2. Treatment-Emergent Adverse Events Occurring in ≥15% of Patients[a]

	n (%)
Skin hyperpigmentation	25 (71.4)
Nausea	17 (48.6)
Headache	13 (37.1)
Injection site pruritis	9 (25.7)
Injection site pain	6 (17.1)
Injection site erythema	6 (17.1)
Vomiting	6 (17.1)
Melanocytic naevus	6 (17.1)

[a]Safety analysis set, defined as all patients who received ≥1 dose of study drug.

Conclusions

- In this trial, patients with *SH2B1* heterozygous variants or 16p11.2 deletion had severe obesity despite a relatively young age
- Hunger was reduced in patients aged ≥12 years regardless of responder classification
- Response rates were similar in those with *SH2B1* variants and 16p11.2 deletion
- Response rates were somewhat higher in those aged <18 years (54%) compared with ≥18 years (36%)
- No new safety events emerged
- A 3-month initial treatment period may be useful to identify individuals with setmelanotide-responsive variants involving *SH2B1* for potential long-term treatment, as will be evaluated in the upcoming Phase 3 EMANATE trial

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