Body Mass Index and Weight Reduction in Patients With SH2B1 Deficiency Obesity After 1 Year of Setmelanotide

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* Potential conflict of interest may exist. Refer to the Meeting App.

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Summary

- **The demonstrated efficacy and tolerability of setmelanotide treatment after ~1 year in patients with *SH2B1* heterozygous variants or chromosome 16p11.2 deletion encompassing *SH2B1* support the continued investigation of setmelanotide in this population, which is underway in the ongoing Phase 3 EMANATE trial (NCT05093634)**

Introduction

- The central melanocortin-4 receptor (MC4R) pathway is a key regulator of energy balance and body weight[1]
  - SH2B adaptor protein 1 (SH2B1) binds to Janus kinase 2 and enhances leptin signaling through the MC4R pathway[1,2]
- Variants in *SH2B1* or a 220–kilobase pair distal deletion of chromosome 16p11.2, encompassing *SH2B1*, is associated with hyperphagia (pathologic insatiable hunger); early-onset, severe obesity; reduced final height; and insulin resistance[2-4]
- Treatment with setmelanotide, an MC4R agonist, was associated with weight loss and hunger reduction after 3 months in patients with *SH2B1* heterozygous variants or chromosome 16p11.2 deletion encompassing *SH2B1* in a Phase 2 trial[5]

Objective

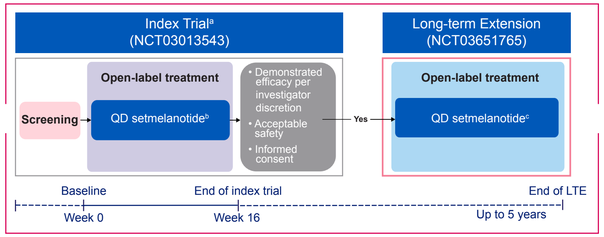
- To assess the continued efficacy of ~1 year of setmelanotide treatment in patients with SH2B1 deficiency obesity

Methods

Trial Design

- Patients were eligible for this long-term extension (LTE) trial (NCT03651765) if they
  - Completed a prior (index) trial in which they received setmelanotide
  - Demonstrated clinical benefit at the discretion of the investigator
- Patients began the LTE immediately following the completion of the index trial (Figure 1)
  - Patients continued the same dose of setmelanotide from the index trial
- Trial visits occurred approximately every 3 months

Figure 1. Trial design.



[a]Index trial data were previously presented at ObesityWeek®; November 1-5, 2021; Virtual. [b]Setmelanotide initiated at 2.0 mg QD for those aged >16 years and 1.0 mg QD for those aged 6 to 16 years. Doses were titrated upward by 1.0 mg every 2 weeks until patients received 3.0 mg QD. [c]Long-term extension continued at the same dose at completion of the index trial. LTE, long-term extension; QD, once daily.

- This analysis was performed in a cohort of patients with *SH2B1* heterozygous variants or a chromosome 16p11.2 deletion that encompasses *SH2B1*
  - These patients received 16 weeks of setmelanotide treatment as part of the index trial
  - Patients were ≥6 years old at the time of enrollment in the index trial
  - Obesity was defined as body mass index (BMI) ≥30 kg/m^2 (for those aged ≥16 years) or BMI ≥95th percentile (for those aged 6-16 years) in the index trial
  - Patients were not eligible for the index trial if they had recent weight loss (>2% within 2 months), received obesity medication (within 3 months), or had gastric bypass (within 6 months or resulting in >10% weight loss)

Outcomes

- Outcomes were assessed after ~1 year of setmelanotide treatment across the index and LTE trials relative to index trial baseline
- Change in BMI was reported for all patients, regardless of age
- Age-relevant weight-related measures were analyzed separately for adult (≥18 years) and pediatric (<18 years) subgroups to minimize the confounding and dilution of treatment effect due to including still-growing pediatric patients with the adult population
  - In adults, changes in weight are reported
  - In pediatric patients, BMI Z score and percentage of the BMI 95th percentile (%BMI$_{95}$) are reported
- A responder is defined as a patient who achieves ≥5% weight loss at Month 3
- Frequency of adverse events was also assessed

Results

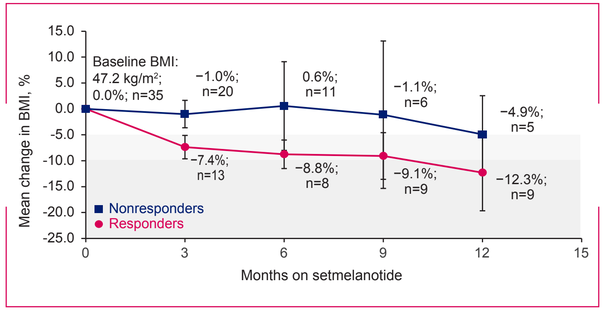
Patient Disposition and Baseline Characteristics

- In total, 35 patients with obesity and *SH2B1* heterozygous variants or chromosome 16p11.2 deletion encompassing *SH2B1* had enrolled in the index trial
  - Nineteen patients entered the LTE trial (8 with *SH2B1* heterozygous variants and 11 with chromosome 16p11.2 deletion encompassing *SH2B1*)
- As of October 29, 2021, 19, 15, and 14 of those patients had received at least 6, 9, and 12 months of treatment, respectively
  - Population sizes decrease at later time points during the LTE trial because some patients have not reached 6, 9, or 12 months
  - Seventeen patients are ongoing, and 2 patients discontinued by voluntary withdrawal during the LTE trial
- At index trial baseline, mean (standard deviation [SD]) age was 31.1 (17.3) years, and 68.6% of patients (24 of 35) were female

Efficacy Outcomes

- Patients had a mean (SD) BMI of 47.2 (12.8) kg/m^2 at index trial baseline
- Mean (SD) percent change in BMI was −3.4% (8.1%; n=19), −5.9% (10.0%; n=15), and −9.7% (8.0%; n=14) at Months 6, 9, and 12, respectively; mean percent change in BMI by responder status is shown in Figure 2

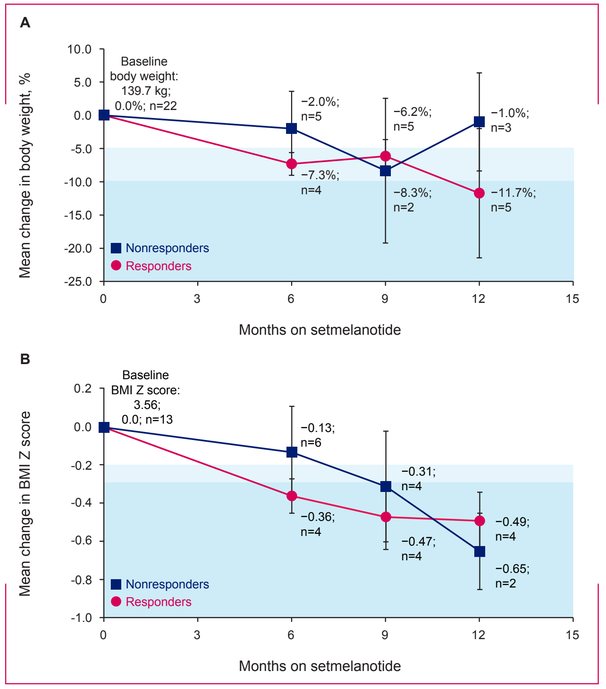
Figure 2. Mean percent change in BMI from index trial baseline by months of setmelanotide treatment.



A responder is defined as a patient who achieves ≥5% weight loss at Month 3. Error bars show standard deviation. Shading denotes benchmarks of −5% and −10% change. This trial is ongoing. BMI, body mass index.

- In patients aged ≥18 years (n=22)
  - Mean (SD) body weight was 139.7 (35.4) kg at index trial baseline
  - Mean (SD) percent change in body weight was −4.4% (5.0%; n=9), −6.8% (5.0%; n=7), and −7.7% (10.0%; n=8) at Months 6, 9, and 12, respectively; mean percent change in body weight by responder status is shown in Figure 3A
- In patients aged <18 years (n=13)
  - Mean (SD) BMI Z score was 3.56 (0.60) and mean (SD) %BMI$_{95}$ was 154.5% (35.5%) at index trial baseline
  - Mean (SD) change in BMI Z score was −0.55 (0.17; n=6) at Month 12; mean change in BMI Z score by responder status is shown in Figure 3B
    - 100% of patients (6 of 6) achieved both a ≥0.3-point and ≥0.2-point reduction in BMI Z score at Month 12
  - Mean (SD) change in %BMI$_{95}$ was −9.7% (11.4%; n=10), −15.9% (12.0%; n=8), and −22.5% (8.5%; n=6) at Months 6, 9, and 12, respectively

Figure 3. (A) Mean percent change in body weight from index trial baseline by months of setmelanotide treatment for patients ≥18 years old. **(B)** Mean change in BMI Z score from index trial baseline by months of setmelanotide treatment for patients <18 years old.



A responder is defined as a patient who achieves ≥5% weight loss at Month 3. Error bars show standard deviation. Shading denotes multiple clinically relevant change thresholds.[4,7] This trial is ongoing. BMI, body mass index.

Safety Outcomes

- No patients discontinued because of adverse events during the LTE
- No new safety concerns emerged during long-term treatment (Table)

Table. Adverse Events Occurring During the Index and LTE Trials in the Safety Population (N=35)

	n (%)
TEAEs	34 (97.1)
Treatment-related TEAEs	34 (97.1)
Serious treatment-related TEAEs	1 (2.9)[a]
TEAEs leading to study drug withdrawal	10 (28.6)
Common TEAEs (≥20%)	
Skin hyperpigmentation	28 (80.0)
Nausea	18 (51.4)
Headache	14 (40.0)
Melanocytic nevus	9 (25.7)

[a]Serious TEAE of melanocytic nevus. This serious TEAE was not considered related to treatment. LTE, long-term extension; TEAE, treatment-emergent adverse event.

CONCLUSION

- One year of MC4R agonist treatment with setmelanotide was associated with clinically meaningful reductions in weight-related measures in patients with SH2B1 deficiency obesity
- Patients who continued setmelanotide treatment after Month 3 generally continued to experience improvements in weight-related measures irrespective of responder classification
  - Small population sizes precluded comparison of the magnitude of effects between responders and nonresponders

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