Body Mass Index and Weight Reductions in Patients With SRC1 Deficiency Obesity After 1 Year of Setmelanotide

ODP605

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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 steroid receptor coactivator 1 (SRC1) deficiency obesity support the continued evaluation 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]
  - The gene nuclear receptor coactivator 1 (*NCOA1*; also known as *SRC1*) encodes a transcriptional coactivator that regulates proopiomelanocortin expression in the MC4R pathway[2,3]
- Certain *NCOA1* (*SRC1*) variants impair MC4R signaling and are associated with hyperphagia (pathologic insatiable hunger) and early-onset, severe obesity[3]
- Treatment with setmelanotide, an MC4R agonist, was associated with significant weight loss and hunger reduction after 3 months in patients with obesity due to SRC1 deficiency caused by a variant in *NCOA1* in a Phase 2 trial[4]

Objective

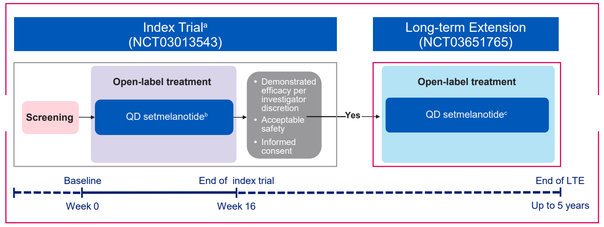
- To assess the continued efficacy of ~1 year of setmelanotide treatment in patients with SRC1 deficiency obesity

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 SRC1 deficiency obesity where 1 allele was either a variant of uncertain significance or pathogenic
  - 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 is reported for all patients, regardless of age
  - BMI was not reported for 2 patients after Month 3 because height data were not available
- 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

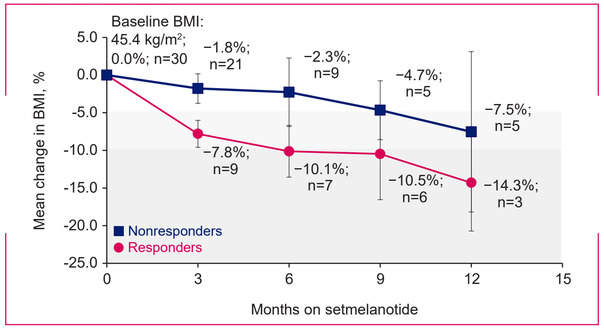
Patient Disposition and Baseline Characteristics

- In total, 30 patients with SRC1 deficiency obesity were treated in the index trial
  - Of these, 17 patients entered the LTE trial
- As of October 29, 2021, 18, 13, and 10 of those patients had received at least 6, 9, and 12 months of treatment, respectively
  - Some patients were able to receive ongoing treatment in the index trial without entering the LTE trial
  - Population sizes decrease at later time points during the LTE trial because some patients have not reached 6, 9, or 12 months
  - At the time of analysis, 15 patients are ongoing, and 2 patients discontinued by voluntary withdrawal during the LTE trial
- At index trial baseline, mean (standard deviation [SD]) age was 30.6 (17.5) years, and 80% of patients (24 of 30) were female

Efficacy Outcomes

- Patients had a mean (SD) BMI of 45.4 (11.3) kg/m^2 at index trial baseline
- Mean (SD) percent change in BMI was −5.7% (5.6%; n=16), −7.8% (5.8%; n=11), and −10.1% (9.4%; n=8) at Months 6, 9, and 12, respectively; percent change in BMI by responder status is shown in Figure 2

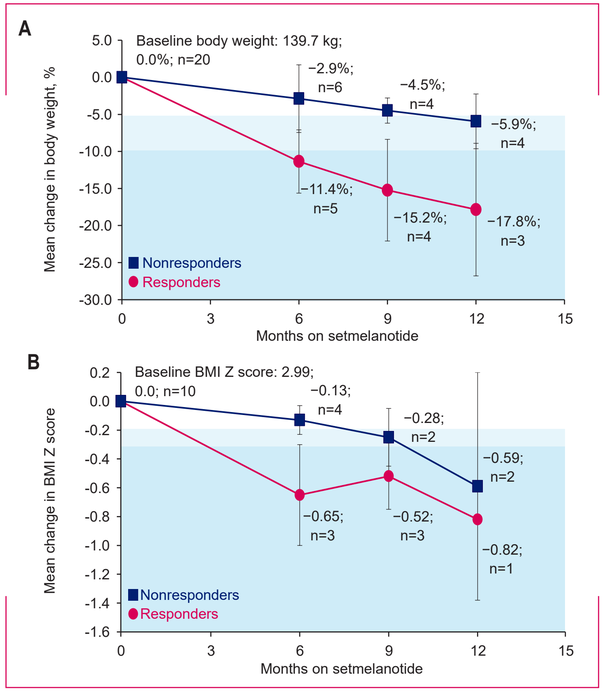
Figure 2. Mean percent change in BMI from index trial baseline by months of setmelanotide treatment.



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=20)
  - Mean (SD) body weight was 139.7 (25.1) kg at index trial baseline
  - Mean (SD) percent change in body weight was −6.7% (6.1%; n=11), −9.9% (7.4%; n=8), and −11.0% (8.6%; n=7) 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=10)
  - Mean (SD) BMI Z score was 2.99 (0.63) and mean (SD) %BMI$_{95}$ was 128.2% (20.5%) at index trial baseline
  - Mean (SD) change in BMI Z score was −0.67 (0.57; n=3) at Month 12; mean change in BMI Z score by responder status is shown in Figure 3B
    - 66.7% of patients (2 of 3) 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 −8.9% (6.5%; n=7), −12.9% (8.1%; n=5), and −21.5% (19.9%; n=3) 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.



BMI was not reported for 2 patients after Month 3 because height data were not available. 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.[5,6] 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=30)

	n (%)
TEAEs	28 (93.3)
Treatment-related TEAEs	27 (90.0)
Serious treatment-related TEAEs	0
TEAEs leading to study drug withdrawal	2 (6.7)
Common TEAEs (≥15%)	
Skin hyperpigmentation	23 (76.7)
Nausea	11 (36.7)
Headache	7 (23.3)
Melanocytic nevus	7 (23.3)
Fatigue	6 (20.0)

LTE, long-term extension; TEAE, treatment-emergent adverse event.

CONCLUSION

- One year of treatment with the MC4R agonist setmelanotide was associated with clinically meaningful reductions in weight-related measures in patients with SRC1 deficiency obesity
- Patients who continued setmelanotide treatment after Month 3 generally continued to experience improvements in weight-related measures irrespective of responder status
  - Small population sizes precluded comparison of the magnitude of effects between responders and nonresponders

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