Efficacy and Safety Analysis of Setmelanotide As a Novel Treatment for Hypothalamic Obesity

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Summary

- **The melanocortin-4 receptor (MC4R) agonist setmelanotide demonstrated significant reduction in body mass index (BMI) and hunger with a manageable safety profile for patients with hypothalamic obesity**

Introduction

- Hypothalamic injury resulting from surgery or radiation for intracranial tumors can impair MC4R pathway signaling, resulting in hypothalamic obesity[1,2]
- The weight gain and appetite changes accompanying hypothalamic obesity are often unresponsive to existing therapies for obesity[2]
- Treatment with setmelanotide, an MC4R agonist, has resulted in weight loss and hunger reduction in patients with MC4R pathway–associated diseases[3,4]

Objective

- To report results from a Phase 2 trial investigating the utility of setmelanotide for the treatment of hypothalamic obesity

Methods

Trial design

- Eligible patients ≥6 to ≤40 years of age with hypothalamic obesity were enrolled across 5 sites in the United States (Table 1)

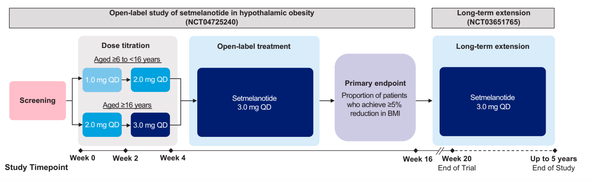
Table 1. Key Eligibility Criteria

Key inclusion criteria	Key exclusion criteria
▪ Age ≥6 to ≤40 years	▪ Glomerular filtration rate <30 mL/min
▪ Obesity • Age ≥6 to <18 years with BMI ≥95th percentile • Age ≥18 years with BMI ≥35 kg/m^2	▪ Dermatologic lesions related to melanoma[a]
▪ Recent (≥6 months and ≤15 years) hypothalamic damage, either unilateral or bilateral, and	▪ Weight gain >5% in the previous 3 months
▪ Diagnosed craniopharyngioma, or	▪ Weight loss ≥2% in the previous 3 months[b]
▪ Brain tumor affecting hypothalamic region, and	▪ Bariatric surgery within the past 6 months
▪ Has undergone surgical resection, radiation, and/or chemotherapy	▪ HbA_{1c} >10%

[a]Those with family history of melanoma were also excluded. [b]Dietary and/or exercise regimens are permitted, including weight loss medications, if the patient plans to keep the regimen/dose stable through treatment duration. BMI, body mass index; HbA_{1c}, glycated hemoglobin.

- Patients underwent open-label dose titration to a final therapeutic dose of 3.0 mg setmelanotide, as tolerated, to be delivered subcutaneously once daily (Figure 1)
  - Patients ≥6 to <16 years of age received 1.0 and 2.0 mg of setmelanotide once daily for 2 sequential 2-week periods followed by 3.0 mg of setmelanotide once daily for 12 weeks
  - Patients ≥16 years of age received 2.0 mg of setmelanotide once daily for 2 weeks followed by 3.0 mg of setmelanotide once daily for 14 weeks
  - Patients who meet the primary endpoint of ≥5% reduction in BMI are eligible to be enrolled in a long-term extension (LTE)

Figure 1. Trial design.



BMI, body mass index; QD, once daily.

Outcomes

- The primary endpoint of the trial was the proportion of patients who achieved ≥5% reduction from baseline in BMI compared with a historical control rate of <5% in this population after 16 weeks of setmelanotide treatment
- Key secondary endpoints included clinically meaningful changes for BMI Z score and weight loss within the population[5,6]
- Additional secondary endpoints included change in daily hunger scores and safety as assessed by the frequency of adverse events

Results

Participant disposition and baseline characteristics

- As of August 31, 2022, there were 18 evaluable patients for analysis within the study; 13 patients were <18 and 5 were ≥18 years of age (Table 2)

Table 2. Baseline Characteristics

	Patients (N=18)
Age, mean (SD), y	15.0 (5.3)
Sex	
Female, n (%)	7 (38.9)
Male, n (%)	11 (61.1)
Baseline weight, mean (SD), kg[a]	102.8 (30.1)
Baseline BMI, mean (SD), kg/m^2	38.0 (6.5)
Baseline BMI Z score, mean (SD)[b]	3.9 (0.9)

[a]Baseline weight reported for patients ≥18 years of age (n=2). [b]Baseline BMI Z score reported for patients ≥6 to <18 years of age (n=9). BMI, body mass index; SD, standard deviation.

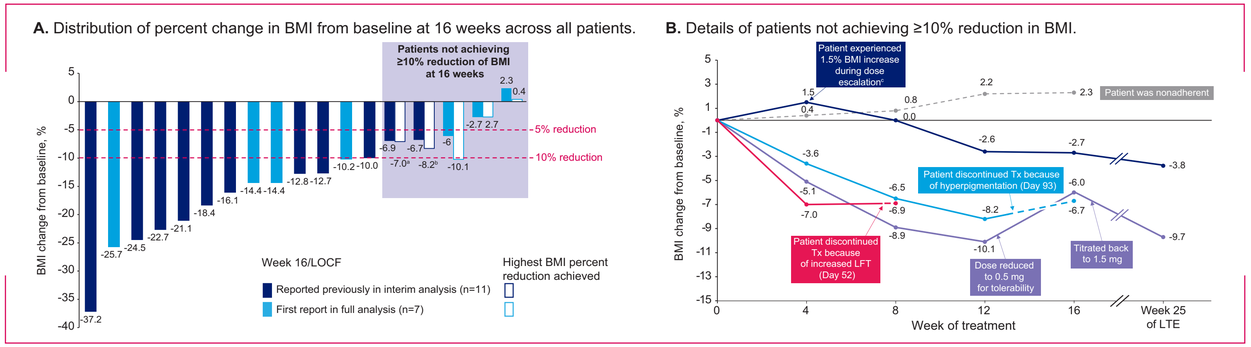
- Setmelanotide treatment resulted in a 12.6% reduction in body weight and 14.5% reduction in BMI at 16 weeks
- Fourteen of 18 patients achieved ≥10% reduction in BMI (Figure 2)
- Mean (standard deviation [SD]) BMI Z score at Week 16 was 2.7 (1.3), a reduction of 1.3 (1.0) points from baseline
- Mean (SD) body weight at Week 16 was 90.4 (28.3) kg, a 12.6% reduction from baseline
- Mean (SD) change in daily hunger score at the patients' most hungry was –2.9 (2.3) (45.0%) for patients ≥12 years of age (n=11) (Table 3)
  - Mean (SD) baseline hunger score was 6.6 (1.6), compared with 3.7 (2.5) at Week 16

Table 3. Efficacy Outcomes

Week 16, change from baseline	n/N	% (90% CI)	*P*
Primary			
Proportion achieving ≥5% reduction in BMI (all ages)	16/18	88.9 (69.0, 98.0)	<0.0001
Secondary			
Proportion achieving ≥0.2-point BMI Z score reduction (age ≥6 to <18 y)	12/13	92.3 (68.4, 99.6)	<0.0001
Proportion achieving ≥5% reduction in BMI (age ≥18 y)	4/5	80 (34.3, 99.0)	<0.0001
Other secondary			
Change in maximal daily hunger score (age ≥12 y)	11/12	−45.0 (−64.8, −25.1)	

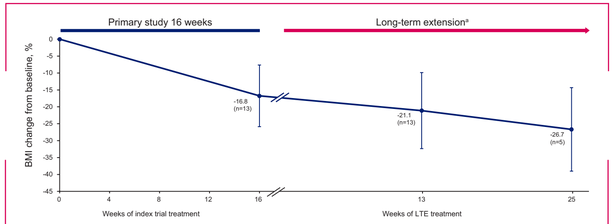
BMI, body mass index; CI, confidence interval.

Figure 2. Mean percent change in BMI from baseline. **(A)** Distribution of percent change in BMI from baseline at 16 weeks. **(B)** Details of patients not achieving ≥10% reduction in BMI.



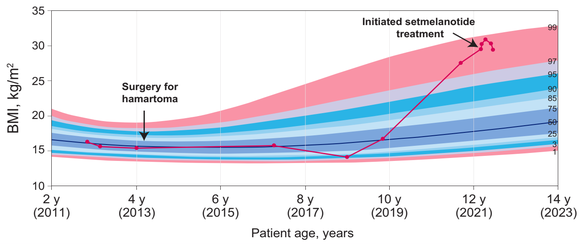
[a]~7.0% last on treatment Week 4. [b]~8.2% last on treatment Week 12. [c]Patient at therapeutic dose of 3 mg setmelanotide; see Figure 4 for detailed information about this patient. BMI, body mass index; LFT, liver function test; LOCF, last observation carried forward; LTE, long-term extension; Tx, treatment.

Figure 3. Mean percent change in BMI in patients with ≥3 months of follow-up in the long-term extension trial.



Errors bars are the standard deviation. [a]Fourteen patients have entered the long-term extension trial; one patient had not reached 3 months of follow-up at the time of analysis. BMI, body mass index.

Figure 4. BMI growth chart of adherent patient who did not achieve ≥5% BMI reduction.



Patient was diagnosed with bilateral hypothalamic hamartoma that was surgically removed in 2013. Patient was 11 years of age at the time of trial participation. Patient initially gained 1.5% BMI during dose escalation but once receiving therapeutic dose of 3 mg, patient experienced 2.7% BMI reduction (4.2% BMI reduction from peak weight), which continued to decline. Shaded bands represent typical trajectory of BMI percentiles over development for children aged 2-20 years (as outlined by the Centers for Disease Control and Prevention). BMI, body mass index.

- Of patients continuing into the LTE, the mean (SD) percent change in BMI was −26.7% (12.3%) at Week 25 among 5 patients with available data at the time of analysis (Figure 3)

Safety outcomes

- Treatment-related adverse events occurred in 83.3% of patients (n=15)
- The most frequent adverse events observed included nausea (61.1%; n=11), vomiting (33.3%; n=6), skin hyperpigmentation (33.3%; n=6), diarrhea (22.2%; n=4), and COVID-19 (22.2%; n=4)
- There was 1 serious treatment-emergent adverse event of *Clostridiodes difficile* colitis, but this was determined not to be related to setmelanotide treatment
- Two patients (11.1%) discontinued because of treatment-related adverse events of hyperpigmentation (n=1) and increased levels of aminotransferase (n=1)

Conclusions

- All patients adhering to setmelanotide treatment (17 of 17) experienced weight loss (see Figure 4 for the BMI growth chart of the patient who did not achieve ≥5% BMI reduction), including those who discontinued because of adverse events
- Our data indicate setmelanotide treatment results in a significant response in a heterogeneous population of patients with hypothalamic obesity who have varied tumor presentation and age
- These encouraging findings support continued development of setmelanotide treatment in patients with hypothalamic obesity; a Phase 3 trial is planned to begin in 2023

Disclosures: GY, EC, and CS are employees of and stockholders in Rhythm Pharmaceuticals, Inc.

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References: 1. Erfurth. *Neuroendocrinology*. 2020;110:767-779. **2.** Abuzzahab et al. *Hom Res Paediatr*. 2019;91:128-136. **3.** Clement et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **4.** Haws et al. *Diabetes Obes Metab*. 2020;22:2133-2140. **5.** US Preventive Services Task Force et al. *JAMA*. 2017;317:2417-2426. **6.** Knowler et al. *N Engl J Med*. 2002;346:393-403.