# Body composition improvements after 12 months of setmelanotide in acquired hypothalamic obesity

PO4.400

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## Introduction

- Acquired hypothalamic obesity (HO) is a form of severe obesity characterised by rapid and excessive weight gain following hypothalamic injury,[1–3] for which there are currently no approved treatments
- Lesions within the hypothalamus have been associated with dysregulation of the melanocortin-4 receptor (MC4R) signaling pathway,[4,5] which is involved in the regulation of hunger and satiety[6–8]
- In a Phase 2 trial of setmelanotide, an MC4R agonist, in patients with acquired HO (NCT04725240), the proportion of patients treated with setmelanotide who exhibited a ≥5% reduction in body mass index (BMI) from baseline to Week 16 was significantly higher than the historic control rate for this population[9]
  - Overall, setmelanotide treatment demonstrated improvements in BMI and BMI z-score at 16 weeks[9]
  - These improvements were maintained for most patients after 12 months in the long-term extension (LTE; NCT03651765), at which the mean percent BMI decrease was 25.5%[10]
- Assessing body composition changes in patients with acquired HO may provide a comprehensive evaluation of treatment efficacy in this patient population
  - A limitation of BMI as a measurement is that it accounts for total body mass only. Therefore, it is not able to convey relative changes in body composition, for example, if a decrease in fat mass was associated with an increase in lean mass, particularly in a growing child or adolescent

## Objective

- To assess body composition changes in patients with HO who received setmelanotide treatment for 12 months in relation to developmental age, treatment adherence, and patient narrative

## Methods

- The Phase 2 multicenter, open-label trial of setmelanotide enrolled patients aged 6 to 40 years with a diagnosis of craniopharyngioma or other non-malignant brain tumour affecting the hypothalamic region who had undergone surgery, chemotherapy, or radiation for intracranial tumours between 6 months and 15 years before screening or had a history of hypothalamic damage supported by magnetic resonance imaging within 8 months before screening
- Patients also had obesity, defined as BMI ≥95th percentile (patients aged 6 to <18 years) or BMI ≥35 kg/m$^2$ (patients aged ≥18 years)
- Patients who experienced a ≥5% reduction in BMI or had an investigator-determined clinically meaningful benefit and exhibited adequate safety after 16 weeks of treatment were eligible to enrol in the LTE; treatment adherence was assessed via patient diaries
- Mean body composition changes were assessed via dual-energy x-ray absorptiometry (DEXA) at index trial baseline and ≥12 months
- For this analysis, patient narratives, safety reports, dose adjustments, and treatment interruptions or discontinuations were reviewed to identify patients who remained on treatment throughout the 12-month period

## Results

### Patient disposition and baseline characteristics

- Of the 18 patients who enrolled in the index trial, 14 (77.8%) continued into the LTE; most patients enrolled in the LTE (n=14) were aged <18 years at study entry (85.7%) and had received treatment for craniopharyngioma (78.6%; Table 1)

### Patient disposition and determination of the on-treatment cohort

- Of the 14 patients who entered the LTE, 11 were confirmed to be on treatment throughout the 1-year period
- While the 3 remaining patients had clinically meaningful age-appropriate weight reductions and greater percent loss of fat mass than lean muscle mass at the end of the index trial, they did not meet the ≥12-month on-treatment criterion, and each had documented treatment discontinuation because of an adverse event (AE), treatment interruption, and non-adherence (Box)

**Table 1.** Demographics and characteristics at index trial baseline of patients entering the LTE (n=14)

| | Total (n=14) |
|---|---|
| **Age, mean (SD), y** | **13.6 (5.0)** |
| **Age range, n (%)** | |
| Adults ≥18 y | 2 (14.3) |
| Children 6 to <18 y | 12 (85.7) |
| **Sex, n (%)** | |
| **Female** | 4 (28.6) |
| **Male** | 10 (71.4) |
| **Tumour type, n (%)** | |
| Craniopharyngioma | 11 (78.6) |
| Hypothalamic hamartoma | 2 (14.3) |
| Juvenile pilocytic astrocytoma | 1 (7.1) |
| Waist circumference, mean (SD), cm | 112.0 (17.9) |
| Weight, mean (SD), kg | 99.1 (32.7) |
| BMI, mean (SD), kg/m$^2$ | 37.0 (7.1) |
| BMI z-score, mean (SD)* | 2.5 (0.3) |
| 95th BMI percentile, mean (SD)† | 145.3 (22.8) |

*BMI z-score was calculated for patients aged <18 years (n=11) using the Centers for Disease Control and Prevention 2022 methodology. †Based on 11 paediatric patients.
SD, standard deviation.

### Box

#### Patient 1

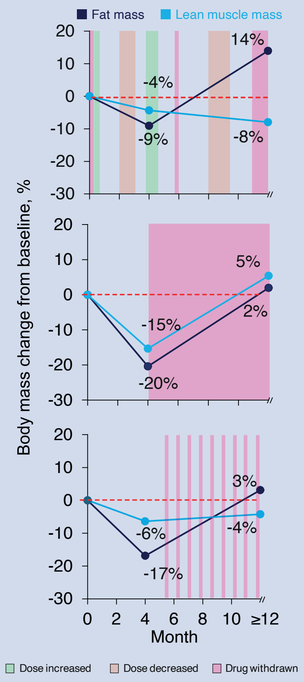
- 23-year-old female patient achieved a percent BMI reduction of 5.9% in the first 4 months after reaching a maximum dosage of 1.5 mg/day
- The patient was not adherent or had multiple treatment withdrawals because of gastrointestinal symptoms and sinusitis. She discontinued treatment at ~8 months but remained on study >12 months, although has now permanently discontinued the trial

#### Patient 2

- 13-year-old male patient achieved a BMI z-score (CDC methodology) reduction of 0.4 in the first 4 months after reaching a maximum dosage of 2.5 mg/day
- The patient was lost to follow-up after entering the LTE, re-entering the trial ~7 months later, noting recurrence of craniopharyngioma
- The patient had issues with adherence to treatment and underwent additional tumour surgery at ~12 months and reinitiated setmelanotide; the BMI z-score subsequently returned to that observed within the first 4 months of treatment (data not shown)

#### Patient 3

- 15-year-old male patient achieved a BMI z-score (CDC methodology) reduction of 0.3 in the first 4 months after reaching a maximum dosage of 3.0 mg/day, which was retained at Month 12
- The patient reported severe depression (including suicidal ideation) and lethargy related to ongoing radiation therapy, which were associated with multiple instances of non-adherence (exact time and duration could not be established)




CDC, Centers for Disease Control and Prevention.

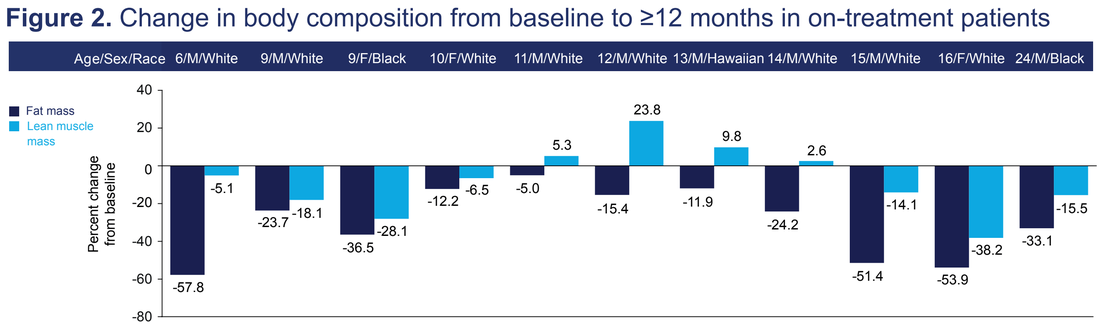
### Efficacy outcomes of confirmed on-treatment patients

- Of the 11 patients who were confirmed to be on treatment for ≥12 months (10 paediatric, 1 adult), the mean (SD) setmelanotide treatment duration at the time of analysis was 477.5 (16.3) days
- The mean (SD) overall percent change in fat mass (−29.6% [17.6%]) was greater than change in lean muscle mass (−7.7% [16.9%]; Figure 1)
- Four male patients (with a baseline age range of 11 to 14 years) exhibited an increase in percent lean muscle mass (Figure 2)
  - Two of the 4 patients progressed in Tanner stage over the same period and had the highest increase in height
  - The average BMI z-score change in these patients was −0.7 (range, −0.1 to −1.2) versus −1.5 in the patients who did not have an increase in percentage of lean muscle mass

**Figure 1.** Mean percent change in fat and lean muscle mass from baseline to ≥12 months in on-treatment patients


Error bars are the standard deviation.

**Figure 2.** Change in body composition from baseline to ≥12 months in on-treatment patients




| Age/Sex/Race | 6/M/White | 9/M/White | 9/F/Black | 10/F/White | 11/M/White | 12/M/White | 13/M/Hawaiian | 14/M/White | 15/M/White | 16/F/White | 24/M/Black |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Change in BMI z-score* | -3.14 | -0.41 | -1.64 | -0.46 | -0.14 | -0.32 | -1.19 | -1.1 | -1.59 | -1.72 | -27.1%* |
| Change in height, cm | +6.2 | +5.3 | +8.3 | +9.5 | +4.6 | +10.4 | +9.5 | +4.0 | +3.6 | 0.0 | NA |
| Change in Tanner stage | No (I) | No (I) | Yes (I→III) | No (I) | No (I) | Yes (IV→V) | Yes (III→IV) | No (V) | No (IV) | No (V) | No (V) |

*Percent change in BMI for 1 adult patient.
F, Female; M, Male; NA, not available.

### Safety outcomes

- All 14 patients who enrolled in the LTE were reported to have had AEs of any causality during the index trial, and 11 (78.6%) reported AEs of any causality during the LTE (Table 2)
  - During the index trial, the most frequent AEs among patients who later enrolled in the LTE were nausea (8 of 14 patients [57.1%]), vomiting (4 of 14 patients [28.6%]), and skin hyperpigmentation (4 of 14 patients [28.6%]); during the LTE, these AEs were reported in 0, 2 (14.3%), and 0 patients, respectively
- There were no serious AE nd no AEs led to study discontinuation during the index trial or LTE
- Although 1 patient did experience elevated liver enzymes, these were determined to be unrelated to setmelanotide treatment; no new safety concerns were observed in the LTE

**Table 2.** Safety summary

| Adverse event | Index trial | LTE |
|---|---|---|
| Any | 14 (100) | 11 (78.6) |
| Related to study drug | 12 (85.7) | 6 (42.8) |
| Leading to study drug interruption or dose | 2 (14.3) | 5 (35.7) |
| Leading to study discontinuation | 0 | 0 |
| Serious | 0 | 0 |
| Resulting in death | 0 | 0 |
| Frequent (≥15%) | | |
| Nausea | 8 (57.1) | 0 |
| Vomiting | 4 (28.6) | 2 (14.3) |
| Skin hyperpigmentation | 4 (28.6) | 0 |
| Injection site pain | 3 (21.4) | 0 |

## Conclusions

- In a heterogeneous population of patients with HO secondary to treatment of hypothalamic tumours, ≥12 months of setmelanotide treatment resulted in greater loss of percent fat mass than lean muscle mass in patients who remained on treatment
- Four peripubertal males (11 to 14 years of age) had a percent increase in lean body mass despite losing fat mass, further highlighting the limitation of BMI as a measurement in this age group
- These results support the beneficial body composition changes associated with previously reported weight reductions with setmelanotide treatment
  - Using measures other than BMI in patients receiving setmelanotide, such as a DEXA scan to assess body composition changes, provides a more complete picture of potential efficacy; patients with a minimal change in BMI may still exhibit clinically relevant decreases in fat mass and increases in muscle mass
  - The observation of increases in percent lean muscle mass in patients aged 11 to 14 years at index trial baseline highlights the importance of accounting for natural changes in body composition during a time of accelerated development and growth while receiving pharmacotherapy
- A randomised, double-blind, placebo-controlled, Phase 3 trial of setmelanotide in patients with HO (NCT05774756) is ongoing

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**References: 1.** Rose, et al. *Obesity (Silver Spring)*. 2018;26:1727–1732. **2.** Erfurth. *Neuroendocrinology.* 2020;110:767–779. **3.** Müller, et al. *Nat Rev Dis Primers.* 2022;8:24. **4.** Roth, et al. *Metabolism*. 2010;59:186–194. **5.** Emet, et al. *Obesity (Silver Spring)*. 2021;29:402–408. **6.** Kühnen, et al. *Trends Mol Med*. 2019;25:136–148. **7.** Sohn, et al. *Cell*. 2013;152:612–619. **8.** Yazdi, et al. *PeerJ*. 2015;3:e856. **9.** Roth, et al. *Lancet Diabetes Endocrinol.* 2024;12:380–389. **10.** Roth, et al. Presented at ObesityWeek; October 14–17, 2023; Dallas, TX.

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