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# Summary

- Patients with hypothalamic obesity (HO) and their caregivers reported unrelenting hunger, drastically reduced energy or physical activity, disrupted sleeping patterns, and substantial weight gain following hypothalamic damage, which was associated with negative impacts on self-esteem, emotions, and family dynamics
- During a clinical trial evaluating setmelanotide, patients and caregivers reported reductions, improvements in eating habits, and increased energy level and activities
- Interviews consistently demonstrated the positive changes of treatment with setmelanotide; these changes were meaningful to both patients with HO and their caregivers because they led to substantial improvements in overall physical and emotional well-being

## Introduction

- Acquired HO is a rapid-onset, severe obesity resulting from hypothalamic damage that impacts the melanocortin-4 receptor (MC4R) pathway, for which there are no approved therapies1
- In patients with HO, rapid weight gain is associated with decreased resting energy expenditure and pathological, insatiable hunger (hyperphagia)<sup>2</sup>
- Results from a Phase 2 clinical trial demonstrated that setmelanotide, an MC4R agonist, was associated with statistically significant reductions in body weight and hunger<sup>3</sup>

# Objective

■ To describe experiences or caregiver observations of hunger, weight, sleep, and energy in patients with HO before and after initiation of setmelanotide

# Methods

- In-depth qualitative interviews were conducted with patients or caregivers of patients who completed a Phase 2 trial of setmelanotide (NCT04725240)
- Eligible patients were aged ≥12 years and enrolled in the open-label long-term extension (LTE; NCT03651765); eligible caregivers were aged ≥18 years and full-time caregivers of patients enrolled in the LTE who were aged <12 or ≥18 years and unable to self-report
- Participants were interviewed via Zoom videoconferencing software between April and July 2023 using a semistructured interview to explore the patient experience and caregiver observations of hunger, eating behaviors, and energy expenditure before and after setmelanotide treatment
- Interview transcripts were analyzed using a thematic approach

#### Results

- A total of 5 participant (3 patients and 2 caregivers) interviews were conducted
- The average age of patient participants was 15 (range, 12-17) years and the average age at surgery was 8 (range 4-14) years; 3 of 5 participants were male and both caregivers were female (ie, the patient's mother;
- **Table 1.** Patient Characteristics and Weight Before and After Setmelanotide

Participant	Patient age at surgery/damage	Weight gain before setmelanotide, lbs*	Weight loss with setmelanotide, lbs*
pIDI 1	14	60	60
pIDI 2	8	100	100
pIDI 3	5	<u>_</u> †	<u>_</u> †
cIDI 1 <sup>‡</sup>	9	50	NA§
cIDI 2"	4	~72¶	84

BMI. body mass index: cIDI. caregiver in-depth interview: pIDI. patient in-depth interview. \*Self- or caregiver-reported. †Patient could not quantify weight, but reported gaining "a lot," which was reduced during treatment with sustained reduction in BMI. †Caregiver report because of cognitive impairment in patient. §Overall loss in weight not reported, reduction in BMI indicated based on height increase over the trial duration. "Caregiver report given because of speech impediment in patient and impaired recall before surgery. Parent reported patient tripled discharge weight of 36 pounds in 4 months after surgery.

#### Patient experiences following hypothalamic damage/surgery and before setmelanotide initiation

- All participants reported that substantial weight gain occurred after damage to the hypothalamus (Table 1)
- All participants experienced or observed unrelenting hunger, drastically reduced energy or physical activity, increased daytime naps, and interrupted nighttime sleep primarily because of hunger (Table 2)

- Additional negative impacts on patients' lives were reported and included self-esteem/self-image, school performance, and social relationships
- Patients and caregivers reported limited or no weight loss with lifestyle and/or other pharmacotherapy interventions before setmelanotide initiation

**Table 2.** Patient Experience Following Hypothalamic Damage/Surgery and Before Setmelanotide

#### Following Hypothalamic Damage/Surgery and Before Setmelanotide Initiation **Energy level and activities** Feelings of hunger "I would wake up and I would be hungry and I would "It was like it would fill me up, but then it could be "Just that I wasn't like a normal kid, and that I didn't "I had trouble. I didn't sleep as much.... It wasn't so much between an hour and 2 hours later, I would think, I had trouble...well, I...yes, because...the reason why have all the energy like all my friends do and stuff... sneak downstairs to get something. And obviously wasn't though is because I felt like I was hungry, so I didn't want supposed to do that or shouldn't need to but felt that I My friend, he would be running around and stuff, where 'I'm hungry again'" - Patient to go to sleep because I felt like I was hungry" - Patient needed to because I was starving" - Patient I would probably just sit down"— Patient

.. when the hunger came, it was really bad. He would throw a fit, he would stomp, he would just insist. And we're talking about between 4 and 6 years old. Very angry, emotional." - Caregiver

"Mostly in school too...if kids had anything in their lunch bag or sitting on their desk, or the teacher had something in her...even that he could see it, he would take it...and he was fast.... We had to lock everything up...." - Caregiver

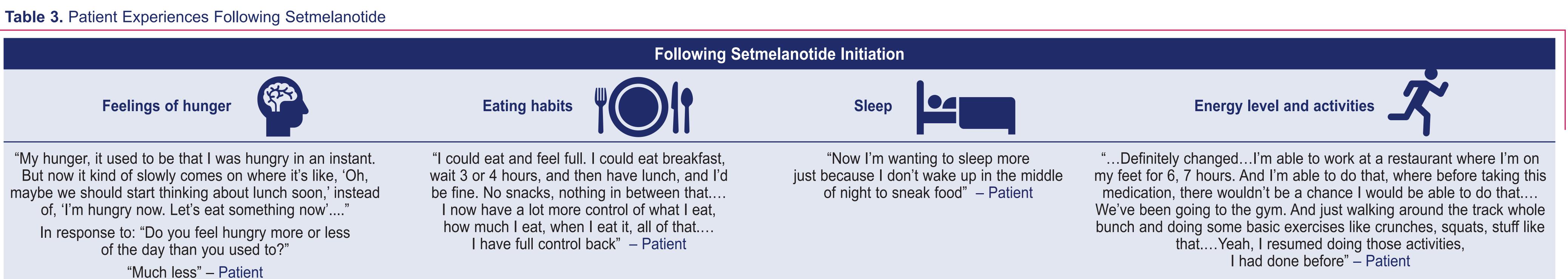
Yes, he'd fall asleep in school often.... He was falling asleep all the time" - Caregiver

"[We'd say,] 'Let's go for a walk. Let's go for a bike ride.' And it was like pulling him out the door. He did not want to leave the couch...when other kids are running around the playground and whatever, he would sit on the side and

want to be next to his teacher. He did not want to play" Caregiver

#### Patient experiences following setmelanotide initiation

- All patients experienced reductions in weight or body mass index (Table 1)
- Most participants (4/5) reported notable reductions in hunger and positive changes in eating behaviors and feelings of satiety with setmelanotide treatment, as well as improvements in sleep, often in the form of reduced or resolved nighttime awakenings due to hunger (Table 3)
- All participants reported improved energy and the ability/desire to be more physically active



In response to: "And does he seem to feel really hungry more or less at the time?" "A lot less" – Caregiver

"He doesn't ask for food anymore. And then, today we went out for breakfast and had pancakes and French toast and he didn't finish it all. He's able to leave food on his plate.... And I'm like, wow...after all these years of this battle, I had to look twice. I'm like, 'Oh, you're bringing it home' and then he didn't even have it yet. So he's still satisfied" - Caregiver

In response to: "How soon after starting setmelanotide did you notice a change in his sleeping?"

"Greatly, probably within...oh, gosh, I would say a month later when he wasn' bringing a snack up to bed or if he didn' need the snack during the night or early morning" – Caregiver

"He was on a stimulant because of the fatigue and low energy. He relied on that stimulant to get through his school day.... So he's been off of a stimulant since May. He's doing remarkably well so that was exciting that just naturally, he doesn't need that. Also, he wears a Fitbit so he counts. He gets so excited to get home from school and tells me how many steps he has. He was in gym class too and just participated

more and didn't complain about the heat or the fatigue or tiredness... He's just more enjoyable. Like I said, I'm just...we go to the pool 3 times a week. We go bike riding. We go for a walk. He used to hate all those things" - Caregiver

#### Treatment satisfaction and desire to continue treatment

- The most important changes reported with treatment were reductions in hunger and weight and improved emotions or mood
- Additional benefits included improved social engagement, physical activity, and school/work performance
- All patients and caregivers reported treatment satisfaction and a strong desire to continue setmelanotide (Table 4)

**Table 4.** Patient- and Caregiver-Reported Meaningfulness of Improvements, Overall Satisfaction of Treatment, and Feelings if Treatment Were Discontinued



Patient

how meaningful it is. It's just been life-changing. And I'm so excited for all other kids to get a hold of this.... I am able to see what it is to feel like normal kid and stuff" – Patient

"It was very exciting. After a week, he skipped his afternoon snack. So that Very satisfied. It's a miracle' was one just super, super [laughter]. It could be...to other people, it's like, 'No big deal.' But for us, I'm like, 'That was a huge, huge progress'... Now we're on...we're enjoying life

"Oh, 100% [satisfied].... Caregiver

to say the least" - Patient "Scared....But I'm also afraid that if he stopped taking it that would we go back to the pound-a-week weight gain. That is a huge fear that I don't know if it'd even occur" Caregiver

every good outcome that is

I know like depression would

be increased, everything

would just go back to normal

and it would be horrible,

come from this medication..

### Conclusions

- The study highlights the unmet needs in effective treatment options for patients with HO and provides additional insights into the patient and caregiver experiences with HO and the potential of setmelanotide
- All 5 patients and caregivers experienced or observed profound changes in hunger, eating-related behaviors, and energy as a result of hypothalamic damage; these changes resulted in negative impacts on patient self-esteem, emotions, and family dynamics
- After receiving setmelanotide, all participants observed reductions in body weight or body mass index and increased energy and physical activity; most participants reported reductions in hunger and improvements in eating behaviors and feelings of satiety
- For patients with HO and their caregivers, setmelanotide was associated with meaningful improvements in their lives that extended beyond clinical outcomes

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