3-Month Real-World Setmelanotide Hunger and Weight Outcomes in Patients with Hypothalamic Obesity

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Introduction

- Acquired hypothalamic obesity (HO) is caused by physical, tumor and/or treatment-related damage or developmental abnormalities to the hypothalamus which can lead to impaired melanocortin-4 receptor (MC4R) pathway signaling, characterized by excessive and often rapid weight gain[1,2]
- The weight gain and appetite changes accompanying acquired HO are often unresponsive to existing therapies for obesity[2,3,4]
- In a Phase 2, open-label trial of setmelanotide, an MC4R agonist, patients with acquired HO experienced consistent and clinically meaningful responses after 16 weeks of treatment, that were maintained or increased for most patients through a 12-month long-term extension trial[3]

Objective

- To report real-world experiences of adult patients with acquired HO with a minimum of 3 months of setmelanotide treatment in France under pre-marketing early access authorization

Methods

- Patients with acquired HO, aged ≥18 years, were treated with setmelanotide in 5 different hospitals in France. This analysis reports efficacy (individual and mean BMI change, changes in hunger scores) and safety (evaluated by adverse event frequency) outcomes
- Physician-reported height and weight information was used to calculate BMI
- Changes in hunger were determined by hunger questionnaires scored from 0 (not hungry at all) to 10 (hungriest possible) comprising of 4 different questions:
  - Over the past 24 hours, on average, how hungry have you felt?
  - Over the past 24 hours, how hungry did you feel when you were most hungry?
  - Over the past 24 hours, how hungry did you feel when you were least hungry?
  - This morning, when you woke up early in the day, how hungry did you feel?
- Meaningful within-person changes in hunger were identified as a reduction of at least 1 point, as normally considered in similar patient populations[3]

Results

Baseline characteristics

- Eight patients (50% male) aged ≥18 years, with a previous resection of craniopharyngioma (n=7) or of Rathke cleft cyst (n=1) were included
- Mean age (standard deviation [SD]) at resection and at setmelanotide treatment initiation (defined as baseline) was 19.3 (8.4) years and 31.4 (7.8) years, respectively
- Mean (SD) weight and BMI at baseline were 132.6 (32.0) kg and 44.1 (6.9) kg/m², respectively
  - Dose varied from 0.5 mg at baseline to 3.0 mg at 6 months based on tolerability
  - Average dose at 3 months of treatment was 2.0 mg
  - 5 patients had 6 months data with a dose of 3.0 mg
- For concomitant obesity medication, 4 patients were on semaglutide/GLP-1 analogues prior to setmelanotide treatment initiation, which was discontinued for 1 patient at setmelanotide initiation

Table 1. Patient baseline characteristics

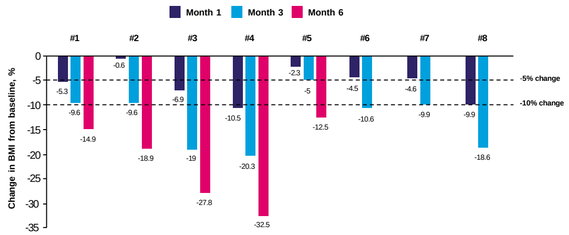
	N=8
Age at setmelanotide treatment initiation, mean (SD), y	**31.4 (7.8)**
Sex, n (%)	
Female	4 (50)
Male	4 (50)
Age at onset of obesity, mean (SD), y [n=7]	**19.1 (8.6)**
Age at tumor resection, mean (SD), y	**19.3 (8.4)**
Weight at baseline, mean (SD), kg	132.6 (32.0)
BMI at baseline, mean (SD), kg/m²	44.1 (6.9)
Concomitant treatment, n (%)	
Semaglutide/GLP-1 analogue*	4 (50)
1 or more hormonal replacement therapy	7 (87.5)

*Discontinued for 1 patient at setmelanotide treatment initiation
BMI, body mass index; SD, standard deviation

Efficacy outcomes

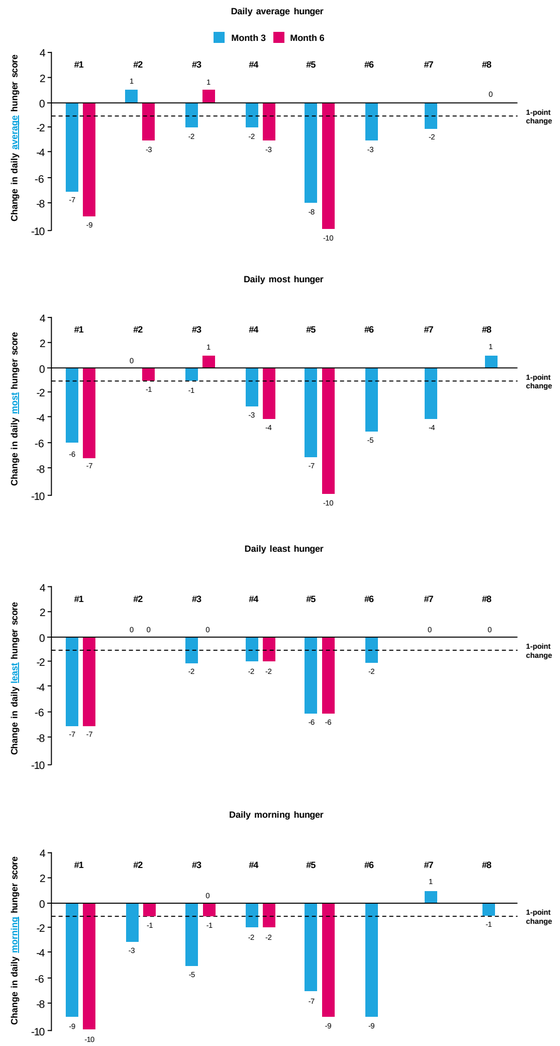
- Overall, a BMI decrease from baseline of 5.6% (2.3 kg/m²), 12.8% (5.7 kg/m²) and 21.3% (7.6 kg/m²) after 1-month (N=8), 3-months (N=8) and 6-months (n=5) of treatment, respectively, was observed, corresponding with a mean decrease in weight of 6.9 kg, 16.8 kg and 29.0 kg, respectively **(Figure 1)**
- At Month 3 of treatment, all patients achieved ≥5% reduction in weight
- By the time of analysis, 5 patients (patient number 1 to 5) had 6-month data
  - All 5 patients achieved ≥12% reduction in weight **(Figure 1)**, with an average BMI decrease of 21.3%
  - Hunger scores at Month 6 were lower or unchanged in each category for 4/5 patients **(Figure 2)**

Figure 1: Individual BMI percent change from baseline by Months 1, 3, and 6



- Overall, patients showed reduction in 3 or more categories of hunger score **(Figure 2)**, with mean scores from baseline to 3 months being:
  - Daily average hunger: 6.0 to 3.1
  - Daily most hunger: 7.4 to 4.3
  - Daily least hunger: 2.9 to 0.5
  - Daily morning hunger: 5.9 to 1.5

Figure 2: Changes in hunger scores from baseline at Months 3 and 6



Safety outcomes

- During treatment, patients reported injection-site pruritus (n=3), asthenia (n=2), frequent, non-prolonged erections (n=2), headache (n=2), hyperpigmentation (n=2), nausea (n=2), anorexia, bacterial angina, bloating, decreased morning erections, diarrhea, erythema, flatulence, increased depressive syndrome, unilateral testicular pain
- At Month 3, one patient had a dose reduction from 2 mg to 1 mg following headaches and nausea however it was declared not related to setmelanotide treatment. The dose was then increased to 3 mg and was well tolerated
- One patient who was on a dose of 1 mg had the dose increased to 2 mg at Day 15 of treatment. In the following 3 days, the patient developed asthenia and anorexia, and the dose was reduced to 0.5 mg. Once the symptoms were resolved, the dose was increased to 0.7 mg at Month 1 and to 1 mg at Month 3, which was well tolerated with no new adverse events
- Combination of GLP-1 analogue and setmelanotide worsened the digestive system adverse events in some patients during the first month

Discussion

- At 1 month, 3 months and 6 months of setmelanotide treatment, a mean decrease in BMI of 5.6%, 12.8% and 21.3%, respectively, was observed in adult patients with acquired HO
- Patients reported meaningful decreases in hunger scores after 3 and 6 months of treatment in each category of the hunger scores
- The mean duration between resection and initiation of setmelanotide treatment was 12.1 years in these adult patients, indicating beneficial outcomes years after injury
- No new safety signals were observed
- Efficacy and safety data are consistent with Phase 2 trial data demonstrating clinically beneficial outcomes of setmelanotide treatment in patients between 6 to 40 years of age[3]

Conclusion

- **These real-world data of adult patients with acquired hypothalamic obesity who received ≥3 months of setmelanotide under pre-marketing early access authorization showed improvements in hunger scores and weight outcomes that were consistent with Phase 2 data and revealed no new safety signals**
- **These results demonstrate the clinical benefits of setmelanotide years after initial hypothalamic injury. As such, setmelanotide has the potential to improve clinical outcomes in adult patients suffering from acquired hypothalamic obesity due to injury experienced more than a decade before**

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References: 1. Erfurth EM. *Neuroendocrinology* 2020;110:767-779; 2. Abuzzahab MJ, et al. *Hom Res Paediatr* 2019;91:128-136; 3. Roth CL, et al. *Lancet Diabetes Endocrinol* 2024;12:380–389; 4. van Iersel L, et al. *Endocr Rev*. 2019;40(1):193-235; 5. Haqq AM, et al. *Lancet Diabetes Endocrinol* 2022;10:859–68.