3-Month real-world setmelanotide hunger and weight outcomes in four French paediatric patients with acquired or congenital hypothalamic obesity

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Presenting Author: Ahlam Azar-Kolakez

Ahlam Azar-Kolakez[1]; Rachel Reynaud[2]; Jean-Claude Carel[1]; Marine Delagrange[3]; Pascal Barat[3]; Natacha Bouhours[4]; Régis Coutant[4]

[1]Endocrinology-Diabetology Department, Reference Center for Endocrine Growth and Developmental Diseases, Robert Debré Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France; [2]Department of Multidisciplinary Paediatrics, Aix Marseille University, MMG, INSERM U1251, Marmara Institute, CRMR HYPO, Marseille 13385, France; [3]Groupe Hospitalier Pellegrin-CHU, Bordeaux, 33076, France; [4]Pediatric endocrinology and diabetology unit and Reference Centre for rare Thyroid Diseases, University Hospital of Angers, Angers, France

Introduction

- Hypothalamic obesity (HO) is a rare and complex disorder characterized by impairment in key regulatory pathways of energy intake and expenditure in the brain
  - Acquired HO is caused by physical, tumour- and/or treatment-related damage or developmental abnormalities to the hypothalamus which can lead to impaired melanocortin-4 receptor (MC4R) pathway signaling, resulting in hyperphagia and characterized by excessive and often rapid weight gain[1,2]
  - Congenital HO occurs due to dysfunction or damage to the hypothalamus from birth, with patients often experiencing hyperphagia and difficulty managing their weight[3]
- The weight gain and appetite changes accompanying HO are often unresponsive to existing therapies for obesity[2,4,5]
- 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 months long-term extension trial[4]

Objective

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

Methods

- Individual case reports from four patients with acquired or congenital HO, aged ≤18 years, who were treated with setmelanotide in 4 different hospitals in France. This analysis reports efficacy (individual BMI z-score, body weight and hunger score change) and safety (evaluated by adverse event frequency) outcomes
- Physician-reported height and weight information was used to calculate BMI z-scores
- 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?

Conclusions

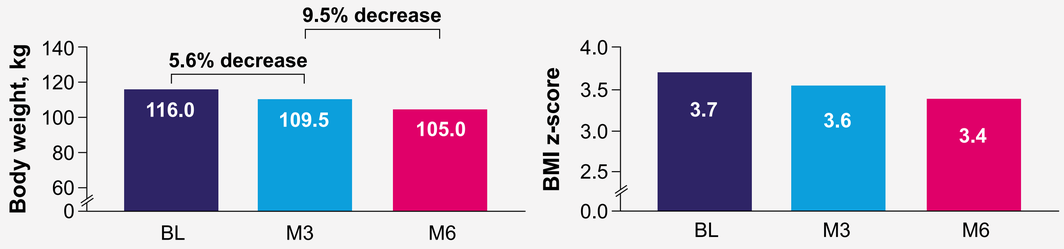
- **These data of 4 paediatric patients with acquired or congenital HO, who received 3 months of setmelanotide under pre-marketing early access authorization, showed improvement in weight measures**
- **Despite the complexities and individual differences associated with hypothalamic injury, these results may suggest that both acquired and congenital forms share a biological mechanism involving disrupted MC4R pathway signaling, allowing for targeted treatment**

Results

Case Report 1 (Acquired HO)

- Patient 1, male, 8 years at onset of obesity, had a previous resection of craniopharyngioma at the age of 9. He had hypopituitarism as a co-morbidity
- Setmelanotide treatment was started at 13 years of age, with dose escalation from 0.5 mg at baseline (BL) to 3 mg at Month 3 (M3), which was maintained through Month 6 (M6)
  - Patient was on semaglutide and the weight was stabilized before the treatment initiation with setmelanotide. Patient was continued on semaglutide throughout the observation period
- Patient had a 5.6% and 9.5% decrease in bodyweight at M3 and M6 of treatment, respectively.
- The BMI z-score change was -0.1 and -0.3, at M3 and M6 of treatment, respectively (**Figure 1**)

Figure 1:

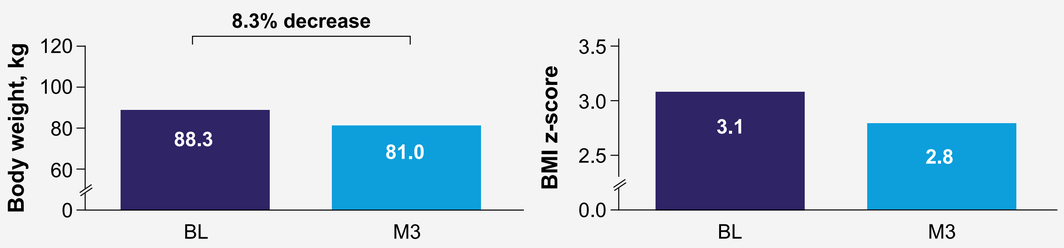


- For the 4 questions included in the scoring of hunger scores, the reported changes were:
  - 1-4-0-0 (BL) to 4-4-4-4 (M3) to 0-5-0-3 (M6)
- Even though an increase in hunger score at M3 and M6 was reported, patient reported to the HCP about being moderately hungry before the meal and not hungry at all after the meal
- During treatment, patient reported abdominal pain and microvesicular eruption of hair follicles on all four limbs and trunk

Case Report 2 (Acquired HO)

- Patient 2, male, 12.9 years at onset of obesity, had radiotherapy for juvenile pilocytic astrocytoma. He had liver cytolysis as co-morbidity
- Setmelanotide treatment was started at 13 years of age, with dose escalation from 0.5 mg at BL to 3 mg at M3
  - As ongoing treatment, patient was on hormonal replacement therapy
- Patient had a 8.3% decrease in body weight and -0.3 BMI z-score change at M3 of treatment **(Figure 2)**

Figure 2:

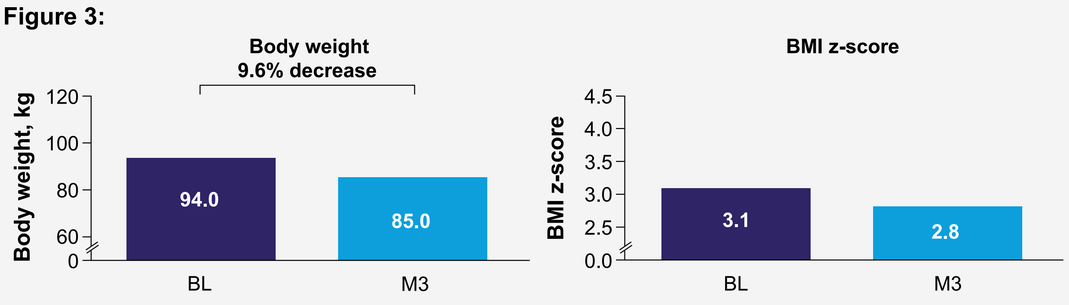


- For the 4 questions included in the scoring of hunger scores, patient reported meaningful change in 3 out of 4 categories with 8-5-8-3 (BL) to 2-3-0-3 (M3)
- Patient had neurological degradation with facial paralysis, right hemiparesis and post-radiation neuritis of the optic nerves, suggestive of radiation necrosis
- During treatment, patient reported induration at injection site at Month 1 (M1) of treatment

Case Report 3 (Congenital HO)

- Patient 3, female, had septo-optic dysplasia (SOD), combined pituitary hormone deficiency and valgus foot as co-morbidity. Age of onset of obesity was not reported
- Setmelanotide treatment was started at 15 years of age, with dose escalation from 0.5 mg at BL to 1 mg at M3
  - As ongoing treatment, patient was on hormonal replacement therapy
- Patient had a 9.6% decrease in body weight and -0.3 BMI z-score change at M3 of treatment **(Figure 3)**

Figure 3:

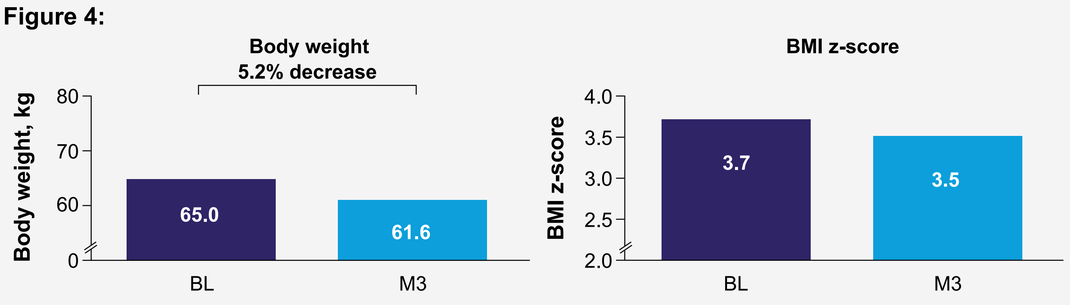


- For the 4 questions included in the scoring of hunger scores, the reported change was 5-5-0-6 (BL) to 5-5-0-5 (M3). Physician noted difficulty in interpretation and scoring with the questionnaire
- During treatment, patient reported injection site reaction and intermittent diarrhoea at 2 weeks of treatment which was resolved. Angina, sore throat and hyperpigmentation was reported at M3

Case Report 4 (Congenital HO)

- Patient 4, male, 2.5 years at onset of obesity, had pituitary stalk interruption syndrome (PSIS), corticotropic, thyrotropic and growth hormone (GH) deficiency as co-morbidity
- Setmelanotide treatment was started at 9 years of age, with dose escalation from 0.5 mg at BL to 2 mg at M3
  - As ongoing treatment, patient was on hormonal replacement therapy
- Patient had a 5.2% decrease in body weight and -0.2 BMI z-score change at M3 of treatment **(Figure 4)**

Figure 4:



- For the hunger outcomes, patient reported a qualitative improvement rather than quantitative, as normally reflected by hunger scores. Initially, the patient described feeling moderately hungry at BL, slightly hungry at M1, and not hungry at all by M3 of treatment
- During treatment, no adverse events were reported for the patient

Discussion

- By the time of analysis, all patients reported ≥5% decrease in body weight by Month 3 of treatment which continued further to 9.5% decrease for one patient with 6 months of treatment data reported
- First reported evidence of setmelanotide treatment in patients with congenital HO (SOD and PSIS) showing >5% decrease in weight by Month 3, suggesting the presence of hypothalamic dysfunction with impaired signaling through the MC4R pathway
- No new safety signals were observed
- Efficacy and safety outcomes in this real-world setting are consistent with Phase 2 trial data demonstrating clinically beneficial outcomes of setmelanotide treatment in a paediatric patient population[4]

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