Treatment History and Comorbidities Reported by Patients With Hypothalamic Obesity Treated With Setmelanotide in a Phase 2 Trial

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Summary

- **Setmelanotide treatment resulted in significant and clinically meaningful body mass index (BMI) reductions in a heterogeneous population of patients with hypothalamic obesity (HO) and with varied tumor presentation and comorbidities**

Introduction

- Hypothalamic damage resulting from intracranial tumors, and their respective treatments, can disrupt leptin-melanocortin signaling leading to HO[1,2]
- Treatment of HO is complex given the varied individual pathophysiology that includes multiple comorbidities and their related management strategies[1,3]
  - Patients are often refractory to lifestyle modifications and traditional pharmacotherapy for treatment of obesity[3]
  - Treatment of patients with HO is complicated by the high level of concomitant medications
- Treatment with the melanocortin-4 receptor (MC4R) agonist setmelanotide resulted in clinically meaningful weight loss in clinical trials of patients with MC4R pathway–associated diseases, including HO[4]
  - In a Phase 2, 16-week trial of setmelanotide in patients with HO, 16 of 18 patients (88.9% [90% confidence interval, 69.0%-98.0%]; *P*<0.0001) achieved ≥5% BMI reduction from baseline, with a mean percent change in BMI of −15.4% at Week 16

Objective

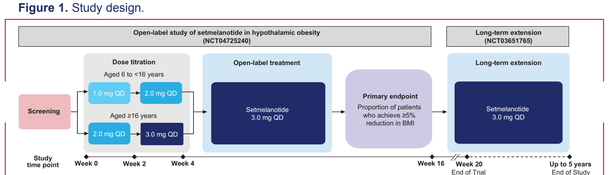
- Here, we report a broad overview of patient histories of all patients entering the Phase 2, 16-week trial of setmelanotide in patients with HO, including tumor treatment, comorbidities, and prior weight loss attempts, to further characterize this population

Methods

Trial design

- Eligible patients were 6 to 40 years of age with evidence of hypothalamic injury within 8 months before screening and a diagnosis of craniopharyngioma, or other nonmalignant brain tumor, with hypothalamic involvement that had been treated with surgery, chemotherapy, or radiation
- Setmelanotide was titrated in an age-dependent manner to a maximum dose of 3.0 mg administered subcutaneously once daily, as tolerated, for 16 weeks of total treatment (Figure 1)

Figure 1. Study design.



BMI, body mass index; QD, once daily.

Outcomes

- The primary endpoint was the proportion of patients achieving ≥5% reduction in BMI after 16 weeks of treatment compared with a historical control rate of <5% in this population
- Patient histories were reviewed and compiled for the following information:
  - Tumor type, laterality, and treatment
  - Comorbid conditions
  - Prior and concomitant medications
  - Prior weight loss attempts
  - Historical growth charts

Results

Patient disposition and baseline characteristics

- A total of 18 patients were enrolled (Table 1)
  - Thirteen patients were <18 years old, and 5 were ≥18 to ≤40 years old
  - Sixteen patients completed the trial (88.9%)
  - Two patients discontinued because of adverse events of hyperpigmentation (n=1) and increased alanine aminotransferase (n=1)
  - One patient was nonadherent to study drug administration

Table 1. Baseline Characteristics

	Patients (N=18)
Age, mean (SD), y	15.0 (5.3)
Age <18, n (%)	13 (7.2)
Age ≥18, n (%)	5 (27.8)
Sex, n (%)	
Female	7 (38.9)
Male	11 (61.1)
Race, n (%)	
White	14 (77.8)
Black or African American	3 (16.7)
Other	1 (5.6)
Ethnicity, n (%)	
Hispanic or Latino	4 (22.2)
Not Hispanic or Latino	14 (77.8)
BMI, mean (SD), kg/m^2	38.0 (6.5)
Weight in patients aged ≥18 years, mean (SD), kg*	120.0 (21.3)
BMI Z score in patients aged ≥6 to <18 years, mean (SD)†	3.9 (0.9)
%BMI95 in patients aged ≥6 to <18 years, mean (SD)†	144.7 (21.4)

†%BMI95, percent of the BMI 95th percentile; BMI, body mass index; SD, standard deviation. *n=5. †n=13.

Tumor details and treatment strategies

- Most patients were diagnosed with craniopharyngioma (77.8%; n=14); 3 (16.7%) had hypothalamic hamartoma and 1 (5.6%) had juvenile pilocytic astrocytoma (Table 2)
  - Patients were primarily treated via surgical resection (88.9%; n=16); 6 additionally received radiotherapy (33.3%), and 1 (5.6%) underwent laser ablation
    - There were 6 patients who underwent multiple procedures: 5 had both craniotomy and radiotherapy (1 had traditional radiotherapy and a gamma knife procedure), and 3 had multiple craniotomies

Table 2. Tumor Type and Treatment Procedure

	Patients, n (%) (N=18)
Tumor type	
Craniopharyngioma	14 (78.8)
Hypothalamic hamartoma	3 (16.7)
Juvenile pilocytic astrocytoma	1 (5.6)
Procedure	
Craniotomy, tumor removal	16 (88.9)
Radiotherapy	6 (33.3)
Laser ablation	1 (5.6)
Gamma knife	1 (5.6)
Hypothalamic involvement	
Bilateral	14 (77.8)
Unilateral	4 (22.2)

Comorbidities and concomitant medications

- The most common comorbidities included hypothyroidism (83.3%; n=15) and diabetes insipidus (77.8; n=14) (Table 3); hyperphagia and increased appetite were reported by 6 patients (33.3%)
- The most commonly reported concomitant medication was thyroid hormones (94.4% [17/18]) (Table 4)

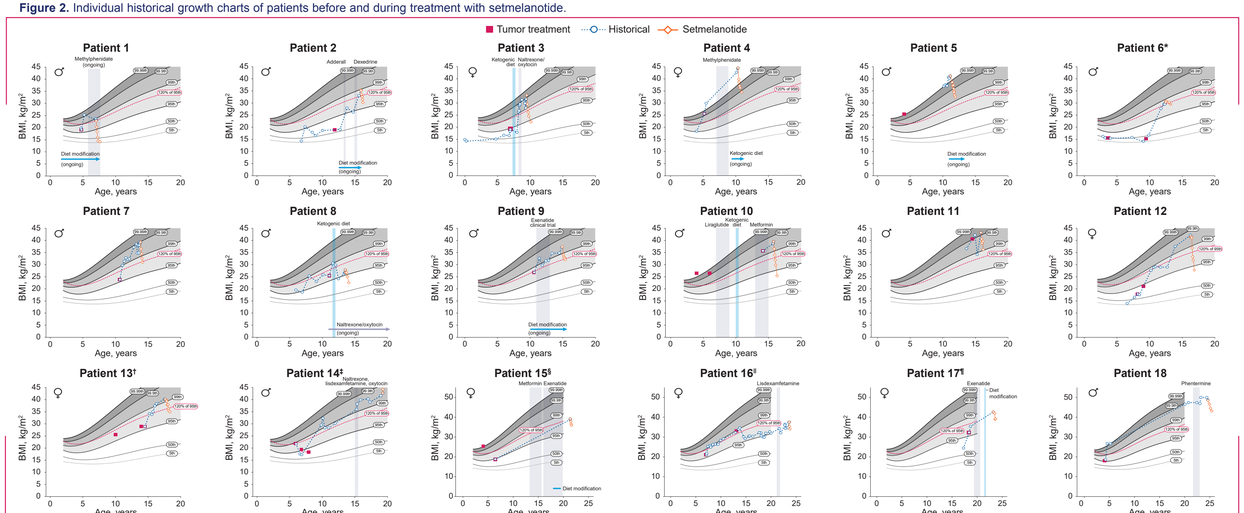
Table 3. Comorbidities Occurring in ≥30% of Patients

	Patients, n (%) (N=18)
Hypothyroidism	15 (83.3)
Diabetes insipidus	14 (77.8)
Growth hormone deficiency	11 (61.1)
Adrenal insufficiency	10 (55.6)
Hypopituitarism	10 (55.6)
Secondary hypogonadism	7 (38.9)
Hyperphagia	6 (33.3)
Headache	6 (33.3)
Anxiety	6 (33.3)

Historical growth charts

- During the clinical trial, 88.9% of patients (16/18) achieved the primary endpoint of ≥5% BMI reduction with setmelanotide treatment; all adherent patients (17/18) experienced reductions in BMI following treatment initiation, including the 2 patients who discontinued therapy because of an adverse event (Figure 2, Patient 15 and Patient 17) and 1 patient who experienced an increase in BMI during dose escalation (Figure 2, Patient 6)

Figure 2. Individual historical growth charts of patients before and during treatment with setmelanotide.



Curves within plots represent the typical trajectory of BMI percentiles over development for children as outlined by the Centers for Disease Control and Prevention. *Patient experienced increased BMI during dose escalation. †Patient reported taking semaglutide and liraglutide each for 2-3 months but date of treatment was not reported. ‡Patient was nonadherent to study drug administration. §Patient discontinued treatment because of adverse event of hyperpigmentation. ¶Patient reported transitioning to a ketogenic diet but date and duration of this attempt were not reported. #Patient discontinued treatment because of adverse event of increased levels of alanine aminotransferase. BMI, body mass index.

Table 4. List of Concomitant Medications Used by ≥50% of Patients

	Patients, n (%) (N=18)
Thyroid hormones*	17 (94.4)
Glucocorticoids†	14 (77.8)
Vasopressin and analogues	14 (77.8)
Somatropin and somatropin agonists‡	12 (66.7)
Serotonin antagonists§	10 (55.6)

*Patients treated included those diagnosed with hypothyroidism (n=15), thyroid disorder (n=1), and panhypopituitarism (n=1). †Patients treated included those with adrenal insufficiency (n=10), pituitary abnormalities (n=2), and panhypopituitarism (n=2). ‡Patients treated included those with growth hormone deficiencies (n=11) and postoperative hypopituitarism (n=1). §Ondansetron was the only serotonin antagonist and was taken for treatment of nausea and vomiting.

Prior and concomitant weight loss attempts

- Fourteen patients (77.8%) reported prior attempts at weight loss (Table 5)
  - Of these, 12 engaged in lifestyle modifications, including dietary modification, ketogenic diet, food restriction, and calorie restriction
    - Four patients reported either some weight loss or perceived lower weight gain with these strategies
  - Pharmacotherapy was used by 9 patients for weight management, and 7 patients used multiple antiobesity medications; no weight loss was experienced or reported with any of the respective medications
    - Four patients were treated for impulse eating with naltrexone/oxytocin and/or lisdexamfetamine
- No prior attempts at weight loss were reported for 4 patients

Table 5. Previous Attempts at Weight Loss (n=18)

Attempt type, n		Lifestyle modifications, n		Pharmacotherapies, n			
No previous attempt	4	Ketogenic diet	5	Exenatide	3	Semaglutide	1
Pharmacotherapy only	1	Dietary modification	5	Metformin	2	Phentermine	1
Lifestyle modification only	1	Calorie restriction	1	Liraglutide	2	Lisdexamfetamine	2
Combined pharmacotherapy and lifestyle modification	12	Food restriction	1	Methylphenidate	2	Oxytocin	3
		Personal trainer	1	Dexedrine	1	Naltrexone	3
				Adderall	1		

Patients may have undergone multiple attempts at either lifestyle modifications or pharmacotherapy or multiple attempts within each of these approaches. Lisdexamfetamine, oxytocin, and naltrexone were administered for control of impulse eating.

Safety outcomes

- Treatment-related adverse events occurred in 83.3% of patients (n=15)
- Frequent adverse events 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)
- A single serious treatment-emergent adverse event of *Clostridioides difficile* colitis occurred but was determined not to be related to setmelanotide treatment
- Discontinuations because of adverse events occurred in 2 patients (11%; hyperpigmentation [n=1] and increased levels of aminotransferase [n=1]) (Figure 2; Patient 15 and Patient 17, respectively)

Conclusions

- This population of patients with HO had complex medical histories including varied tumor presentation, degree of hypothalamic damage, associated pituitary hormone deficiencies, and other comorbid conditions
  - Many of the patients also had a history of unsuccessful weight loss attempts
- Regardless of a high level of common comorbidities and concomitant treatments, all adherent patients in this Phase 2 trial experienced a reduction in BMI with 16 weeks of setmelanotide treatment, with a safety profile consistent with previous clinical trials of setmelanotide in MC4R pathway–associated diseases

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