4-Year Setmelanotide Weight Outcomes in Patients With POMC and LEPR Deficiency Obesity

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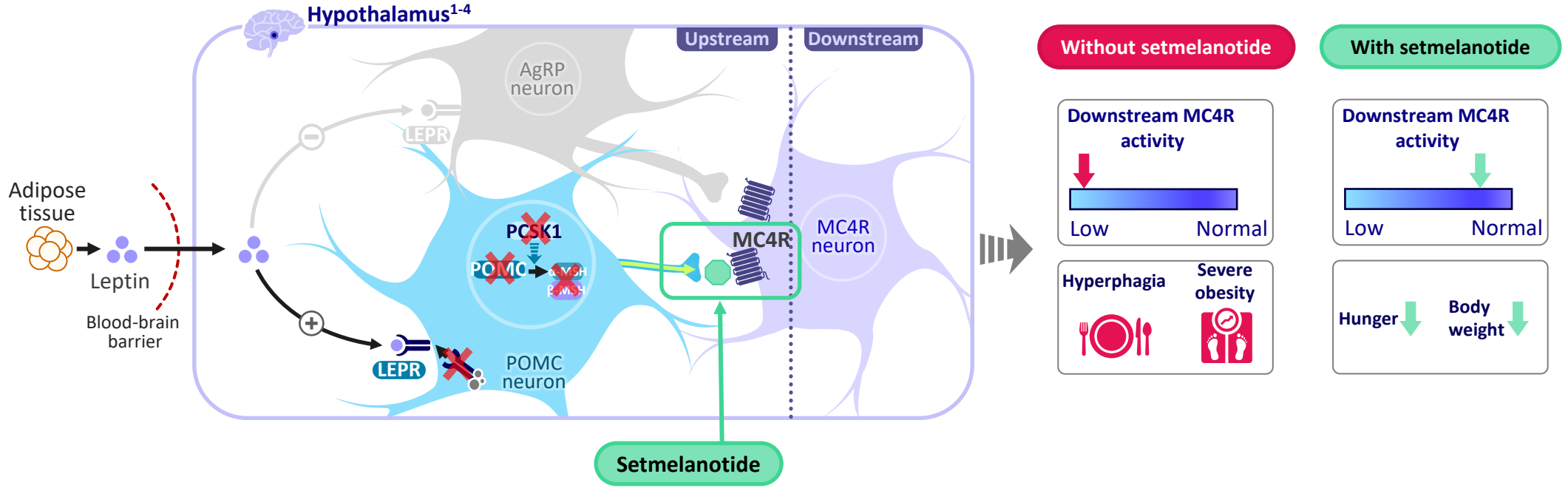
POMC and LEPR Deficiency Are Rare Forms of MC4R Pathway–Associated Obesity

- Under physiologic conditions, the hypothalamic MC4R pathway regulates hunger, satiety, energy expenditure, and, consequently, body weight[1-4]
- Rare variants in key genes of the MC4R pathway are associated with hyperphagia and severe, early-onset obesity[5,6]
  - Biallelic variants in *POMC* and *PCSK1* lead to POMC deficiency; biallelic variants in *LEPR* lead to LEPR deficiency[6]
- The MC4R agonist setmelanotide is associated with reduced weight-related outcomes and hunger in patients with obesity due to POMC or LEPR deficiency[7]



AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

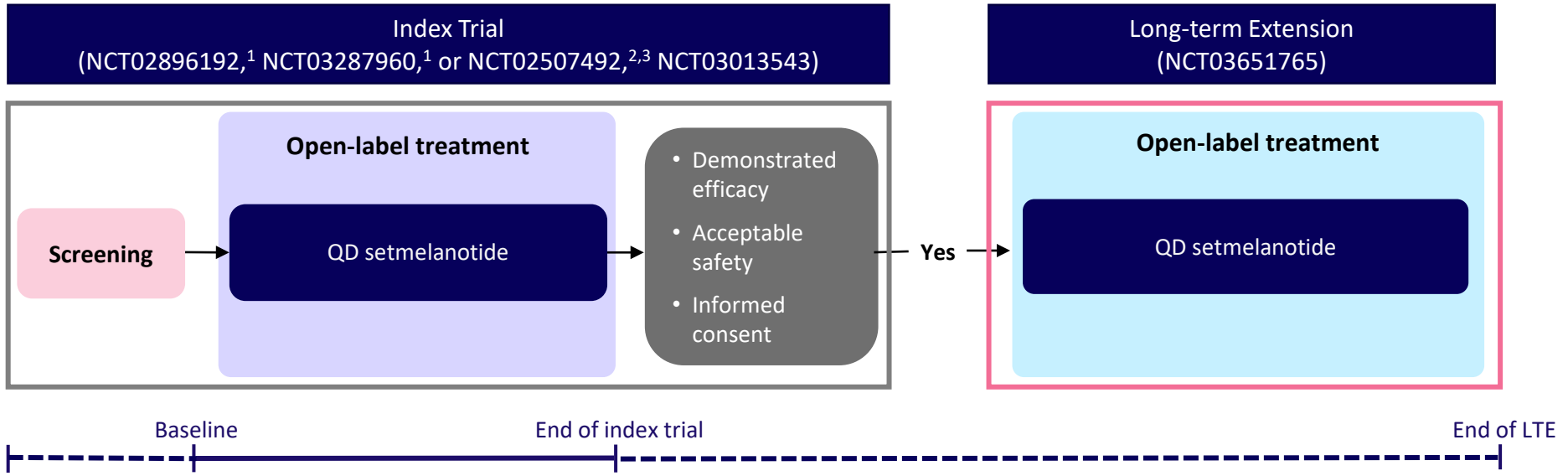
1. da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **2.** Yazdi et al. *PeerJ*. 2015;3:e856. **3.** Farooqi, O'Rahilly. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **4.** Vaisse et al. *Cold Spring Harb Perspect Biol*. 2017;9:a028217. **5.** Huvenne et al. *Obes Facts*. 2016;9:158-173. **6.** Clément et al. *Physiol Behav*. 2020;227:113134. **7.** Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970.

Objective

The objective of this analysis was to assess the long-term efficacy of setmelanotide therapy in patients with POMC and LEPR deficiency obesity who had a clinically meaningful weight response at the end of the initial 12 months of therapy and who had long-term, on-treatment outcomes at Year 4

%BMI95, percent of the 95th BMI percentile; BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin.

Clinical Trials Overview



Key inclusion criteria
- Obesity due to POMC, including PCSK1, or LEPR deficiency and ≥6 years of age

Key exclusion criteria
- Recent diet, exercise, or gastric bypass surgery resulting in weight loss or stabilization
- Significant or concerning dermatologic findings (eg, melanoma or skin lesions)
- History of suicidal ideation or behavior
- Moderate-to-severe renal dysfunction

Key inclusion criteria
- Completed a prior index trial in which the participant received setmelanotide and achieved clinically beneficial weight loss[†]

Key exclusion criteria
- Considered not suitable to participate in the opinion of the study investigator

BMI, body mass index; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin; QD, once daily.
*Not all patients received 52 weeks of setmelanotide treatment in their respective index trial; treatment duration reported in this analysis accurately reflects total exposure time. [†]Defined as ≥10% body weight reduction after 52 weeks in patients aged ≥18 years or ≥0.3 BMI Z score reduction after 52 weeks in patients aged <18 years.

1. Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. **2.** Kühnen et al. *N Engl J Med*. 2016;375:240-246**. 3.** Clément et al. *Nat Med*. 2018;24:551-555.

Patient Disposition and Baseline Characteristics

Enrolled in LTE with a meaningful weight response* (N=27)

Not included (n=8)
- Transitioned to commercial therapy (n=4)
- Withdrawal by patient or caregiver (n=1)
- Discontinued because of AE (n=1)
- Nonadherence to injected study drug (n=1)
- Lost to follow-up (n=1)

Patients with Year 4 data† (n=19)

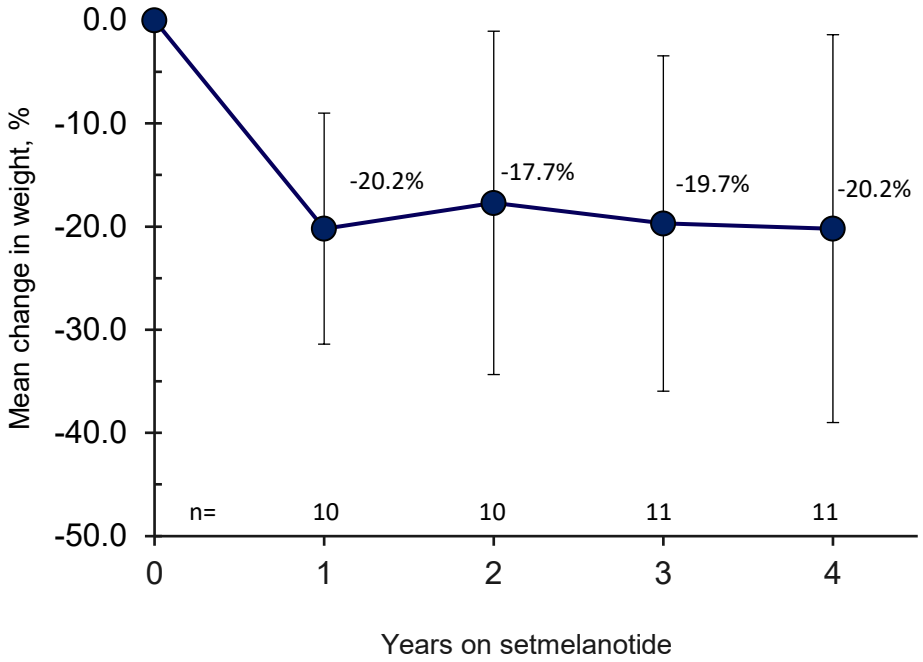
Index trial baseline characteristics	Total (n=19)
Age, mean (SD; range)	**20.2 (6.7; 10-36)**
Age range, n (%)	
≥18 years	**11 (57.9)**
<18 years	**8 (42.1)**
Sex, n (%)	
Male	**9 (47.4)**
Female	**10 (52.6)**
Race	
White	**13 (68.4)**
Other	**6 (31.6)**
Weight, mean (SD), kg	**133.4 (32.6)**
BMI, mean (SD), kg/m^2	**45.8 (10.1)**
BMI Z score, mean (SD)‡	**3.2 (0.6)**
%BMI95, mean (SD)‡	**152.7 (16.0)**
Waist circumference, mean (SD), cm	**127.2 (19.1)**

%BMI95, percent of the 95th BMI percentile; AE, adverse event; BMI, body mass index; LTE, long-term extension; SD, standard deviation.
Data cutoff: June 13, 2023. *Meaningful response defined as ≥10% body weight reduction after 52 weeks in patients aged ≥18 years or ≥0.3 BMI Z score reduction after 52 weeks in patients aged <18 years. †Includes 3 patients falling outside the prespecified 4-year visit window (range, 3.5-3.7 years on treatment). ‡Calculated on the basis of Centers for Disease Control and Prevention (CDC) 2022 methodology for children (aged <18 years) only (n=8).

Sustained Improvements in Weight and BMI Across Adult Patients Over 4 Years

Percent change in body weight, adults

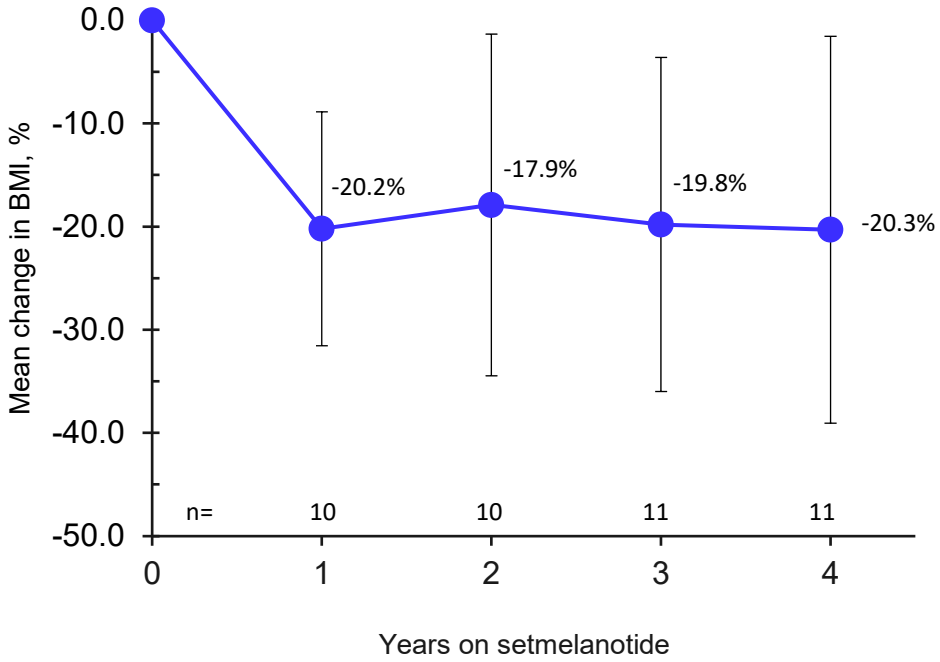
Baseline weight: 148.6 (32.4) kg (n=11)



Year-4 range in percent weight change: **–49.0% to 8.0%**

Percent change in BMI, adults

Baseline BMI: 49.2 (11.6) kg/m^2 (n=11)



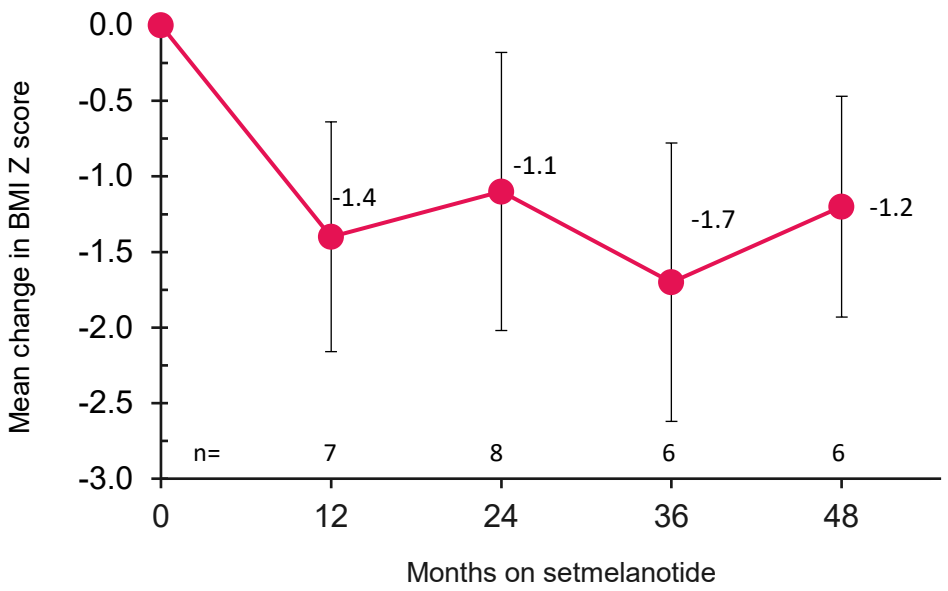
Year-4 range in percent BMI change: **–49.0% to 6.8%**

BMI, body mass index.
Data cutoff: June 13, 2023. Error bars are the standard deviation.

Age-Appropriate Weight Measures Were Reduced in Pediatric Patients Over 4 Years of Treatment

Change in BMI Z score, patients <18 years

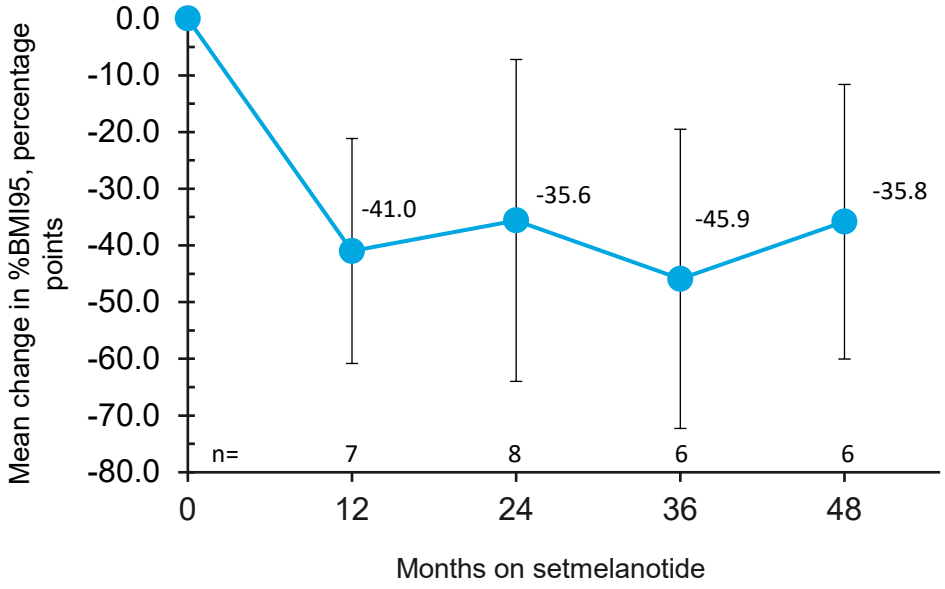
Baseline BMI Z score: 3.2 (0.57; n=8)



Year-4 range in BMI Z score change:
–2.1 to –0.2

Change in %BMI95, patients <18 years

Baseline %BMI95: 152.7 (16.0; n=8)



Year-4 range in %BMI95 change:
–68.3 to –4.8

%BMI95, percent of the 95th BMI percentile; BMI, body mass index.
Data cutoff: June 13, 2023. Error bars are the standard deviation.

The Safety Profile of Setmelanotide At Year 3 Was Consistent With Previous Studies of POMC or LEPR Deficiency Obesity

AEs occurring during the index and LTE trials in the overall population	Patients, n (%) (N=24)*
Any AE	**24 (100.0)**
Any treatment-related AE	**24 (100.0)**
Serious AEs	**11 (45.8)**
Serious treatment-related AEs	**0 (0.0)**
AEs leading to drug discontinuation	**1 (4.2)**
AEs reported in ≥25% of the population	
Injection site reactions[†,‡]	**23 (95.8)**
Other disorders[†,§]	**22 (91.7)**
Skin hyperpigmentation[†,‖]	**22 (91.7)**
Nausea	**17 (70.8)**
Diarrhea	**12 (50.0)**
Mood disorders[†,¶]	**11 (45.8)**
Abdominal pain, upper	**8 (33.3)**
Abdominal pain	**7 (29.2)**
Vomiting	**7 (29.2)**
Gastroenteritis	**6 (25.0)**
Spontaneous penile erection[#]	**5 (33.3)**

AE, adverse event; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin.

*Data as of October 4, 2022; represents an earlier data cut of patients with ≥3 years of data at the time of analysis. †If a patient experienced >1 event with a given AE group, that patient is counted only once for that AE group. ‡Injection site reactions include injection site erythema, injection site edema, injection site pruritis, injection site induration, injection site pain, injection site bruising, and injection site reaction. §Other disorders include headache, upper respiratory tract infection, back pain, arthralgia, dry mouth, asthenia, fatigue, pain in extremity, alopecia, dizziness, pyrexia, vertigo, chills, dry skin, influenza, nasopharyngitis, and oropharyngeal pain. ‖Skin hyperpigmentation includes skin hyperpigmentation and melanocytic nevus. ¶Mood disorders are depressed mood and suicidal ideation. Most mood disorder events were reported in patients with a history of psychiatric disease and were considered not or unlikely related to study drug. #Percentage of male patients (n=15).

Summary and Conclusions

- Long-term treatment with setmelanotide demonstrated sustained weight-related efficacy in pediatric and adult patients with POMC or LEPR deficiency
- The safety profile of setmelanotide was consistent with previous studies
- The limitations of this study include lack of a control group and small sample sizes

These data support long-term use of setmelanotide in patients with obesity due to POMC and LEPR deficiency

LEPR, leptin receptor; POMC, proopiomelanocortin.