Weight Outcomes With Setmelanotide Over 3 Years in Patients With POMC or LEPR Deficiency Obesity

Presenter: Dr. Sonali Malhotra

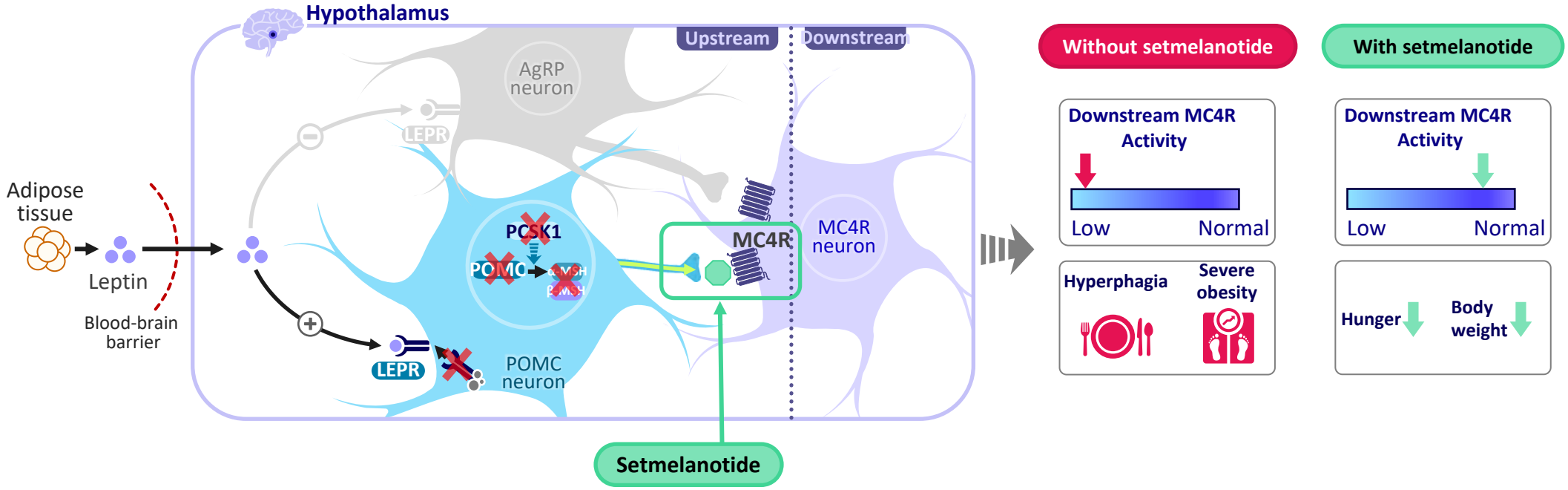
Oral presentation 037

Clément, K[1,2]; Wabitsch, M[3]; Van den Akker, E[4]; Argente, J[5,6]; Navarria, A[7]; Srinivasan, M[7]; Yuan, G[7]; Malhotra, S[7-9]; Kühnen, P[10]

[1]Assistance Publique Hôpitaux de Paris, Nutrition Department, Pitié–Salpêtrière Hospital, Paris, France; [2]Sorbonne Université, Inserm, NutriOmics Research Unit, Paris, France; [3]Division of Pediatric Endocrinology and Diabetes, Center for Rare Endocrine Diseases, Department of Pediatrics and Adolescent Medicine, University of Ulm, Ulm, Germany; [4]Division of Pediatric Endocrinology, Department of Pediatrics, Sophia Children's Hospital and Obesity Center CGG, Erasmus University Medical Center, Rotterdam, The Netherlands; [5]Department of Pediatrics and Pediatric Endocrinology, Universidad Autónoma de Madrid, University Hospital Niño Jesús, CIBER "Fisiopatología de la obesidad y nutrición" (CIBEROBN), Instituto de Salud Carlos III, Madrid, Spain; [6]IMDEA Food Institute, Madrid, Spain; [7]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [8]Massachusetts General Hospital, Boston, MA, USA; [9]Harvard Medical School, Boston, MA, USA; [10]Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin und Humboldt–Universität zu Berlin, Institute for Experimental Pediatric Endocrinology, Berlin, Germany

Energy Expenditure Is Regulated by the Hypothalamic MC4R Pathway

- Under physiologic conditions, the hypothalamic melanocortin-4 receptor (MC4R) pathway regulates hunger, satiety, energy expenditure, and, consequently, body weight[1-4]
- Rare variants in the MC4R pathway are associated with hyperphagia and early-onset, severe obesity[5]
- The MC4R agonist setmelanotide reduced BMI and hunger in patients with obesity due to POMC or leptin receptor (LEPR) deficiency in Phase 3 trials[6]

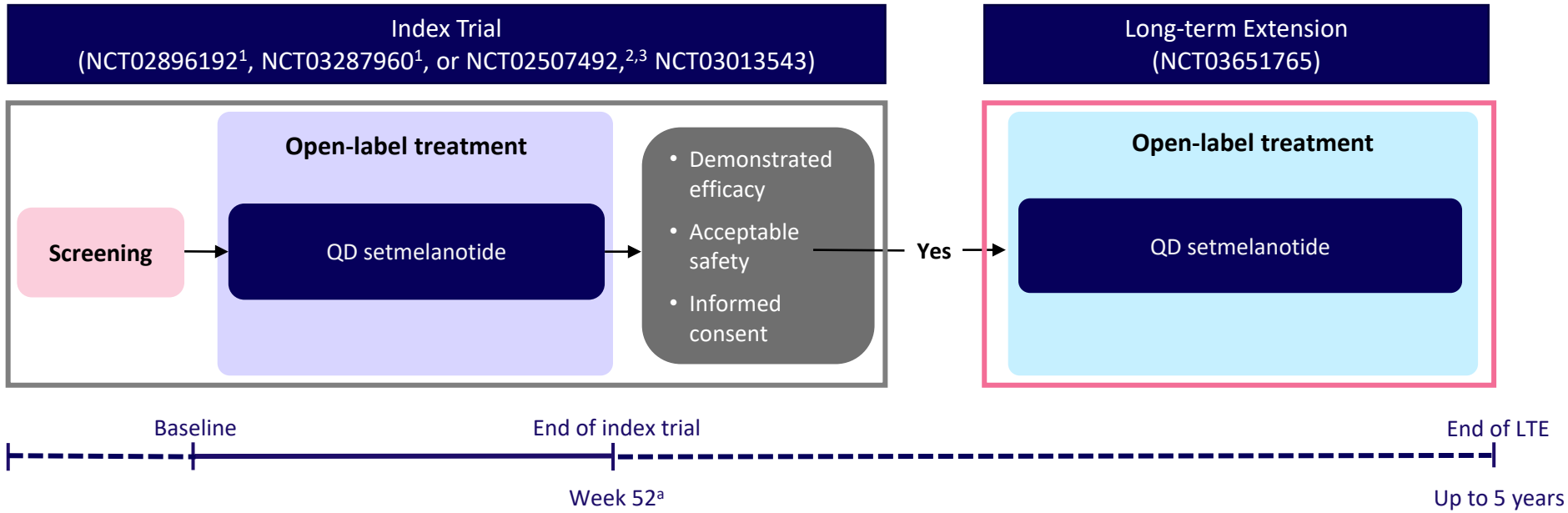


AgRP, agouti-related peptide; BMI, body mass index; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

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. *Lancet Diabetes Endocrinol*. 2020;8:960-970.

Methods

Objective: This analysis of a long-term extension trial (NCT03651765) assessed weight-related measures following setmelanotide treatment over 3 years among patients with POMC or LEPR deficiency obesity who achieved clinically beneficial weight loss in the index Phase 2 and 3 trials after 1 year of treatment



Inclusion criteria

- Obesity due to POMC, including PCSK1, or LEPR deficiency and ≥6 years of age
- Completed a prior index trial in which they received setmelanotide and achieved clinically beneficial weight loss of
  - ≥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

Key exclusion criteria

- Significant or concerning dermatologic findings (eg, melanoma or skin lesions)
- History of suicidal ideation or behavior
- Moderate to severe renal dysfunction
- Considered not suitable to participate in the opinion of the study investigator

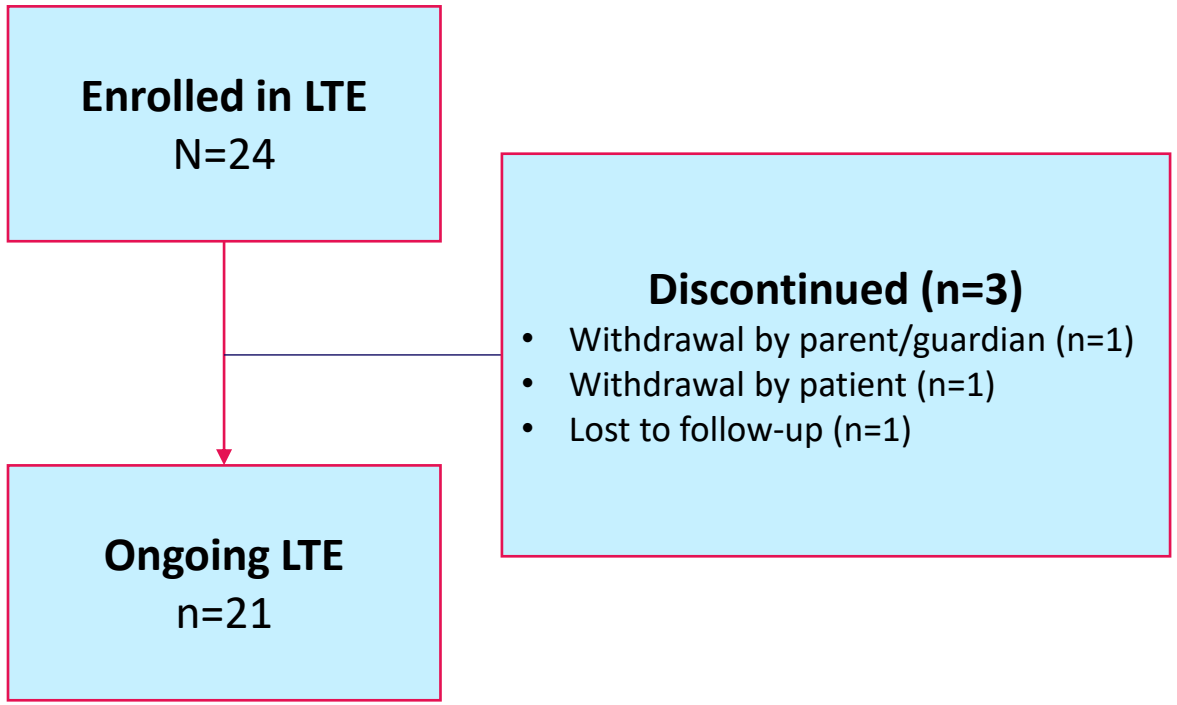
LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin; QD, once daily.

[a]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.

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

24 patients demonstrated meaningful response[a] to setmelanotide after 1 year of treatment and were included in this analysis

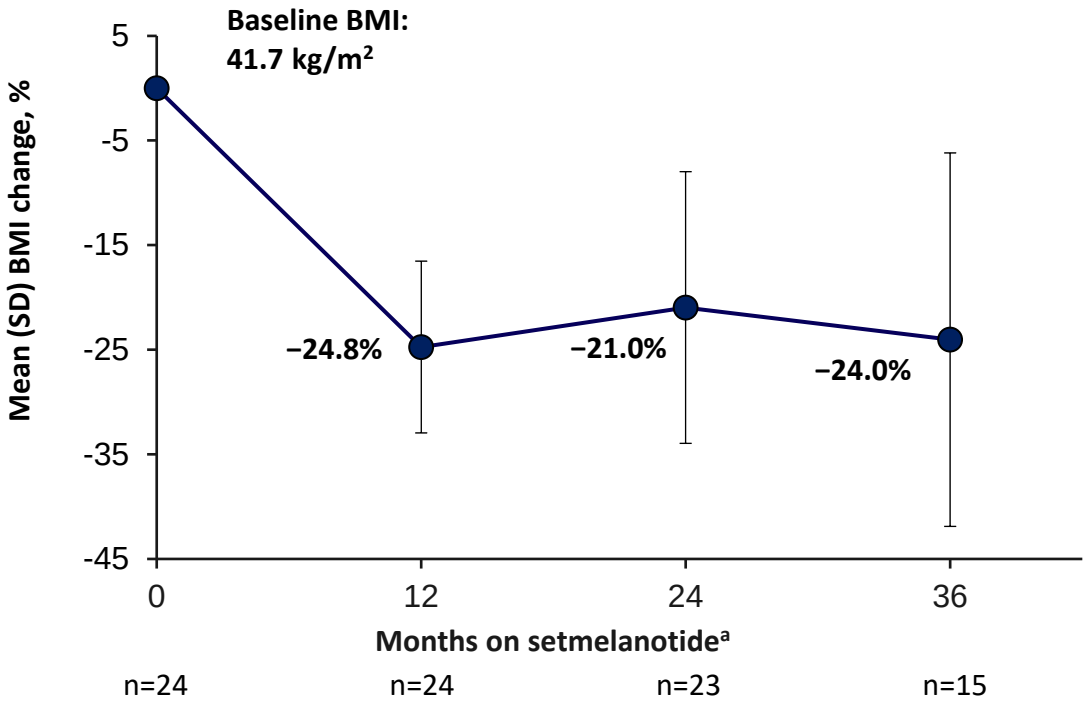


Index trial baseline characteristics	Total (N=24)
Age, years	
Mean (SD)	**18.6 (7.4)**
Age categories, n (%)	
<18	**13 (54.2)**
≥18	**11 (45.8)**
Sex, n (%)	
Male	**15 (62.5)**
Race, n (%)	
White	**16 (66.7)**
Black or African American	**1 (4.2)**
Other	**7 (29.2)**
Type of obesity, n (%)	
POMC deficiency	**15 (62.5)**
LEPR deficiency	**9 (37.5)**
Weight, kg	
Mean (SD)	**120.5 (37.9)**
BMI, kg/m^2	
Mean (SD)	**41.5 (10.2)**
BMI Z score	
Mean (SD)	**3.4 (0.5)[b]**

[a]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. [b]Patients aged <18 years (n=13).
BMI, body mass index; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin; SD, standard deviation.

Reduced BMI Sustained Over 3 Years Across Patients

Mean BMI change was **−10.6 kg/m²** after 3 years of setmelanotide treatment (SD, 8.0 kg/m² [n=15])
Mean BMI was 32.5 kg/m² after 3 years of setmelanotide treatment (SD, 9.8 kg/m² [n=15])

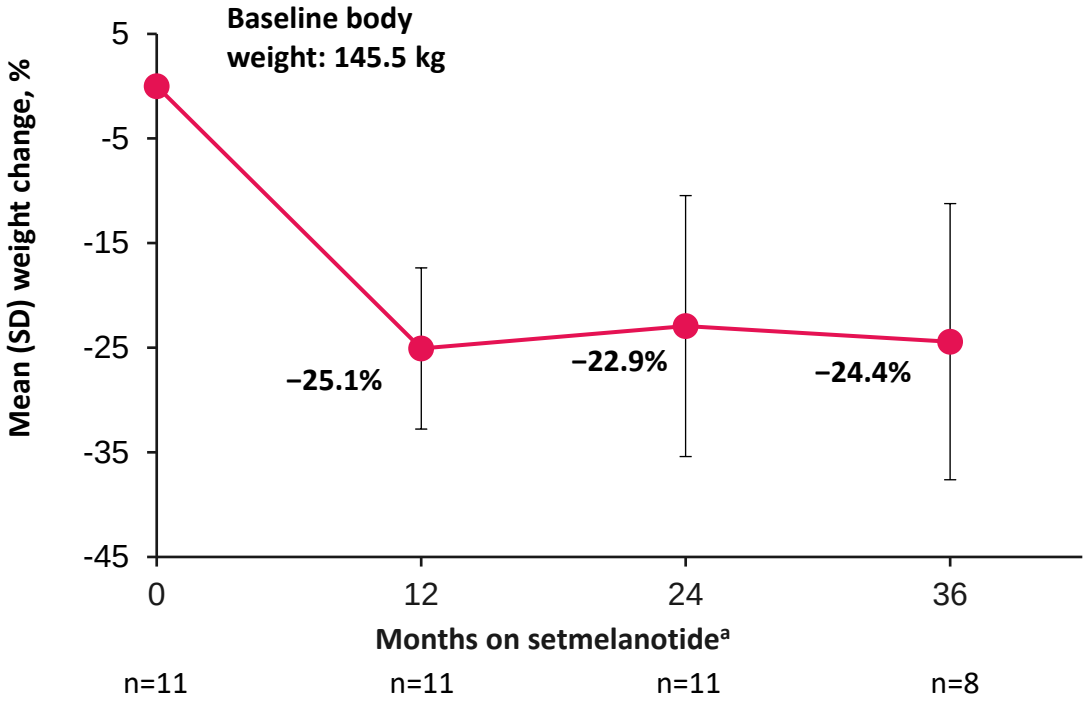


	Month 12	Month 24	Month 36
≥10% BMI reduction, n/N (%)	23/24 (95.8)	20/23 (87.0)	12/15 (80.0)

[a]The long-term extension trial is ongoing, and not all patients have reached 24 or 36 months of treatment. BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation.

Sustained Body Weight Reductions in Patients Aged ≥18 Years

Mean weight change was **−35.4 kg** in adult patients after 3 years of setmelanotide treatment (SD, 23.6 kg [n=8])
Mean weight was 105.0 kg in adult patients after 3 years of setmelanotide treatment (SD, 25.7 kg [n=8])



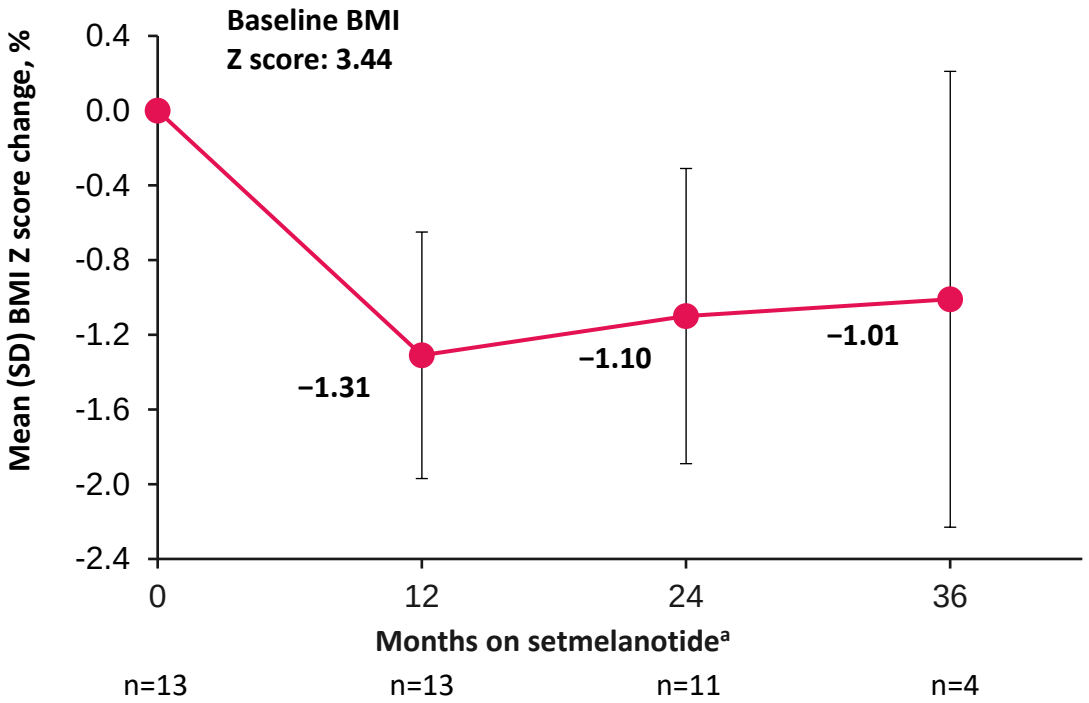
	Month 12	Month 24	Month 36
≥10% weight reduction, n/N (%)	11/11 (100)	9/11 (81.8)	7/8 (87.5)

[a]The long-term extension trial is ongoing, and not all patients have reached 24 or 36 months of treatment. LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation.

Reduced BMI Z Score in Patients Aged <18 Years With LEPR or POMC Deficiency Obesity

Mean BMI Z score change was **−1.01 points** in pediatric patients after 3 years of setmelanotide treatment (SD, 1.22 [n=4])

Mean BMI Z score was 2.42 points in pediatric patients after 3 years of setmelanotide treatment (SD, 1.22 [n=4])



	Month 12	Month 24	Month 36
≥0.3-point reduction, n/N (%)	13/13 (100)	10/11 (90.9)	3/4 (75.0)

[a]The long-term extension trial is ongoing, and not all patients have reached 24 or 36 months of treatment. BMI, body mass index; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation.

The Safety Profile[a] of Setmelanotide Was Consistent With Previous Studies of Patients With LEPR or POMC Deficiency Obesity

	n (%)
Any AE	24 (100.0)
Any treatment-related AEs	24 (100.0)
Serious AEs	11 (45.8)
Serious treatment-related AEs	0 (0.0)
AEs leading to drug discontinuation	1 (4.2)
AE leading to death	0 (0.0)

- 1 patient experienced hypoglycemia and headache, which led to discontinuation during an index trial, and did not continue into the LTE trial, but no AEs led to discontinuation during the LTE trial

AEs reported in ≥15% of population	n (%)
Injection site reactions[b,c]	23 (95.8)
Other disorders[b,d]	22 (91.7)
Skin hyperpigmentation[b,e]	22 (91.7)
Nausea	17 (70.8)
Diarrhea	12 (50.0)
Mood disorders[b,f]	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[g])

[a]AEs were aggregated across index and extension trials to provide more complete information. [b]If a patient experienced >1 event with a given AE group, that patient is counted only once for that AE group. [c]Injection site reactions includes injection site erythema, injection site edema, injection site pruritis, injection site induration, injection site pain, injection site bruising, and injection site reaction. [d]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. [e]Skin hyperpigmentation includes skin hyperpigmentation and melanocytic nevus. [f]Mood disorders are depressed mood and suicidal ideation. The majority of mood disorder events were reported in patients with a history of psychiatric disease and were considered not or unlikely related to study drug. [g]Percentage of 15 total male patients.

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

Summary and Conclusions

- Patients with a meaningful clinical response in weight-related measures after 1 year of setmelanotide therapy continued to demonstrate sustained clinical benefit at 3 years of setmelanotide treatment

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- The safety profile of setmelanotide was consistent with previous reports
- Limitations of this study include lack of a control group, and only patients who responded to setmelanotide treatment during the index trials (85.7%) were included

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

AE, adverse event; LEPR, leptin receptor; POMC, proopiomelanocortin.