Effect of Long-term Setmelanotide Use on Body Composition in Patients With POMC or LEPR Deficiency Obesity

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Summary

- **In this long-term extension (LTE) trial (NCT03651765), setmelanotide showed sustained reduction in fat mass with relatively preserved lean mass**
- **The safety profile of setmelanotide in patients with obesity due to proopiomelanocortin (POMC) deficiency, attributable to biallelic variants in *POMC* or *PCSK1*, or leptin receptor (LEPR) deficiency over 2 years of treatment was generally consistent with previous studies, supporting the efficacy and safety of long-term setmelanotide use in these patients**

Introduction

- The hypothalamic melanocortin-4 receptor (MC4R) pathway regulates hunger, satiety, and energy expenditure, thus affecting body weight[1-3]
- Variants in genes upstream of MC4R, including those encoding POMC, proprotein convertase subtilisin/kexin type 1 (PCSK1), and LEPR, can lead to hyperphagia and early-onset, severe obesity[1-4]
- In 2 pivotal Phase 3 trials, the MC4R agonist setmelanotide was associated with significant reductions in body weight, body mass index (BMI), and hunger in patients with POMC deficiency obesity, attributable to biallelic variants in *POMC* or *PCSK1*, and LEPR deficiency obesity[5]
  - These results supported the US Food and Drug Administration approval of setmelanotide for chronic weight management in adult and pediatric patients aged ≥6 years with obesity due to POMC, PCSK1, or LEPR deficiency or BBS[6]
- Treatments designed to reduce weight or BMI in patients with obesity should reduce fat mass while preserving lean mass because reduced lean mass can have multiple negative impacts, including worsened overall health and decreased energy expenditure[7]
- Understanding the long-term effects of setmelanotide on body composition is critical

Objective

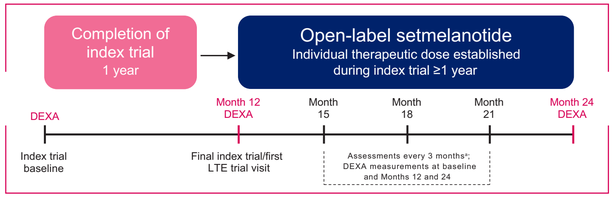
- To assess changes in total fat and lean mass over 2 years in adult and pediatric patients who demonstrated beneficial weight loss and acceptable tolerability after 1 year of setmelanotide treatment in an index trial

Methods

Trial design

- Patients aged ≥6 years with POMC or LEPR deficiency obesity were eligible for enrollment in the LTE trial if they
  - Completed an index trial (NCT02896192, NCT03287960, NCT02507492, NCT03013543) in which they received setmelanotide
  - Demonstrated clinical benefit (ie, patients aged ≥18 years who achieved ≥10% body weight reduction and patients aged <18 years who achieved ≥0.3-point BMI Z score reduction) and acceptable tolerability as determined by the investigator
- Patients initiated the LTE trial immediately following index trial completion (Figure 1)
  - Body composition was measured using dual-energy x-ray absorptiometry or bioelectrical impedance at index trial baseline, Month 12, and Month 24
  - Frequency and severity of adverse events (AEs) were assessed during the index and LTE trials in aggregate

Figure 1. Trial design.



*Adverse events were assessed during study visits every 3 months during the LTE trial. DEXA, dual-energy x-ray absorptiometry; LTE, long-term extension.

Results

Patient disposition

- Fifteen patients with POMC deficiency and 9 patients with LEPR deficiency who achieved clinical benefit following setmelanotide in an index trial were enrolled in the LTE trial
- As of November 2021, 21 patients were ongoing with setmelanotide treatment in the LTE trial (Table 1)

Table 1. Disposition for All Patients Enrolled in the LTE Trial

	All patients, n (%) (N=24)
Enrolled in LTE trial	24 (100)
Ongoing in LTE trial	21 (87.5)
Discontinued from LTE trial	3 (12.5)
Withdrawal by parent or guardian	1 (4.2)
Withdrawal by patient	1 (4.2)
Lost to follow-up	1 (4.2)

LTE, long-term extension.

Demographics and baseline characteristics

- Patients were primarily male and White with mean (standard deviation [SD]) age of 18.58 (7.35) years and mean (SD) BMI of 41.47 (10.24) kg/m^2 at index trial baseline (Table 2)

Table 2. Demographic and Baseline Characteristics of All Patients Enrolled in the LTE Trial

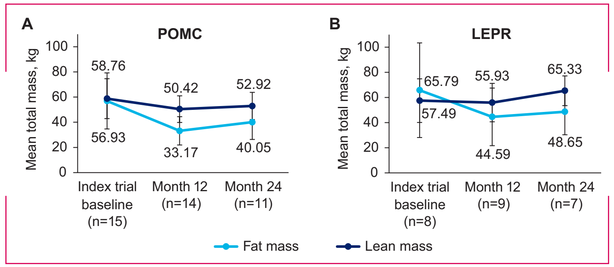
	All patients (N=24)
Age, mean (SD), y	18.58 (7.35)
<18 years old, n (%)	13 (54.2)
≥18 years old, n (%)	11 (45.8)
Sex	
Male, n (%)	15 (62.5)
Female, n (%)	9 (37.5)
Race	
White, n (%)	16 (66.7)
Black, n (%)	1 (4.2)
Other, n (%)	7 (29.2)
Type of obesity	
POMC deficiency, n (%)	15 (62.5)
LEPR deficiency, n (%)	9 (37.5)
Body weight, mean (SD), kg	120.48 (37.89)
Height, mean (SD), cm	168.25 (13.81)
BMI, mean (SD), kg/m^2	41.47 (10.24)
BMI Z score in patients <18 years old, mean (SD)	3.44 (0.45)

BMI, body mass index; LEPR, leptin receptor; LTE, long-term extension; POMC, proopiomelanocortin; SD, standard deviation.

Body composition

- Across all patients, there was a decrease in total fat mass from index trial baseline to Month 12 that was maintained through Month 24; total lean mass remained relatively stable throughout the index and LTE trials (Figure 2)

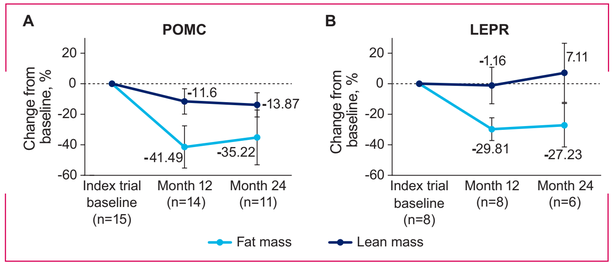
Figure 2. (A) Mean total fat and lean mass for patients with POMC deficiency. **(B)** Mean total fat and lean mass for patients with LEPR deficiency.



Error bars are the standard deviation. LEPR, leptin receptor; POMC, proopiomelanocortin.

- In patients with POMC and LEPR deficiency, the mean (SD) percent change from index trial baseline in total fat mass was −41.49% (13.83%; n=14) and −29.81% (7.44%; n=8), respectively, at Month 12 and −35.22% (17.92%; n=11) and −27.23% (14.26%; n=6), respectively, at Month 24 (Figure 3)
  - There were smaller mean percent changes in lean mass from index trial baseline to Month 12 and Month 24

Figure 3. (A) Mean percent change from index trial baseline in total fat and lean mass for patients with POMC deficiency. **(B)** Mean percent change from index trial baseline in total fat and lean mass for patients with LEPR deficiency.



Error bars are the standard deviation. LEPR, leptin receptor; POMC, proopiomelanocortin.

Safety and tolerability

- The safety profile of setmelanotide was consistent throughout the index and LTE trials and with previous studies in patients with rare MC4R pathway diseases; the most common AEs were skin hyperpigmentation, injection site reactions, nausea, headache, and diarrhea (Table 3)

Table 3. AEs Across Index and LTE Trials for All Patients Enrolled in the LTE Trial

	All patients
Any AE, n (%)	24 (100)
AEs by MedDRA grouped preferred term occurring in ≥15% of patients, n (%)	
Injection site reactions[a]	23 (95.8)
Other disorders[b]	22 (91.7)
Skin hyperpigmentation[c]	22 (91.7)
Nausea	17 (70.8)
Diarrhea	12 (50.0)
Mood disorders[d]	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 (20.8)
Any TRAE, n (%)	24 (100)
Any SAE, n (%)	11 (45.9)
Treatment-related SAE, n (%)	0
AE leading to discontinuation, n (%)[e]	1 (4.2)
AE leading to death, n (%)	0

[a]Injection site reactions included injection site erythema, injection site edema, injection site pruritis, injection site induration, injection site pain, injection site bruising, and injection site reaction. [b]Other disorders included 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. [c]Skin hyperpigmentation included skin hyperpigmentation and melanocytic nevus. [d]Mood disorders included depressed mood and suicidal ideation; for mood disorders, the majority of events were reported in patients with a history of psychiatric disease and were considered not or unlikely related to study drug. [e]One patient had AEs leading to discontinuation during an index trial (hypoglycemia, headache); there were no AEs that led to discontinuation during the LTE trial. AE, adverse event; LTE, long-term extension; MedDRA, Medical Dictionary for Regulatory Activities; SAE, serious AE; TRAE, treatment-related AE.

Conclusions

- Setmelanotide showed sustained reduction in total fat mass with moderately reduced lean mass in patients with POMC deficiency and sustained reduction in total fat mass with preserved lean mass in patients with LEPR deficiency over 2 years of treatment, as well as a safety profile consistent with clinical trials of setmelanotide in patients with other rare MC4R pathway diseases with no new safety concerns
- These results support the persistence of beneficial therapeutic effect on weight-related parameters with long-term use of setmelanotide in patients with POMC or LEPR deficiency obesity

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