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Adipose Tissue, Appetite, & Obesity

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Body Mass Index and Weight Reductions in Patients With Obesity Due to Heterozygous Variants in POMC, PCSK1, and LEPR After 1 Year of Setmelanotide

Sadaf Farooqi, Jennifer Miller, Olga Ohayan, Cecilia Scimia, Christopher Still, Marianne Yohn, Guojun Yuan, Jesús Argente, and Brieana Buckley

Background: The melanocortin-4 receptor (MC4R) pathway is a key regulator of energy balance. Heterozygous variants of the genes for proopiomelanocortin (POMC), leptin receptor (LEPR), and proprotein convertase subtilisin/kexin type 1 (PCSK1) upstream of MC4R can result in impaired signaling in the MC4R pathway. This impaired signaling can lead to hyperphagia and early-onset, severe obesity. Setmelanotide (SET), an MC4R agonist, reduced weight and hunger after 3 months in patients with obesity due to these heterozygous variants in an earlier Phase 2 study. The current analysis is the first to assess continued efficacy of an additional year of SET treatment in patients with obesity due to heterozygous affectation of POMC, PCSK1, and LEPR.

Methods: Patients aged ≥6 years with obesity due to heterozygous variants in POMC, PCSK1, and LEPR were eligible for this long-term extension (LTE) trial (NCT03651765) after completing an index trial in which they received SET and demonstrated clinical benefit and acceptable safety as determined by the investigator. Patients received a minimum of 4 months of SET treatment in the index trial and began the LTE immediately following the completion of the index trial. Study visits occurred every 3 months and evaluated changes in body weight measures and assessed safety and tolerability. The current analysis reports outcomes after 1 year total of SET treatment across the index and LTE trials, relative to index trial baseline.

Results: As of October 29, 2021, 35 patients with obesity heterozygous for POMC, PCSK1, and LEPR had enrolled in the index trial, with 16, 17, and 17 patients continuing into the LTE trial and receiving at least 6, 9, and 12 months of treatment with SET, respectively. At index trial baseline, mean (standard deviation [SD]) body mass index (BMI) for all index trial patients was 50.26 (9.41) kg/m^2, body weight in patients ≥18 years old was 142.97 (28.70) kg, and BMI Z score in patients <18 years old was 4.04 (0.65). Mean (SD) percent change in BMI was −6.93% (9.13%; n=16), −8.14% (10.13%; n=17), and −7.83% (9.69%; n=17) after 6, 9, and 12 months of treatment, respectively. Of 15 patients ≥18 years old, the mean (SD) percent change in body weight was −10.24% (7.90%; n=15) after 12 months. For the 1 patient <18 years old, mean change in BMI Z score was 0.64 after 12 months. No new safety concerns emerged during the LTE and 1 patient discontinued due to an adverse event, likely unrelated to treatment.

Conclusions: Treatment with SET had continued efficacy in patients with obesity due to heterozygous variants in POMC, PCSK1, and LEPR after 1 year of treatment. These data support the continued investigation of SET in these patients, which is underway in the Phase 3 EMANATE trial (NCT05093634).

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