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Adipose Tissue, Appetite, & Obesity

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Body Mass Index and Weight Reductions in Patients With SRC1 Genetic Variant Obesity After 1 Year of Setmelanotide

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Background: The melanocortin-4 receptor (MC4R) pathway is a key regulator of energy balance. Steroid receptor coactivator 1 (SRC1; also known as NCOA1) is a transcriptional coactivator that regulates proopiomelanocortin (POMC) expression in the MC4R pathway. Certain SRC1 variants impair MC4R signaling and are associated with hyperphagia (pathologic insatiable hunger) and early-

onset, severe obesity. Treatment with setmelanotide, an MC4R agonist, resulted in weight and hunger reductions after 3 months in patients with SRC1 variant obesity in a Phase 2 study. This analysis is the first to assess the continued efficacy of 1 year of setmelanotide treatment in patients with SRC1 variant obesity.

Methods: Patients with SRC1 variant obesity aged ≥6 years were eligible for this long-term extension (LTE) trial (NCT03651765) if they completed an index trial in which they received setmelanotide and demonstrated clinical benefit on the basis of efficacy and acceptable safety as determined by the investigator. Patients received a minimum of 4 months of setmelanotide treatment as part of the index trial and began the LTE immediately following completion. Study visits occurred approximately every 3 months. Study objectives included evaluating changes in weight-related measures and tolerability. The current analysis reports outcomes after 1 year of setmelanotide treatment across the index and LTE trials, relative to index trial baseline.

Results: As of October 29, 2021, 30 patients (20 ≥18 years old and 10 <18 years old) with SRC1 variant obesity enrolled in the index trial. Seventeen patients entered the LTE; at the time of analysis, 16, 11, and 8 patients had received at least 6, 9, and 12 months of treatment, respectively. At index trial baseline, mean (standard deviation [SD]) body mass index (BMI) for all patients was 45.4 (11.3) kg/m2, body weight in patients ≥18 years old was 139.7 (25.1) kg, and BMI Z score in patients <18 years old was 2.99 (0.63). After 6, 9, and 12 months of treatment, mean (SD) percent change in BMI was −5.7% (5.6%; n=16), −7.8% (5.8%; n=11), and −10.1% (9.4%; n=8), respectively. Mean (SD) percent change in body weight in patients ≥18 years old at 6, 9, and 12 months was −6.7% (6.1%; n=11), −9.9% (7.4%; n=8), and −11. 0% (8.6%; n=7), respectively. The mean (SD) change in BMI Z score was −0.35 (0.35; n=7), −0.42 (0.23; n=5), and −0.67 (0.57; n=3) after 6, 9, and 12 months, respectively. No new safety concerns emerged during long-term treatment, and no patients discontinued because of an adverse event.

Conclusions: One year of setmelanotide treatment led to clinical weight benefits in patients with SRC1 variant obesity. These data support the continued investigation of setmelanotide in this population, which is underway in the Phase 3 EMANATE trial (NCT05093634).

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