Abstract citation ID: bvac150.073

Adipose Tissue, Appetite, & Obesity

RF24 | PSUN91

Body Mass Index and Weight Reduction in Patients With SH2B1 Genetic Variant Obesity After One Year of Setmelanotide

Jesús Argente, MD, PhD, Sadaf Farooqi, MB, ChB, PhD, Wendy Chung, MD, PhD, Martin Wabitsch, MD, PhD, Cecilia Scimia, MD, PhD, Madhura Srinivasan, MS, and Shuang Hu, MS

Background: SH2B adaptor protein 1 (SH2B1) binds to Janus kinase 2 and enhances leptin signaling through the central melanocortin-4 receptor (MC4R) pathway, a key regulator of energy balance. Variants in SH2B1 or a 220–kilobase pair distal deletion of chromosome 16p11.2, including SH2B1, are associated with hyperphagia (pathologic insatiable hunger), severe early-onset obesity, reduced final height, and insulin resistance. Setmelanotide, an MC4R agonist, produced significant weight and hunger reduction after 3 months in patients with SH2B1 heterozygous variants or 16p11.2 deletion in a Phase 2 study. This analysis is the first to assess the continued efficacy of ~1 year of setmelanotide treatment in patients with SH2B1 genetic obesity.

Methods: Patients aged ≥6 years with SH2B1 heterozygous variants or 16p11.2 deletion encompassing SH2B1 were eligible for this long-term extension (LTE) trial (NCT03651765) if they completed a prior (index) trial in which they received setmelanotide and demonstrated clinical benefit based on weight and hunger results, 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 the completion of the index trial. Study visits occurred approximately every 3 months. Study objectives included evaluating changes in body weight measures and assessing 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, 35 patients with obesity and SH2B1 heterozygous variants or 16p11.2 deletion had enrolled in the index trial. Of patients entering the LTE, 19, 15, and 14 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 47.2 (12.8) kg/m2, body weight in patients aged ≥18 years (n=22) was 139.7 (35.4) kg, and BMI Z-score in patients aged <18 years (n=13) was 3.56 (0.60). Mean (SD) percent change in BMI was −3.4% (8.1%; n=19), −5.9% (10.0%; n=15), and −9.7% (8.0%; n=14) after 6, 9, and 12 months of treatment. Mean (SD) percent change in body weight in patients aged ≥18 years was −4.4% (5.0%; n=9), −6.8% (5.0%; n=7), and −7.7% (10.0%; n=8) after 6, 9, and 12 months, respectively. Mean (SD) change in BMI Z-score was −0.55 (0.17; n=6) after 12 months. No patients discontinued due to adverse events during the LTE . No new safety concerns emerged during long-term treatment.

Conclusions: Setmelanotide treatment provided clinically meaningful reductions in weight-related measures in patients with SH2B1 heterozygous variants or 16p11.2 deletion up to ~1 year. These data support the continued investigation of setmelanotide in this population, which is underway in the planned Phase 3 EMANATE trial (NCT05093634).

Presentation: Sunday, June 12, 2022 12:30 p.m. - 2:30 p.m., Sunday, June 12, 2022 12:30 p.m. - 12:35 p.m.