Abstract citation ID: bvac150.076

Adipose Tissue, Appetite, & Obesity

RF24 | PSUN96

Setmelanotide in Patients With Heterozygous POMC, LEPR, SRC1, or SH2B1 Obesity: Design of EMANATE – A Placebo-Controlled Phase 3 Trial

Martin Wabitsch, MD, PhD, Sadaf Farooqi, MBChB, PhD, Jesús Argente, MD, PhD, Erica van den Akker, MD, Guojun Yuan, PhD, Olga Ohayon, RN, BA, MSc, and Cecilia Scimia, MD, PhD

Background: The central hypothalamic melanocortin-4 receptor (MC4R) pathway is a key regulator of energy balance. Certain variants in genes upstream of MC4R, including those encoding the leptin receptor (LEPR), proopiomelanocortin (POMC), steroid receptor coactivator 1 (SRC1; also known as NCOA1), prohormone convertase (PC)1/3 (encoded by the gene PCSK1), and SH2B adaptor protein 1 (SH2B1) genes, lead to impaired MC4R pathway signaling and rare genetic diseases of obesity. While the deficiencies resulting from these genetic variants differ in some clinical features, they are all characterized by hyperphagia (pathologic insatiable hunger) and early-onset obesity during childhood. Setmelanotide, an MC4R agonist, reduced body weight and hyperphagia (assessed by hunger scores) after 3 months in patients with heterozygous POMC, including patients with the N221D variant in PCSK1; LEPR; SRC1; and SH2B1 (including a 220–kilobase pair distal deletion of chromosome 16p11.2) variants in an earlier Phase 2 trial. In the Phase 2 trial, 12 of 35 (34%) patients with heterozygous POMC, PCSK1, or LEPR variants; 9 of 30 patients (30%) with heterozygous SRC1 variants; and 13 of 35 (37%) patients with heterozygous SH2B1 variants achieved ≥5% weight loss after 3 months of setmelanotide treatment. **Methods:** EMANATE is a randomized, double-blind, placebo-controlled Phase 3 trial (NCT05093634) comprising 5 similar independent sub-studies based on genetic variants. For eligibility, patients must be 6-65 years old, have history of hyperphagia and childhood obesity, current obesity defined as BMI ≥30 kg/m^2 (in those ≥18 years old), and BMI ≥95th percentile (in those 6-17 years old). Patients must also have a heterozygous genetic variant in POMC or PCSK1; heterozygous genetic variant in LEPR; a homozygous, heterozygous, or compound heterozygous variant in SRC1 or SH2B1 (including a chromosomal deletion of 16p11.2 including SH2B1); or a heterozygous N221D variant in PCSK1. Patients with ≥2% weight loss in the prior 3 months, HbA1C >10%, clinically significant pulmonary, cardiac, or oncological disease, or history of significant liver or serious kidney disease are not eligible. Within each sub-study, patients will be randomized 1: 1 to receive daily subcutaneous injections of setmelanotide or placebo for 52 weeks. The primary outcome is the mean change in body weight in patients who receive setmelanotide compared with placebo. Safety will be assessed by frequency and severity of adverse events.

Current Status: EMANATE is currently underway and began enrolling patients in early 2022. The planned enrollment is 560 patients. If successful, this placebo-controlled Phase 3 trial will support setmelanotide treatment for improvements in body weight–related measures and hunger in an expanded population of patients living with rare genetic diseases of obesity.

Presentation: Sunday, June 12, 2022 12:30 p.m. - 2:30 p.m., Sunday, June 12, 2022 1:12 p.m. - 1:17 p.m.