Background
BARDET-BIE LD Syndrome (BBS) is a genetic obesity syndrome characterized by early onset obesity and hyperphagia. Proteins encoded by BBS genes facilitate leptin-melanocortin (LEP-MC) signaling critical to anorexigenic regulation. Effective drug therapies for obesity in BBS have not been reported. Setmelanotide, a melanocortin-4 receptor (MC4R) peptide agonist, has induced weight loss in patients with monogenic defects on LEP-MC signaling pathway. We report preliminary data in an ongoing proof-of-concept trial using setmelanotide in BBS.

Methods: Five subjects (age 12-61 years, 4 females) diagnosed as BBS with 4 distinct mutations were enrolled in a 52-week trial. Setmelanotide was administered daily by SQ injection with dose titration every 2 weeks to a maximum of 3 mg/day based on weight and hunger response. The primary endpoint is percent body weight change at week 52, and secondary endpoints include metabolic & biometric parameters, hunger/hyperphagia scores, and safety/tolerability assessments.

Results: Subjects exhibited morbid obesity and hyperphagia at initiation (BMI: 44.6 ± 2.5 kg/m²). Mean BMI, weight and waist circumference decreased 6.0%, 7.1% and 4%, respectively, in 4 subjects within 30 weeks of treatment (including the multi-week titration). 1 subject showed no weight loss. Hunger/hyperphagia scores markedly improved in all subjects. Improvement in lipids, hsCRP, liver transaminases, and glycemic indices was generally observed in all subjects. Therapeutic responses were observed in each genotype. Therapy was not associated with adverse changes in BP or HR. Adverse effects included mild injection site reactions and increased skin pigmentation; otherwise MC4R agonist therapy was well tolerated.

Conclusions: Favorable anorexigenic effects and good tolerability achieved with the MC4R agonist setmelanotide in this ongoing proof-of-concept study supports the importance of continued evaluation of MC4R agonist therapy in BBS and other monogenic disorders of the LEP-MC signaling pathway.

Abstract

BBS Obesity Phase 2 Study: Patients #1 & #2

Study Drug

Setmelanotide is a β-amino acid cyclic peptide also known as RM-493 that functions as an MC4R agonist with 50% effective concentration (EC50) = 0.27 mM. Setmelanotide has been studied in more than 200 healthy and impaired volunteers without known genetic obesity defects; it has demonstrated tolerability if any signal of increased blood pressure or heart rate and moderate weight loss efficacy. Setmelanotide is formulated to provide PK exposures sufficient for once daily long-term injection therapy.

Conclusions:

• Setmelanotide led to body weight reductions in 4 of 5 BBS patients treated and apparent weight stabilization in the youngest BBS patient treated (12 year old patient with a BBS1 mutation). Hunger/hyperphagia symptoms improved promptly in all 5 BBS patients.

• Response was evident in patients carrying 4 distinct BBS mutations (BBS1, BBS2, BBS3D, and BBS12).

• Favorable anorexigenic effects and good tolerability achieved with the MC4R agonist setmelanotide in this ongoing proof-of-concept study supports the importance of continued evaluation of MC4R agonist therapy in BBS patients and other monogenic disorders of the LEP-MC signaling pathway.

References


