Obesity and Hyperphagia Therapy in Bardet-Biedl Syndrome With a Melanocortin-4 Receptor Agonist

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Abstract

Background: Bardet-Biedl 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 in LEP-MC signaling pathways. 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 genotypes 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 responses. The primary endpoint is percent body weight change; secondary end-points include metabolic & biometric parameters, hunger/hyperphagia scores, and safety & tolerability assessments.

Results: Subjects exhibited morbid obesity and hyperphagia at initiation (BMI = 44.8 +/- 2.5 kg/m^2). Mean BMI, weight and waist circumference decreased 6.9%, 7.1% and 6%, respectively, in 4 subjects within 6 to 19 weeks of starting 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.

Conclusion: 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.

Background

The hypothalamic Leptin - POMC - MC4R pathway ("MC4 Pathway") is a critical coordinated regulator of appetite and weight (Figure 1) and includes several genes for anorexigenic peptides and receptors that reduce hunger and increase energy expenditure as components of integrated weight control. Several genes in this pathway have been identified as major monogenic causes of early-onset extreme obesity, including POMC and Leptin Receptor (LEPR) deficiencies. Syndromic genetic forms of extreme obesity such as the Bardet-Biedl syndrome (BBS) appear to arise from impairment of this critical pathway as a consequence of ciliopathy gene defects impairing LEPR signaling function in the hypothalamus[1].

The MC4R agonist peptide setmelanotide (RM-493) provides a once daily injectable form of therapy to restore impaired function in this pathway, serving in essence as replacement or rescue therapy for specific genetic deficiencies. Setmelanotide is being studied in several ongoing clinical studies of patients with deficiencies in the MC4 pathway. Here we report preliminary results on the use of setmelanotide in obese and hyperphagic patients with BBS.

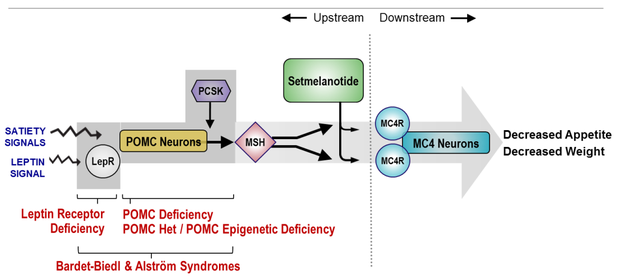

Figure 1. A simplified schematic diagram of the hypothalamic MC4 pathway, showing the site of setmelanotide (RM-493) action, as well as potential deficiencies in humans for which setmelanotide might function as replacement or rescue therapy. LepR = leptin receptor; PCSK = gene symbol for prohormone convertase 1/3; MSH = melanocyte stimulating hormone; MC4R = melanocortin-4 receptor.

Study Drug

Setmelanotide is an 8-amino-acid cyclic peptide also known as RM-493 that functions as an MC4R agonist with 50% effective concentration [EC50] = 0.27 nM.[2] Setmelanotide has been studied in more than 200 healthy and obese individuals without known genetic obesity defects; it has demonstrated little 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.

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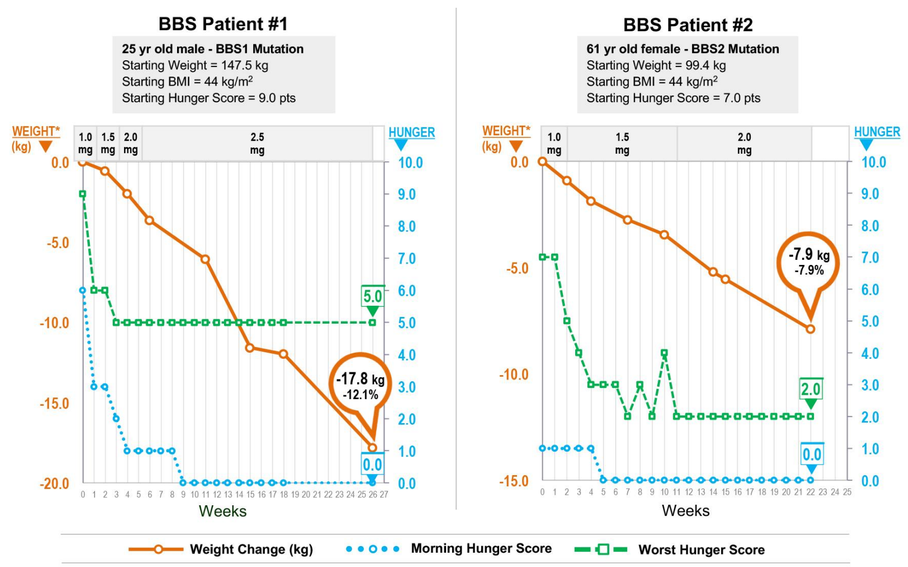
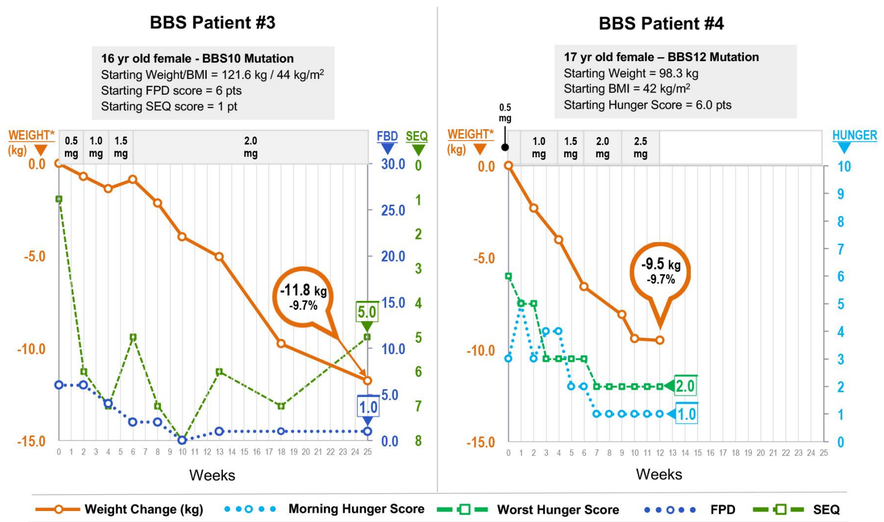
BBS Obesity Phase 2 Study : Patients #1 & #2



* Figures represent cumulative weight lost in kgs

BBS Obesity Phase 2 Study : Patients #3 & #4



* Figures represent cumulative weight lost in kgs

FPD: Food Problem Diary; Score Range 0 to 30, higher score means worse result

SEQ: Significant Event Questionnaire, which counts significant food behavior events rarely seen in this population (Y/N for 8 behaviors), so maximum score of 8 points means greatest improvement. Shown in reverse scale so downward movement equals improvement for clarity

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.
- Responses were evident in patients carrying 4 distinct BBS mutations (*BBS1*, *BBS2*, *BBS10* 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.

Study Methods

Study RM-493-014 (EudraCT #2017-000387-14; clintrials.gov identifier #NCT03013543) is a Phase 2 open-label, escalating titrated dosing, proof-of-concept study designed to investigate setmelanotide as a treatment for BBS and several other potential MC4 pathway genetic forms of obesity. Recently, setmelanotide treatment demonstrated progressive weight loss in 2 sentinel POMC deficiency obesity patients with early-onset extreme obesity due to bi-allelic *POMC* gene mutations.[3] Substantial reduction in body weight and self-reported hunger was also shown in a LEPR-/-patient, providing a second proof-of concept demonstration that setmelanotide has potential to provide meaningful efficacy in appropriately identified forms of genetic obesity by restoring absent LEPR-POMC signaling.[4]

Setmelanotide dosing starts at either 0.5 or 1.0 mg daily (depending on patient age) with stepwise upward dose titration by 0.5 mg occurring every 2 weeks until a recognizable therapeutic effect on weight reduction is established. Hunger/hyperphagia is evaluated using 2 different methods. For patients older than 12 years of age and without cognitive impairment, patient self-reported hunger scores using a numeric rating scale (NRS) from 0 = no hunger to 10 = extreme hunger are assessed for both morning hunger and worst hunger in past 24 hours. BBS patients age 12 or younger or with cognitive impairment are evaluated using 2 observer-reported outcome (ORO) scales relating to hyperphagia: A) the Food Problem Diary (FPD) is a 6-question scale (NRS from 0 = no observed hyperphagia to 30 = extreme hyperphagia) derived from an instrument used for Prader-Willi syndrome patients[5] and B) the Significant Event Questionnaire (SEQ) is a novel instrument assessing 8 distinct observable behaviors such as sharing food, etc. with 1 point for each question and higher scores indicating less hyperphagic behaviors (NRS from 0 to 8). We now report preliminary efficacy and safety/tolerability data in 5 BBS patients with defects in 4 different *BBS* genes.

Study Results

Two BBS patients with *BBS1* mutations and one each with *BBS2*, *BBS10* and *BBS12* mutations were enrolled. Body weight and hunger scores (3 subjects) or hyperphagia score (1 subject) time courses are depicted for 4 BBS patients demonstrating therapeutic responses to setmelanotide, with both endpoints evaluated over total treatment durations lasting between 12 to 26 weeks. The youngest BBS patient, a 12-year old subject with a *BBS1* mutation, did not demonstrate any body weight change with setmelanotide dosing after 33 weeks on treatment, including a final 12-week test period on 3.0 mg daily. Nonetheless, the weight curve for this patient did indicate apparent slowing of prior childhood weight gain as shown in her pediatric growth chart (Figure 2). Overall, all 5 BBS patients demonstrated clear > 50% reductions from baseline in either hunger or hyperphagia scores.

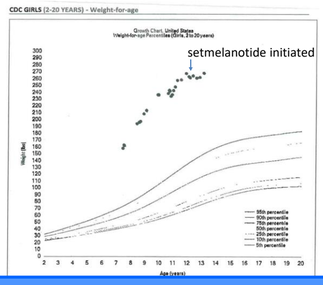


Figure 2. Pediatric growth chart of BBS Patient #5 (12 yr old female with BBS1 mutation): while not demonstrating any body weight change, the weight curve indicates apprarent slowing of prior weight gain.

Safety and Tolerability

Setmelanotide treatment was associated with intermittent injection site reactions, especially during the first 2-4 weeks of dosing; variable degrees of skin hyperpigmentation was also noted in all patients, presumably due to the activation of the closely-related MC1 (tanning) receptor. Otherwise, preliminary safety and tolerability of setmelanotide was unremarkable with no clinically significant findings in blood pressure, vital signs, or laboratory evaluations noted.

References

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