Methods: Setmelanotide, an 8-amino-acid cyclic peptide also known as RM-493, is a melanocortin-4 receptor (MC4R) agonist with a 50% effective concentration (EC50) 0.27 nM.1 Setmelanotide has been studied in more than 200 healthy and obese individuals without known genetic defects, demonstrating little if any signal of increased blood pressure and moderate weight loss efficacy. Setmelanotide is currently formulated to provide PK exposures sufficient for once daily long-term injection therapy. Recently, setmelanotide treatment demonstrated encouraging and progressive weight loss in 2 sentinel POMC deficiency obesity patients with early-onset extreme obesity due to bi-allelic POMC gene mutations.2,3 We have now enrolled a patient with bi-allelic loss-of-function mutations in the Leptin Receptor (lepr) gene, a second rare genetic disorder of obesity related to the MC4 pathway, to evaluate the applicability of setmelanotide treatment in treating other forms of MC4 pathway monogenic obesity.

An investigator-initiated clinical trial (RM-493-011 study) was amended to allow enrollment of other MC4 pathway monogenic forms of obesity, including Lepr deficiency, and POMC epigenetic or J-/heterozygous extreme obesity (EudraCT #2011-004632-02, clinicaltrials.gov identifier NCT02507492). Setmelanotide treatment is individualized for each patient, starting at 0.5 mg daily and escalating in dose by 0.5 mg every 2 weeks until a initial recognizable effect on weight reduction and hunger score (Likert scale ranging from 0 = no hunger to 10 = extreme hunger) was established. Thereafter, this Lepr deficient patient was seen at 2-4 week intervals, and a final clinical evaluation was conducted after 13 weeks of treatment. It is anticipated that he will continue in this study long term with clinical observations every 4-8 weeks through 12 months in total, with an option for subsequently enrolling in a long-term extension.

Safety and Tolerability

Safety and tolerability in this patient and in 2 POMC deficiency patients has been mostly unremarkable. Mild pain and intermittent induration at injection sites, occasional headaches and dry mouth, and fatigue have been reported. Patients have also reported increased darkening of skin, nevi and hair due to cross-reactivity of setmelanotide with the MC1R located in skin.

Conclusions

- Setmelanotide produced substantial reduction in both weight and self-reported hunger in this sentinel Lepr-/- patient.
- Weight loss occurred at a steady rate of 1 to 2 kg per week and escalated to ~26% from baseline at 12 weeks, demonstrating a clinically meaningful reduction during this initial treatment period.
- Resting energy expenditure decreased during treatment but remained stable when measured per kg body weight, suggesting that daily energy expenditure is not decreasing and thereby interfering mechanistically with further weight reduction, as has been demonstrated in common polygenic forms of obesity.
- Lipid parameters were reduced from baseline with no observed impact on baseline normal glycemic measures.
- Intermittent injection site reactions were noted; neither impacted continuation with daily therapy.
- These pilot efficacy data in a Lepr-/- patient provide a second proof-of-concept demonstration that setmelanotide has the potential to provide meaningful efficacy in appropriately identified genetic forms of obesity due to MC4 pathway deficiency by restoring absent Leptin-POMC signaling.


References


T-P-LB-3656: Proof of Concept for Treatment of a Second Rare Genetic Disorder of the Leptin-Melanocortin Pathway: Successful Therapy of Extreme Obesity in a Leptin-Receptor (LepR) Deficient Patient with Setmelanotide

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