# 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

Peter Kühnen[1] Karine Clément[2], Christine Poitou-Bernert[2], Fred Fiedorek[3], Lex van der Ploeg[3], Hillori Connors[3], Keith Gottesdiener[3], Sadaf Farooqi[4], Susanna Wiegand[1], Annette Grüters[1], Heiko Krude[1].

Affiliations: [1]Charité Universitätsmedizin, Berlin, GE; [2]ICAN, Paris, FR; [3]Rhythm Pharmaceuticals, MA; [4]University of Cambridge, UK.

## Abstract

Background: The hypothalamic Leptin-Proopiomelanocortin (POMC)-Melanocortin-4 (MC4) receptor (R) pathway is a critical regulator of appetite and body weight. The synthetic peptide setmelanotide (RM-493), a first in class MC4R agonist, is ideally positioned for the treatment of monogenic defects characterized by severe, early-onset obesity arising in this MC4 pathway. Proof of concept in POMC deficiency obesity, a first rare genetic disorder of this pathway, demonstrated substantial weight loss in two adult patients (NEJM 2016; 375(3): 240-246). We hypothesized that LepR deficiency obesity, a second rare form of monogenic obesity set in the MC4 pathway, would also respond to setmelanotide. Methods: A 22-year-old adult male LepR deficient patient was treated in an investigator-initiated, Phase 2, non-randomized, open label pilot study with setmelanotide for ~3 months (EudraCT No. 2014-002392-28; clinicaltrials.gov identifier No. NCT02507492). Setmelanotide was injected subcutaneously once per day. Results: The patient demonstrated prompt and striking reductions in appetite and body weight with a total loss of 17.5 kg body weight after initiation and up titration of 13 weeks of setmelanotide (13.4% of his initial body weight). Hunger (measured on a 10-point scale ranging from 0=no hunger to 10=extreme hunger) decreased from 9 points at baseline to 1-2 points at 13 weeks. The weight loss was predominantly caused by a reduction in body fat and resting energy expenditure stayed stable during this period. Setmelanotide was generally well tolerated without serious adverse events and a second LepR deficiency patient has initiated treatment. Conclusion: We describe a successful treatment of extreme obesity and hunger in a LepR deficient patient based on a "replacement" strategy to provide the missing activation of the MC4 pathway in this disorder. While very preliminary, these data support the potential benefit of setmelanotide in additional rare monogenic obesity disorders that impact the MC4 pathway.

## Background

A "personalized" approach to obesity drug development is to leverage new understanding of the major monogenic causes of early-onset and extreme obesity to select patients likely to respond to therapy targeted to such underlying genetic mutations. The hypothalamic Leptin - POMC - MC4R pathway ("MC4 Pathway") is a critical coordinated regulator of appetite and weight (Figure 1) and includes several genes for anorexogenic 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. 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 therapy for specific genetic deficiencies. Setmelanotide in being studied in several, ongoing proof-of-concept clinical studies in patients with deficiencies in the MC4 pathway. Here we report initial results on the use of setmelanotide in LepR deficiency obesity, a second form of monogenic obesity arising from mutations in the MC4 pathway.

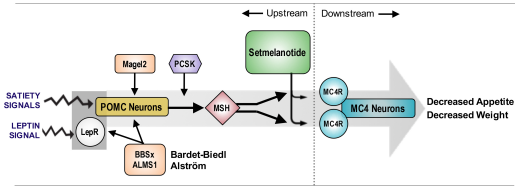


*Figure 1. A simplified schematic diagram of the hypothalamic MC4 pathway, showing the site of RM-493 (setmelanotide) action, as well as potential deficiencies in humans for which setmelanotide might function as replacement therapy. LepR = leptin receptor; Magel2 = Mage-L2 gene, located in the human chromosome 15 Prader-Willi syndrome locus; PCSK = gene symbol for prohormone convertase 1/3; MSH = melanocyte stimulating hormone; BBSx = Bardet-Biedl syndrome; ALMS1 = gene symbol for Alström syndrome.*

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## Study Drug and Study Methods

Methods: Setmelanotide, an 8-amino-acid cyclic peptide also known as RM-493, is a melanocorting-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] 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 -/+ heterozygous extreme obesity (EudraCT #2014-002392-28; 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 full 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.

## Pediatric Weight & Height Curves

LepR monogenic obesity #1

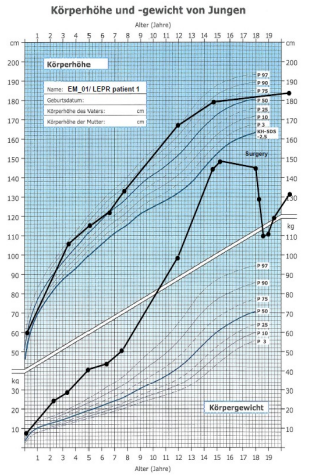
21 year old male from France.

-/- LepR obesity diagnosed by K. Clément, ICAN, Pitié-Salpêtrière Hospital, Paris.

Failed bariatric surgery (gastric banding) ~ 2 years ago (see right); regained over 20 kg in last year.

Starting weight = 130.6 kg; initial hunger score = 9/10

Pediatric height and weight curves for this patient since infancy at right.




## References

(1) Chen et al. RM-493, a melanocortin-4 receptor (MC4R) agonist, increases resting energy expenditure in obese individuals. J Clin Endo Metab 2015. 100: 1639-45.

(2) Kuhnen et al. Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. NEJM 2016. 375:240-46.

## Weight and Hunger Score Responses in LepR Patient #1


**Body Weight and Composition, Energy Expenditure and Metabolic Laboratory Values during Treatment**

| Variable | Baseline | 13 Weeks | Normal Range |
|---|---|---|---|
| Weight (kg)<br>Change from prestudy (%) | 130.6 | 113.1<br>13.4% | |
| Body Mass Index (kg/m2)<br>Change from prestudy | 39.9 | 34.5<br>-5.4 | |
| REE (kcal/24 hr)<br>Change from prestudy | 2610.9 | 2381.8<br>-229.1 | |
| REE per kg body weight<br>Change from prestudy | 20.0 | 21.1<br>+1.1 | |
| Fat mass (kg)<br>Change from prestudy | 56.3 | 36.5<br>-19.8 | |
| Lean body mass (kg)<br>Change from prestudy | 73.7 | 76.9<br>+3.2 | |
| Cholesterol Measures<br>Total (mg/dL) | 168 | 135 | <200 |
| LDL-C (mg/dL)<br>HDL-C (mg/dL) | 102<br>52 | 78<br>46 | <130<br>>45 |
| Triglyceride (mg/dL) | 57 | 53 | <200 |
| HbA1c (%) | 5.1 | 5.1 | <6.0 |

## 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 headache 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. lost per week and amounted to ~ 20% from baseline at 22 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 and skin darkening 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 LepR-POMC signaling.