Setmelanotide in Patients With Obesity Due to Certain MC4R Variants Stratified as Rescuable or Nonrescuable Based on an In Vitro Functional Assay

Summary

- **In a Phase 2 trial, weight loss response to treatment with setmelanotide was not strongly predicted by the presence of melanocortin-4 receptor (MC4R) variants determined to be rescuable or nonrescuable by in vitro assay**

Introduction

- The MC4R pathway is a key regulator of energy expenditure and hunger; rare variants in key genes involved in the pathway can lead to hyperphagia and early-onset, severe obesity[1,2]
- In addition, variants disrupting MC4R trafficking to the cell membrane or binding affinity to its ligand lead to reduced downstream signaling[3]
- Setmelanotide is an MC4R agonist that is indicated in the United States and European Union for the treatment of patients ≥6 years of age with obesity due to biallelic proopiomelanocortin (POMC), biallelic proprotein convertase subtilisin/kexin type 1 (PCSK1), and biallelic leptin receptor (LEPR) deficiency and Bardet-Biedl syndrome
- Variants in *MC4R* are relatively more common than variants in the previously mentioned genes and may account for 2%-6% of early-onset, severe obesity in adults and children in the general population[1,4,5]
- Given the mechanism of action of setmelanotide, an MC4R agonist, it might be expected that loss of function (LOF) variants would prevent receptor activation by setmelanotide[6]
- Pharmacologic studies show setmelanotide can bind wild-type MC4R with higher affinity than the endogenous ligand α–melanocyte-stimulating hormone (α-MSH), suggesting setmelanotide could induce signaling in some *MC4R* variants[7]
  - An established cell-based assay[8] was used to determine agonist activity of α-MSH and setmelanotide across 346 *MC4R* variants that are potentially rescuable with setmelanotide treatment

Objectives

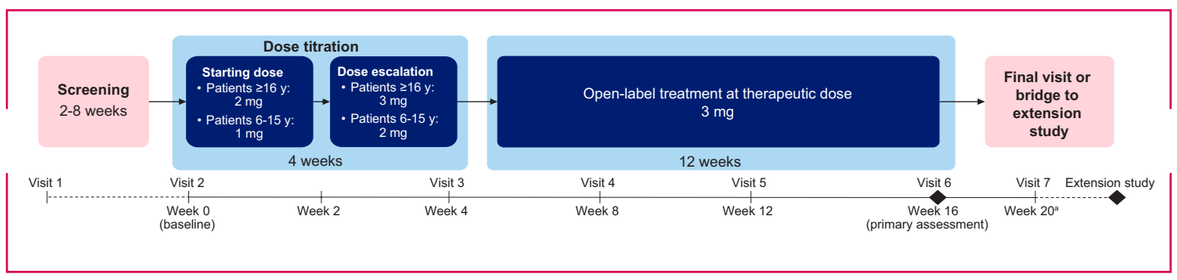
- To categorize patients with obesity due to MC4R deficiency in an ongoing clinical trial (NCT03013543) on the basis of variants predicted to be rescuable or nonrescuable by setmelanotide treatment
- To determine if these categories might predict responders to setmelanotide treatment, defined as those achieving ≥5% body mass index (BMI) reduction after 3 months of treatment

Methods

Clinical trial design and patients

- Patients were enrolled in a basket-design, open-label, Phase 2 study investigating setmelanotide in individuals ≥6 years old with obesity due to rare variants in genes of the MC4R pathway, including in *MC4R*
  - Obesity was defined as BMI ≥95th percentile for those aged 6-15 years or BMI ≥30 kg/m^2 for those aged ≥16 years
  - Key exclusion criteria included weight loss of >2% within the prior 2 months, use of approved medication for obesity within 3 months, gastric bypass within 6 months or any prior bypass resulting in >10% durable weight loss, glycated hemoglobin >9.0% at screening, and glomerular filtration rate <30 mL/min at screening
- Patients received open-label setmelanotide treatment for 3 months (Figure 1)

Figure 1. Study design.



[a]Final visit at Week 20 for patients not enrolling in a separate extension study.

- The primary endpoint was the proportion of patients achieving ≥5% body weight reduction from baseline at Month 3
- Response to setmelanotide was evaluated on the basis of BMI change at Month 3
  - Responders were defined as those achieving ≥5% BMI reduction from baseline
- In this post hoc analysis, efficacy outcomes were compared by grouping patients with the MC4R assay variants predicted to be rescuable versus nonrescuable

In vitro MC4R functional assay

- A cyclic adenosine monophosphate (cAMP) assay with an α-MSH dose-response curve was performed to determine variants with moderate and strong LOF
  - A full dose-response curve was performed for wild-type controls, and cAMP response to α-MSH was performed for *MC4R* variants
    - Half-maximal effective concentration [EC_{50}]: the effective concentration of α-MSH that produces half of the maximal cAMP response produced by wild-type controls[8]
    - Maximum efficacy [E_{max}]: the concentration of α-MSH that produces the maximal cAMP response for that variant[8]
    - Assays did not measure downstream intracellular cascades or other pathways that can be engaged by MC4R activation
  - A total of 346 variants were screened, 29 of which were identified by Rhythm sequencing initiatives
  - Variants were classified as wild type (EC_{50} <140 nM and E_{max} >70%), ambiguous (EC_{50} 140-220 nM and E_{max} 40%-70%), moderate LOF (EC_{50} 220-1000 nM or E_{max} <40%), or strong LOF (EC_{50} >1000 nM or E_{max} <20%)
    - These classifications are comparable to those used in published studies
- A dose-response curve with setmelanotide was performed with variants classified as moderate or strong LOF to determine those that could or could not be rescued by setmelanotide
  - Variants were defined as rescuable if EC_{50} was <44 nM and E_{max} was >70%

Results

Patient demographics

- Twenty-three patients with predicted rescuable MC4R deficiency and 24 patients with predicted nonrescuable MC4R deficiency were enrolled (Table)
  - Mean age was 24.7 and 19.2 years for patients with predicted rescuable and nonrescuable MC4R deficiency, respectively; 52.2% of the rescuable MC4R cohort and 62.5% of the nonrescuable MC4R cohort were female
  - Mean (standard deviation [SD]) BMI at baseline was 42.4 (7.1) kg/m^2 and 42.3 (10.0) kg/m^2 for the predicted rescuable and nonrescuable populations, respectively

Variant classification

- Of 346 variants assayed, 149 were classified as wild type, 62 as ambiguous, 44 as moderate LOF, and 91 as strong LOF
  - Of 135 moderate-to-strong variants analyzed, 19 (14%) were rescued by setmelanotide (14 moderate LOF; 5 strong LOF)

Efficacy outcomes

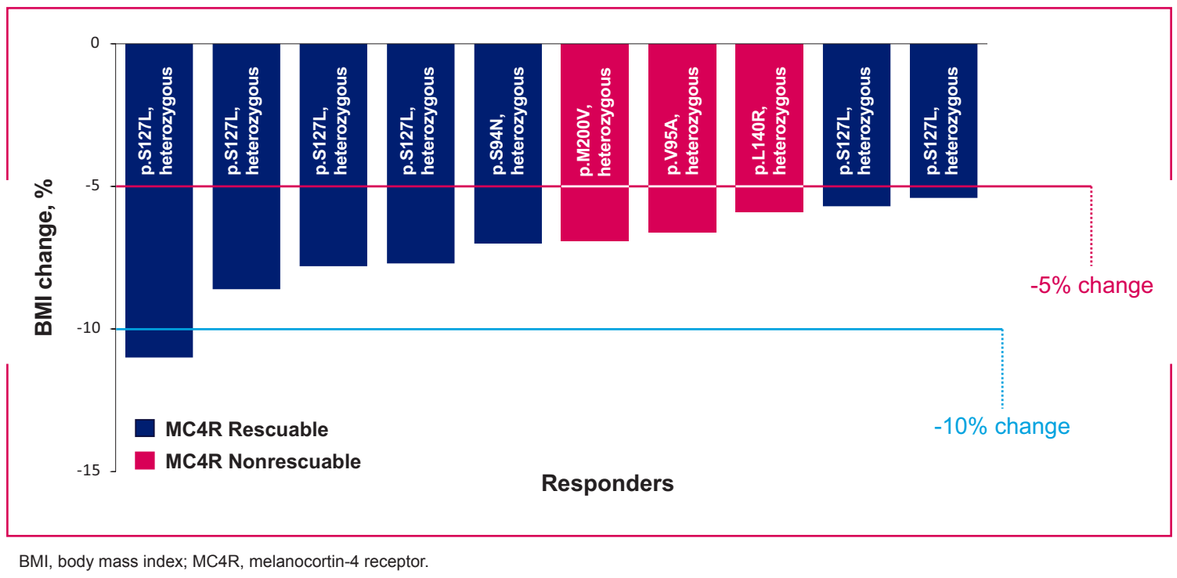
- The in vitro MC4R functional assay had limited predictive value, given that it had a low level ability to discriminate responders and nonresponders (Figure 2)
  - Of patients with variants predicted to be rescuable by setmelanotide, 7 of 23 (30.4% [90% confidence interval (CI), 15.3%-49.6%]) achieved a ≥5% BMI reduction at Month 3
  - Of patients with variants predicted to be nonrescuable by setmelanotide, 3 of 24 (12.5% [90% CI, 3.5%-29.2%]) achieved ≥5% BMI reduction at Month 3

Table. Genotypes of Patients Grouped by Predicted Setmelanotide Function

Rescuable MC4R variant (n=23)	No. of patients	Nonrescuable MC4R variant (n=24)	No. of patients
p.S127L, heterozygous	16	p.D37V, heterozygous	4
p.I301T, heterozygous	2	p.P260Q, heterozygous	2
p.S94N, heterozygous	2	p.V95A, heterozygous	2
p.N240S, heterozygous	2	p.R165Q, heterozygous	2
p.P272R, heterozygous	1	p.I291del, heterozygous	2
		p.T150I, heterozygous	2
		p.S85G, homozygous	1
		p.L140R, heterozygous	1
		p.Q115fs, heterozygous	1
		p.I269N, heterozygous	1
		p.S58Afs*7, heterozygous	1
		p.E61K, heterozygous	1
		p.P260Q, homozygous	1
		p.L54P, heterozygous	1
		p.D122Y, heterozygous	1
		p.M200V, heterozygous	1

MC4R, melanocortin-4 receptor.

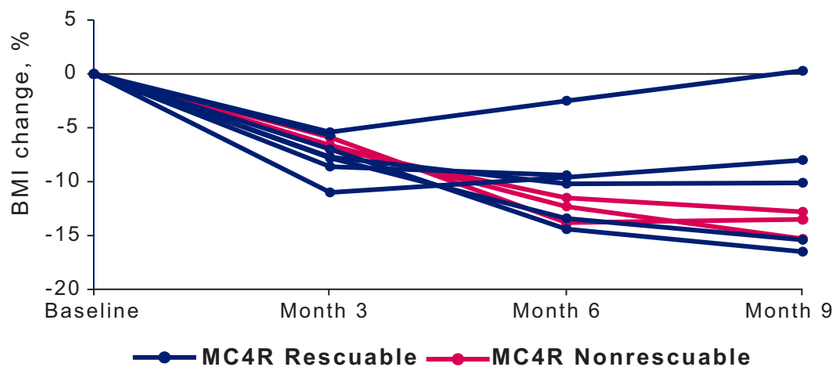
Figure 2. Percent change in BMI at Month 3 for patients responding to setmelanotide treatment.



BMI, body mass index; MC4R, melanocortin-4 receptor.

- Among responders, mean percent change in BMI from baseline was generally similar between patients in the rescuable and nonrescuable MC4R cohorts over time, with patients in the nonrescuable MC4R cohort showing numerically higher percent reduction in BMI at Month 6 and 9 (Figure 3)

Figure 3. Change in mean percent BMI over time with setmelanotide treatment in the responder population.



Responders				
MC4R Rescuable				
n	7	7	6	5
Percent BMI change, mean (SD)		-7.6 (1.9)	-9.9 (4.2)	-9.9 (6.7)
MC4R Nonrescuable				
n	3	3	3	3
Percent BMI change, mean (SD)		-6.5 (0.5)	-12.5 (1.2)	-13.9 (1.3)

BMI, body mass index; MC4R, melanocortin-4 receptor.

Conclusions

- The in vitro assay had limited predictive value but did directionally identify a larger proportion of responders in the rescuable group versus the nonrescuable group
  - Most responders were carriers of the p.S127L heterozygous variant in the rescuable group; 6 of 16 patients with this variant showed response to setmelanotide on the basis of BMI
- Weight loss, as determined by percent change in BMI, tended to increase over time in patients achieving ≥5% BMI reduction at Month 3, with continued weight loss in responders in both predicted rescuable and nonrescuable groups at 6 and 9 months of treatment with setmelanotide
- The assay for rescuable versus nonrescuable MC4R variants had limited predictive value for response, suggesting that a range of patients with MC4R deficiency may respond to setmelanotide
  - Further assessment of this assay is underway to investigate if predicted values result from interactions with other clinical factors

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References: 1. Huvenne et al. *Obes Facts*. 2016;9:158-173. **2.** Farooqi. *Biol Psychiatry*. 2022;91:856-859. **3.** Yeo et al. *Hum Mol Genet*. 2003;12:561-574. **4.** Vaisse et al. *J Clin Invest*. 2000;106:253-262. **5.** Farooqi et al. *N Engl J Med*. 2003;348:1085-1095. **6.** Collet et al. *Mol Metab*. 2017;6:1321-1329. **7.** Hammad et al. *Life Sci*. 2022;307:120857. **8.** Holford. *Transl Clin Pharmacol*. 2017;25:157-161.