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## Summary

- After 1 year on setmelanotide, clinical trial participants with certain rare melanocortin-4 receptor (MC4R)-related diseases had reduced body weight and severity of obesity
- While improvements in weight and weight categories were seen across all indications, the magnitude of response differed by MC4R pathway disease type, which may be attributable to the variable mechanisms and location of dysfunction in the MC4R pathway

## Introduction

- The hypothalamic MC4R pathway is a key regulator of energy balance and food intake<sup>1,2</sup>
- Impaired signaling in the MC4R pathway in patients with acquired hypothalamic obesity (HO), proopiomelanocortin (POMC; including biallelic variants in *POMC* or *PCSK1*) deficiency or leptin receptor (LEPR) deficiency, or Bardet-Biedl syndrome (BBS) can cause hyperphagia and severe obesity<sup>2-4</sup>
- The MC4R agonist setmelanotide has demonstrated clinically meaningful weight and hunger reduction in these populations<sup>2-4</sup>

# Objective

 To report weight trajectories of individual patients with acquired HO, POMC deficiency, LEPR deficiency, or BBS stratified by weight category after 1 year of setmelanotide treatment

### Methods

### Study design

Patients aged ≥6 years with obesity and acquired HO, POMC deficiency (including variants in POMC or PCSK1), LEPR deficiency, or BBS enrolled across 4 index clinical trials (NCT04725240, NCT02896192, NCT03287960, and NCT03746522) and a long-term extension trial (NCT03651765) of setmelanotide who had on-treatment measurements at both baseline and 1 year were included in this post hoc analysis²-4

### Outcomes

- Changes in body mass index (BMI) and percent of the 95th percentile for BMI (%BMI95) from index trial baseline to 1 year of setmelanotide were assessed and stratified by weight categories
- In adults aged ≥18 years, weight categories were defined in adult patients as healthy weight (BMI ≥18.5 to <25 kg/m²), overweight (BMI ≥25 to <30 kg/m²), class I obesity (BMI ≥30 to <35 kg/m²), class II severe obesity (BMI ≥35 to <40 kg/m²), or class III extreme obesity (BMI ≥40 kg/m²)<sup>5,6</sup>
- In pediatric patients aged <18 years, weight categories were defined based on age and sex as healthy weight (≥5th to <85th BMI percentile), overweight (≥85th to <95th BMI percentile), class I obesity (percent of the 95th percentile for BMI [%BMI95] ≥95% to <120% or BMI ≥30 to <35 kg/m², whichever was lower), class II severe obesity (%BMI95 ≥120% to <140% or BMI ≥35 to <40 kg/m², whichever was lower), or class III extreme obesity (%BMI95 ≥140% or BMI ≥40 kg/m², whichever was lower)<sup>5-7</sup>
- For pediatric patients at a BMI percentile of ≥95%, data are reported as %BMI95; for pediatric patients at a BMI percentile <95%, data are reported as BMI percentile

# Results

#### **Baseline characteristics**

- In total, 58 patients were included (acquired HO: n=12; POMC deficiency: n=9; LEPR deficiency: n=11; BBS: n=26) (Table)
- Most patients had class III extreme obesity at baseline (acquired HO: 67%; POMC deficiency: 44%; LEPR deficiency: 82%; BBS: 77%)

### Table. Demographics and Baseline Characteristics

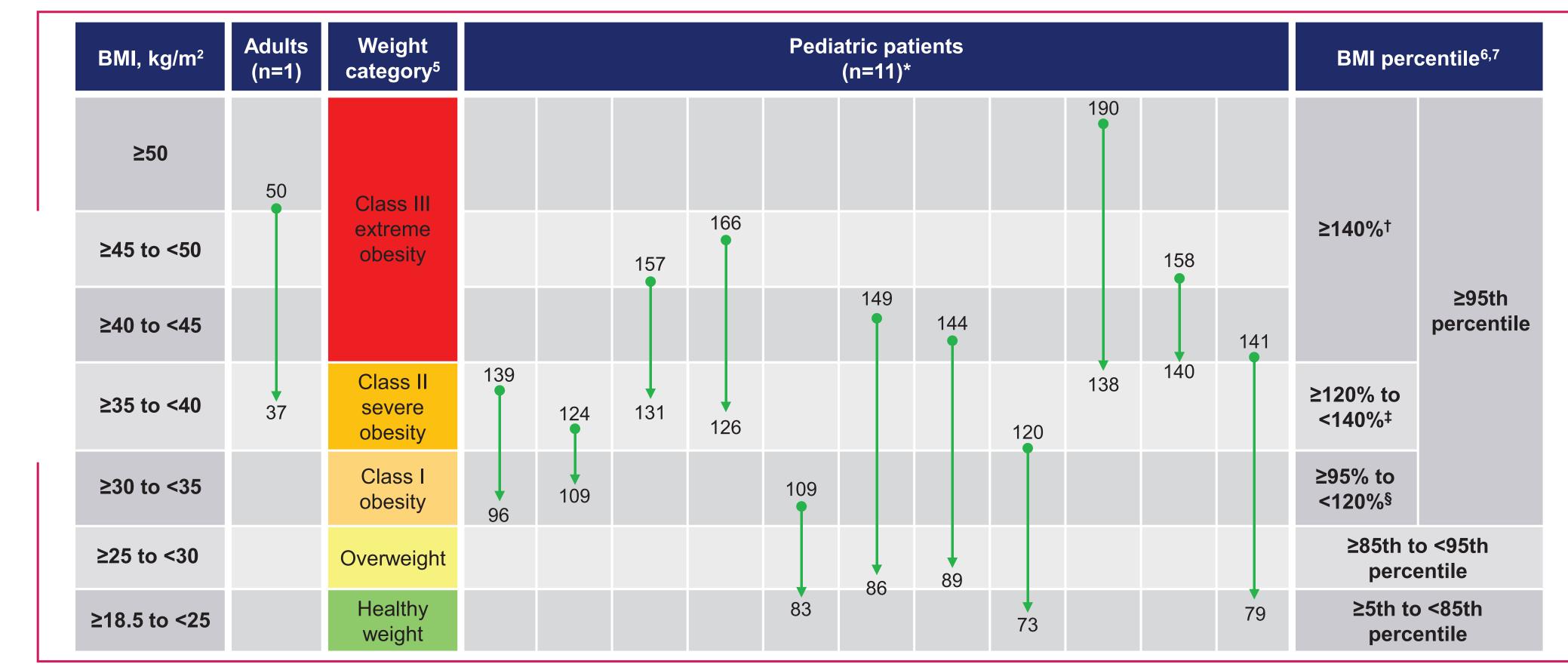
Parameter	All patients (n=58)	HO (n=12)	POMC deficiency* (n=9)	LEPR deficiency (n=11)	BBS (n=26)
<18 years	34 (59)	11 (92)	6 (67)	3 (27)	14 (54)
≥18 years	24 (41)	1 (8)	3 (33)	8 (73)	12 (46)
Sex, n (%)					
Male	29 (50)	8 (67)	5 (56)	5 (45)	11 (42)
Female	29 (50)	4 (33)	4 (44)	6 (55)	15 (58)
Race, n (%)					
White	49 (84)	10 (83)	7 (78)	9 (82)	23 (88)
Black or African American	3 (5)	2 (17)	0	0	1 (4)
Other	6 (10)	0	2 (22)	2 (18)	2 (8)
Ethnicity, n (%)					
Not Hispanic or Latino	52 (90)	9 (75)	8 (89)	10 (91)	24 (96)
Hispanic or Latino	4 (7)	2 (17)	1 (11)	0	1 (4)
Other or unknown	2 (3)	1 (8)	0	1 (9)	0
%BMI95, mean (SD) <sup>†</sup>					
<18 years	151.2 (34.6) n=34	145.3 (22.8) n=11	141.2 (22.5) n=6	151.7 (23.0) n=3	160.1 (48.8) n=14
BMI, mean (SD), kg/m <sup>2‡</sup>					
≥18 years	49.2 (9.5) n=24	NA	40.7 (7.6) n=3	54.3 (12.5) n=8	47.9 (6.1) n=12

for BMI; BBS, Bardet-Biedl syndrome; BMI, body mass index; HO, hypothalamic obesity; LEPR, leptin receptor; NA, not applicable; POMC, proopiomelanocortin; SD, standard deviation.

#### Changes in weight category

- Of 12 patients with HO, 11 (92%) improved by ≥1 weight category (Figure 1)
- The remaining patient, categorized as having class III extreme obesity at baseline, experienced a 7.0% absolute reduction in BMI and 17.4—percentage point reduction in %BMI95 from baseline

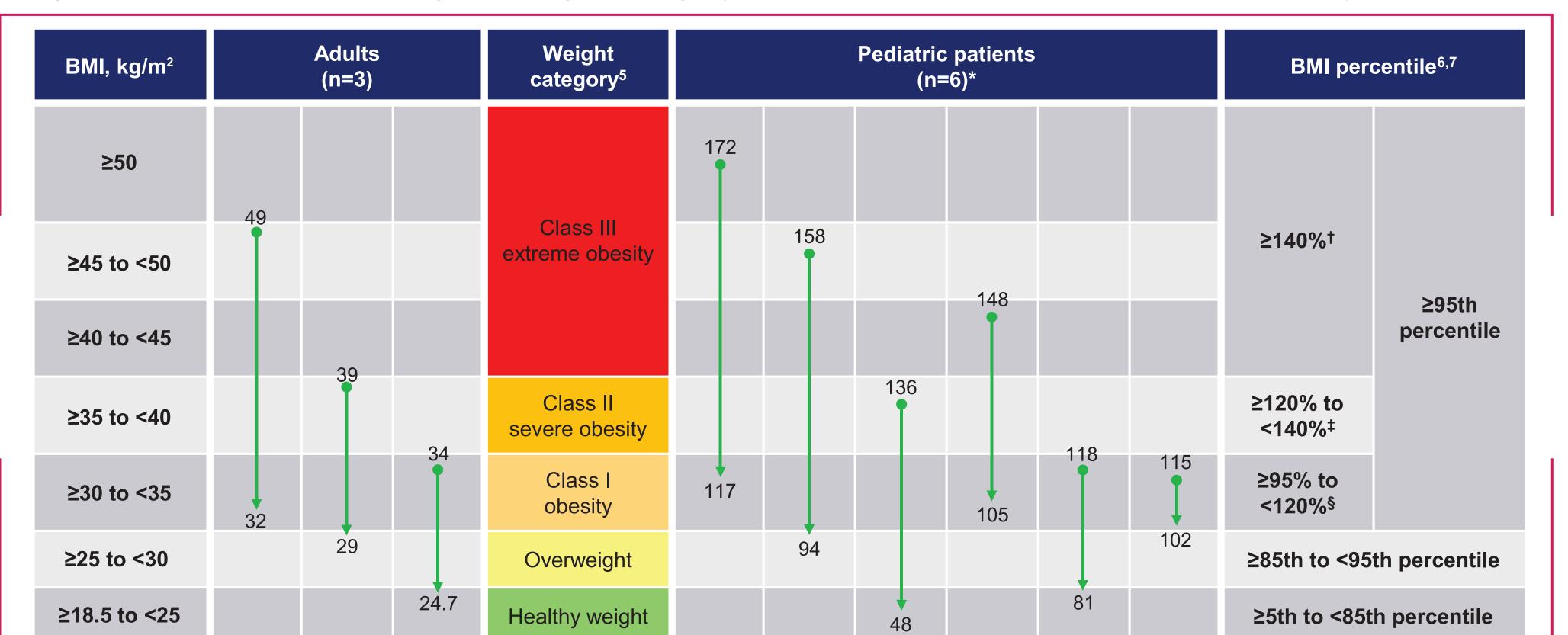
Figure 1. On-treatment change in weight category at Year 1 in patients with acquired HO.



\*At a BMI percentile of ≥95%, pediatric patients are reported as %BMI95. †Or BMI ≥40 kg/m² (whichever is lower). ‡Or BMI ≥35 to <40 kg/m² (whichever is lower). §Or BMI ≥30 to <35 kg/m² (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; HO, hypothalamic obesity.

- Of 9 patients with POMC deficiency, 8 (89%) improved by ≥2 weight categories (Figure 2)
- Three patients (33%) achieved healthy weight
- All patients experienced improvements in BMI or %BMI95

Figure 2. On-treatment change in weight category at Year 1 in patients with POMC deficiency.



\*At a BMI percentile of ≥95%, pediatric patients are reported as %BMI95. †Or BMI ≥40 kg/m² (whichever is lower). ‡Or BMI ≥35 to <40 kg/m² (whichever is lower). §Or BMI ≥30 to <35 kg/m² (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; POMC, proopiomelanocortin.

- Of 11 patients with LEPR deficiency, 4 (36%) improved by ≥1 weight category (Figure 3)
- One patient (9%) improved by 2 weight categories, achieving a weight category of overweight
- All patients experienced improvements in BMI or %BMI95

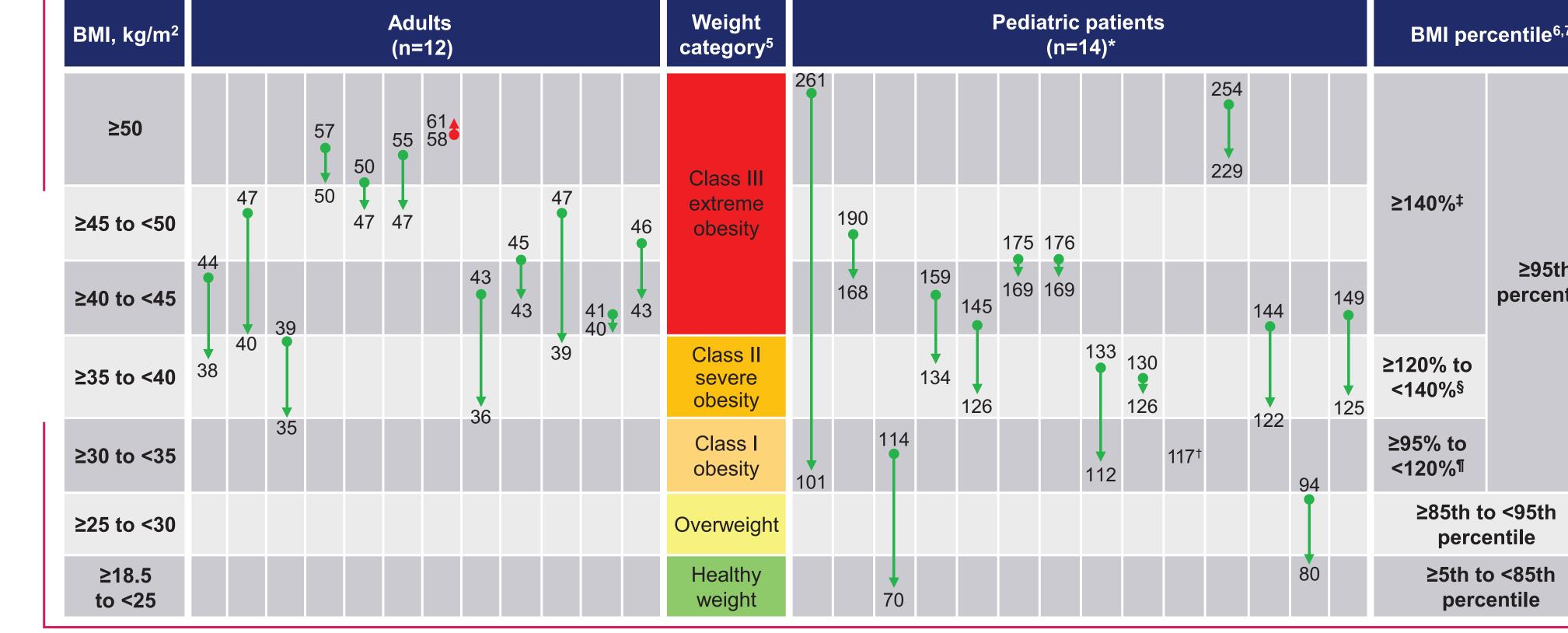
Figure 3. On-treatment change in weight category at Year 1 in patients with LEPR deficiency.



\*At a BMI percentile of ≥95%, pediatric patients are reported as %BMI95. †Or BMI ≥40 kg/m² (whichever is lower). ‡Or BMI ≥35 to <40 kg/m² (whichever is lower). §Or BI ≥30 to <35 kg/m² (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; LEPR, leptin receptor.

- Of 26 patients with BBS, 11 (42%) improved by ≥1 weight category (Figure 4)
- Two patients (8%) improved by ≥2 weight categories, and 2 patients (8%) achieved a healthy weight
- Twenty-four patients (92%) experienced improvements in BMI or %BMI95

Figure 4. On-treatment change in weight category at Year 1 in patients with BBS.



\*At a BMI percentile of ≥95%, pediatric patients are reported as %BMI95. †Patient %BMI95 was the same at baseline and 1 year of treatment. ‡Or BMI ≥40 kg/m² (whichever is lower). §Or BMI ≥35 to <40 kg/m² (whichever is lower). ¶Or BMI ≥30 to <35 kg/m² (whichever is lower). %BMI95, percent of the 95th percentile for BMI BBS, Bardet-Biedl syndrome; BMI, body mass index.

#### Safety outcomes

 Setmelanotide was well tolerated; common adverse events across cohorts included skin hyperpigmentation, nausea, and vomiting<sup>2-4</sup>

### Conclusions

- After 1 year of setmelanotide, despite small samples sizes, improvements of ≥1 weight category or reduced severity of obesity were observed across all cohorts (acquired HO: 92%; POMC deficiency: 89%; LEPR deficiency: 36%; BBS: 42%)
- For patients with acquired HO and POMC deficiency, the weight category improved from obesity to overweight in 4 patients, and the weight category improved from obesity to healthy weight in 6 patients
- Patients with LEPR deficiency and BBS had more severe weight categories at baseline but still showed general improvement in weight categories after 1 year of treatment
- Of patients with LEPR deficiency who had BMI ≥50 kg/m², 3 decreased by ≥5 kg/m², which is the respective interval of lower weight categories
- In distinct patient populations with obesity, setmelanotide generally reduced body weight and led to an improved weight category, albeit with differing intensity depending on MC4R pathway disease type, which may be due to the variable mechanisms and location of MC4R pathway dysfunction

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