Setmelanotide in Bardet-Biedl syndrome: A 52-week indirect comparison of phase 3 trial participants aged 2–5 years with a natural history cohort from the international Clinical Registry Investigating Bardet-Biedl Syndrome

PO3.010

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Introduction

- Bardet-Biedl syndrome (BBS) is a rare, heterogenous ciliopathy primarily characterised by progressive retinal degeneration, polydactyly, hyperphagia, early-onset obesity, renal dysfunction, hypogonadism, and neurodevelopmental/neurocognitive manifestations
- Central to BBS is the disruption of the hypothalamic melanocortin-4 receptor (MC4R) pathway, associated with variants in ≥26 BBS genes and 4 modifier genes[1]
  - Disrupted signalling in this pathway may lead to impaired appetite regulation, hyperphagia, and early-onset obesity, thereby impacting quality of life and increasing the risk of obesity-related complications, morbidity and mortality[2,3]
- Setmelanotide, an MC4R agonist, has been shown to reduce hunger and body weight outcomes in participants aged 2–5 years with hyperphagia and obesity associated with BBS in the 52-week open-label phase 3 VENTURE (NCT04966741) clinical trial[4]

Objectives

- In the absence of a placebo-controlled comparison in the VENTURE clinical trial, we performed an indirect treatment comparison of weight-related parameters over 52 weeks using a natural history cohort from the international Clinical Registry Investigating BBS (CRIBBS)

Methods

- Participants with BBS aged 2–5 years with obesity treated with setmelanotide in the phase 3 VENTURE clinical trial (n=5) and a control group from CRIBBS receiving usual care (n=75) were included
  - In the phase 3 trial, eligible participants had obesity with a BMI ≥97th percentile for age and sex, and a body weight of ≥15 kg at enrollment
- Inverse probability of treatment weighting (IPTW) was used to establish two balanced cohorts and quantify the treatment effects on change in BMI z-score, BMI, and BMI percentage of the 95th percentile
- The primary endpoint was the responder rate at 52 weeks, defined as a ≥0.2-point reduction in the BMI z-score
  - A reduction of ≥0.2 points is considered clinically relevant in a paediatric population[4]
- Key secondary endpoints were the mean absolute change in BMI z-score, BMI, and the mean percent change of BMI 95th percentile from baseline to follow-up at Week 52

Results

- Mean age at baseline of treated and control participants was 3.8 years
- The primary endpoint of a ≥0.2-point reduction in BMI z-score from baseline to 52 weeks was met by 80% (n=4) of the treated participants compared with 50.6% (n=38) of the CRIBBS participants, reflecting a 29.5% difference between the two groups (p=0.56)
- BMI endpoints are summarised in **Table**
  - After 52 weeks, the mean baseline BMI z-scores (4.2 vs 3.2) changed by −1.5 for treated participants vs −0.1 for controls with a treatment difference estimate (95% CI) of −1.5 (−2.8, −0.3; p=0.02)
  - From mean baseline BMI (23.7 vs 23.8), treated participants showed a reduction of −2.3 kg/m^2, whereas controls experienced an increase of +1.4 kg/m^2. The treatment difference was −3.7 (−6.1, −1.4; p=0.002)
  - For percent of the 95th BMI percentile (128.8% vs 116.9% at baseline), this changed by −14.5% in treated participants vs −0.2% among controls with a treatment difference of −14.3% (−28.4, −0.2%; p=0.05) at 52 weeks

Table: BMI endpoints in setmelanotide-treated participants with BBS compared with the matched CRIBBS participants

	Treated participants with BBS (n=5)	Matched CRIBBS participants (n=75)	CTE estimate (95% CI)	*p* value
BMI z-score				
Baseline	4.2 (3.4, 5.1)	3.2 (2.8, 3.5)		
52 weeks	2.7 (1.6, 3.7)	3.1 (2.8, 3.4)		
Change from baseline	-1.5 (-2.6, -0.6)	-0.1 (-0.3, 0.1)	-1.5 (-2.8, -0.3)	0.02
BMI (kg/m^2)				
Baseline	23.7 (20.9, 26.5)	23.8 (22.6, 25.0)		
52 weeks	21.4 (18.8, 23.9)	25.2 (24.1, 26.3)		
Change from baseline	-2.3 (-4.1, -0.6)	1.4 (0.8, 2.0)	-3.7 (-6.1, -1.4)	0.002
Percent of the BMI 95th percentile (%)				
Baseline	128.8 (117.0,143.5)	116.9 (109.8, 123.5)		
52 weeks	114.3 (102.7,126.2)	116.7 (110.4, 122.7)		
Change from baseline	-14.5 (-25.3, -3.6)	-0.2 (-2.4, 2.1)	-14.3 (-28.4, -0.2)	0.05

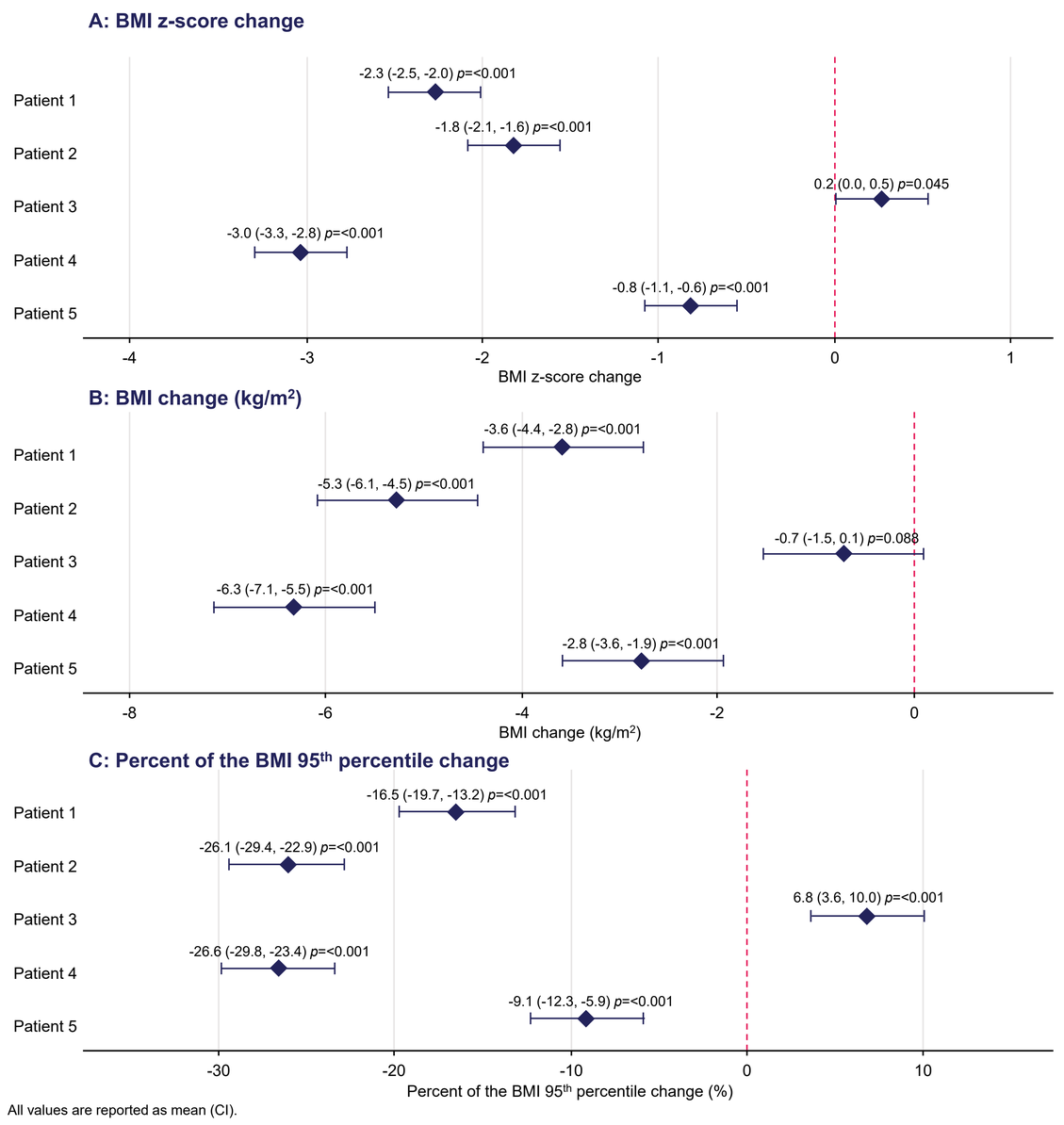
All values are reported as mean (CI).
BBS, Bardet-Biedl syndrome; BMI, body mass index; CI, confidence interval; CRIBBS, Clinical Registry Investigating BBS; CTE, controlled treatment effect.

- Sensitivity analyses using Bayesian additive regression trees (BART) matching, neural network matching (NNET), and logistic regression matching (LOGIT) methodology demonstrated similar statistically significant improvements in weight-related endpoints with setmelanotide compared with usual care

Results (continued)

- Individual BMI endpoints in setmelanotide-treated participants with BBS compared with the matched participants from CRIBBS are shown in **Figure**
  - One participant (patient 3) showed an initial reduction in BMI z-score (-1.7) at 12 weeks. However, due to an adverse event not related to treatment, they underwent a dose reduction; resulting in an increased BMI z-score (+0.2) at 52 weeks compared with baseline

Figure: Individual estimated treatment effects on BMI outcomes in setmelanotide-treated participants with BBS compared with the matched participants from CRIBBS



All values are reported as mean (CI).
BBS, Bardet-Biedl syndrome; BMI, body mass index; CI, confidence interval; CRIBBS, Clinical Registry Investigating BBS

Limitations

- The number of treated participants with BBS was small (n=5), which limits the precision of comparative analyses and increases sensitivity to individual patient responses
- Information on lifestyle and dietary interventions in participants from CRIBBS was not systematically captured. However, increased parental awareness following early diagnosis in the CRIBBS participants included in this analysis (aged 2–5 years) may have resulted in intensive lifestyle and dietary modifications. Such early, proactive management could explain the high rate of responders observed in the matched CRIBBS participants and may have contributed to attenuating observable differences between treated and untreated groups

Conclusions

- This indirect treatment comparison provides additional evidence that setmelanotide offers clinically and statistically significant weight-related benefits over 52 weeks in paediatric patients with BBS aged 2–5 years, reinforcing its therapeutic value in managing BBS compared with usual care
- Sensitivity analyses using alternative indirect comparison methodologies confirmed the robustness of these findings across multiple analytical approaches, strengthening confidence in the validity of the observed treatment benefits of setmelanotide in this paediatric population
- These findings support early intervention in patients with BBS to help improve weight-related outcomes, and mitigate the risk of obesity-related complications; ultimately improving quality of life and life expectancy

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