Quality of Life in Patients With Bardet-Biedl Syndrome in a Setmelanotide Phase 3 Trial

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Background and Objective

- In randomized placebo-controlled Phase 3 clinical studies of proopiomelanocortin and leptin receptor deficiency, setmelanotide has demonstrated a well-tolerated safety profile and significant body weight loss and hunger score reductions in patients ≥6 years old[1]
- Bardet-Biedl syndrome (BBS) is a rare genetic disease characterized by a range of features, including hyperphagia and early-onset obesity,[2,3] which significantly and negatively impacts health-related quality of life (HRQOL) for patients and their families living with this disease[2-4]
- In a randomized placebo-controlled Phase 3 trial of patients ≥6 years old with BBS and Alström syndrome, setmelanotide reduced body weight by ≥10% and maximal hunger by ≥25% in significant proportions of patients ≥12 years old (and without cognitive impairment for hunger scores) after 1 year[5]
- Here, we evaluate changes in HRQOL in adults and children with BBS after 1 year of setmelanotide treatment
  - We additionally examined the association of HRQOL with clinical and secondary patient-reported outcomes, including among a subset of patients from this trial who did not have cognitive impairment

Methods

- A Phase 3 trial (NCT03746522) investigated the effects of 1 year of setmelanotide in patients with BBS and obesity; patients received either double-blinded placebo or setmelanotide treatment for 14 weeks and then received open-label setmelanotide for ≥52 weeks of total setmelanotide treatment
  - Obesity was defined as weight >97th percentile for those aged 6–15 years and body mass index ≥30 kg/m^2 for those aged ≥16 years
  - Average hunger in the past 24 hours, maximal hunger in the past 24 hours, and morning hunger were self-reported daily using a numerical rating scale score ranging from 0–10, with 0 = "not hungry at all" and 10 = "hungriest possible"; scores for maximal daily hunger are reported herein
  - HRQOL was investigated using the self-reported Pediatric Quality of Life Inventory (PedsQL) or the Impact of Weight on Quality of Life Questionnaire-Lite (IWQOL-Lite); scores ranged from 0 to 100, where 0 = the worst possible HRQOL and 100 = the best possible HRQOL[6,7]
    - For PedsQL, age-appropriate assessment tools (PedsQL-Child [for those 8 to 12 years old] and PedsQL-Teen [for those 13 to 17 years old]) were used, and outcomes were reported together
    - For PedsQL, impairment was defined as a self-reported total score <68.2, and clinically meaningful improvement was defined as a total score change >4.44[7]
    - For IWQOL-Lite, impairment was defined based on total score, with definitions for severe (<71.8), moderate (71.9–79.4), mild (79.5–87.0), or no (87.1–94.6) impairment; the clinically meaningful improvement cutoff was defined as a total score change ranging from 7.7 to 12 points[6]
- Descriptive analyses were conducted on data reported at baseline and with ~52 weeks of active setmelanotide treatment (Tables 1-4)
- Spaghetti plots were produced to illustrate the individual patient HRQOL course during the clinical trial period (Figure)

Results

Table 1. Baseline Characteristics

	All patients[a]	Patients without cognitive impairment
Patients, n[b]	31	15
Patients who reported HRQOL assessments, n[c]	24	13
Age, mean (SD) [range], years[c]	21.5 (10.9) [10–44]	23.2 (10.7) [12–43]
Body mass index,[c] mean (SD) [n], kg/m^2	42.9 (9.3) [24]	43.9 (10.5) [13]
Maximal hunger score, mean (SD) [n][c]	–	6.8 (1.8) [11]

[a]Includes adults and children with and without cognitive impairment. [b]All randomized patients who received ≥1 dose of setmelanotide or placebo and have baseline data. [c]Of patients who completed HRQOL assessments used in this analysis and had baseline total scores. HRQOL, health-related quality of life; SD, standard deviation.

Results, continued

Table 2. Summary of Impact of Setmelanotide in Children (8–17 Years Old; Self-Reported) With Baseline and Week-52 HRQOL Data

	All patients	Patients without cognitive impairment
Patients, n	9	3
PedsQL total score at baseline, mean (SD)	67.2 (18.9)	83.3 (2.7)
Change in PedsQL total score at Week 52, mean (SD)	+11.2 (14.4)	+3.3 (6.6)
Body mass index Z score change at Week 52, mean (SD)	−0.7 (0.5)	−1.0 (0.7)
Maximal hunger, percent change at Week 52, mean (SD) [range]	-	−43.4 (14.8) [−64.1, −30.2]

HRQOL, health-related quality of life; PedsQL, Pediatric Quality of Life Inventory; SD, standard deviation.

- All children with HRQOL impairment at baseline (n=4) experienced clinically meaningful improvement after 52 weeks of setmelanotide
- Among children with no impairment of HRQOL at baseline (n=5), all preserved or improved their nonimpaired HRQOL status (clinically meaningful improvement: n=2; preserved HRQOL: n=3)
- 82% of patients had no HRQOL impairment after 52 weeks of treatment

Table 3. Categorization of HRQOL Impairment at Baseline as Measured by IWQOL-Lite in Adults (≥18 Years Old)

	All patients with baseline HRQOL		Patients with baseline and Week-52 HRQOL data	
	All patients	Patients without cognitive impairment	All patients	Patients without cognitive impairment
Patients, n[a]	13	9	11	7
n (%) with impairment at baseline	10 (76.9)	8 (88.9)	8 (72.7)	6 (85.7)
Severe, n	4	3	4	3
Moderate, n	4	3	4	3
Mild, n	2	2	0	0

[a]All randomized patients who received ≥1 dose of setmelanotide or placebo, completed HRQOL assessments used in this analysis, and had baseline total scores. HRQOL, health-related quality of life; IWQOL-Lite, Impact of Weight on Quality of Life-Lite.

- The majority of adult patients (76.9%) reported a high HRQOL burden at baseline (of these patients, 80% experienced moderate-to-severe impairment)
  - In patients who also reported Week-52 data, 73% had moderate or severe impairment at baseline

Table 4. Impact of Setmelanotide in Adults (≥18 Years Old) With Baseline and Week-52 HRQOL Data

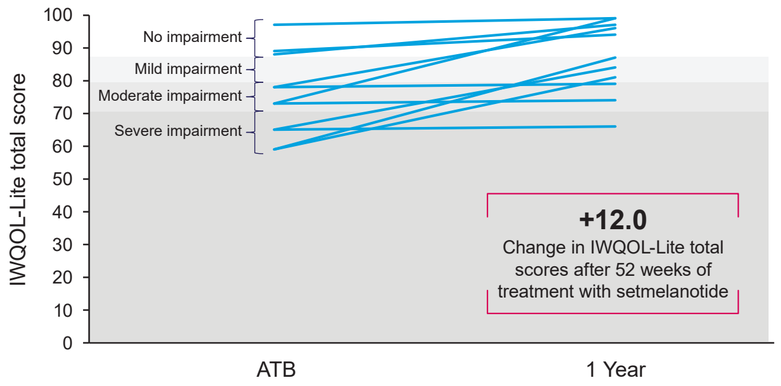
	All patients	Patients without cognitive impairment
Patients, n	11	7
IWQOL-Lite total score at baseline, mean (SD)	74.9 (12.6)	70.7 (10.6)
Change in IWQOL-Lite total score at Week 52, mean (SD)	+12.0 (10.8)	+17.6 (9.6)
Body mass index, percent change at Week 52, mean (SD)	−9.4 (7.0)	−10.1 (8.0)
Maximal hunger, percent change at Week 52, mean (SD) [range]	–	−39.3 (27.5) [−77.0, −4.8]

HRQOL, health-related quality of life; IWQOL-Lite, Impact of Weight on Quality of Life-Lite; SD, standard deviation.

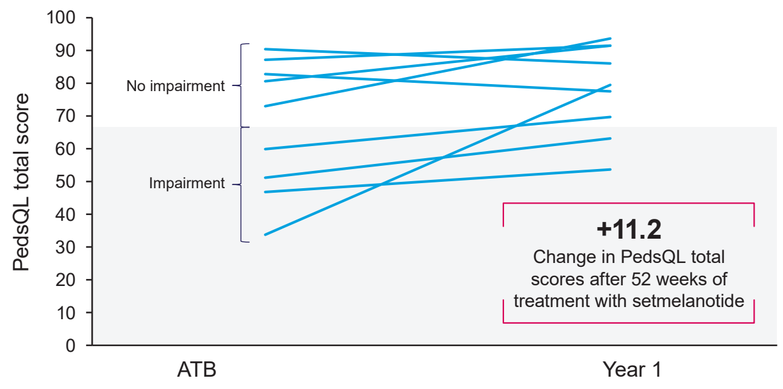
- Of adults with HRQOL impairment at baseline (n=8), 63% (5/8) had clinically meaningful improvement after 52 weeks of setmelanotide
- Among adults without impairment of HRQOL at baseline (n=3), all improved or preserved their nonimpaired HRQOL status (clinically meaningful improvement: n=1; preserved HRQOL: n=2)

Figure. Improved health-related quality of life measures in patients after 1 year of treatment

A. Self-Reported IWQOL-Lite Total Scores



B. Self-Reported PedsQL Total Scores[a]



[a]Includes patients who reported PedsQL-Child or PedsQL-Teen score.

Blue lines represent patient-level scores. Higher scores indicate better quality of life. ATB was defined as the last available measurement prior to starting setmelanotide (Week 0 for patients in setmelanotide group and Week 14 for patients in placebo group). Only the patients with nonmissing ATB visit 11 scores were included.

ATB, active treatment baseline; HRQOL, health-related quality of life; IWQOL-Lite, Impact of Weight on Quality of Life Questionnaire-Lite; PedsQL, Pediatric Quality of Life Inventory.

Conclusions

- After 1 year of treatment with setmelanotide, 85% of patients reported clinically meaningful improvements in or preserved their nonimpaired HRQOL status
  - 75% of patients with impaired HRQOL at baseline experienced clinically meaningful improvement; among patients with no impaired HRQOL at baseline, all patients improved or preserved their nonimpaired HRQOL status
- For the subset of patients without cognitive impairment, clinically meaningful improvements in clinical outcomes such as body mass index and hunger also mirrored their improvements in HRQOL
- At the patient level, improvements were sustained over the 52-week trial period
- In this rare disease, our research underscores the need to address the high HRQOL burden experienced by patients; additional research is warranted to confirm findings in clinical practice

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