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

Elizabeth Forsythe,[1] Robert Haws,[2] Jesús Argente,[3,4,5] Philip Beales,[1] Costel Chirila,[6] Karine Clément,[7,8] Hélène Dollfus,[9] Gabriel Á Martos-Moreno,[3,4] Ari Gnanasakthy,[6] Brieana C. Buckley,[10] Usha G. Mallya,[10] Andrea M. Haqq[11]

[1]Genetics and Genomic Medicine Programme, University College London Great Ormond Street Institute of Child Health, London, UK; [2]Marshfield Clinic Research Institute, Marshfield, WI, USA; [3]Department of Endocrinology, Hospital Infantil Universitario Niño Jesús, Instituto de Investigación La Princesa, Department of Pediatrics, Universidad Autónoma de Madrid, Madrid, Spain; [4]CIBER Fisiopatología de la obesidad y nutrición (CIBERobn), Instituto de Salud Carlos III, Madrid, Spain; [5]IMDEA Institute, Madrid, Spain; [6]RTI Health Solutions, Research Triangle Park, NC, USA; [7]Nutrition Department, Assistance Publique Hôpitaux de Paris, Pitié-Salpêtrière Hospital, Paris, France; [8]Sorbonne Université, INSERM, NutriOmics Research Unit, Paris, France; [9]Hôpitaux Universitaires de Strasbourg, CARGO and Department of Medical Genetics, Strasbourg, France; [10]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [11]Department of Pediatrics, University of Alberta, Edmonton, AB, Canada

257

Presenting Author:
Elizabeth Forsythe
elizabeth.forsythe@ucl.ac.uk

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 an ultra-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.

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

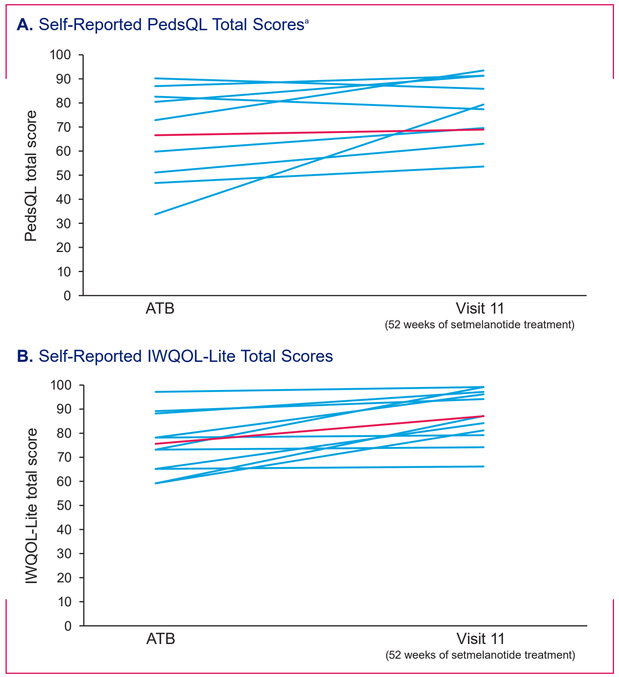
Table 4. Impact of Setmelanotide in Adults (≥18 Years Old) With Baseline and Week-52 HRQOL Data

	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. Spaghetti plots of individual patient HRQOL course.



[a]Includes patients who reported PedsQL-Child or PedsQL-Teen score.
Blue lines represent patient-level scores and red lines represent the group mean at each visit. 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 ultra-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

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided under the direction of the authors by MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

References: 1. Clement et al. *Lancet Diabetes Endocrinol.* 2020;8:960-970. **2.** Forsythe et al. *Front Pediatr.* 2018;6:23. **3.** Haws et al. *Contemp Clin Trials Commun.* 2021;22:100780. **4.** Schwimmer et al. *JAMA.* 2003;289:1813-1819. **5.** Haws et al. Poster presented at: Pediatric Endocrine Society Annual Meeting; April 30-May 3, 2021; Virtual. **6.** Crosby et al. *J Clin Epidemiol.* 2004;57:1153-1160. **7.** Varni et al. *Ambul Pediatr.* 2003;3:329-341.