Quality of Life in POMC or LEPR Deficiency: Setmelanotide Phase 3 Trials

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Summary

- After treatment with setmelanotide, patients with severe obesity and hyperphagia due to proopiomelanocortin (POMC) and leptin receptor (LEPR) deficiency reported meaningful improvements in health-related quality of life (HRQOL)

Introduction

- Genetic variants impacting the melanocortin-4 receptor pathway may lead to rare genetic diseases of obesity, including POMC and LEPR deficiency[1]
- Individuals with these diseases experience insatiable hunger and associated severe obesity at a young age, along with a high comorbidity burden.[1-3] All of these can impair QOL in both individuals with the diseases and their caregivers[4-6]
- There is a need for an efficacious therapy that preserves or improves HRQOL for patients with rare genetic diseases of obesity
- Setmelanotide was previously shown to reduce hunger and body weight in individuals with rare genetic diseases of obesity, including POMC and LEPR deficiency[3,7]

Objective

- To assess HRQOL burden prior to and after ~52 weeks of treatment with setmelanotide in patients with POMC and LEPR deficiency

Methods

Study Design and Key Entry Criteria

- Patients with obesity due to POMC and LEPR deficiency received setmelanotide for ~52 weeks in two Phase 3 trials (POMC trial, NCT02896192; LEPR trial, NCT03287960)
  - Obesity was defined as body mass index ≥95th percentile for ages 6–17 years and ≥30 kg/m^2 for ages ≥18 years
  - Exclusion criteria included recent weight loss from a diet and/or exercise regimen, >10% durable weight loss from prior gastric bypass surgery, a Patient Health Questionnaire-9 score ≥15, suicidal ideation of type 4 or 5 on the Columbia Suicide Severity Rating Scale, or history of suicidal behavior in the last month

Assessments

- HRQOL was investigated using the self-reported Impact of Weight on Quality of Life-Lite (IWQOL-Lite; for patients aged ≥18 years) or Pediatric Quality of Life Inventory (PedsQL; PedsQL-Child for patients aged 8–12 years and PedsQL-Teen for patients aged 13–17 years)
  - Assessments were completed at baseline and Weeks 4, 12, 26, 38, and 52
  - Analysis was performed in those who demonstrated weight loss (≥5-kg or ≥5% for those with baseline body weight <100 kg) with 12 weeks of setmelanotide
  - Scores ranged from 0 to 100, where 0 represents the worst possible HRQOL and 100 represents the best possible HRQOL[8,9]
  - For IWQOL-Lite, impairment was defined based on total score as severe (<71.8), moderate (range, 71.9–79.4), mild (range, 79.5–87.0), or none (range, 87.1–94.6)[8]
    - Previously published studies in the literature were used to define clinically meaningful improvement cutoff as a total score change ranging from 7.7 to 12 points, depending on baseline IWQOL-Lite total score[8]
  - For PedsQL, impairment was defined as a total score <68.2[4]
    - Clinically meaningful improvement was defined as a total score change >4.4[9]
  - Mean and standard deviation were calculated; *P*-values were not calculated because population sizes were small
- Patient-level analyses are important in rare genetic diseases where each patient's journey is unique
- Hunger was previously investigated using patient self-reports[3]

Results

Patient Disposition and Baseline Characteristics

- 13 patients met weight loss endpoints and completed HRQOL assessments (Table 1)
- In total, 11 of 13 patients reported impaired HRQOL at baseline
  - All adults reported moderate-to-severe impairment in their HRQOL at baseline
  - Both children reported impaired HRQOL at baseline
  - 2 of 4 adolescents reported impaired HRQOL at baseline

Table 1. Patient Disposition and Demographics

	POMC and LEPR trials
Patients enrolled, n	21
Patients with ≥5-kg (or ≥5%) weight loss, n (%)	16 (76.2)
Patients with ≥5-kg (or ≥5%) weight loss who completed HRQOL assessments, n (%)	13 (81.2)
Age of patients with ≥5-kg (or ≥5%) weight loss who completed HRQOL assessments, mean (SD) [range], years	20.4 (7.6) [11–37]
Age ≥18 years, n (%)	7 (53.8)
Age 13–17 years, n (%)	4 (30.7)
Age 8–12 years, n (%)	2 (15.4)

HRQOL, health-related quality of life; LEPR, leptin receptor; POMC, proopiomelanocortin; SD, standard deviation.

Patient-Reported and Clinical Outcomes Associated With Setmelanotide

- The majority (73%) of patients who reported scores at Week 52 experienced clinically meaningful improvement in HRQOL while receiving setmelanotide (Table 2)
  - 5 of 6 adults, 1 of 2 children, and 2 of 3 adolescents had clinically meaningful improvement in HRQOL at Week 52
- HRQOL improvements were observed as early as Week 5 and were maintained throughout the study (Figure 1)
- Weight loss and hunger reduction were clinically meaningful for the patients included in this analysis (weight loss range, −35.6% to −2.3%; hunger reduction range, −72.2% to −1.4%)

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

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Table 2. Patient-Reported and Clinical Outcomes Associated With Setmelanotide

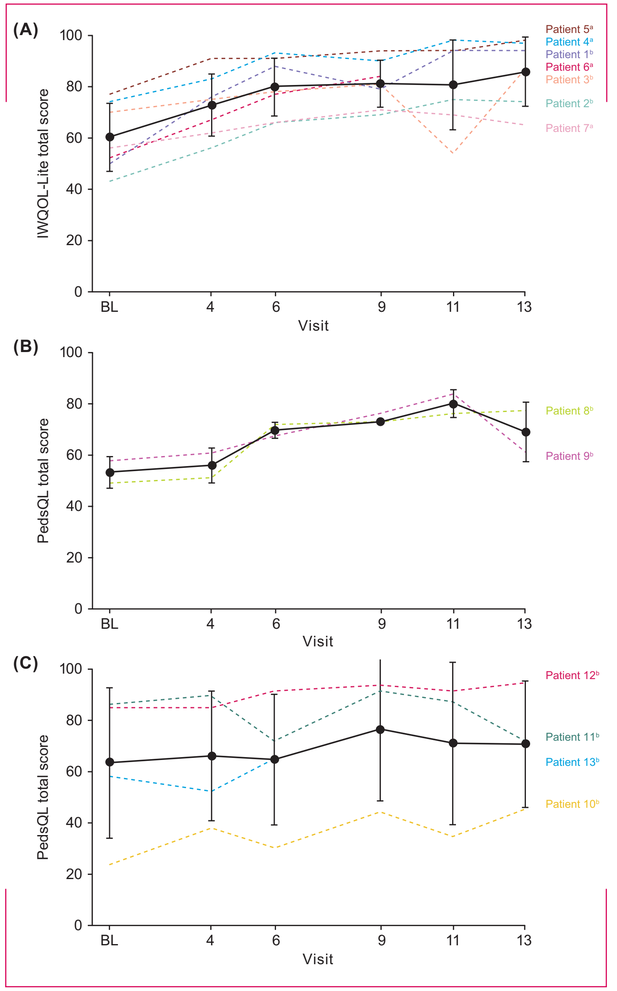
	Patient 1[a]	Patient 2[a]	Patient 3[a]	Patient 4[b]	Patient 5[b]	Patient 6[b]	Patient 7[b]	Mean (SD)
IWQOL-Lite Summary								
IWQOL-Lite total score at baseline	50	43	70	74	77	52	56	60.3 (13.2)
Change in IWQOL-Lite total score at Week 52	+44	+31	+17	+23	+21	–	+9	+24.2 (+12.1)
Relevant improvement cutoffs for IWQOL-Lite total score[7,c]	12.0	12.0	12.0	8.3	8.2	12.0	12.0	–
Body weight, percent change at Week 52	−34.8	−25.8	−27.7	−21.0	−15.6	–	−2.3	−21.2 (11.3)
Most hunger, percent change at Week 52	−14.3	−5.8	−72.2	−64.3	−66.7	–	−37.5	−43.5 (26.7)
PedsQL-Child Summary								
	Patient 8[a]	Patient 9[a]						Mean (SD)
PedsQL total score at baseline	48.9	57.6	–	–	–	–	–	53.3 (6.1)
Change in PedsQL total score at Week 52	+28.3	+3.3	–	–	–	–	–	+15.8 (+17.7)
Body weight, percent change at Week 52	−20.1	−2.4	–	–	–	–	–	−11.2 (12.5)
PedsQL-Teen Summary								
	Patient 10[a]	Patient 11[a]	Patient 12[a]	Patient 13[a]				Mean (SD)
PedsQL total score at baseline	23.9	85.9	84.8	58.7	–	–	–	63.3 (29.1)
Change in PedsQL total score at Week 52	+21.7	−14.1	+9.8	–	–	–	–	+5.8 (+18.3)
Body weight, percent change at Week 52	−26.2	−30.2	−35.6	−27.3	–	–	–	−29.8 (+4.2)
Most hunger, percent change at Week 52	−54.7	−37.5	−1.4	−3.5	–	–	–	−24.3 (26.2)

[a]Patient enrolled in POMC trial. [b]Patient enrolled in LEPR trial. [c]Improvement and deterioration cutoff scores are dependent on baseline IWQOL-Lite total scores. IWQOL-Lite, Impact of Weight on Quality of Life-Lite; LEPR, leptin receptor; PedsQL, Pediatric Quality of Life Inventory; POMC, proopiomelanocortin; SD, standard deviation.

Conclusions

- Setmelanotide resulted in clinically meaningful improvement in HRQOL in the majority (73%) of patients after ~52 weeks of treatment
  - Numerical improvements in HRQOL were 2 to 3 times larger than the relevant meaningful threshold
- Meaningful HRQOL improvements were observed as early as Week 5, were maintained throughout the study, and were mirrored by clinically meaningful hunger reductions and weight loss
- The results of this study indicate that it is essential to support patients and their families psychologically, independent of pharmacologic treatment; further, psychological support is warranted during pharmacologic treatment, such as treatment with setmelanotide

Figure 1. Health-related quality of life throughout the trials as assessed by **(A)** IWQOL-Lite, **(B)** PedsQL-Child, and **(C)** PedsQL-Teen.



[a]Patient enrolled in LEPR trial. [b]Patient enrolled in POMC trial. BL, baseline; IWQOL-Lite, Impact of Weight on Quality of Life-Lite; PedsQL, Pediatric Quality of Life Inventory.