Long-term Efficacy of Setmelanotide in Patients With POMC or LEPR Deficiency Obesity

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* Potential conflict of interest may exist. Refer to the Meeting App.

ODP607

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Summary

- **Long-term use of setmelanotide demonstrated durable weight loss in patients with biallelic variants in *POMC*, *PCSK1*, or *LEPR* for up to 36 months of treatment**
- **There were no new safety concerns that emerged during long-term use of setmelanotide**
- **These data support the long-term use of setmelanotide in patients with POMC or LEPR deficiency obesity**

Introduction

- The central melanocortin-4 receptor (MC4R) signaling pathway is important for regulating energy balance and body weight[1]
- Rare variants in genes encoding proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) can cause impairment in MC4R signaling, resulting in early-onset, severe obesity[1,2]
- Pivotal Phase 3 trials have demonstrated treatment with setmelanotide, an MC4R agonist, leads to reduced weight and hunger in patients with POMC or LEPR deficiency obesity[1]
- The current analysis examines the continuation of these effects of setmelanotide in this population over 3 years of treatment

Objective

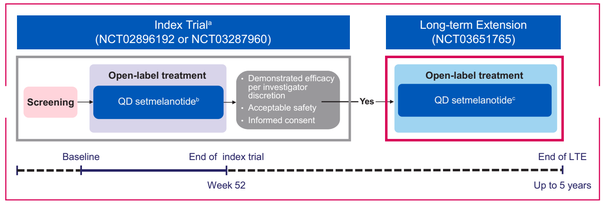
- To assess the continued efficacy of up to 3 years of setmelanotide treatment in patients with POMC or LEPR deficiency obesity

Methods

Study Design

- Patients who were ≥6 years of age and carried a biallelic variant in *POMC*, *PCSK1*, or *LEPR* were eligible for this long-term extension (LTE) trial (NCT03651765)
- Patients must also have completed a prior (index) trial and demonstrated clinical benefit and acceptable safety with setmelanotide treatment, as determined by the investigator
- Patients were excluded from the study if they had a history of melanoma, liver disease or injury, or a glomerular filtration rate <30 mL/min
- Patients began the LTE upon completion of the index trial, continuing the individual dosage determined in the index trial (Figure 1)
- Adverse events and weight were assessed every 3 months in the LTE
  - Weight-related measures were analyzed by adult (≥18 years old) and pediatric (<18 years old) subgroups separately to minimize dilution of treatment effect and prioritize appropriate evaluations according to age group
  - Body mass index (BMI) changes were reported in the overall population, with change in body weight provided for patients ≥18 years old and change in BMI Z score and percent of the BMI 95th percentile (%BMI_{95}) for those <18 years of age

Figure 1. Trial design.



[a]Index trial data were previously presented at ObesityWeek®[1]; November 1-5, 2021; Virtual. [b]Setmelanotide treatment during the index trial occurred for up to 52 weeks. [c]Setmelanotide treatment continued for up to 5 years within the LTE. LTE, long-term extension; QD, once daily.

Outcomes

- Outcomes including percent change in body weight from baseline, as well as safety and tolerability, were assessed every 3 months

Results

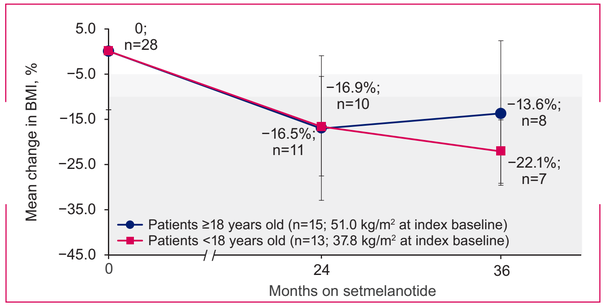
Participant Disposition and Baseline Characteristics

- As of October 29, 2021, 28 patients with POMC or LEPR deficiency obesity received setmelanotide treatment in an index trial (<18 years old, n=13; ≥18 years old, n=15)
- Patients were evenly distributed across sex and were predominately White (n=18; 64.3%) with a mean (SD) age of 19.8 (8.1) years
- There were 24 patients who continued on to the LTE; 2 patients withdrew from the study and 1 patient was withdrawn by their parent/guardian
- Patients in the LTE received at least 24 (n=21) or 36 (n=15) months of setmelanotide treatment
  - The LTE is ongoing, and not all patients have reached 24 or 36 months of treatment
- At index trial baseline, mean (standard deviation [SD]) BMI for all patients was 44.9 (11.8) kg/m^2

Efficacy Outcomes

- Mean (SD) BMI for all patients in the LTE was 36.3 kg/m^2 (11.3) at 24 months and 36.8 kg/m^2 (13.1) at 36 months
- Mean (SD) percent change in BMI was −16.7% (16.0%; n=21) and −17.5% (20.5%; n=15) after 24 and 36 months of treatment, respectively; mean percent change in BMI by age is shown in Figure 2

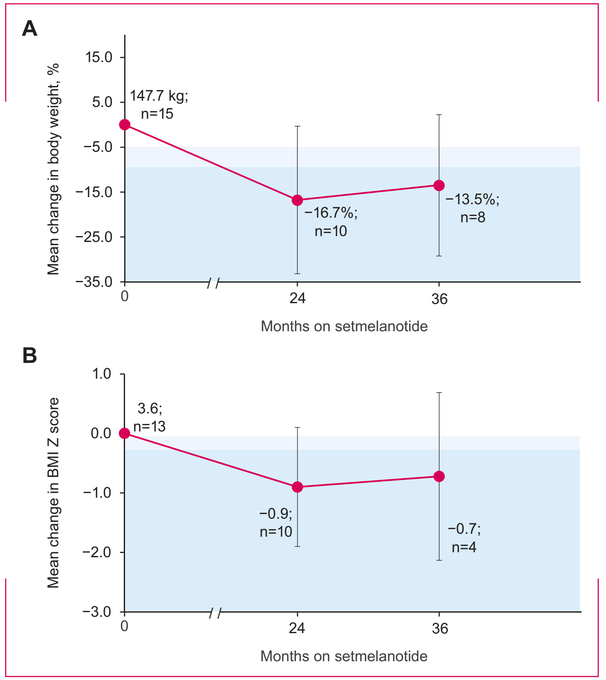
Figure 2. Mean percent change in BMI from index trial baseline by duration of setmelanotide treatment in the overall population.



Error bars indicate standard deviation. Shading represents benchmarks of at least −5% or −10% change. This trial is ongoing. BMI, body mass index.

- Patients ≥18 years of age had a mean (SD) body weight of 147.7 kg (28.7; n=15) at index trial baseline and exhibited a percent change in body weight of −16.7% (16.2%; n=10) and −13.5% (15.9%; n=8) after 24 and 36 months of treatment, respectively (Figure 3A)
  - Seven of 10 patients ≥18 years of age (70%) achieved ≥10% reduction in body weight from baseline at 24 months of treatment; 5 of 8 patients (62.5%) achieved this outcome at 36 months
- Patients <18 years old had a mean (SD) BMI Z score of 3.6 (0.4; n=13) at index trial baseline and exhibited a change in BMI Z score after 24 and 36 months of −0.9 (0.9; n=10) and −0.7 (1.4; n=4), respectively (Figure 3B)
  - Eight of 10 patients <18 years of age (80%) achieved ≥0.3-point reduction in BMI Z score from baseline at 24 months of treatment; 2 of 4 patients (50%) achieved this outcome at 36 months
- Patients <18 years old had a mean (SD) %BMI_{95} of 147.7 (17.7; n=13) and experienced a reduction in mean (SD) %BMI_{95} of –34.3% (24.5%; n=11) and −38.7% (33.7%; n=6) after 24 and 36 months respectively

Figure 3. Effects of setmelanotide on weight-related measures. **(A)** Mean percent change in body weight from index trial baseline by months of setmelanotide treatment in patients ≥18 years old. **(B)** Mean change in BMI Z score from index trial baseline by months of setmelanotide treatment in patients <18 years old.



Error bars indicate standard deviation. Shading represents multiple clinically relevant change thresholds of 5% and 10% body weight reduction and 0.2 and 0.3 BMI Z score reduction.[3,4] This trial is ongoing. %BMI_{95}, percent of the BMI 95th percentile; BMI, body mass index.

Safety Outcomes

- No patients discontinued because of adverse events during the LTE
- No new safety concerns emerged during long-term treatment
- Adverse events for the safety population across the index and LTE trials (N=28) are shown in the Table

Table. Adverse Events Occurring During the Index and LTE Trials in the Safety Population (N=28)

	n (%)
TEAEs	28 (100)
Treatment-related TEAEs	28 (100)
Serious treatment-related TEAEs	0 (0)
TEAEs leading to study drug withdrawal	3 (10.7)
Common TEAEs (≥50%)	
Skin hyperpigmentation	25 (89.3)
Injection site erythema	23 (82.1)
Nausea	17 (60.7)
Injection site edema	16 (57.1)
Injection site pruritus	16 (57.1)
Headache	15 (53.6)
Diarrhea	14 (50.0)

LTE, long-term extension; TEAE, treatment-emergent adverse event.

CONCLUSION

- Setmelanotide treatment provided continued efficacy for maintaining weight loss and an acceptable safety profile for up to 3 years of treatment in patients with POMC or LEPR deficiency obesity

Acknowledgments:
This study was sponsored by Rhythm Pharmaceuticals, Inc. Writing and editorial support for this poster was provided under the direction of the authors by Dorothy Dobbins, PhD, and David Boffa, ELS, of MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

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