# A Randomized Trial of a Once-Weekly Formulation of Setmelanotide in Individuals With Obesity

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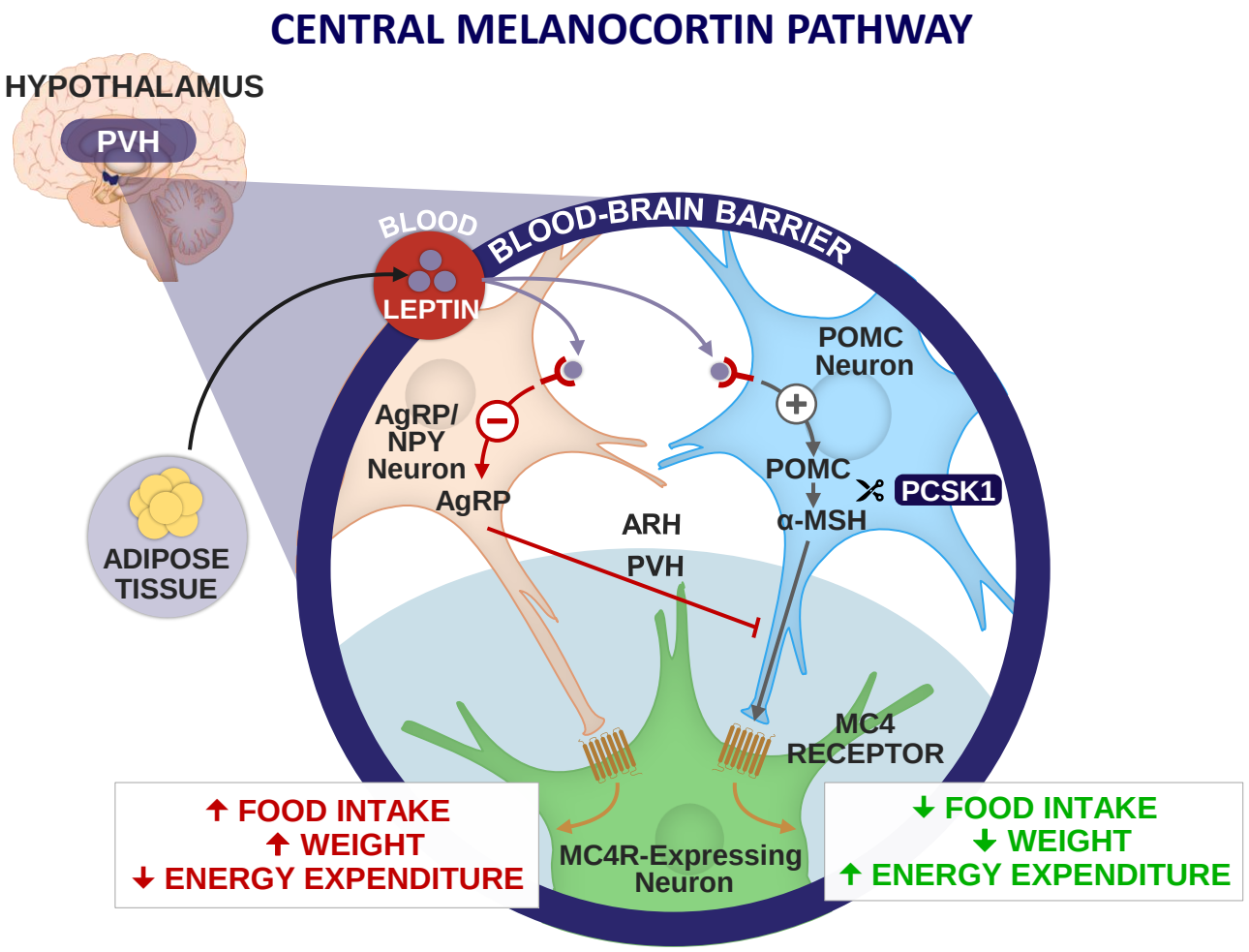
# Rare Genetic Disorders of Obesity Can Result From Dysfunction of the Central Melanocortin Pathway

- The MC4R pathway is a part of the central melanocortin pathway and regulates satiety and energy expenditure[1-4]
  - Monogenic disorders of obesity associated with the MC4R pathway include variants in *POMC, LEPR, PCSK1,* and *MC4R*[2]
  - Syndromic forms of obesity, including Bardet-Biedl syndrome and Alström syndrome, may involve dysregulation of the MC4R pathway[5,6]
- Targeting the MC4R pathway for the treatment of rare genetic disorders of obesity has become an area of development for potential innovative therapies[2]




AgRP, agouti-related protein; ARH, arcuate nucleus of the hypothalamus; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVH, paraventricular nucleus of the hypothalamus.

**1**. Huvenne et al. *Obes Facts.* 2016;9:158-173. **2**. Clément et al. *Physiol Behav.* 2020;227:113134. **3**. Yazdi et al. *PeerJ*. 2015;3:e856. **4**. Shen et al. *Biochim Biophys Acta.* 2017;1863:2477-2485. **5**. Haws et al. *Diabetes Obes Metab.* 2020 [Epub ahead of print]. **6**. Haws et al. Poster presented at: Keystone Symposia on Molecular and Cellular Biology: Functional Neurocircuitry of Feeding and Feeding Disorders; February 10-14, 2019; Banff, Alberta, Canada.

# Once-Daily Treatment With the MC4R Agonist Setmelanotide Demonstrates Weight and Hunger Reductions in Individuals With Rare Genetic Disorders of Obesity

- Setmelanotide is an MC4R agonist being investigated for the treatment of rare genetic disorders of obesity[1,2]
- QD subcutaneous setmelanotide has demonstrated weight and hunger reduction benefits in phase 3 trials in individuals with POMC or LEPR deficiency obesity and in phase 2 trials of individuals with Bardet-Biedl syndrome or Alström syndrome[3-6]
- QW dosing of injected therapies may decrease patient burden and improve adherence compared with QD dosing[7]
- A long-acting formulation of setmelanotide using FluidCrystal® technology with QW administration is being investigated as an alternative to the QD formulation

**OBJECTIVE**

To evaluate the safety, pharmacokinetics, and efficacy of a long-acting, once-weekly formulation of setmelanotide in comparison to once-daily setmelanotide injections in healthy individuals with obesity (interim analysis)

LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin; QD, once-daily; QW, once-weekly.

**1**. Collet et al. *Mol Metab.* 2017;6:1321-1329. **2**. Clément et al. *Physiol Behav.* 2020;227:113134. **3**. Clément et al. Poster presented at: ObesityWeek; November 3-7, 2019; Las Vegas, NV. **4**. van den Akker et al. Poster presented at: ObesityWeek; November 3-7, 2019; Las Vegas, NV. **5**. Haws et al. *Diabetes Obes Metab.* 2020 [Epub ahead of print]. **6**. Haws et al. Poster presented at: Keystone Symposia on Molecular and Cellular Biology: Functional Neurocircuitry of Feeding and Feeding Disorders; February 10-14, 2019; Banff, Alberta, Canada. **7.** Qiao Q et al. *Diabetes Metab Syndr Obes*. 2016;9:201-205.

# Study Design

## Participants

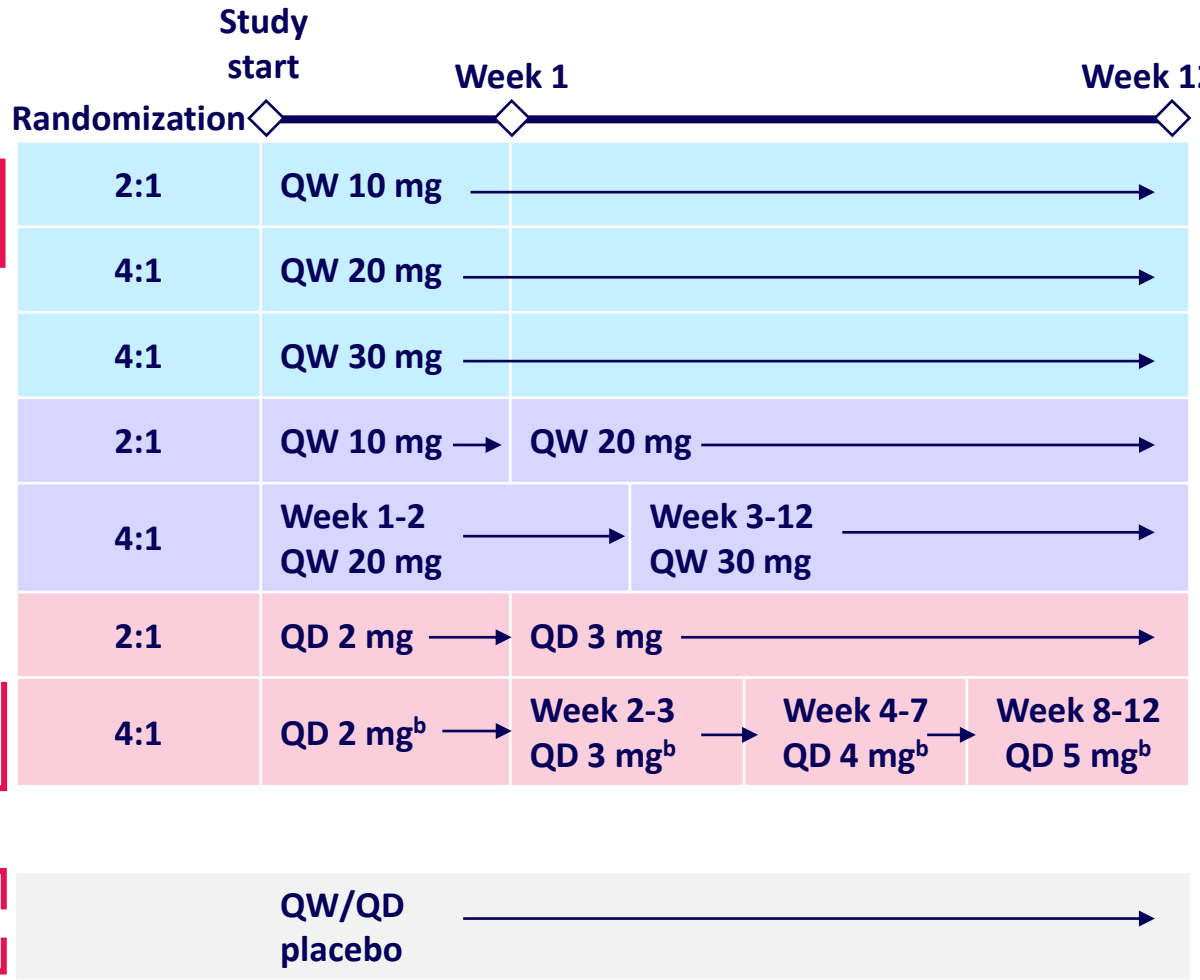
- Key inclusion criteria
  - Adults (aged 18–55 years)
  - BMI[a] ≥35 kg/m$^2$
  - Medically healthy at screening
- Key exclusion criteria
  - Clinically significant physical or laboratory abnormalities
  - Suicidal ideations, behaviors, or attempts
  - Significant dermatologic findings
  - Recent bariatric surgery

**Randomized**

## Setmelanotide

- QW with or without dose titration
- QD with dose titration

## Placebo




[a]Inclusion criteria updated from BMI ≥40 mg/kg$^2$ in the November 2019 amended protocol. [b]Data to be determined.
BMI, body mass index; QD, once daily; QW, once weekly.

# Trial Objectives

## Primary Objective

- Evaluate the safety and tolerability of QW setmelanotide formulation
- Evaluate body weight change from baseline at 12 weeks with QW setmelanotide compared with QD setmelanotide

## Secondary Objective

- Evaluate pharmacokinetics of QW and QD setmelanotide
- Evaluate body weight change from baseline at week 12 with QW setmelanotide compared with placebo

## Exploratory Objective

- Evaluate the efficacy of QW and QD setmelanotide on hunger, body mass index, waist circumference, and health status



QD, once-daily; QW, once-weekly.

# Results

# Baseline Participant Characteristics

| | | Setmelanotide dose/schedule | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall (N=85) | 10 mg QW (n=12) | 20 mg QW (n=8) | 30 mg QW (n=8) | 10 mg/20 mg QW (n=12) | 20 mg/30 mg QW (n=8) | 2 mg/3 mg QD (n=13) | Placebo (n=24) |
| Age, mean (SD), y | 40.5 (8.5) | 38.1 (9.8) | 40.3 (7.5) | 39.5 (10.8) | 40.1 (7.6) | 39.4 (9.0) | 42.8 (7.8) | 41.6 (8.5) |
| Sex, n (%) | | | | | | | | |
| Male | 22 (25.9) | 4 (33.3) | 0 | 2 (25) | 3 (25) | 2 (25) | 5 (38.5) | 6 (25) |
| Female | 63 (74.1) | 8 (66.7) | 8 (100) | 6 (75) | 9 (75) | 6 (75) | 8 (61.5) | 18 (75) |
| Race, n (%) | | | | | | | | |
| Black/African American | 22 (25.9) | 0 (0) | 4 (50) | 1 (12.5) | 2 (16.7) | 2 (25) | 4 (30.8) | 9 (37.5) |
| White | 63 (74.1) | 12 (100) | 4 (50) | 7 (87.5) | 10 (83.3) | 6 (75) | 9 (69.2) | 15 (62.5) |
| Ethnicity, n (%) | | | | | | | | |
| Hispanic or Latino | 45 (52.9) | 8 (66.7) | 0 | 1 (12.5) | 7 (58.3) | 3 (37.5) | 9 (69.2) | 17 (70.8) |
| Not Hispanic or Latino | 40 (47.1) | 4 (33.3) | 8 (100) | 7 (87.5) | 5 (41.7) | 5 (62.5) | 4 (30.8) | 7 (29.2) |
| Weight, mean (SD), kg | 126.6 (20.8) | 127.0 (20.6) | 124.7 (16.9) | 129.4 (17.2) | 128.9 (25.0) | 136.0 (15.5) | 120.5 (23.0) | 125.0 (22.0) |
| BMI, mean (SD), kg/m$^2$ | 45.7 (5.6) | 44.3 (4.1) | 45.5 (3.7) | 46.9 (4.2) | 46.2 (7.5) | 47.7 (3.6) | 44.2 (6.7) | 45.8 (6.2) |

- Baseline weight and BMI were generally similar across treatment groups
- 71 of 85 participants (83.5%) completed the study, and 14 (16.5%) discontinued; 7 participants (QW setmelanotide, n=3; QD setmelanotide, n=4; placebo, n=0) discontinued the study because of adverse events[a]

[a]Additional reasons for study discontinuation were withdrawal by participant (n=3), investigator decision (n=1), lack of participant adherence (n=1), removed from study (n=1), and other (n=1).
BMI, body mas index; QD, once daily; QW, once weekly; SD, standard deviation.

# Safety of Setmelanotide QW

| | | Setmelanotide dose/schedule | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Overall (N=85) | 10 mg QW (n=12) | 20 mg QW (n=8) | 30 mg QW (n=8) | 10 mg/20 mg QW (n=12) | 20 mg/30 mg QW (n=8) | 2 mg/3 mg QD (n=13) | Placebo (n=24) |
| TEAEs, n (%) | 80 (94.1) | 12 (100) | 8 (100) | 8 (100) | 12 (100) | 8 (100) | 12 (92.3) | 20 (83.3) |
| TEAEs related to study drug, n (%) | 79 (92.9) | 12 (100) | 8 (100) | 8 (100) | 12 (100) | 8 (100) | 12 (92.3) | 19 (79.2) |
| Serious TEAEs, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |
| TEAEs leading to study drug withdrawal, n (%) | 8 (9.4) | 0 (0) | 1 (12.5) | 1 (12.5) | 0 (0) | 1 (12.5) | 4 (30.8) | 1 (4.2) |
| Nausea | 2 (2.4) | 0 | 0 | 1 (12.5) | 0 | 0 | 1 (7.7) | 0 |
| Vomiting | 1 (1.2) | 0 | 0 | 0 | 0 | 0 | 1 (7.7) | 0 |
| Injection site reaction[a] | 2 (2.4) | 0 | 0 | 0 | 0 | 0 | 1 (7.7) | 1 (4.2) |
| Back pain | 1 (1.2) | 0 | 1 (12.5) | 0 | 0 | 0 | 0 | 0 |
| Dizziness | 1 (1.2) | 0 | 0 | 0 | 0 | 1 (12.5) | 0 | 0 |
| Erectile dysfunction | 1 (1.2) | 0 | 0 | 0 | 0 | 0 | 1 (7.7) | 0 |
| TEAEs leading to death, n (%) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) |

- The safety profile of setmelanotide QW was similar to that of setmelanotide QD
- No serious TEAEs or deaths occurred

[a]Represents system organ class group.

QD, once daily; QW, once weekly; TEAE, treatment-emergent adverse event.

# TEAEs of Interest With Setmelanotide QW

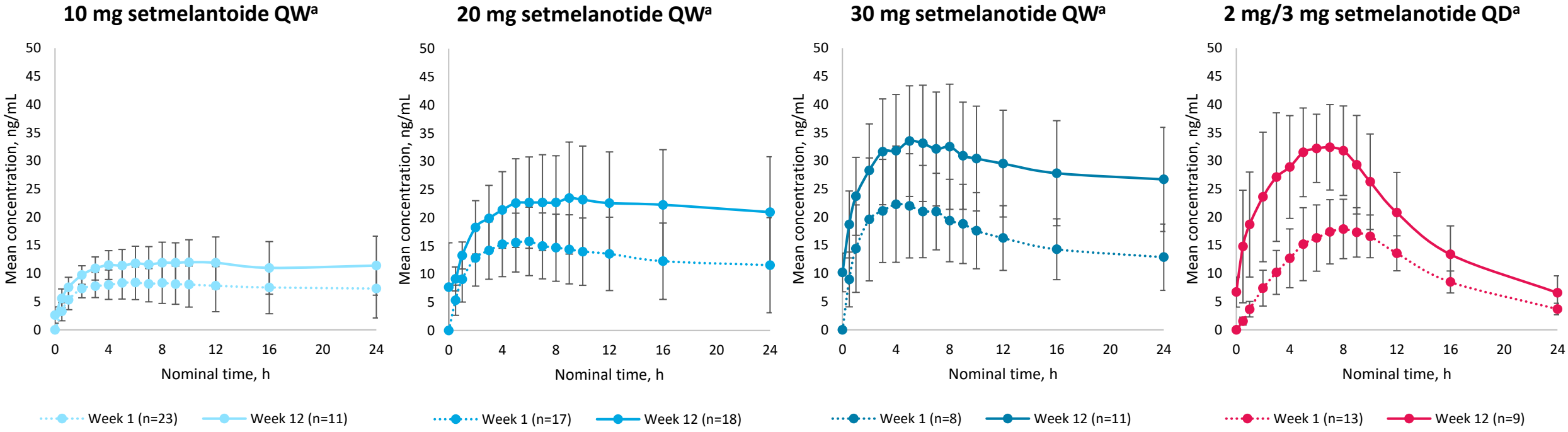
**AEs occurring in ≥10% of the overall population**

| | | Setmelanotide dose/schedule | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **TEAEs of interest, n (%)** | **Overall (N=85)** | **10 mg QW (n=12)** | **20 mg QW (n=8)** | **30 mg QW (n=8)** | **10 mg/20 mg QW (n=12)** | **20 mg/30 mg QW (n=8)** | **2 mg/3 mg QD (n=13)** | **Placebo (n=24)** |
| Injection site reaction[a] | 55 (64.7) | 10 (83.3) | 2 (25.0) | 2 (25.0) | 11 (91.7) | 4 (50.0) | 8 (61.5) | 18 (75.0) |
| Skin hyperpigmentation | 50 (58.5) | 11 (91.7) | 6 (75.0) | 5 (62.5) | 10 (83.3) | 5 (62.5) | 9 (69.2) | 4 (16.7) |
| Nausea | 34 (40.0) | 4 (33.3) | 7 (87.5) | 6 (75.0) | 3 (25.0) | 5 (62.5) | 6 (46.2) | 3 (12.5) |
| Headache | 23 (27.1) | 1 (8.3) | 5 (62.5) | 6 (75.0) | 2 (16.7) | 2 (25.0) | 3 (23.1) | 4 (16.7) |
| Vomiting | 18 (21.2) | 3 (25.0) | 4 (50.0) | 3 (37.5) | 3 (25.0) | 1 (12.5) | 2 (15.4) | 2 (8.3) |

- Rates of TEAEs of interest were generally similar between setmelanotide QW and QD, with some variation between dosing levels
- All injection site reactions were classified as mild

[a]Represents system organ class group.
AE, adverse event; QD, once daily; QW, once weekly; TEAE, treatment-emergent AE.

# Setmelanotide QW Demonstrated a Consistent 24-Hour PK Range and Is Detected Steadily Over 1 Week

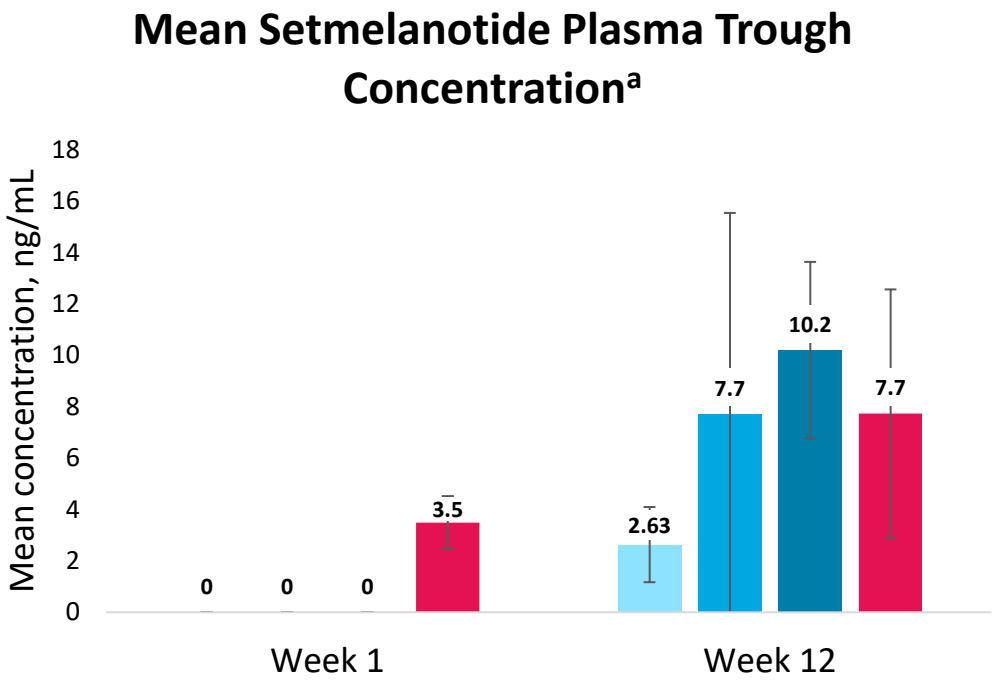


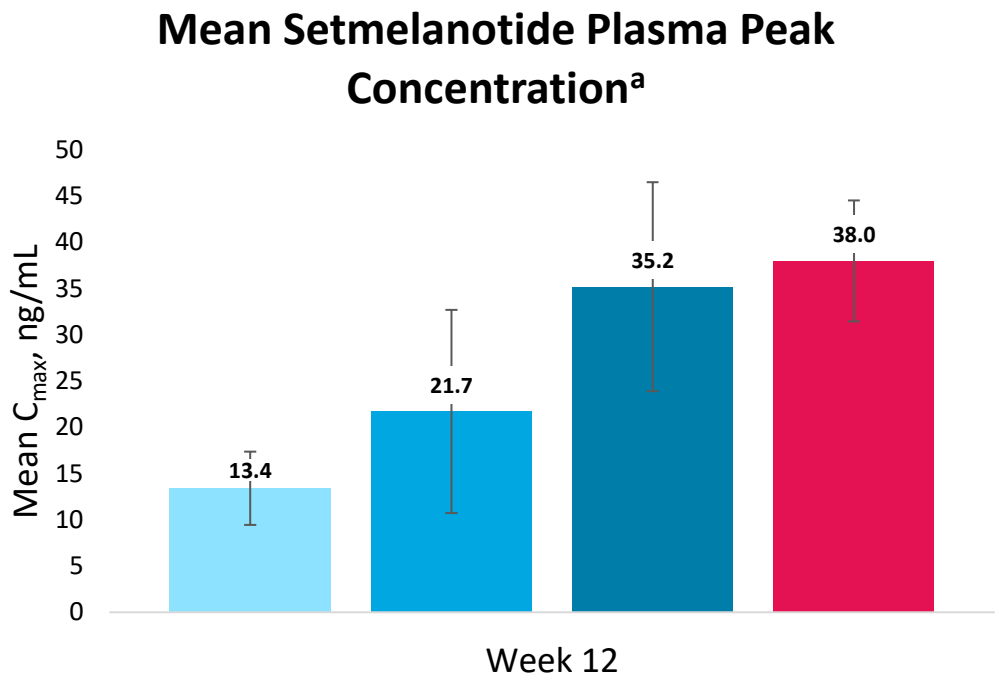

| Week-1 plasma concentration, mean (SD), ng/mL | Hours after delivery | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | 0.5 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 12 | 16 | 24 | 48 | 72 | 96 | 120 | 168 |
| Pooled setmelanotide QW | 0 (0) | 5.0 (3.3) | 8.2 (5.2) | 11.3 (7.0) | 12.3 (7.0) | 13.0 (7.7) | 13.2 (7.2) | 13.1 (7.1) | 12.5 (6.6) | 12.4 (6.5) | 12.1 (6.5) | 11.8 (6.2) | 11.3 (6.1) | 10.4 (5.8) | 9.8 (6.5) | 7.4 (4.5) | 5.1 (3.2) | 4.0 (2.9) | 3.2 (2.1) | 3.0 (2.3) |
| 2 mg/3 mg setmelanotide QD | 0 (0) | 1.6 (0.7) | 3.7 (1.4) | 7.4 (3.2) | 10.2 (3.9) | 12.7 (5.2) | 15.2 (6.5) | 16.3 (5.9) | 17.4 (5.7) | 17.9 (5.3) | 17.3 (4.4) | 16.6 (3.8) | 13.6 (3.1) | 8.5 (1.9) | 3.8 (1.0) | NA | NA | NA | NA | NA |

[a]Error bars represent standard deviation.

NA, not applicable; PK, pharmacokinetic; QD, once daily; QW, once weekly; SD, standard deviation.

# Mean Setmelanotide Trough and Peak Plasma Concentrations



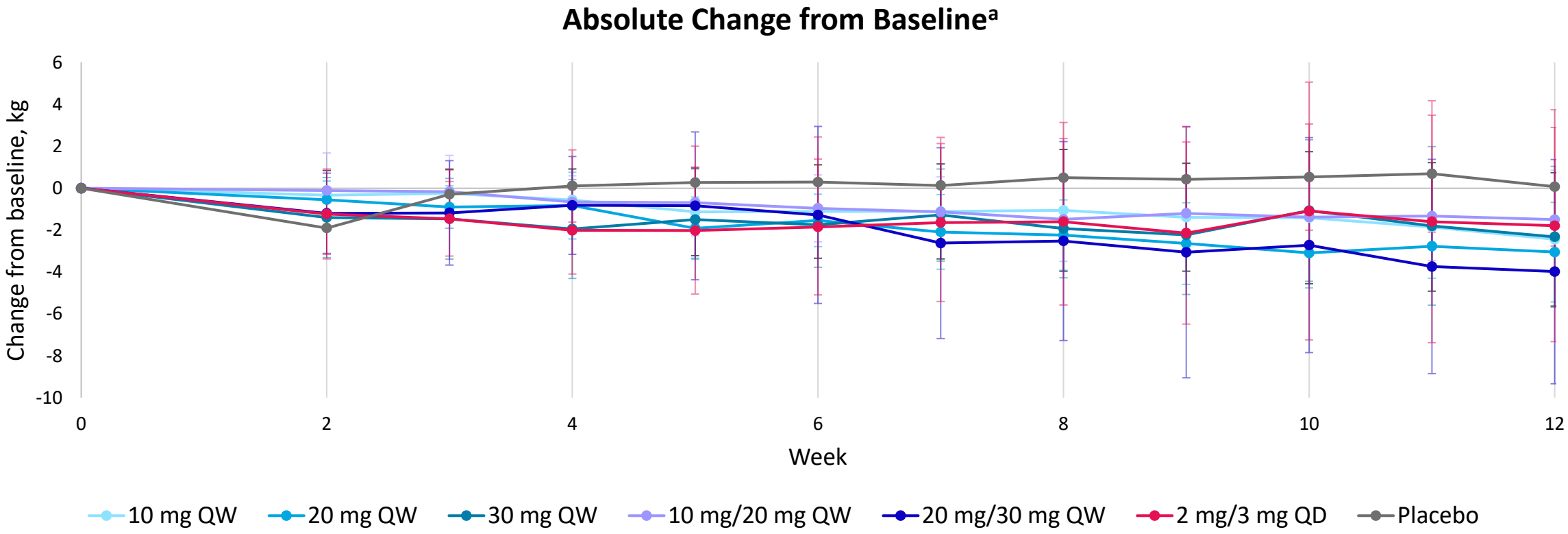




10 mg QW (n=11) | 20 mg QW (n=18) | 30 mg QW (n=11) | 2 mg/3 mg QD (n=13)

- Week-12 mean trough setmelanotide concentration was comparable between formulations
- Peak setmelanotide concentration at week 12 was numerically higher with setmelanotide QD compared with setmelanotide QW

[a]Error bars represent standard deviation.
QD, once daily; QW, once weekly.

# Weight Loss Was Similar Between Setmelanotide QW and QD




| Change from baseline at week 12, kg (percent change from baseline) | | | | | | |
|---|---|---|---|---|---|---|
| 10 mg QW | 20 mg QW | 30 mg QW | 10 mg/20 mg QW | 20 mg/30 mg QW | 2 mg/3 mg QD | Placebo |
| −2.6 (−2.3)[b] | −3.3 (−2.6)[b] | −3.0 (−2.2)[b] | −1.1 (−0.9) | −3.6 (−2.8)[b] | −2.1 (−1.6) | 0.5 (0.3) |

[a]Error bars represent the standard deviation. [b]Weight loss was statistically significant compared with placebo.
QD, once daily; QW, once weekly.

# Change in Hunger Was Similar Between Setmelanotide Formulations

| | Setmelanotide dose/schedule | | | | | | |
|---|---|---|---|---|---|---|---|
| **Outcome** | **10 mg QW** | **20 mg QW** | **30 mg QW** | **10 mg/20 mg QW** | **20 mg/30 mg QW** | **2 mg/3 mg QD** | **Placebo** |
| Baseline most hungry score, mean (SD) | 5.0 (2.0) (n=11) | 3.8 (2.3) (n=8) | 4.1 (2.4) (n=8) | 4.6 (2.9) (n=11) | 6.4 (2.1) (n=8) | 6.0 (2.7) (n=13) | 4.2 (3.3) (n=22) |
| Week 12 most hungry score, mean (SD) | 2.9 (2.0) (n=11) | 2.5 (1.9) (n=7) | 4.1 (2.6) (n=6) | 2.9 (2.1) (n=12) | 3.2 (3.6) (n=5) | 4.0 (1.8) (n=10) | 4.1 (3.1) (n=23) |
| Absolute change from baseline, mean (SD) | −2.1 (1.3) (n=11) | −1.6 (1.6) (n=7) | 0.3 (2.6) (n=6) | −1.9 (3.0) (n=11) | −3.9 (4.8) (n=5) | −2.3 (2.4) (n=10) | −0.3 (3.3) (n=21) |
| Percent change from baseline, % (SD) | −44.6 (26.1) (n=11) | −39.8 (44.9) (n=7) | 45.5 (158.3)[a] (n=5) | 83.5 (405.1)[a] (n=11) | −50.2 (62.6) (n=5) | −35.6 (28.9) (n=9) | 10.1 (128.1) (n=18) |
| Percent change from baseline LSM difference compared with placebo (*P* value) | −53.1 (0.44) | −70.6 (0.38) | 26.1 (0.77) | 64.7 (0.34) | −4.0 (0.97) | −116.3 (0.91) | -- |
| Percent change from baseline LSM difference compared with 2 mg/3 mg QD (*P* value) | −61.3 (0.45) | −78.8 (0.40) | 17.9 (0.86) | 56.5 (0.50) | −12.2 (0.90) | -- | -- |

[a]Increased percent change from baseline due to missing data values and outliers.
LSM, least squares mean; QD, once daily; QW, once weekly; SD, standard deviation.

# Conclusions

- A long-acting QW formulation of setmelanotide had similar pharmacokinetics, safety, and efficacy as QD dosing in this interim analysis
  - The safety profile of QW setmelanotide was similar to that of the QD formulation
  - In healthy volunteers, the trough concentration of setmelanotide with the QW formulation was consistent with the trough concentration of the efficacious QD formulation
  - Weight and hunger change at week 12 was comparable between QW and QD setmelanotide
- Together, the evidence from this interim analysis supports further investigation of QW setmelanotide in individuals with rare genetic disorders of obesity



QD, once-daily; QW, once-weekly.