Summary
- The Phase 2 DAYBREAK trial will evaluate setmelanotide for weight loss and hunger reduction in individuals who have a variant in at least one of 31 genes associated with the melanocortin-4 receptor (MC4R) pathway.
- Understanding the effect of setmelanotide in individuals with genetic variants within the MC4R pathway can expand access to those living with rare genetic diseases of obesity.
- Enrollment of the first patient is expected by the end of 2021.

Introduction
- Rare genetic diseases of obesity are distinct from general obesity and are often driven by variants in the MC4R pathway, which regulates energy balance and body weight homeostasis.
- Rare variants in key MC4R pathway genes, such as LEPR, POMC, and PCSK1, have been associated with obesity irrespective of environmental factors.
- Other genes within the MC4R pathway, including LEPR, SIM1, MRAP2, and KRAS, are also associated with obesity.
- Setmelanotide, a selective agonist of MC4R, is approved to treat obesity and is currently being evaluated in clinical trials.
- Treatment with setmelanotide in two Phase 3 trials resulted in ≥10% weight loss from baseline and ≥0.3-point reduction from baseline in BMI Z score for those aged ≥18 years old or <18 years old, respectively, compared with placebo.
- If a patient’s weight increases by ≥5% from the Stage 2 entry weight, the patient will be considered a nonresponder and will be discontinued from the study.
- There is no additional weight loss (≥0.6 cm) for those aged ≥12 years old compared with placebo.
- Key exclusion criteria include pregnancy, active malignancy, or concurrent use of certain medications.

Methods
- Participants and Eligibility Criteria
  - Stage 1 of the study will enroll ~500 eligible patients (Table 1 and Box 1) with the intention to include ~130 of those patients in Stage 2.
  - Sample size was determined by a power analysis to detect significance between the 2 groups (pooled treatment across genotype versus pooled placebo) with a 2-sided alpha level of 5% and an expected premature dropout rate of 5% in Stage 2.
- Key inclusion criteria (Stage 1):
  - Preidentified variant in the MC4R pathway
  - Aged 26 to 65 years
  - BMI ≥ 24.0 kg/m² (18 years old) or BMI ≥ 77th percentile (6 to ≤17 years old)
- Key exclusion criteria (Stage 1):
  - Recent diet or exercise resulting in ≥3% weight loss
  - Bariatric surgery within 6 months of enrollment
  - Diagnosis or features of syndromic obesity
  - Glycated hemoglobin >10.0%
  - Glomerular filtration rate <60 ml/min

Figure 1. Study design for Stage 1 and Stage 2 of a Phase 2 trial of setmelanotide.

Stage 1
- Open-label run-in period
  - Visit 1(1): Screening
  - Visit 2(2): 2 weeks
  - Visit 3(3): Week 2
  - Visit 4(4): Week 6
  - Visit 5(5): Week 8
  - Visit 6(6): Week 12
- Open-label dose titration
  - Visit 7: Baseline
  - Visit 8: Week 1
  - Visit 9: Week 2
  - Visit 10: Week 4
  - Visit 11: Week 6
  - Visit 12: Week 8
  - Visit 13: Week 12
  - Visit 14: Week 18
  - Visit 15: Week 20
  - Visit 16: Week 24
- Randomized, double-blind
  - Visit 17: Visit 22
  - Visit 18: Visit 24
  - Visit 19: Visit 26
  - Visit 20: Visit 28
  - Visit 21: Visit 30
  - Visit 22: Visit 32
  - Visit 23: Visit 34
  - Visit 24: Visit 36
  - Visit 25: Visit 38
  - Visit 26: Visit 40
  - Visit 27: Visit 42
  - Visit 28: Visit 44
- End of study visit

Stage 2
- Open-label treatment at therapeutic dose 3 mg
  - Visit 1(1): Baseline
  - Visit 2(2): Week 2
  - Visit 3(3): Week 4
  - Visit 4(4): Week 6
  - Visit 5(5): Week 8
  - Visit 6(6): Week 10
  - Visit 7(7): Week 12
  - Visit 8(8): Week 14
  - Visit 9(9): Week 16
  - Visit 10(10): Week 18
  - Visit 11(11): Week 20
  - Visit 12(12): Week 22
  - Visit 13(13): Week 24
  - Visit 14(14): Week 26
  - Visit 15(15): Week 28
  - Visit 16(16): Week 30
  - Visit 17(17): Week 32
  - Visit 18(18): Week 34
  - Visit 19(19): Week 36
  - Visit 20(20): Week 38
  - Visit 21(21): Week 40
  - Visit 22(22): Week 42
  - Visit 23(23): Week 44
- Responders
  - Yes
  - R=
  - 2
  - 1
  - No
  - End of study visit

Stage 2
- Randomized, double-blind
  - Visit 24(24): 24 weeks
  - Visit 25(25): End of study visit

References: