Setmelanotide Treatment in Individuals With Obesity and *PHIP* Variants: Results From the DAYBREAK Trial

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Peter Kuhnen, MD[1]; Vidhu Thaker, MD[2]; Christopher Still, DO, FACN, FACP, FTOS[3]; Douglas Denham, DO, CPI[4]; Heidi Shea, MD[5]; Svetlana Ten, MD[6]; Whitney Herring, MD[7]; Dorit Koren, MD, MTR[8]; Jill C. Garrison, PhD[8]; Fabian Zuiderwijk,[8] Patrick Sleiman, PhD[8]; Orit Pinhas-Hamiel, MD[9,10]; Antje Koerner, MD[11]; Erica van den Akker, MD[12] on behalf of the DAYBREAK Trial Investigators

[1]Charité - Universitätsmedizin Berlin, Berlin, Germany; [2]Columbia University Irving Medical Center, New York, NY; [3]Geisinger Clinic, Danville, PA; [4]Clinical Trials of Texas, San Antonio, TX; [5]Endocrine Associates of Dallas and Plano, Plano, TX; [6]Ten's Medical Center – Pediatric Endocrinology Clinic, Brooklyn, NY; [7]Mississippi Center for Advanced Medicine, Madison, MS; [8]Rhythm Pharmaceuticals, Inc., Boston, MA; [9]Tel Aviv University, Tel Aviv, Israel; [10]Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [11]Universitaetsklinikum Leipzig, Leipzig, Germany; [12]Erasmus University Medical Center, Rotterdam, The Netherlands

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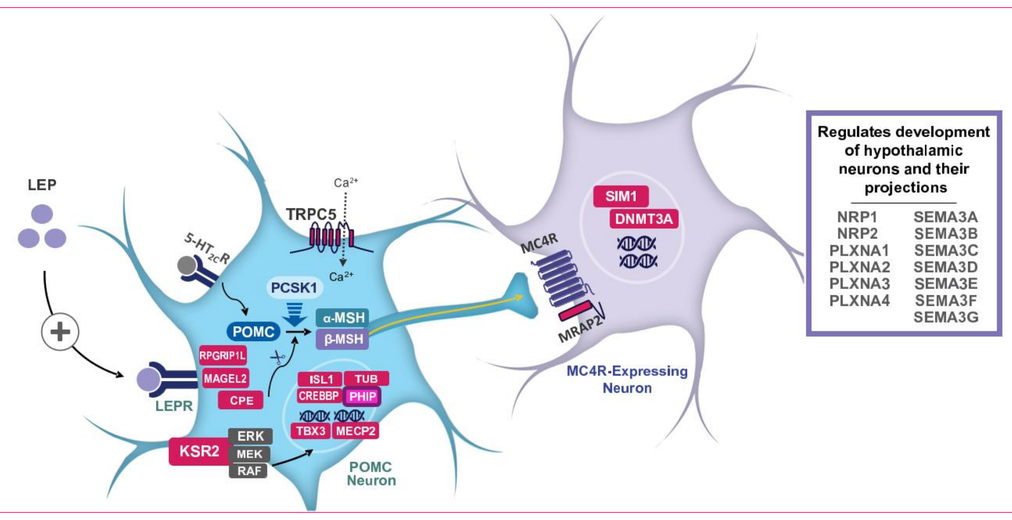
Introduction

- The melanocortin-4 receptor (MC4R) pathway regulates energy balance, hunger, and satiety[1-4]
- DAYBREAK (NCT04963231) was a 2-stage clinical trial evaluating setmelanotide in individuals with a variant in ≥1 of 31 genes involved in the MC4R pathway, including *PHIP*, which enhances *POMC* transcription (Figure 1)

Figure 1. Genes Studied in the DAYBREAK Trial



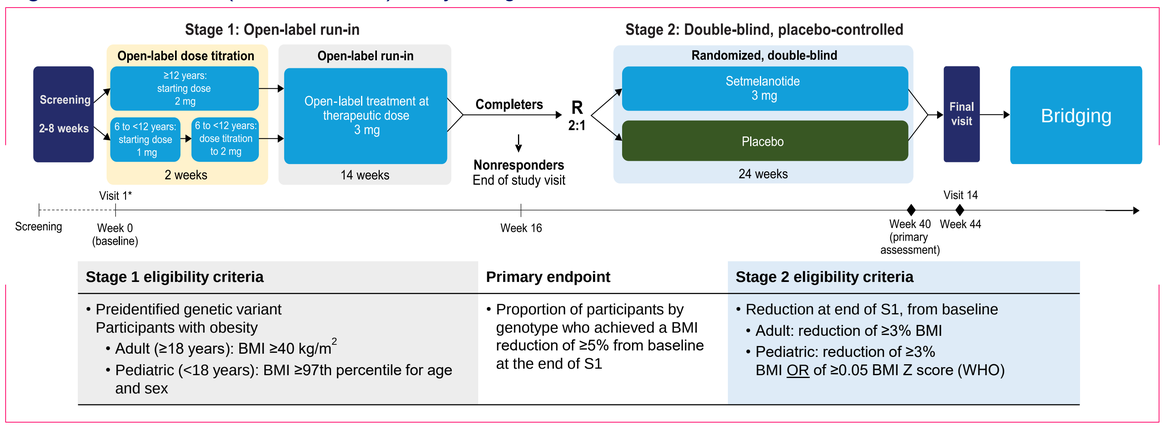
- Heterozygous deleterious *PHIP* variants are associated with obesity as well as intellectual disability, developmental delay, behavioral disorders (autism spectrum disorder and attention deficit hyperactivity disorder), often with dysmorphic features (eg, a high forehead and hypertelorism)[5-7]

Objective

- To determine the efficacy of setmelanotide in achieving weight loss and reduction in hunger in children and adults with *PHIP* variants and obesity in the DAYBREAK trial

Methods

Figure 2. DAYBREAK (NCT049463231) Study Design



Stage 1 eligibility criteria	Primary endpoint	Stage 2 eligibility criteria
• Preidentified genetic variant Participants with obesity • Adult (≥18 years): BMI ≥40 kg/m^2 • Pediatric (<18 years): BMI ≥97th percentile for age and sex	• Proportion of participants by genotype who achieved a BMI reduction of ≥5% from baseline at the end of S1	• Reduction at end of S1, from baseline • Adult: reduction of ≥3% BMI • Pediatric: reduction of ≥3% BMI OR of ≥0.05 BMI Z score (WHO)

*Virtual visit.
BMI, body mass index; R, randomization; S, stage; WHO, World Health Organization.

- Daily "most hunger" was assessed at Week 0, 6, 12, and 16 (Figure 2)
  - The daily hunger questionnaire for participants ≥12 years of age was a self-administered questionnaire in which 1 item was used (maximal hunger)
    - "In the last 24 hours, how hungry did you feel when you were the most hungry? (averaged on weekly basis)"; participants could respond from 0 to 10, where 0 = not hungry at all and 10 = hungriest possible
- Participants could reinitiate open-label setmelanotide if body mass index (BMI) increased by ≥5% from stage 2 entry (switch to setmelanotide within stage 2 or exit from stage 2 early and transition early to bridging)

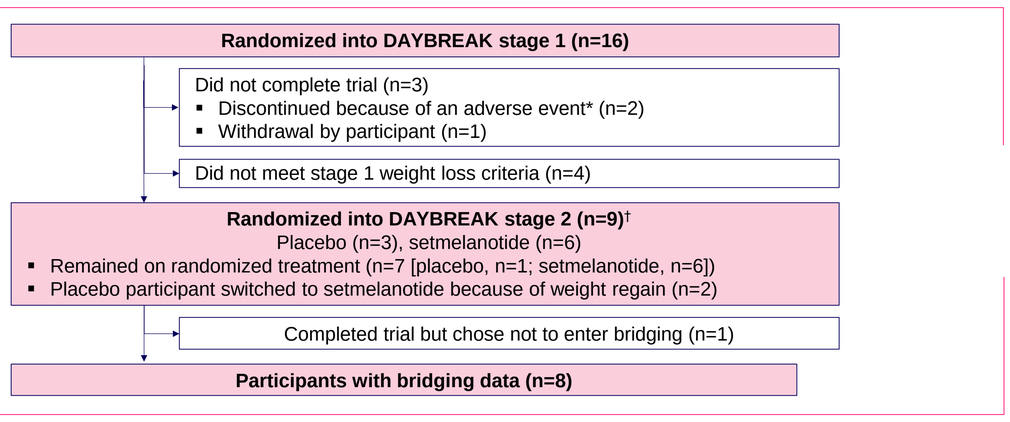
Outcomes

- Primary analyses were related to stage 1; stage 2 analyses, shown here, were exploratory or ad hoc

Participant Disposition and Baseline Characteristics

- Of 16 participants randomized into the DAYBREAK trial in stage 1, 9 continued into stage 2 and 8 had available bridging data (Figure 3; Table 1)

Figure 3. Participant Disposition



*Skin darkening and asthma attack. †Met end of stage 1 weight loss criteria (body mass index reduction of ≥5% from baseline).

Table 1. Demographics and Participant Characteristics

	Participants with *PHIP* variant
Enrolled participants, n	16
Age range, y	7-58
Age, mean (SD), y	26.6 (16.6)
6-17 y, n (%)	6 (37.5)
≥18 y, n (%)	10 (62.5)
Male, n (%)	8 (50.0)
Race, n (%)	
White	13 (81.3)
Other	1 (6.3)
Not reported or unknown	2 (12.5)
Ethnicity, n (%)	
Hispanic or Latino	4 (25.0)
Not Hispanic or Latino	12 (75.0)
BMI (≥18 y), mean (SD), kg/m^2	45.34 (7.01)
BMI Z score (age 6-17 y), mean (SD)	2.46 (0.45)
Waist circumference, mean (SD), cm	119.7 (25.4)

BMI, body mass index; SD, standard deviation.

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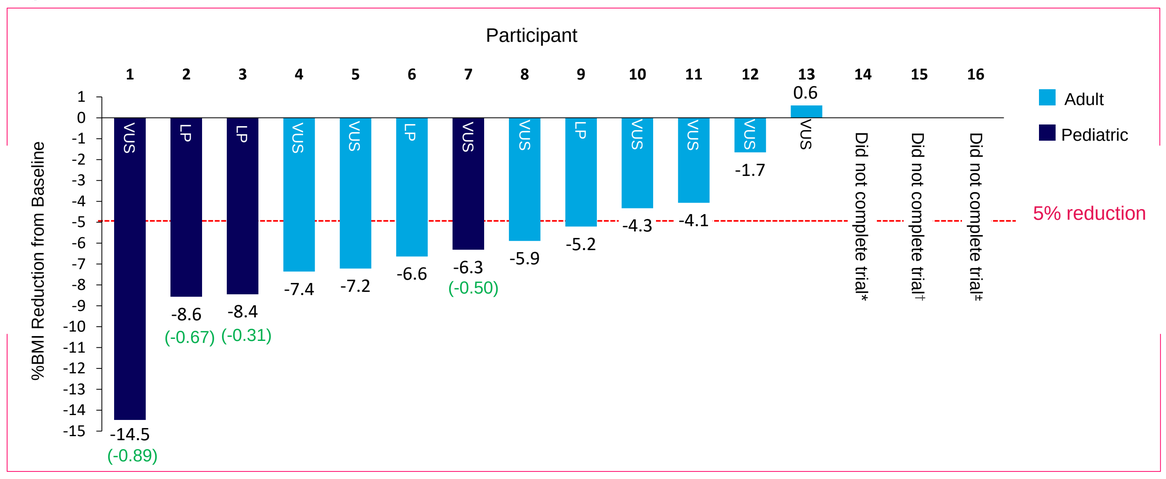
Reference: 1. Farooqi, O'Rahilly. *Nat Clin Pract Endocrinol Metab*. 2008;4:569-577. **2.** Kühnen et al. *Mol Med*. 2019;25:136-148. **3.** Sohn et al. *Cell*. 2013;152:612-619. **4.** Yazdi et al. *PeerJ*. 2015;3:e856. **5.** Craddock et al. *Cold Spring Harb Mol Case Stud*. 2019;5:a004200. **6.** Webster et al. *Cold Spring Harb Mol Case Stud.* 2:a001172. **7.** Jansen et al. *Eur J Hum Genet*. 26:54-63.

Results

Efficacy Outcomes

- 9 of 16 participants (56.3%) met age-related weight loss criteria of ≥5% BMI reduction from baseline (Figure 4)
- The mean (standard deviation [SD]) BMI percent change in the 13 participants who completed stage 1 of the trial was −6.12% (3.62%)

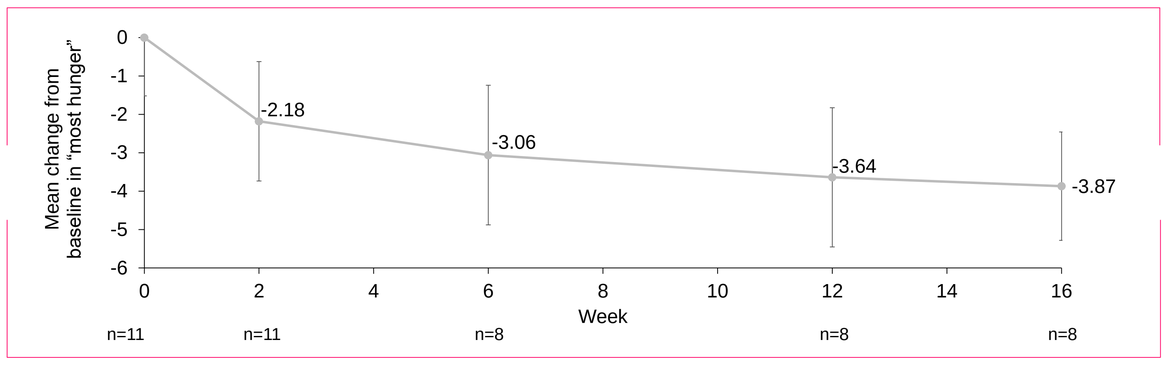
Figure 4. Stage 1 BMI Reduction at 16 Weeks



Corresponding BMI Z score (WHO) reductions in green. *Discontinued because of an adverse event (skin darkening). †Discontinued because of an adverse event (asthma attack). ‡Participant withdrew from trial. Pathogenicity within bar graphs (LP and VUS) according to ACMG criteria. ACMG, American College of Medical Genetics; BMI, body mass index; LP, likely pathogenic; VUS, variant of uncertain significance.

- Eight of 11 participants ≥12 years old with baseline "most hunger" data had Week-16 follow-up for daily "most hunger" scores and exhibited a mean (SD) score change of −3.87 (1.41; Figure 5)
  - 7 participants achieved a score reduction of ≥2

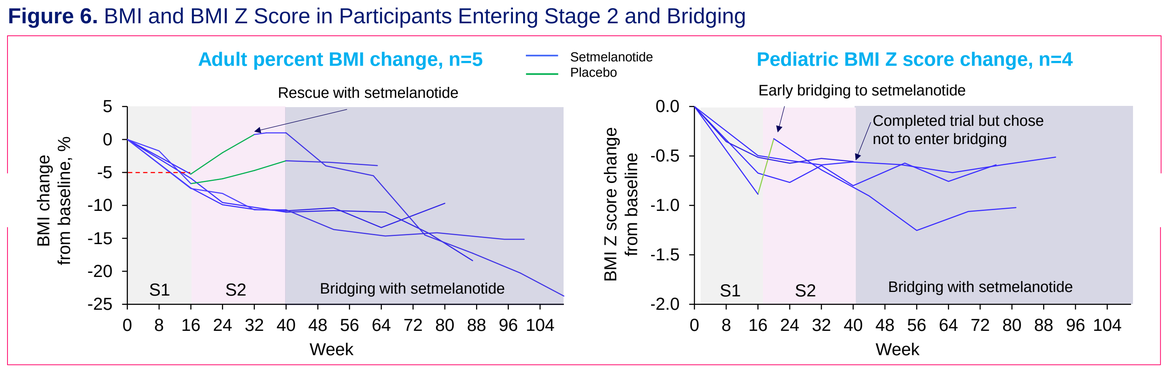
Figure 5. Reduction of "Most Hunger" Score From Baseline



Error bars are the standard deviation.

- Nine participants entered stage 2 (5 adult and 4 pediatric)
  - Participants receiving setmelanotide maintained consistent weight loss, whereas those receiving placebo did not (Figure 6)
  - One pediatric participant completed the trial but chose not to enter bridging
- For post stage 2 data, 8 participants continued on treatment, with a mean (SD) bridging duration of 48.7 (14.1) weeks
  - From baseline, 5 adult and 3 pediatric participants exhibited a final mean (SD) percent change in BMI of −14.18% (7.66%) and BMI Z score change of −0.71 (0.27), respectively, at the latest available measurement
    - In adults, the latest available data ranged from 64 to 110 weeks from baseline
    - In pediatric participants, the latest available data ranged from 76 to 91 weeks from baseline

Figure 6. BMI and BMI Z Score in Participants Entering Stage 2 and Bridging



BMI, body mass index; S, stage.

Safety

- In stage 1, the most commonly observed adverse events were skin hyperpigmentation (93.4%), injection induration (37.5%), and nausea (37.5%), and a similar safety profile was observed in stage 2 and during bridging (Table 2)

Table 2. Safety Summary

	Stage 1	Stage 2		Bridging
	SET (n=16)	SET (n=7)	PBO (n=2)	SET (n=8)
Any SAE, n (%)	1 (6.3)	0	0	1 (12.5)
Any TRSAE, n (%)	1 (6.3)	0	0	0
Any AE leading to study drug discontinuation, n (%)	2 (12.5)	0	0	0
Any AE leading to study discontinuation, n (%)	2 (12.5)	0	0	0
Any AE, n (%)	16 (100)	6 (85.7)	1 (50.0)	4 (50.0)
AE in ≥3 participants in stage 1				
Skin hyperpigmentation	15 (93.4)	1 (14.3)	0	1 (11.1)
Injection site induration	6 (37.5)	0	0	1 (11.1)
Nausea	6 (37.5)	1 (14.3)	0	0
Headache	5 (31.3)	2 (28.6)	0	0
Injection site pruritus	5 (31.3)	0	0	0
Melanocytic nevus	5 (31.3)	0	0	1 (11.1)
Nasopharyngitis	3 (18.8)	2 (28.6)	0	2 (22.2)
Injection site erythema	4 (25.0)	0	0	1 (11.1)
Injection site pain	4 (25.0)	0	0	0
COVID-19	3 (18.8)	1 (14.3)	0	1 (11.1)
Injection site bruising	3 (18.8)	0	0	0
Injection site discoloration	3 (18.8)	0	0	0
Any TRAE, n (%)	16 (100)	3 (42.9)	0	1 (12.5)
TRAE in ≥3 participants in stage 1				
Skin hyperpigmentation	14 (87.5)	1 (14.3)	0	1 (12.5)
Injection site induration	6 (37.5)	0	0	1 (12.5)
Nausea	6 (37.5)	0	0	0
Injection site pruritus	5 (31.3)	0	0	0
Melanocytic naevus	5 (31.3)	0	0	0
Injection site erythema	4 (25.0)	0	0	1 (12.5)
Headache	4 (25.0)	1 (14.3)	0	0
Injection site pain	4 (25.0)	0	0	0
Injection site bruising	3 (18.8)	0	0	0
Injection site discoloration	3 (18.8)	0	0	0

AE, adverse event; PBO, placebo; SAE, serious AE; SET, setmelanotide; TRAE, treatment-related AE; TRSAE, treatment-related serious AE.

Conclusions

- Individuals with *PHIP* variants receiving setmelanotide who continued into stage 2 of the DAYBREAK trial maintained consistent weight loss throughout the trial
- Where hunger could be assessed (in those ≥12 years old), a clinically relevant decrease in hunger scores was observed for participants receiving setmelanotide
- The observed clinical response to setmelanotide, a highly selective MC4R agonist, suggests the MC4R pathway is a key biologic driver of obesity in individuals with *PHIP* variants of interest and merits further investigation