DAYBREAK Trial: Setmelanotide Versus Placebo in Patients With Melanocortin-4 Receptor Pathway Variants

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Introduction

- The hypothalamic melanocortin-4 receptor (MC4R) pathway is a key regulator of energy balance and food intake[1-4]
- Impairment in MC4R pathway signaling resulting from rare variants in genes within this pathway can cause hyperphagia (a pathologic, insatiable hunger accompanied by abnormal food-seeking behaviors) and early-onset, severe obesity[4-7]
- The MC4R agonist setmelanotide is approved by the US Food and Drug Administration and European Medicines Agency for the treatment of certain MC4R pathway diseases (biallelic variants in *POMC*, *PCSK1*, or *LEPR*, and Bardet-Biedl syndrome)[8-12]
- DAYBREAK (NCT04963231) was a 2-stage Phase 2 study designed to evaluate the efficacy of setmelanotide in individuals carrying confirmed variants in ≥1 gene with strong or very strong relevance to the MC4R pathway

Objective

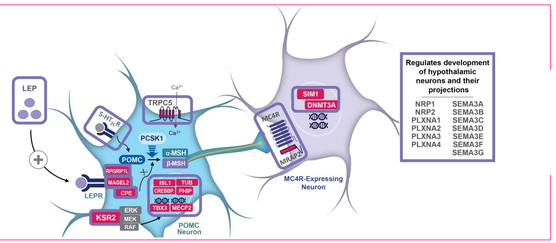
- The objective of the DAYBREAK trial was to determine the efficacy of setmelanotide in achieving weight loss in children and adults with obesity relating to variants in genes selected by Rhythm's ClinGen-based framework as having very strong relevance to the MC4R pathway[13] to identify which populations may have the best potential to benefit from setmelanotide therapy

Methods

Trial design

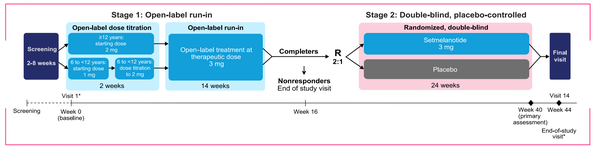
- DAYBREAK is a 2-stage, double-blind, placebo-controlled trial conducted at 37 sites across 8 countries
- Individuals aged 6 to 65 years with body mass index (BMI) ≥40 kg/m^2 (aged ≥18 years) or ≥97th percentile (aged ≥6 to <18 years) and hyperphagia who carried variants classified as uncertain significance, likely pathogenic, or pathogenic according to American College of Medical Genetics criteria in ≥1 of the 31 genes (Figure 1) were eligible

Figure 1. Genes studied in the DAYBREAK trial.



- Individuals meeting prespecified weight loss criteria from baseline at the end of the 16-week, open-label run-in period (Stage 1 [S1]) were eligible to enter a 24-week, double-blind, randomized, placebo-controlled period (Stage 2 [S2]) (Figure 2, Table 1)

Figure 2. DAYBREAK study design.



*Virtual visit. BMI, body mass index; R, randomization.

Table 1. DAYBREAK Primary Endpoint and Eligibility Criteria

Stage 1 eligibility criteria	Primary endpoint	Stage 2 eligibility criteria

• Genetic confirmation in patients 6-65 years
• Patients with obesity
  • Adult (≥18 years): BMI ≥40 kg/m^2
  • Pediatric (<18 years): BMI ≥97th percentile for age and sex
	• Proportion of patients 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

BMI, body mass index.

- Patients could reinitiate open-label setmelanotide if BMI increased by ≥5% from S2 entry (switch to setmelanotide within S2 or exit from S2 early and transition early to bridging)

Outcomes

- Primary analyses were related to S1; S2 analyses, shown here, were exploratory or ad hoc

Patient disposition and baseline characteristics

- In total, 164 individuals were enrolled; 100 completed
- At S1, participants were divided into 15 gene cohorts; of 7 cohorts with ≥5 patients, 6 (*MAGEL2*, *PLXNA* [*1-4*], *PHIP*, *SEMA3* [*A-G*], *SIM1*, and *TBX3*) showed potential setmelanotide efficacy (*KSR2* did not)
- After S1, 49 patients with *MAGEL2*, *PHIP*, *PLXNA* (*1-4*), *SEMA3* (*A-G*), *SIM1*, *RPGRIP1L*, or *TBX3* variants were randomized 2:1 to receive setmelanotide or placebo (Figure 3)
  - Thirty-nine patients completed S2; 3 patients in the placebo arm switched to setmelanotide in S2, and 6 (n=4 placebo; n=2 setmelanotide) exited S2 early for bridging
- S2 cohort demographics are shown in Table 2

Figure 3. S2 patient disposition (*MAGEL2*, *PHIP*, *PLXNA* [*1-4*], *SEMA3* [*A-G*], *RPGRIP1L*, *SIM1*, or *TBX3* variants).

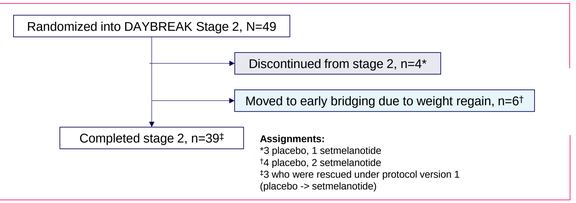


Table 2. Stage 2 Cohort Demographics (N=49)

	All	<18 y	≥18 y
Male, n (%)	22 (44.9)	10 (45.5)	12 (54.5)
Female, n (%)	27 (55.1)	14 (51.9)	13 (48.1)

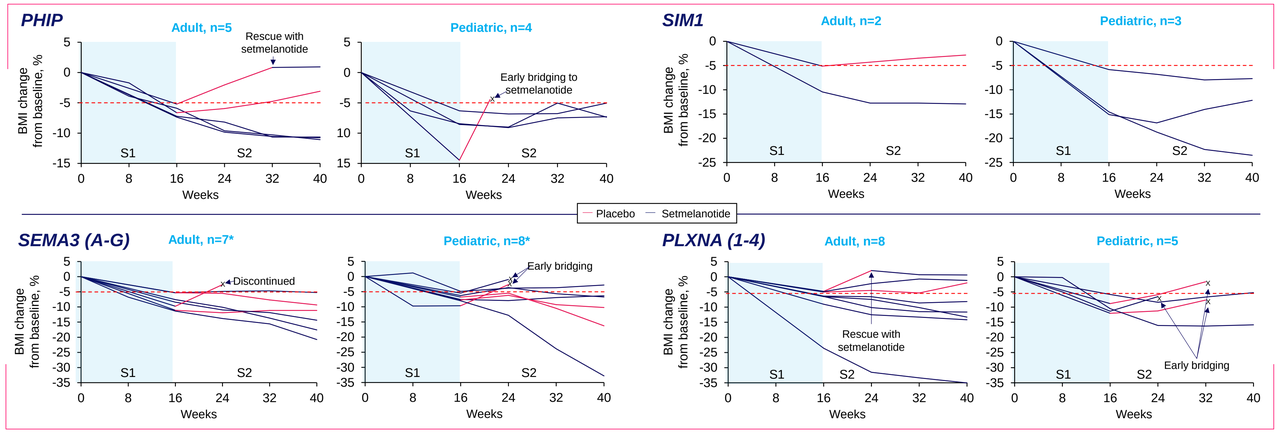
	Mean (SD)	Range	% of S1 starters (n/N)
BMI, kg/m^2			
Adult baseline (n=25)	46.1 (7.2)	40.4-69.9	23 (25/109)
Adult S2 start (n=25)	42.6 (7.0)	36.2-66.3	-
BMI Z score (CDC)			
Pediatric baseline (n=24)	2.5 (0.3)	1.83-2.97	44 (24/55)
Pediatric S2 start (n=24)	2.25 (0.4)	1.48-2.92	-

Results

Efficacy outcomes

- A higher proportion of patients in the setmelanotide arm achieved or maintained 5% BMI reduction from study baseline to the end of S2 (27/32 receiving setmelanotide [84.4%] vs 5/17 receiving placebo [29.4%]; *P*=0.001)
- Per-genotype analyses were limited by the small number of placebo-treated patients; from study baseline to the end of S2, mean (SD; range) percent BMI change was −12.4% (8.0%; 1.2%-35.0%) in the continuous setmelanotide arm
- Results of the gene cohort analyses were consistent with S1 trends, as shown in Figure 4; individuals with *PHIP* variants, which can lead to obesity by disrupting *POMC* transcription, maintained a consistent weight loss response, while the response in individuals with other gene variants was more variable
  - *PLXNA* (*1-4*), *SEMA3* (*A-D*, *F*, *G*), and *SIM1* had a more variable degree of weight loss, some of substantially greater magnitude than *PHIP* (eg, *PLXNA4*)
  - *SEMA3E* had excellent response, but was limited by the sample size (n=3)
- Results from patients with variants in *MAGEL2* (n=1 adult; n=2 children) and *RPGRIP1L* (n=1 adult) were consistent, with patients randomized to setmelanotide continuing or maintaining weight loss in S2; the patient with a *TBX3* variant (n=1 child) was assigned to placebo, regained weight, received rescue setmelanotide open-label therapy, and resumed losing weight

Figure 4. Individual weight response of patients entering S2 by cohorts of interest.



*One adult and 1 pediatric patient with a *SEMA3G* variant dropped out of stage 2 before having any data and are not shown.

Safety

- Setmelanotide was well tolerated with no new safety concerns across the entire study
- The most common adverse events (incidence >20%) were skin hyperpigmentation, injection site reactions, nausea, melanocytic nevus, headache, and vomiting

Conclusions

- Clinical response to setmelanotide treatment, a highly selective MC4R agonist, suggests that the MC4R pathway may be a key biologic driver of obesity in patients with variants of interest
- The design of the exploratory DAYBREAK trial, which utilized an open-label run-in period to identify patients with impaired MC4R signaling (S1) followed by confirmation of response in the randomized withdrawal period (S2), successfully identified multiple genes of interest that merit further investigation
  - The percent change in BMI from baseline to the end of S2 varied between gene cohorts
- Further studies may elucidate whether the genetic variants of interest explored in DAYBREAK contribute to a loss of function in the MC4R pathway or can identify other patient-specific factors that can modulate response to setmelanotide treatment

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