DAYBREAK Trial: Setmelanotide vs placebo in patients with melanocortin-4 receptor pathway variants

Gloria Ortiz, MD[1]; Svetlana Ten, MD[2]; Whitney Herring, MD[3]; Orit Pinhas-Hamiel, MD[4]; Elif A. Oral, MD[5]; Nina Rosano, MD[6]; Dorit Koren, MD, MTR[7]; Hak-myung Lee, PhD[7]; Jill C. Garrison, PhD[7]; Olga Ohayon, RN BA, MSc[7]; Patrick Sleiman, PhD[7]; Martin Wabitsch, MD, PhD[8]; Erica van den Akker, MD[9]; Jesús Argente, MD, PhD[10–12]; I. Sadaf Farooqi, PhD[13] on behalf of the DAYBREAK Trial Investigators

[1]Rio Grande Valley Endocrine Center, McAllen, TX; [2]Ten's Medical Center – Pediatric Endocrinology Clinic, Brooklyn, NY; [3]Mississippi Center for Advanced Medicine, Madison, MS; [4]Tel Aviv University, Tel Aviv, Israel; Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [5]University of Michigan, Ann Arbor, MI; [6]UMass Chan Medical School, Worcester, MA; [7]Rhythm Pharmaceuticals, Inc., Boston, MA; [8]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, Universitätsklinikum Ulm, Ulm, Germany; [9]Erasmus University Medical Center, Rotterdam, The Netherlands; [10]Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [11]CIBER fisiopatología de la obesidad y nutrición, Instituto de Salud Carlos III, Madrid, Spain; [12]Universidad Autónoma de Madrid, Madrid, Spain; [13]Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK

ECO 2025 - Conflict Of Interest

Name: Erica van den Akker

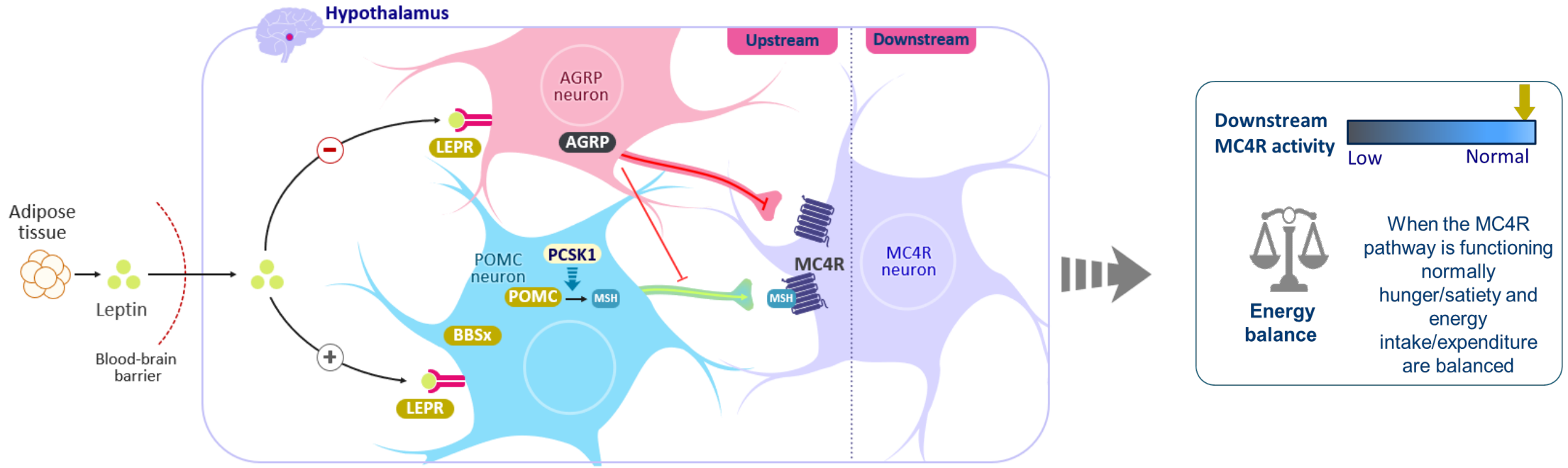
☐ I have the following potential conflicts of interest to report:

- **X Research Contracts**
- **X Consulting**
- **☐ Employment in the Industry**
- **☐ Stockholder of a healthcare company**
- **☐ Owner of a healthcare company**
- **☐ Other(s)**

☐ I declare that I have no potential conflict of interest.

The central hypothalamus is a key regulator of energy balance, appetite, and bodyweight

- The hypothalamic melanocortin-4 receptor (MC4R) pathway is a key regulator of energy balance and food intake[1,2]

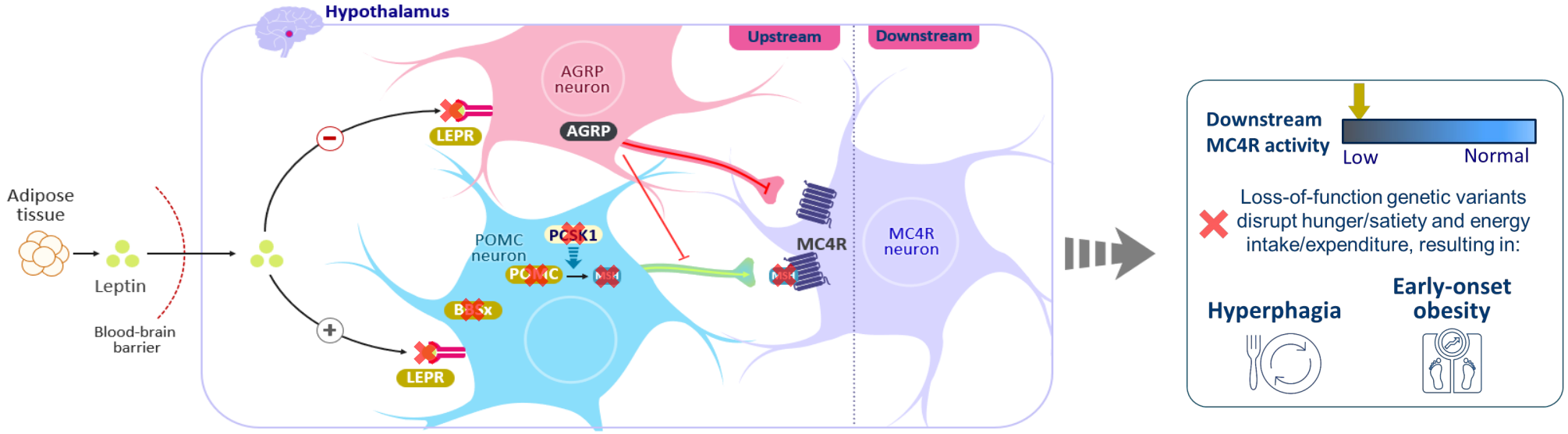


AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Farooqi IS. *Biol Psychiatry*. 2022;91:856–59; **2.** Yeo GSH, et al. *Mol. Metab*. 2021;48:101206.

Impaired MC4R signalling due to rare genetic variants may result in hyperphagia and obesity from the first years of life[1–4]

- The MC4R agonist setmelanotide is approved by the FDA and EMA for the treatment of certain MC4R pathway diseases, controlling hyperphagia* and treating obesity[5,6]
- DAYBREAK (NCT04963231) was a two-stage Phase 2 study designed to evaluate the efficacy of setmelanotide in individuals carrying confirmed variants in ≥1 of 31 genes with strong or very strong relevance to the MC4R pathway[7]



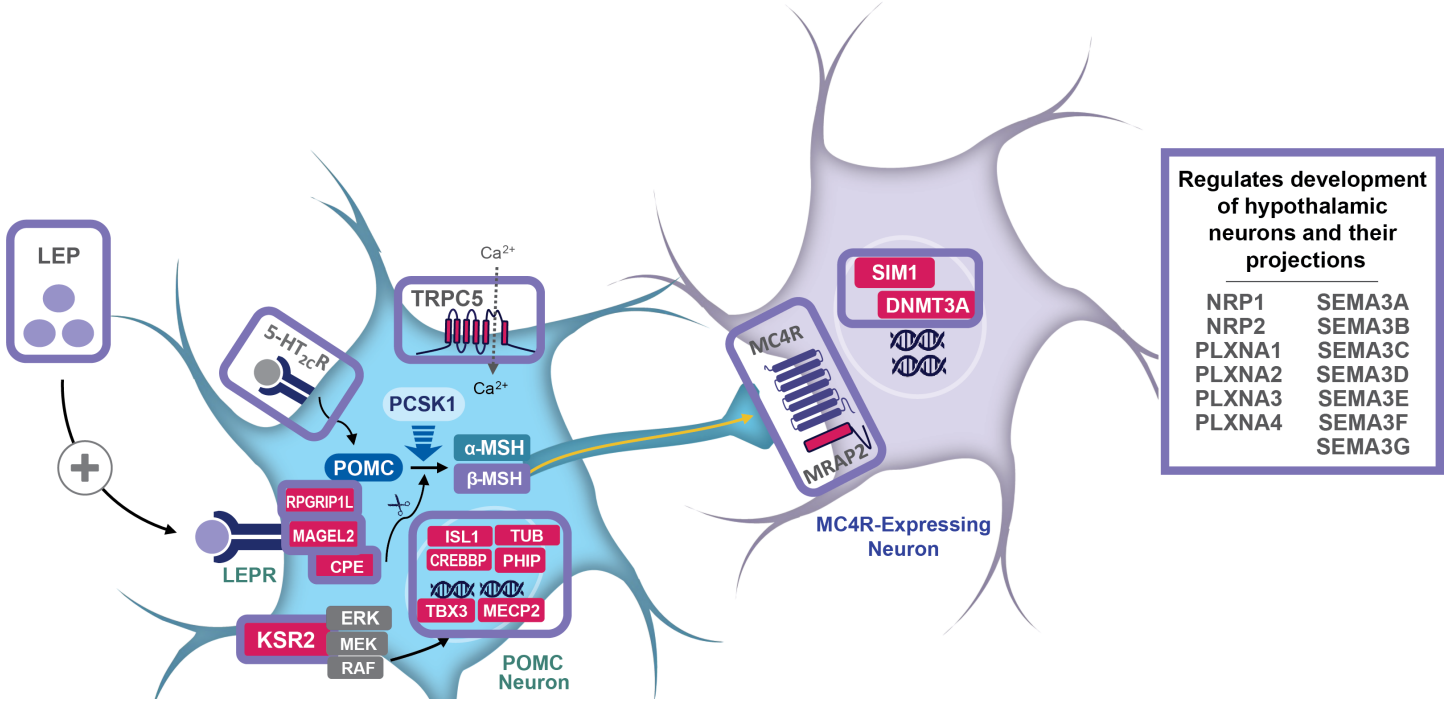
*Absence of satiety and pathologic, insatiable hunger accompanied by abnormal food-seeking behaviors.

AgRP, agouti-related peptide; EMA, European Medicines Agency; FDA, Food and Drug Administration; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Farooqi IS. *Biol Psychiatry.* 2022;91:856–59; **2.** Haqq AM, et al, La*n Diabetes Endocrinol.* 2022;10:859–868; **3.** Forsythe E, et al. *Front Pediatr.* 2018;6:23; **4.** Pomeroy J, et al. *Pediatr Obes.* 2021;16:e12703; **5.** European Medicines Agency. Available at: https://www.ema.europa.eu/en/documents/product-information/imcivree-epar-product-information_en.pdf. **6.** US Food and Drug Administration. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213793s001lbl.pdf. **7.** Vogel et al. Presented at: European Society for Paediatric Endocrinology; September 22–26, 2021; Virtual.

Objectives of this study

- To determine the efficacy of setmelanotide in achieving weight loss in children and adults with obesity related to gene variants selected by Rhythm's ClinGen-based framework based on their strong association with the MC4R pathway[1]
- To identify which populations may have the best potential to benefit from setmelanotide therapy



1. Vogel et al. Presented at: European Society for Paediatric Endocrinology; September 22–26, 2021; Virtual.

Inclusion criteria and primary endpoint

Stage 1 eligibility criteria

- Genetic confirmation in patients 6–65 years
- Patients with obesity
  - Adults (≥18 years): BMI ≥40 kg/m^2
  - Paediatric (<18 years): BMI ≥97th percentile for age and sex

Primary endpoint

- Proportion of patients by genotype who achieved a BMI reduction of ≥5% from baseline at the end of Stage 1

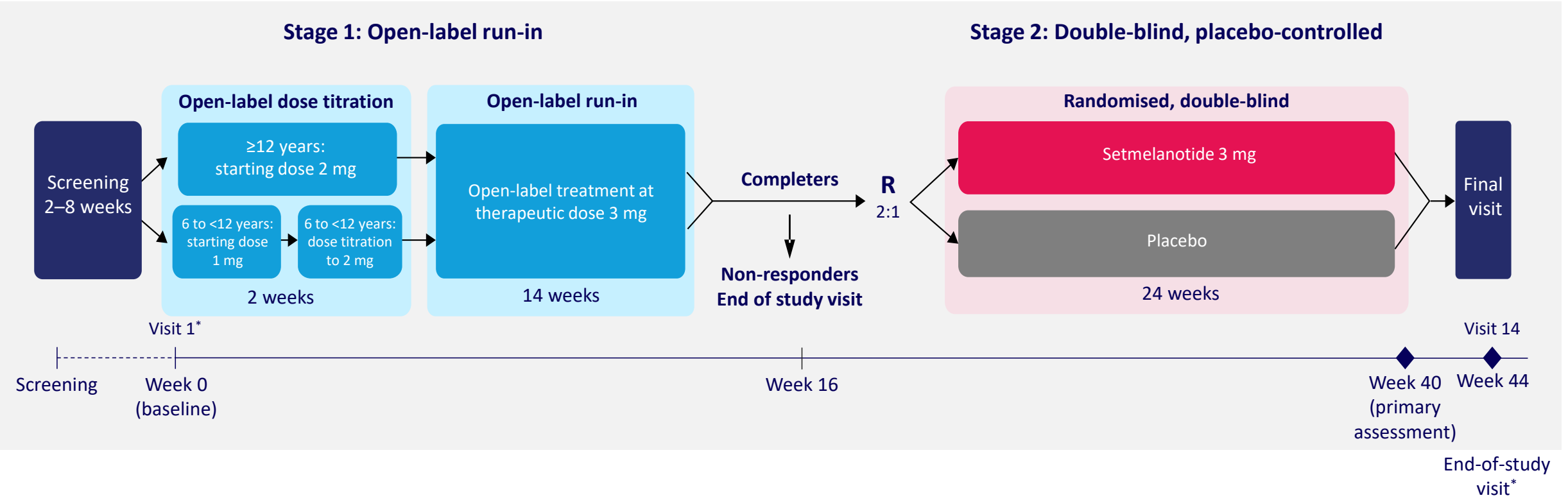
Stage 2 eligibility criteria

- Reduction at end of Stage 1, from baseline
  - Adult: reduction of ≥3% BMI
  - Paediatric: reduction of ≥3% BMI OR ≥0.05 BMI z-score

BMI, body mass index.

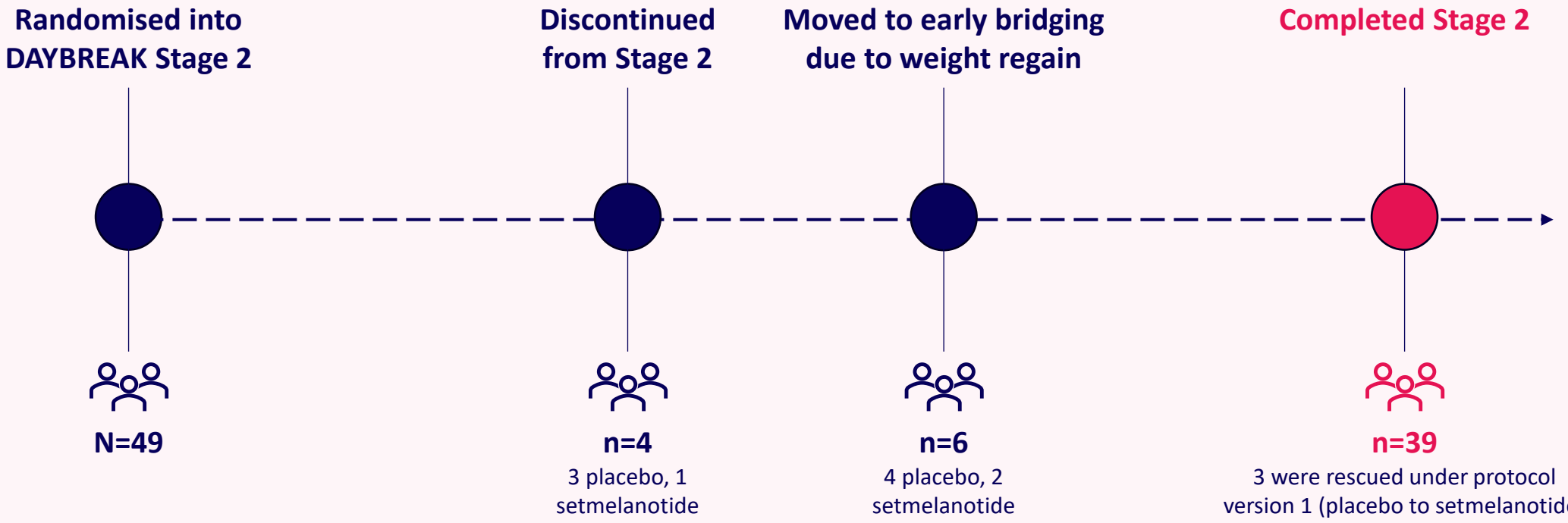
Study design

- Efficacy outcome assessed at end of Stage 2 was change from baseline in BMI (kg/m^2)



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

Patient disposition



Patient and demographics

- After Stage 1, 49 patients with *PHIP*, *PLXNA(1-4)*, *SEMA3(A-G)*, *SIM1*, *MAGEL2*, *TBX3*, or *RPGRIP1L* variants were randomised 2:1 to receive setmelanotide or placebo

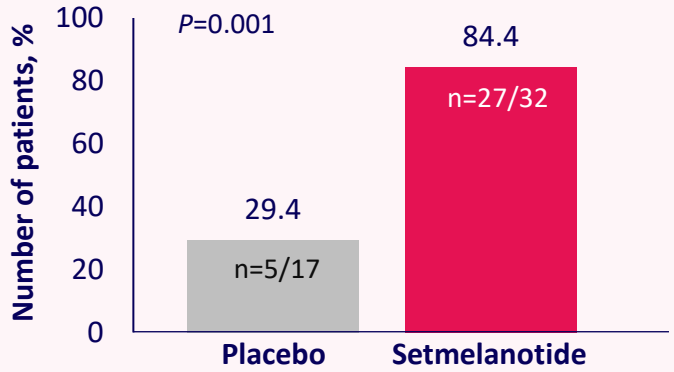
Stage 2 cohort demographics

	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 Stage 1 starters (n/N)**
BMI, kg/m^2			
Adult baseline (n=25)	46.1 (7.2)	40.4–69.9	23 (25/109)
Adult Stage 2 start (n=25)	42.6 (7.0)	36.2–66.3	-
BMI z-score (CDC)			
Paediatric baseline (n=24)	2.5 (0.3)	1.83–2.97	44 (24/55)
Paediatric Stage 2 start (n=24)	2.25 (0.4)	1.48–2.92	-

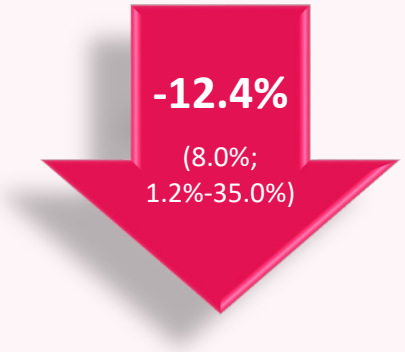
BMI, body mass index; CDC, Centers for Disease Control and Prevention; MAGEL2, melanoma-associated antigen gene L2; PHIP, pleckstrin homology domain interacting protein; PLXNA1-4, plexin A1-4; RPGRIP1L, retinitis pigmentosa GTPase regulator-interacting protein-1 like; SD, standard deviation; SEMA3A-G, semaphorin 3A-G; SIM1, single-minded homolog 1; TBX3, T-box transcription factor.

Results

A higher proportion of patients in the setmelanotide arm achieved or maintained 5% BMI reduction from study baseline to the end of Stage 2



Mean (SD; range) percent BMI change in the continuous setmelanotide arm from baseline to the end of Stage 2

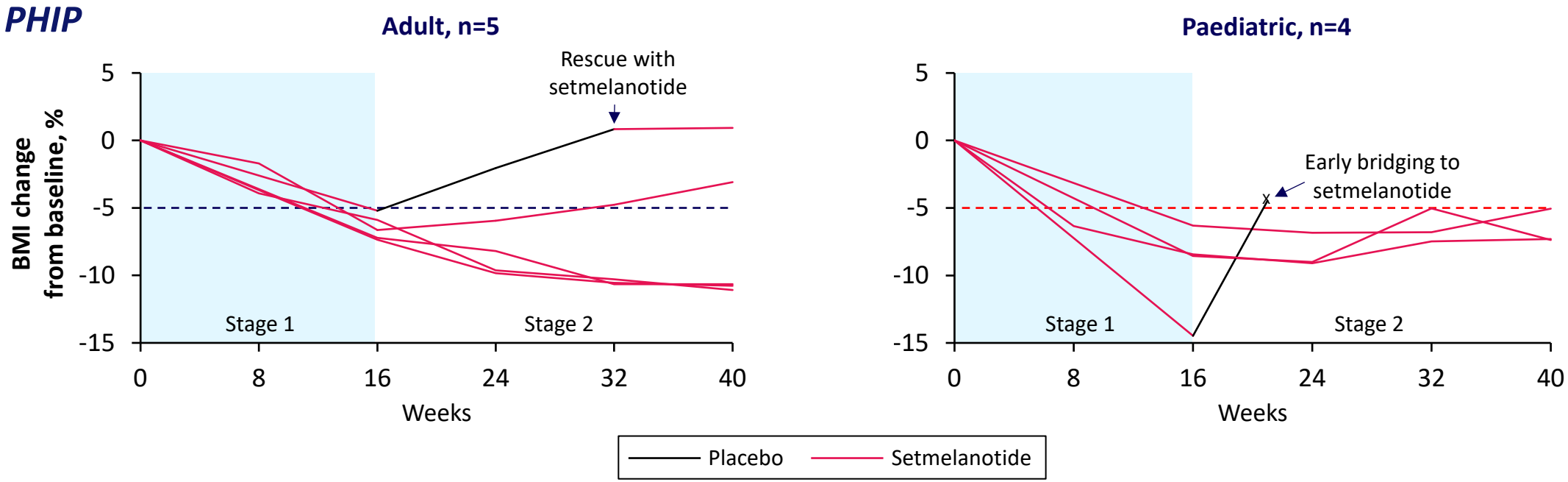


- Results from patients with variants in MAGEL2 (n=1 adult; n=2 children) and RPGRIP1L (n=1 adult) were consistent: patients randomised to setmelanotide **continued or maintained weight loss** in Stage 2
- The patient with a TBX3 variant (n=1 child) was assigned to placebo, regained weight, received rescue setmelanotide open-label therapy, and **resumed losing weight**

BMI, body mass index; MAGEL2, melanoma-associated antigen gene L2; RPGRIP1L, retinitis pigmentosa GTPase regulator-interacting protein-1 like; SD, standard deviation; TBX3, T-box transcription factor.

Results in patients with *PHIP* variants

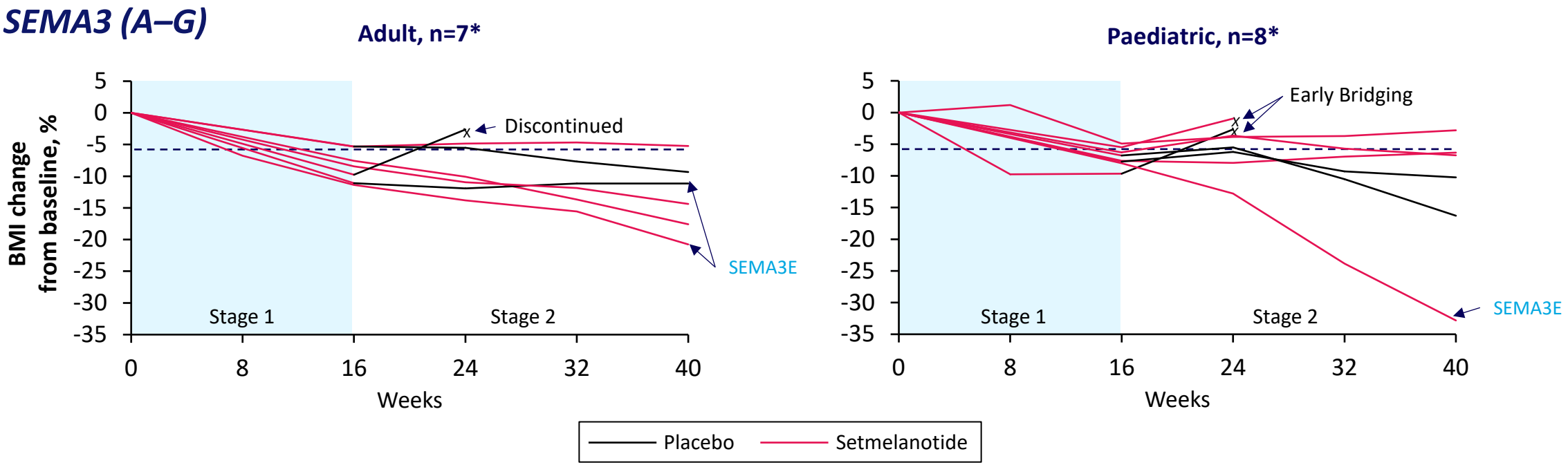
- Individuals with *PHIP* variants, which can lead to obesity by disrupting *POMC* transcription, maintained a consistent weight loss response



BMI, body mass index; PHIP, pleckstrin homology domain interacting protein; POMC, proopiomelanocortin.

Results in patients with *SEMA3E* variants

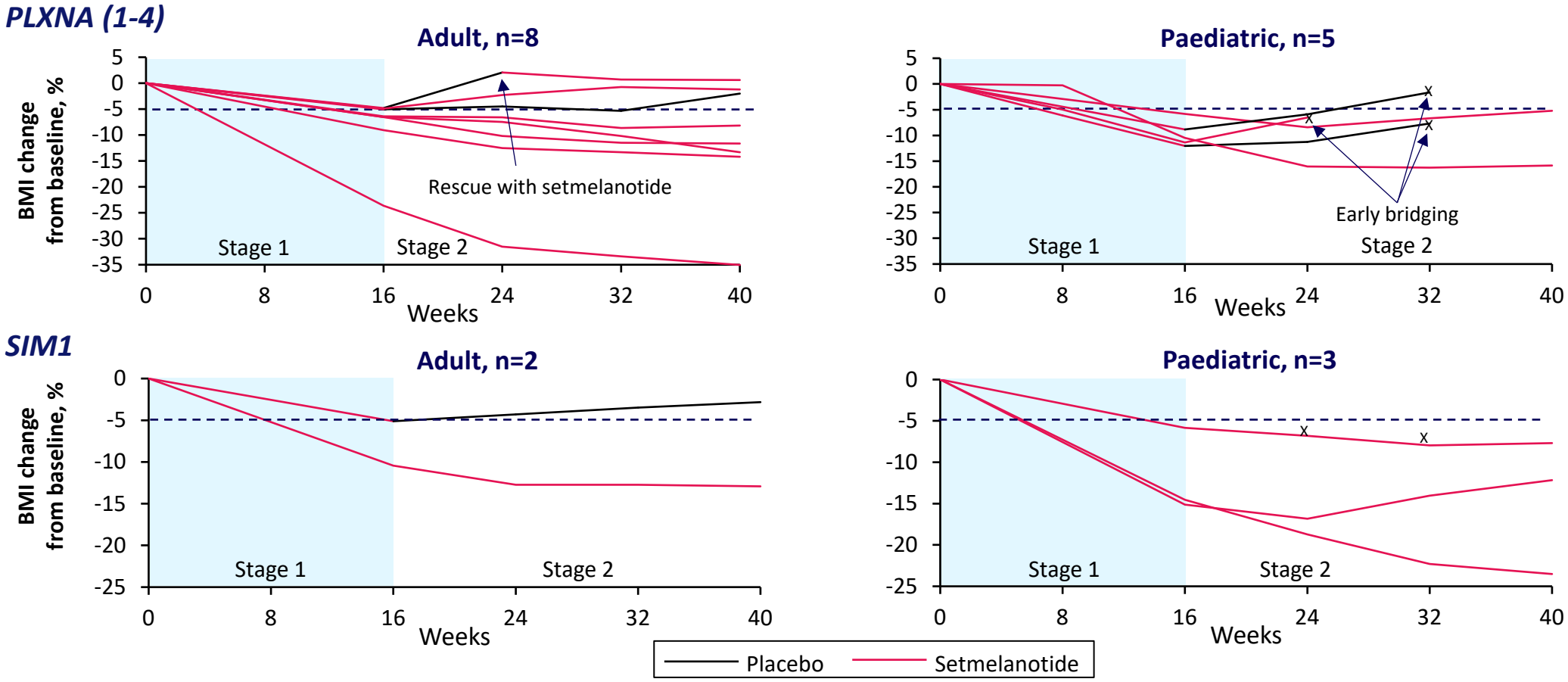
- SEMA3E had excellent response, but was limited by the sample size (n=3)
- SEMA3 (A D, F, G) had a more variable degree of weight loss



*One adult and 1 paediatric patient with a *SEMA3G* variant dropped out of Stage 2 before having any data and are not shown.
BMI, body mass index; SEMA3A–G, semaphorin 3A–G.

Results in patients with *PLXNA* and *SIM1* variants

- PLXNA (1-4) and SIM1 had a more variable degree of weight loss, some of substantially greater magnitude than PHIP



BMI, body mass index; PHIP, pleckstrin homology domain interacting protein; PLXNA1-4, plexin A1-4; SIM1, single-minded homolog 1.

Safety

- Setmelanotide was well tolerated with no new safety concerns across the entire study

Most common adverse events (incidence >20%)

- Skin hyperpigmentation
- Injection site reactions
- Nausea
- Melanocytic naevus
- Headache
- Vomiting

Conclusion

- 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 enabled the **identification of multiple genes of interest** that merit further investigation, by utilising
  - Stage 1 open-label run-in period to identify patients with impaired MC4R signalling
  - Stage 2 confirmation of response in the randomised withdrawal period
- The **percent change in BMI** from baseline to the end of Stage 2 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**

BMI, body mass index; MC4R, melanocortin-4 receptor.