Stage 1 Results of the Phase 2 DAYBREAK Trial Assessing Setmelanotide in Patients With Early-Onset, Severe Obesity and Hyperphagia Who Carried a Variant Related to the Melanocortin-4 Receptor Pathway

MON-788

Gloria Ortiz, MD[1]; Svetlana Ten, MD[2]; Maria Contreras, MD[3]; Whitney Herring, MD[4]; Orit Pinhas-Hamiel, MD[5,6]; Elif A. Oral, MD[7]; Nina Rosano, MD[8]; Dorit Koren, MD, MTR[9]; Hak-myung Lee, PhD[8]; Jill C. Garrison, PhD[8]; Olga Ohayon, RN, MSc, BA[8]; Patrick Sleiman, PhD[8]; Martin Wabitsch, MD, PhD[10]; Erica van den Akker, MD[11]; Jesús Argente, MD, PhD[12-14]; I. Sadaf Farooqi, PhD[15]; 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]Texas Tech Physicians of Amarillo, Amarillo, TX; [4]Mississippi Center for Advanced Medicine, Madison, MS; [5]Tel Aviv University, Tel Aviv, Israel; [6]Pediatric Endocrine and Diabetes Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [7]University of Michigan, Ann Arbor, MI; [8]UMass Chan Medical School, Worcester, MA; [9]Rhythm Pharmaceuticals, Inc., Boston, MA; [10]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, Universitätsklinikum Ulm, Ulm, Germany; [11]Erasmus University Medical Center, Rotterdam, The Netherlands; [12]Hospital Infantil Universitario Niño Jesús, Madrid, Spain; [13]CIBER fisiopatología de la obesidad y nutrición. Instituto de Salud Carlos III, Madrid, Spain; [14]Universidad Autónoma de Madrid, Madrid, Spain; [15]Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre, University of Cambridge, Cambridge, UK

Presenting Author:
Elif Oral, MD
eliforal@med.umich.edu

Summary

- **The DAYBREAK study investigated response to setmelanotide melanocortin-4 receptor (MC4R) agonist therapy in patients with genetic variants in the MC4R pathway linked to obesity and hyperphagia**
  - **Stage 1 found that 6 genes or gene families responded to setmelanotide MC4R agonist therapy, with the most consistent responses seen in individuals with variants in *PHIP* and *SEMA3* genes**

Introduction

- The hypothalamic 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 has been shown to reduce weight and hunger in patients with certain MC4R pathway diseases caused by variants in genes central to this pathway, namely proopiomelanocortin and leptin receptor deficiency, and Bardet-Biedl syndrome[8-10]
- DAYBREAK (NCT04963231) was a 2-stage Phase 2 study designed to evaluate the efficacy of setmelanotide in individuals carrying a variant 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 for achieving weight loss in children and adults with obesity related to variants in genes identified by Rhythm's ClinGen-based framework[11] as having strong or very strong relevance to the MC4R pathway, in order to identify which populations may be most likely to benefit from setmelanotide therapy

Methods

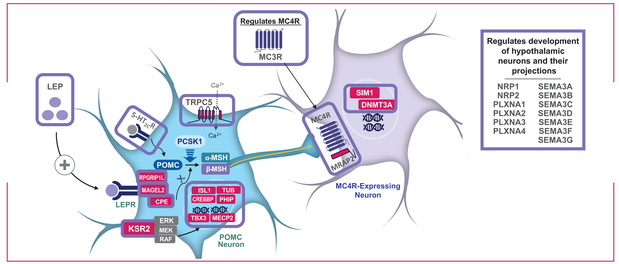
Trial design

- 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 variants of uncertain significance (VUS), likely pathogenic, or pathogenic according to the American College of Medical Genetics (ACMG) criteria in ≥1 of the 31 genes (Figure 1, Table) were eligible
- Individuals with ≥5% BMI reduction from baseline (ie, responders) at the end of the 16-week, open-label, run-in period (Stage 1) were eligible to enter a 24-week, double-blind, randomized, placebo-controlled period (Stage 2)

Outcomes

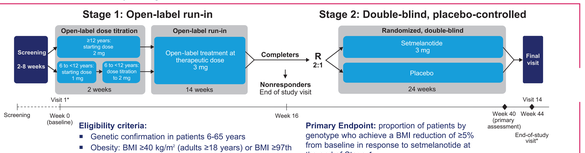
- The primary endpoint of Stage 1 was the proportion of responders per gene cohort at the end of the Stage (Figure 2)

Figure 1. Genes under study in the DAYBREAK Trial.[12]



α-MSH, alpha–melanocyte stimulating hormone; β-MSH, beta–melanocyte stimulating hormone; 5-HT$_{2C}$R, serotonin 2C receptor; CPE, carboxypeptidase E; CREBBP, CREB binding protein; DNMT3A, DNA methyltransferase 3 alpha; ERK, extracellular signal-regulated kinase; ISL1, insulin gene enhancer protein; KSR2, kinase suppressor of ras 2; LEP, leptin; LEPR, leptin receptor; MAGEL2, melanoma antigen gene family member L2; MC3R, melanocortin-3 receptor; MC4R, melanocortin-4 receptor; MECP2, methyl-CpG binding protein 2; MEK, mitogen-activated protein kinase; MRAP2, melanocortin receptor accessory protein 2; MSH, melanocyte-stimulating hormone; NRP, neuropilin; PCSK1, proprotein convertase subtilisin/kexin type 1; PHIP, pleckstrin homology domain interacting protein; PLXNA, plexin A; POMC, proopiomelanocortin; RAF, rapidly accelerated fibrosarcoma; RPGRIP1L, RPGRIP 1 like; SEMA, semaphorin; SIM1, single-minded homolog 1; TBX3, T-Box transcription factor 3; TRPC5, transient receptor potential cation channel subfamily C member 5; TUB, TUB bipartite transcription factor.

Figure 2. DAYBREAK study design.



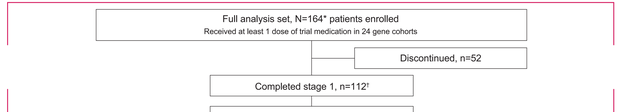
*Virtual visit. BMI, body mass index; R, randomization.

Table. Baseline Demographics

Parameter	Total (N=164)
Age, mean (SD)	30.2 (16.9)
Male, n (%)	54 (32.9)
Female, n (%)	110 (67.1)
BMI at baseline, mean (SD; range; n), kg/m^2 (age ≥18 years)	48.5 (8.1; 40-74.4; 109)
BMI Z score at baseline, mean (SD; n) (age <18 years)	2.6 (0.4; 55)

BMI, body mass index; SD, standard deviation.

Figure 3. Patient disposition.



*165 patients consented and enrolled and 1 discontinued before 1 dose. †Includes 12 discontinued patients who withdrew prior to week 16 but had their end-of-study visit within 2 weeks of week 16; their data are included in completer analysis.

Results

Patient disposition and baseline characteristics

- 164 individuals were enrolled (Figure 3); 100 patients who completed Stage 1 and 12 patients who discontinued treatment within a prespecified 2 weeks before the end of Stage 1 were included in the completer analysis (Figure 3)
- Patients were divided into 15 gene cohorts. Of 7 cohorts with ≥5 patients, 6 (*SEMA3[A-G], PLXNA[1-4], PHIP, TBX3, MAGEL2*, and *SIM1*) showed potential setmelanotide efficacy (*KSR2* did not) and are discussed further below

Efficacy outcomes

- Response rate was highest in the *PHIP* cohort (56.3% of the full cohort and 69.2% of completers; Figures 4 and 5)
  - ≥1 patient per cohort achieved ≥10% BMI reduction (Figure 6)

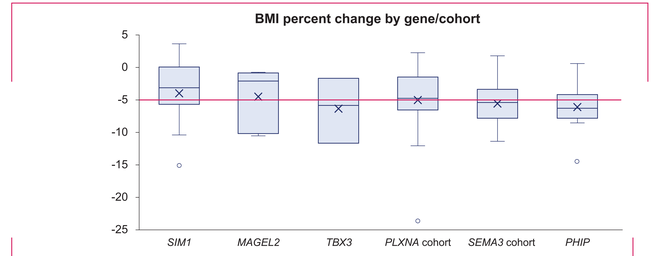
Figure 4. Proportion of responders per cohort.

PLXNA	*SEMA3*	*PHIP*	*TBX3*	*MAGEL2*	*SIM1*
30% (12 of 40)	35.6% (16 of 45)	56.3% (9 of 16)	40% (2 of 5)	30% (3 of 10)	25% (5 of 20)

Patients with **≥5% reduction in BMI** at 16 weeks

BMI, body mass index.

Figure 5. BMI percent change by cohort (completer analysis).



Number, average and median BMI % change per gene/cohort	*SIM1*: (n=16) Mean: −4.02 Median: −3.14	*MAGEL2*: (n=7) Mean: −4.60 Median: −2.06	*TBX3*: (n=3) Mean: −6.41 Median: −5.86	*PLXNA1-4*: (n=27) Mean: −5.09 Median: −4.84	*SEMA3A-G*: (n=26) Mean: −5.60 Median: −5.40	*PHIP*: (n=13) Mean: −6.12 Median: −6.32

BMI, body mass index.

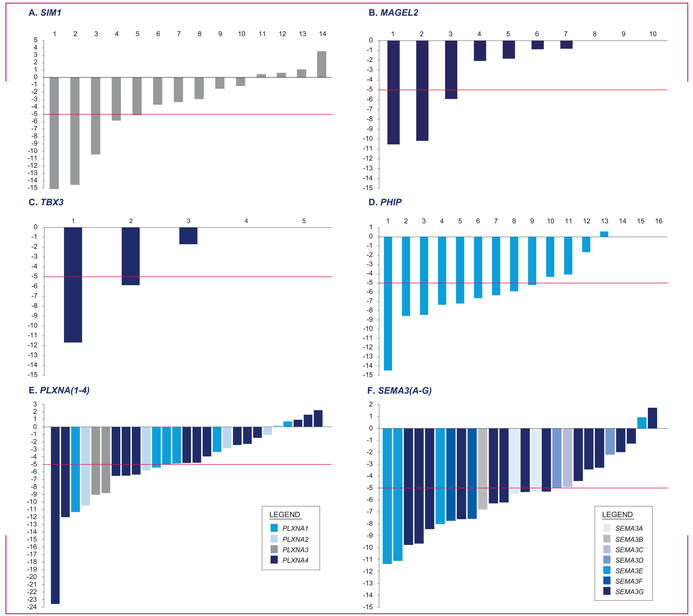
Ad hoc genetic analysis

- As ~80% of VUS are reclassified to benign or likely benign, VUS inclusion may have contributed to response variability
- An ad hoc analysis showed an increased response rate with updated versus starting ACMG variant classification
  - For example, in the *SEMA3G* cohort, 5 variants were reclassified from VUS or likely pathogenic to likely benign. Excluding these variants from the analysis of those who completed Stage 1 would result in a shift in response rate from 8/14 or 57% to 7/9 or 78%

Safety

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

Figure 6. Individual percent BMI change from baseline to 16 weeks within cohorts.



BMI, body mass index.

- Overall, 49 responders across 6 gene cohorts were randomized into Stage 2

Conclusions

- DAYBREAK Stage 1 identified 6 additional genes or gene families within the MC4R pathway that respond to setmelanotide MC4R agonist therapy
- There was variable response within cohorts, with at least 1 individual displaying >10% BMI reduction within each of these 6 cohorts
  - Within-group differences in response may be partially reflective of genetic burden as well as nongenetic factors
- An ad hoc analysis showed an increased response rate with updated versus initial ACMG variant classification
- Response was associated with predicted variant pathogenicity, allowing for further refinement of patient selection
- Stage 2 of the trial will enable further elucidation of Stage 1 results by demonstrating the response to randomized withdrawal of therapy

Acknowledgments: The authors thank the DAYBREAK Trial Investigators: Heidi Shea (Endocrine Associates of Dallas and Plano), Vidhu Thaker (Irving Medical Center, Columbia University), Andrea Acosta (Mayo Clinic), Christopher Still (Geisinger Clinic), James Swain (Honor Health Research Institute), Marta Ramón (Hospital Sant Joan de Deu), Bessie Spilliotis and Neoklis Georgopoulos (University of Patras School of Medicine), Opada Alzohaili (Metro Detroit Endocrinology Center), Stephanie Sisley (Texas Children's Hospital; Baylor College of Medicine), Andrea Hagq (University of Alberta), Antje Koerner (Universitaetsklinikum Leipzig), Joan Han (Icahn School of Medicine at Mount Sinai; Mount Sinai Kravis Children's Hospital), Paul Piper (Javara Research), Shana McCormack (Children's Hospital of Philadelphia), Klara Klein (University of North Carolina), William White (The London Diabetes Centre), Michal Ben-Ami (Sheba Medical Center), Janine Makaronidis (University College London Hospitals NHS Foundation Trust), Dror Dicker (Hasharon Hospital), Leonardo Soriano (Hospital Fundación Jimenez Díaz), Anthony Goldstone (Imperial College Healthcare Trust), Wendy Chung (Columbia University Medical Center), Aramis Cosme (Accurate Clinical Research), Cecilia Scimia (Rhythm Pharmaceuticals, Inc.), Bhavik Shah (Rhythm Pharmaceuticals, Inc.), and Murray Stewart (Rhythm Pharmaceuticals, Inc.).

This study was sponsored by Rhythm Pharmaceuticals, Inc. Writing and editorial support for this poster was provided under the direction of the authors by MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

Disclosures: GO, **ST**, **WH**, **EAO**, **NR**, **MW**, **EvdA**, and **JA** and/or their institutions have received study funding and/or compensation for speaking engagements, writing, consulting, advisory board participation, and/or educational events from Rhythm Pharmaceuticals, Inc. **WH** and **WH's** institution have received study funding or compensation for advisory board participation from Novo Nordisk. **OP-H** and **ISF** declare no competing interests. **EAO** has received study funding, royalties, consulting fees, and/or lecture fees from Alcea Therapeutics, Ionis Pharmaceuticals, Morphic Medical, Fractyl, Regeneron Pharmaceuticals, Amryt Pharmaceuticals (now Chiesi), Third Rock Ventures, Rejuvenate Bio, and NIDDK, and has patents for use of metreleptin in lipodystrophy and recombinant leptin or analogues in NASH. **NR** has received consulting fees from Novo Nordisk. **DK**, **HL**, **JCG**, **OO**, and **PS** are employees and may own stock in Rhythm Pharmaceuticals, Inc. **EvdA** and **EvdA's** institution have received research funding and/or compensation for speaking engagements, writing, and/or educational events from Federatie Medisch Specialisten, Stichting Kwaliteitsgelden Medisch Specialisten, Medialane TV, Pfizer, Nederlandse Hartstichting/ZonMW, and Stichting Erasmus Trustfonds.

References: 1. Farooqi and O'Rahilly. *Nat Clin Pract Endocrinol Metab.* 2008;4:569-577. **2.** Kühnen et al. *Trends Mol Med.* 2019;25:136-148. **3.** Sohn et al. *Cell.* 2013;152:612-619. **4.** Yazdi et al. *Peer J.* 2015;3:e856. **5.** da Fonseca et al. *J Diabetes Complications.* 2017;31:1549-1561. **6.** Huvenne et al. *Obes Facts.* 2016;9:158-173. **7.** Duborn et al. *Pharmacol Res.* 2023;191:106763. **8.** Clément et al. *Lancet Diabetes Endocrinol.* 2020;8:960-970. **9.** Haqq et al. *Lancet Diabetes Endocrinol.* 2022;10:859-868. **10.** Roth et al. *Lancet Diabetes Endocrinol.* 2024 [Epub ahead of print]. **11.** Vogel et al. Presented at: European Society for Paediatric Endocrinology; September 22-26, 2021; Virtual. **12.** Rhythm Pharmaceuticals, Inc. https://ir.rhythmtx.com/static-files/93a3db32-fbcd-4fe3-b121-78c5feb658b8. Accessed May 13, 2024.