Rhythm Pharmaceuticals

Positive Topline Results from Phase 3 Trial Evaluating Setmelanotide in Patients with Acquired Hypothalamic Obesity

April 7, 2025

Forward-looking Statements

This presentation and the accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding our pivotal Phase 3 TRANSCEND study evaluating setmelanotide for the treatment of acquired hypothalamic obesity and the potential for setmelanotide to treat hypothalamic obesity; the safety, efficacy, potential benefits of, and clinical design or progress of any of our products or product candidates at any dosage or in any indication; our expectations surrounding potential regulatory submissions, progress, or approvals and timing thereof for any of our product candidates, including the anticipated supplemental New Drug Application to the FDA and a Type II variation request to the European Medicines Agency; the estimated market size and addressable population for our drug products, including setmelanotide for the treatment of hypothalamic obesity; the future announcement of data from our other ongoing clinical trials, including the Japanese cohort of our Phase 3 trial evaluating setmelanotide for patients with acquired hypothalamic obesity; our participation in and presentation of the full data from the TRANSCEND study at an upcoming medical meeting; and the timing of any of the foregoing. Statements using words such as “expect”, “anticipate”, “believe”, “may”, “will”, “aim” and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, positive results from earlier clinical trials of setmelanotide may not be predictive of the results of later clinical trials of setmelanotide, interim, topline and preliminary data that we announced may change as more patient data become available, setmelanotide may cause undesirable side effects that could delay or prevent additional regulatory approvals or limit the commercial profile of approved labeling, Breakthrough Therapy designation by the FDA may not lead to a faster development, regulatory review or approval process, and nor does it increase the likelihood that setmelanotide will receive additional marketing approvals in the United States, failure to identify and develop additional product candidates, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, the impact of competition, risks related to the commercialization and market acceptance of IMCIVREE for the treatment of hypothalamic obesity in the medical community and with third-party payors, and the other important factors discussed under the caption “Risk Factors” in our Annual Report on Form 10-K for the year ended December 31, 2024 and our other filings with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this press release or to update them to reflect events or circumstances occurring after the date of this press release, whether as a result of new information, future developments or otherwise.

Industry and Other Data

Unless otherwise indicated, information contained in this presentation concerning our industry and the markets in which Rhythm operates, including its general expectations, market position and market opportunity, is based on its management’s estimates and research, as well as industry and general publications and research, surveys and studies conducted by third parties. While we believe the information from these third-party publications, research, surveys and studies is reliable, it does not guarantee the accuracy or completeness of such information, and Rhythm has not independently verified this information. Management’s estimates are derived from publicly available information, their knowledge of the company's industry and their assumptions based on such information and knowledge, which they believe to be reasonable. This data involves a number of assumptions and limitations which are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in our periodic reports filed with the Securities and Exchange Commission under the captions “Cautionary Note Regarding Forward Looking Statements,” “Summary Risk Factors” and “Risk Factors.” These and other factors could cause Rhythm’s future performance and market expectations to differ materially from its assumptions and estimates.

On Today's Call

Susan Phillips, MD

Pediatric Endocrinologist at Rady Children's Hospital-San Diego

Professor of Pediatrics at UC San Diego School of Medicine

David Meeker, MD

Chair, President and Chief Executive Officer

Hunter C. Smith

Chief Financial Officer

David Meeker, MD

Chair, President and CEO

Acquired Hypothalamic Obesity Represents Significant Global Opportunity

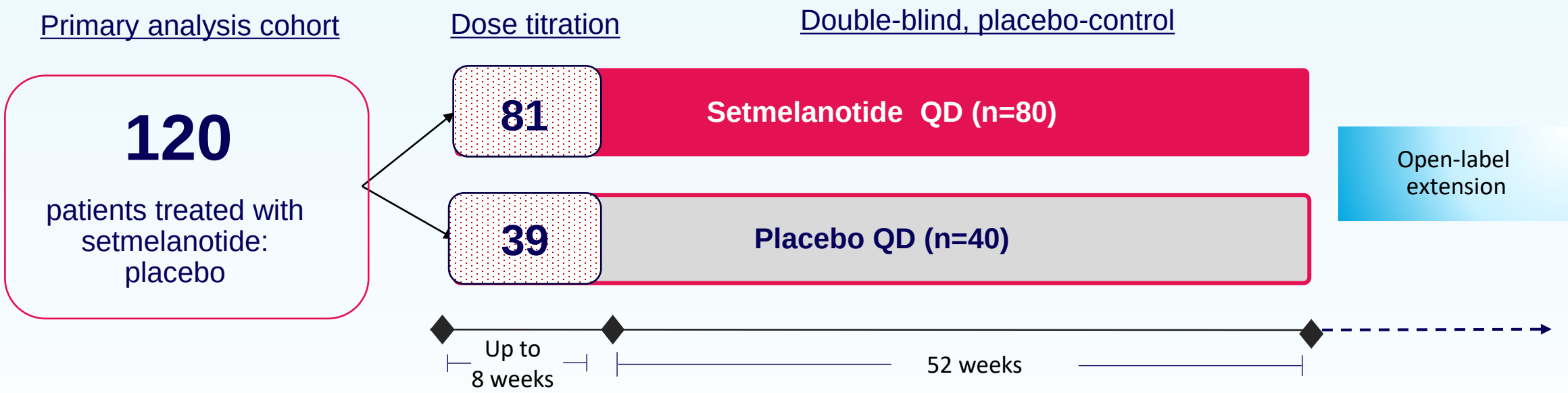
Rare, life-changing disease with severe impact and burden on patients and families

Significant unmet need with no approved therapies

Identified, actively engaged **patient community**

Setmelanotide achieved **highly clinically meaningful BMI reduction** in largest, placebo-controlled study ever conducted in acquired hypothalamic obesity

Phase 3 TRANSCEND Trial: Largest and Longest Placebo-controlled Trial in Acquired Hypothalamic Obesity Trial



+12 Japanese patients remain blinded in ongoing supplemental cohort; Data from this supplemental cohort will serve as the basis for a regulatory submission in Japan.

Demographics of Primary Analysis Cohort

BASELINE CHARACTERISTIC		Total (n=120)
Age, years	Mean (SD) (Range) <12 years old, n ≥12 years and <18, n ≥18 years old, n	19.9 (13.8) (4 – 66) 31 (25.8) 40 (33.3) 49 (40.8)
Sex, n (%)	Female / Male	72/48 (60/40)
Race, n (%)	White	100 (83)
Ethnicity, n (%)	Hispanic or Latino Not Hispanic or Latino	14 (11.7) 105 (87.5) 1 unknown
Weight, kg	Mean (SD) Range	93.3 (38.5) 23.9-226.9
BMI, kg/m^2	Mean (SD) Range	36.1 (9.2) 21.3 – 70.0
BMI-Z (n=71)	Mean (SD) Range	3.61 (1.7) 1.9 – 10.4

As of the data cutoff date of April 3, 2025; BMI, body mass index; SD, standard deviation; BMI Z calculated for patients younger than 18 to measure relative weight adjusted by child's age, sex and height.

Vast Majority of Patients Completed Trial, Transitioned to Extension Study

PRIMARY ANALYSIS COHORT

(N=120)

DISCONTINUED

Treatment	Placebo
(n=9)	*(n=5)*

AE *(n=7)*
Withdrawal *(n=7)*

COMPLETED 52 WEEKS
at therapeutic regimen

(n=106)

101
PATIENTS ENROLLED IN OPEN-LABEL EXTENSION*

*As of data cutoff, April 3, 2025.

Setmelanotide Achieved Statistically Significant and Highly Clinically Meaningful Reduction in BMI

Primary analysis cohort (N=120)

-16.5%

BMI change from baseline in

Setmelanotide arm

(n=81)

-19.8%

Placebo-adjusted difference in BMI reduction from baseline

(P<0.0001)

+3.3%

BMI change from baseline in

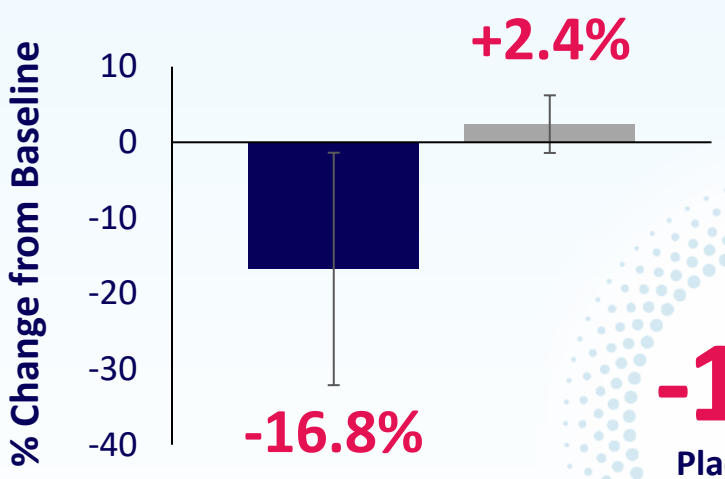
Placebo arm

(n=39)

NOTE: Shown are the least square (LS) means for setmelanotide and placebo groups and the LS mean difference in mean percentage change from baseline in BMI at Week 52, obtained from an analysis of covariance (ANCOVA) model. Rubin's Rule was used to provide the overall estimates of differences in LS means and p-value.

Significant Reductions in BMI Observed in both Adults and Children

≥18 Years Old *(n=49)*



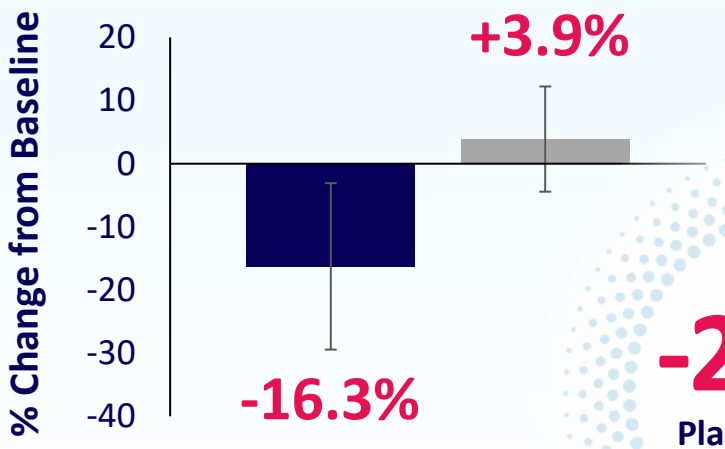
-19.2%
Placebo-adjusted Difference

(P<0.0001)

Setmelanotide (n=33)

Placebo (n=16)

<18 Years Old *(n=71)*



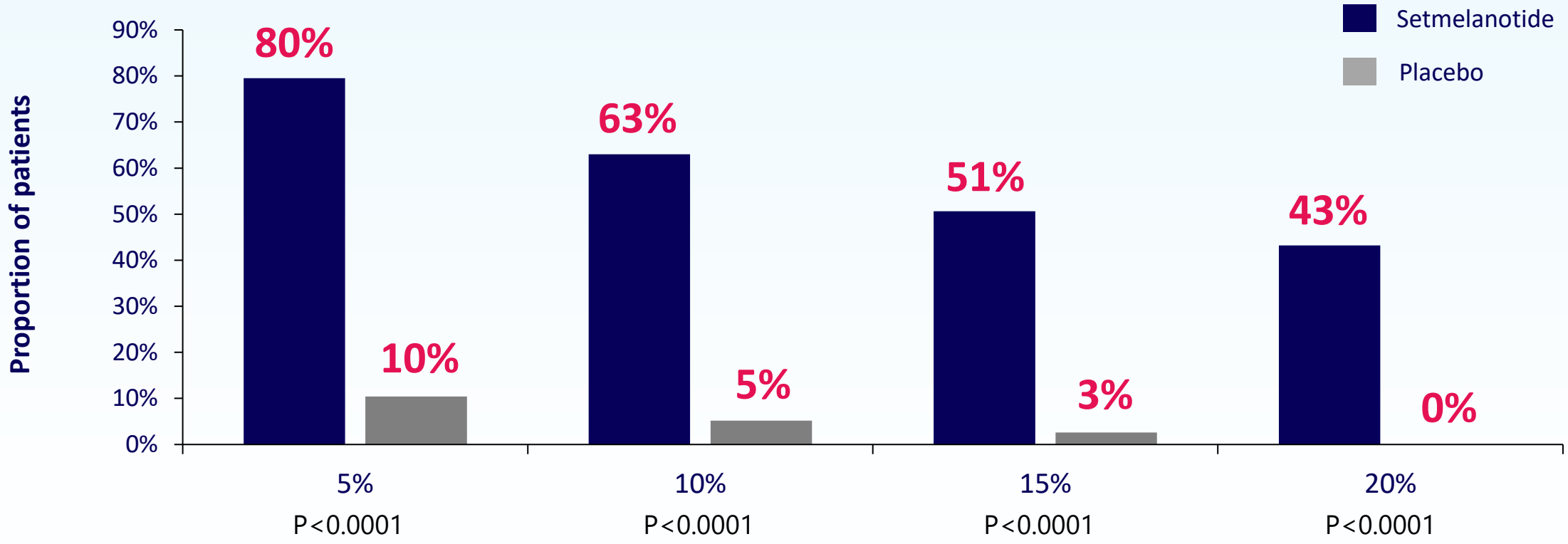
-20.2%
Placebo-adjusted Difference

(P<0.0001)

Setmelanotide (n=48)

Placebo (n=23)

Consistent Response to Setmelanotide Therapy Observed across Majority of Patients



Further Explanation on a Few Patient Outliers

Adult patient on setmelanotide

23yo female

- No BMI decrease during 52-week trial period
- Achieved -27% BMI decrease at 9 months in OLE

Pediatric patients on setmelanotide

(BMI Z-score reduction of 0.2 considered clinically significant)

6yo male

- BMI decrease of -2.5% during 52-week trial
- BMI Z-score 5.59 at baseline decreased to 4.74 for reduction of -0.85

7yo female

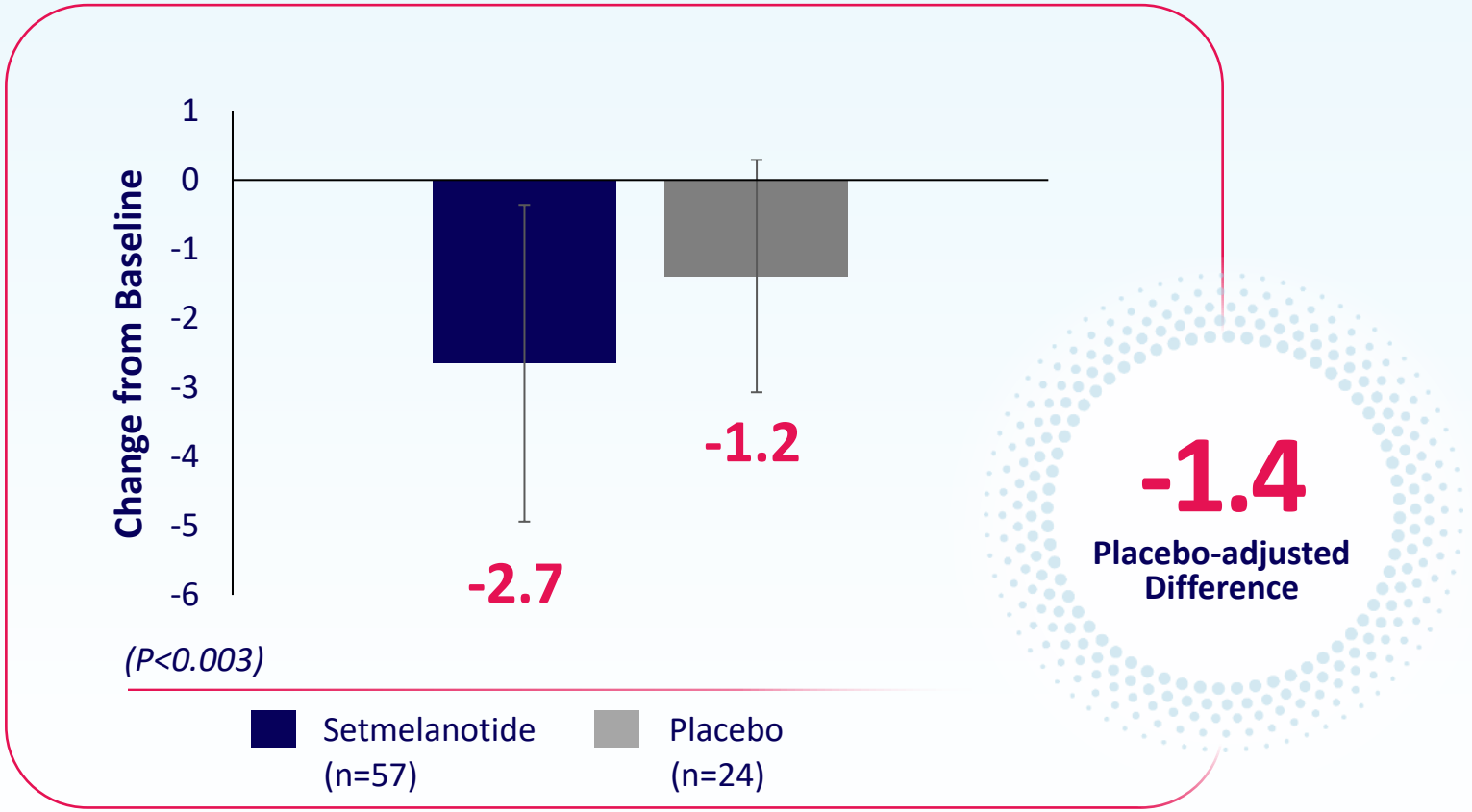
- BMI decrease from baseline of -13.3% at visit 8; BMI decrease of -2.8% at 52 weeks
- BMI Z-score of 6.45 at baseline decreased to 5.1 at 52 weeks for reduction of -1.3

Adolescent patient on placebo

12yo female

- Complex medical history, adrenal crisis, nausea and vomiting, other endocrine medicine changes
- 17% BMI decrease at 52 weeks
- In OLE, BMI decrease of -33%; Investigator: “Looks fantastic!”

Setmelanotide Achieved Statistically Significant Reduction in Hunger Compared with Placebo in Patients ≥12 Years Old



Note: Patients ≥12 years of age were administered the questionnaire. Patients rated their hunger on an 11-point numeric rating scale ranging from 0 to 10 (0 = not hungry at all and 10 = hungriest possible) with a recall period of 24 hours.

Significant BMI Reductions Observed in Patients with Prior Use or Concomitant Use of GLP-1s

Prior use of GLP-1 *(n=16)*

-24.7%

Placebo-adjusted difference in BMI reduction from baseline

Concomitant GLP-1 *(n=15)*

-27.1%

Placebo-adjusted difference in BMI reduction from baseline

Setmelanotide Generally Well Tolerated with No New Safety Signals

Parameter	Setmelanotide n (%) *(n=81)*	Placebo n (%) *(n=39)*	Overall n (%) *(n=120)*
At Least 1 AE	81 (100.0)	35 (89.7)	116 (96.7)
At Least 1 Drug-Related AE	71 (87.7)	26 (66.7)	97 (80.8)
At Least 1 Serious AE	23 (28.4)	3 (7.7)	26 (21.7)
At Least 1 Drug-Related Serious AE	1 (1.2)	0	1 (0.8)
At Least 1 AE Which Resulted in Death	1 (1.2)	0	1 (0.8)
At Least 1 AE Leading to Study Drug Withdrawal	6 (7.4)	5 (12.8)	11 (9.2)
At Least 1 AE Leading to Study Discontinuation	4 (4.9)	0	4 (3.3)

One SAE considered related to study drug: hypernatremia; sodium levels 150-158 (normal upper limit 145) mmol/L, resolved after 2 days following medication

One death due to seizures considered not related to study drug

Setmelanotide Generally Well Tolerated with No New Safety Signals

Most Common (≥20% Overall)	Setmelanotide n (%) *(n=81)*	Placebo n (%) *(n=39)*	Overall n (%) *(n=120)*
Skin hyperpigmentation	45 (55.6)	3 (7.7)	48 (40.0)
Nausea	41 (50.6)	15 (38.5)	56 (46.7)
Headache	32 (39.5)	12 (30.8)	44 (36.7)
Vomiting	32 (39.5)	8 (20.5)	40 (33.3)
Diarrhea	19 (23.5)	8 (20.5)	27 (22.5)
Injection site reaction	19 (23.5)	9 (23.1)	28 (23.3)

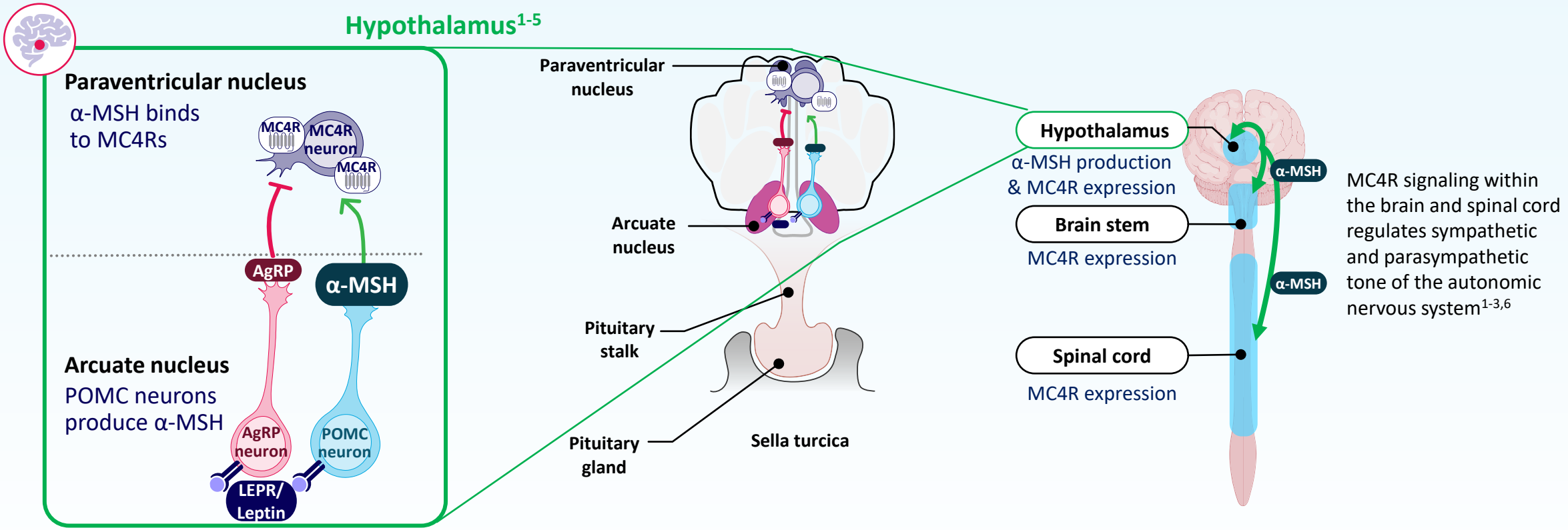
Safety was generally consistent with previously reported AEs in other clinical trials

Susan Phillips, MD

Pediatric endocrinologist at Rady Children's Hospital-San Diego;

Professor of pediatrics at UC San Diego School of Medicine

α-MSH Drives MC4R Pathway Signaling to Regulate Energy Balance and Body Weight[1-3]



α-MSH activation of MC4R regulates[1-3]:

- Hunger & food intake
- Energy expenditure

→ **Body weight**

α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

1. Baldini et al. *J Endocrinol.* 2019;241:R1-R33. **2.** Dimitri. *Front Endocrinol.* 2022;13:846880. **3.** Hill et al. *Neuroendocrinol.* 2017;104:330-346. **4.** Hochberg et al. *Obes Rev*. 2010;11:709-721. **5.** Roth et al. *Obesity (Silver Spring).* 2011;19:36-42. **6.** Sohn et al. *Cell.* 2013;152:612-619.

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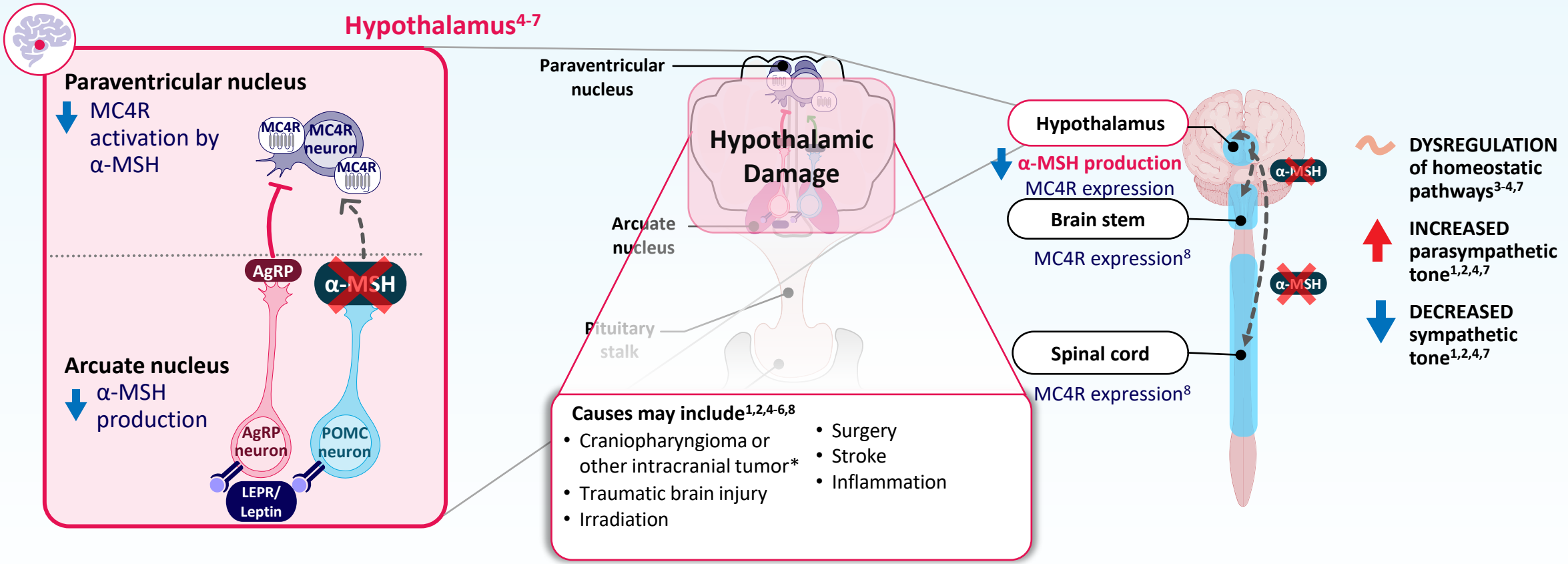
Hypothalamic Damage Can Impair MC4R Pathway Signaling and Lead to Acquired Hypothalamic Obesity[1-3]



Decreased α-MSH activation of MC4R may result in[1-3,7]:

- Hyperphagia
- Reduced energy expenditure

→ **Accelerated and sustained weight gain**

*Suprasellar tumors such as astrocytoma.[1,7]

α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

1. Abuzzahab et al. *Horm Res Paediatr.* 2019;91:128-136. **2.** Roth. *Front Endocrinol (Lausanne).* 2011;2:49. **3.** Roth et al. *Metabolism.* 2010;59:186-194. **4.** Dimitri. *Front Endocrinol (Lusanne).* 2022;13:846880. **5.** Baldini et al. *J Endocrinol.* 2019;241:R1-R33. **6.** Hochberg et al. *Obes Rev*. 2010;11:709-721. **7.** Roth et al. *Obesity (Silver Spring).* 2011;19:36-42. **8.** Sohn et al. *Cell.* 2013;152:612-619.

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Acquired Hypothalamic Obesity: Rare Disease with Accelerated Weight Gain Following Various Injuries to the Hypothalamic Region

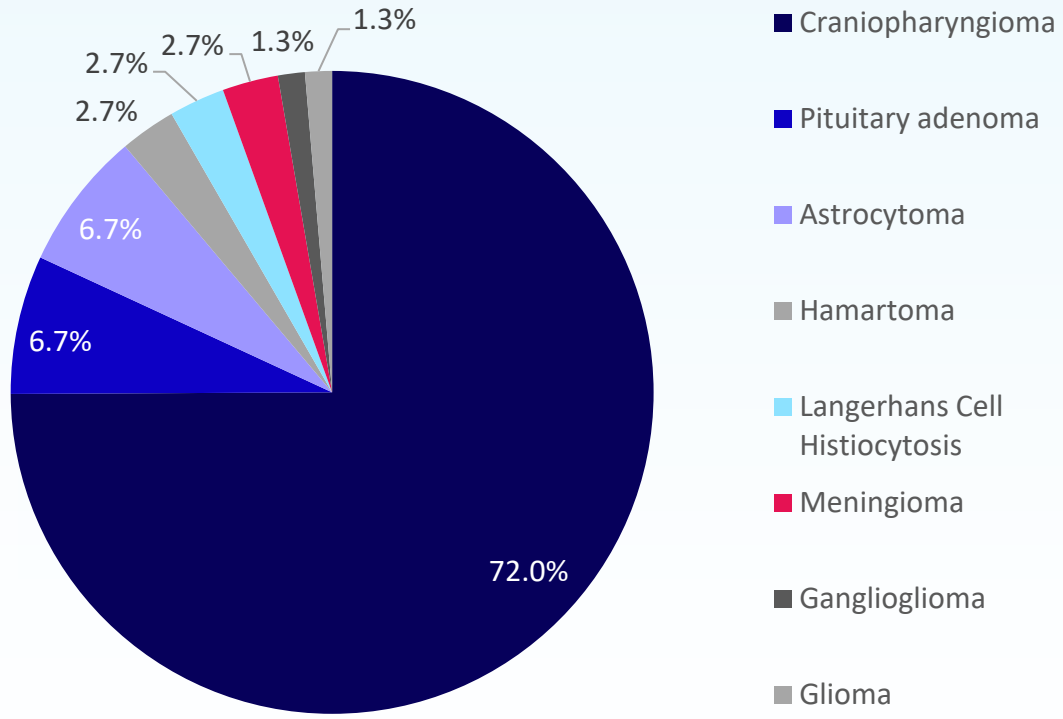
MC4R pathway deficiency following injury to hypothalamic region causes reduced energy, hyperphagia and accelerated, sustained weight gain

Craniopharyngioma and **other tumors** and treatment—tumor resection surgery and radiation—is most common cause

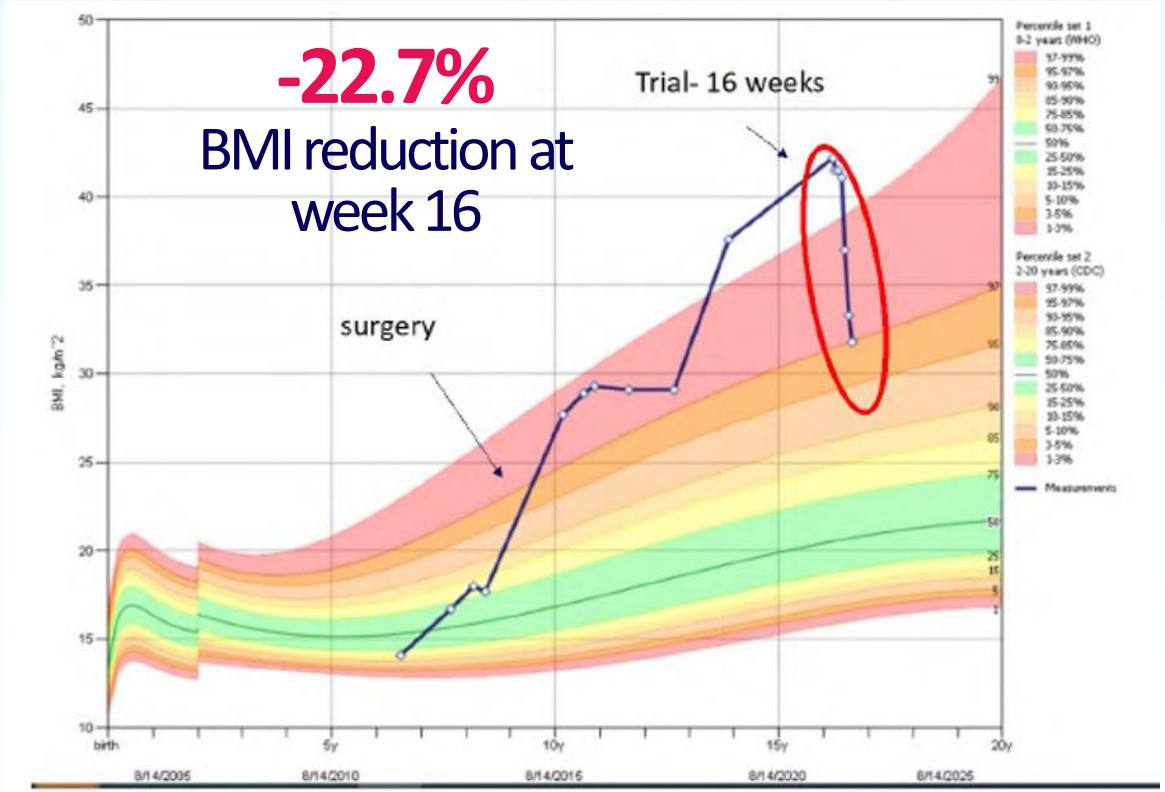
Additional causes include traumatic brain injury, inflammation, surgery, stroke, irradiation and other injuries

No approved treatments available

Tumor Frequency in the International Registry of Hypothalamic Obesity Disorders (IHROD)



Patient Case Report: 16yo Female Achieved 22.7% BMI Reduction at 16 weeks on Setmelanotide Therapy in Phase 2 Trial



Individual patient results varied

8yo: Diagnosed with craniopharyngioma

2014
surgical resection

2015
radiotherapy

16yo: Enters Setmelanotide Ph2 trial in **2021**

41.1kg/m² → **31.8kg/m²**

122.8kg → **94.6kg**

at baseline

at 16 weeks of setmelanotide therapy

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2013

7yo before tumor diagnosis

AUGUST 2021

AUGUST 2024

David Meeker, MD

Chair, President and CEO

Hypothalamic Obesity: A Potentially Transformative Opportunity

5,000 – 10,000

estimated U.S. prevalence[1]

3,500 – 10,000

estimated European prevalence[2]

5,000 – 8,000

estimated Japanese prevalence[3]

- ✓ Unmet medical need is high
- ✓ Patients are identified
- ✓ Patients engaged with system

~500 Estimated incidence in each U.S., Europe and Japan[1, 2, 3]

1. U.S. estimates based on reported incidence of hypothalamic obesity following craniopharyngioma and long-term survival rates, (Zacharia, et al., *Neuro-Oncology* 14(8):1070–1078, 2012. doi:10.1093/neuonc/nos142; and Muller, et al., *Neuro-Oncology* 17(7), 1029–1038, 2015 doi:10.1093/neuonc/nov044.); 2. European estimates limited to the EU4 (Germany, France, Spain, Italy), UK and the Netherlands and prevalence of 0.1-0.3 in 10,000 patients; 3. Rhythm estimates the prevalence of acquired hypothalamic obesity in Japan to be approximately 5,000 to 8,000 based on our review of tumor registries and claims data; Prevalence is 2-3 times higher than in the USA & Europe due to a higher reported frequency of craniopharyngioma.

Focus on Global Regulatory Strategy

US

EU

UK

CANADA

JAPAN

Regulatory submissions in the U.S. and EU expected to be completed in Q3 2025

Additional Important Milestones and Data Readouts Anticipated

RM-718
First patient to be dosed in **Ph1, Part C in acquired HO** anticipated in **April 2025**

Setmelanotide
First patient to be dosed in **Ph3 congenital HO substudy** anticipated in **Q2 2025**

Bivamelagon
Topline data from **Phase 2 trial in acquired HO** anticipated in **H2 2025**

Setmelanotide
Phase 2 trial in **Prader-Willi syndrome** enrollment completion anticipated in **Q3 2025**

Setmelanotide
Topline data from **12-patient Japanese cohort** in acquired HO anticipated in **Q1 2026**

Setmelanotide
Topline data from **Ph3 EMANATE trial** in MC4R pathway diseases anticipated in **Q1 2026**

RYTM expects cash to be sufficient to fund planned operations into 2027

Questions?