# Commercial Readiness for Acquired Hypothalamic Obesity

**September 24, 2025**



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# Forward-looking Statements

This presentation contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, and that involve risks and uncertainties, including without limitation statements regarding the potential, safety, efficacy, and regulatory and clinical progress of our products and product candidates, including setmelanotide, and including the anticipated timing for our expectations surrounding regulatory submissions, approvals and timing thereof, our business strategy and plans, including regarding commercialization of setmelanotide and our other product candidates, the announcement of data from our clinical trials, including our global Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity, the ongoing enrollment of patients in our clinical trials, the potential benefits of any of the Company's products or product candidates for any specific disease indication or at any dosage, expectations surrounding the potential market opportunity for our product candidates, anticipated milestones, our future financial performance and the sufficiency of our cash, cash equivalents and short-term investments to fund our operations, and strategy, prospects and plans, including regarding the commercialization of setmelanotide, our anticipated financial performance for any period of time, our participation in investor events, including our Commercial Readiness in acquired Hypothalamic Obesity event and webcast, and the timing of any of the foregoing. Statements using words such as "expect", "anticipate", "believe", "may" 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 outcome of clinical trials, the impact of competition, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our liquidity and expenses, the impact of global events on our business and operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and other reports we file 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 presentation or to update them to reflect events or circumstances occurring after the date of this presentation, whether as a result of new information, future developments or otherwise.

# Speaker Disclosures

Dr. Shoemaker and Dr. Blevins have been compensated for their time to prepare for and participate in today's investor presentation. Karmelo Bragg and his mother Miracle Bragg were compensated for their time to participate in the making of the video about Karmelo's experience with acquired HO.

# Today's Speakers

**David Meeker, MD**
*Chairman, President, and CEO*

**Jennifer Lee**
*Executive Vice President, Head of North America*

**Ashley Shoemaker, MD, MSCI**
*Associate Professor of Pediatrics, Vanderbilt University Medical Center*

**Lewis Blevins, MD**
*Medical Director, UCSF Medical Center*

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# Agenda

| | |
|---|---|
| **Welcome & Introduction** | **David Connolly**, *Head of Investor Relations and Corporate Communications* |
| **Setmelanotide Overview** | **David Meeker, MD**, *Chairman, President, and CEO* |
| **Physician Panel** | **Ashley Shoemaker, MD, MSCI**, *Associate Professor of Pediatrics, Vanderbilt University Medical Center*<br>**Lewis Blevins, MD**, *Medical Director, UCSF Medical Center*<br>*Moderator:* **David Meeker, MD**, *Chairman, President, and CEO* |
| **Break** | |
| **U.S. Commercial Strategy** | **Jennifer Lee**, *Executive Vice President, Head of North America* |
| **Q&A** | |
| **Closing** | **David Meeker, MD**, *Chairman, President, and CEO* |



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# Setmelanotide Overview

**David Meeker, MD**

***Chairman, CEO and President***

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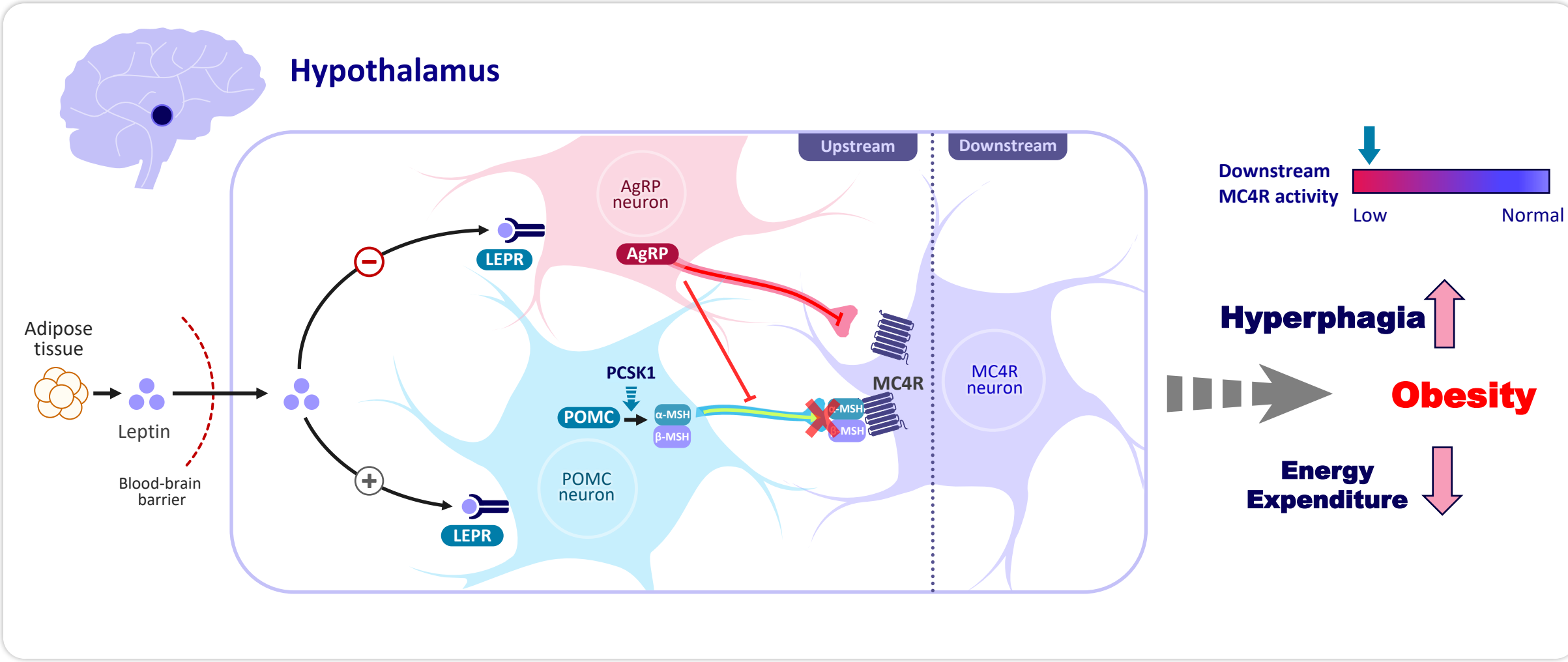
# Rhythm is Ready for a Successful U.S. Launch

**Significant unmet need**

**Setmelanotide's proven efficacy**

**Transformative opportunity**

# MC4R Pathway Biology is Clear




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**. Abuzzahab et al. *Horm Res Paediatr.* 2019;91:128-136. **2.** Erfurth. *Neuroendocrinology.* 2020;110:767-779. **3.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732. **4.** Roth. *Front Endocrinol (Lausanne).* 2011;2:49.



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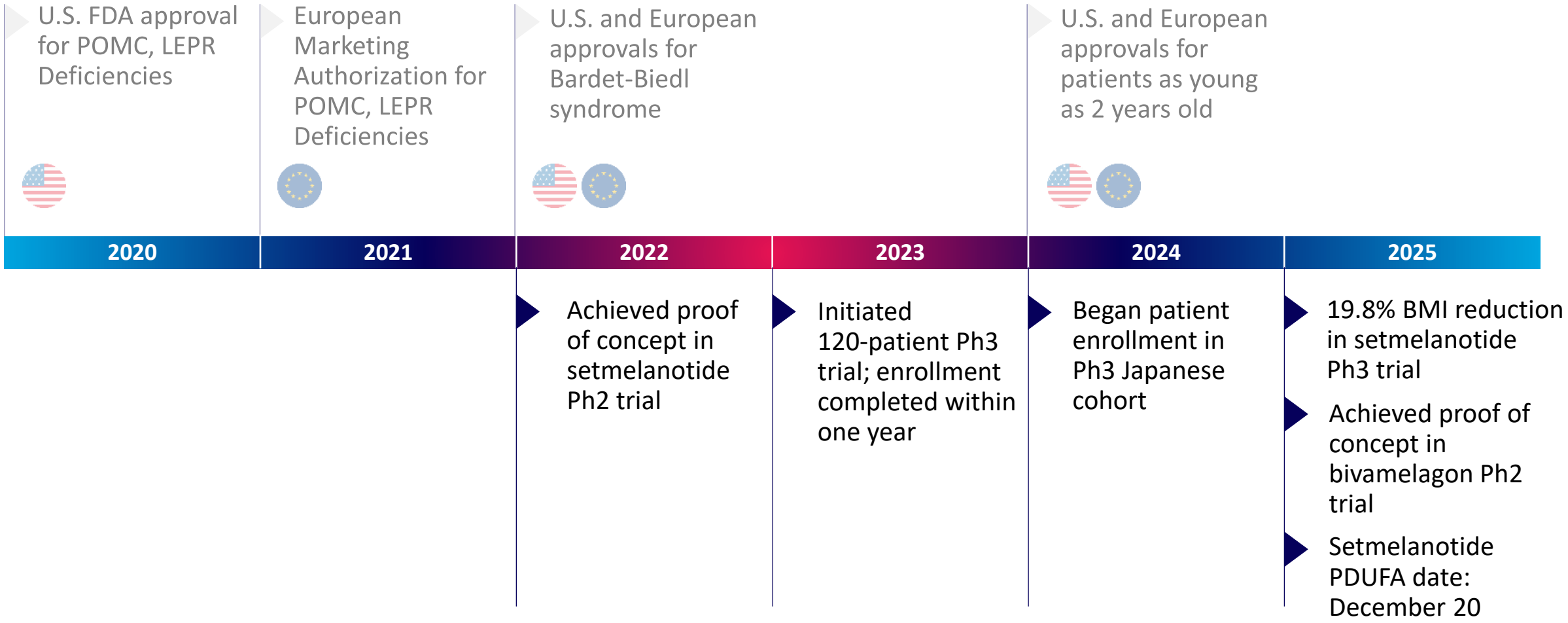
# IMCIVREE (setmelanotide) has Secured Multiple FDA Approvals, EU Authorizations for Label Expansion

# Rapid Development in Acquired Hypothalamic Obesity



IMCIVREE™
(setmelanotide) injection

# Solid Global Foundation in Place

**>25**
countries where IMCIVREE is available

**>350**
employees in

**15**
different countries

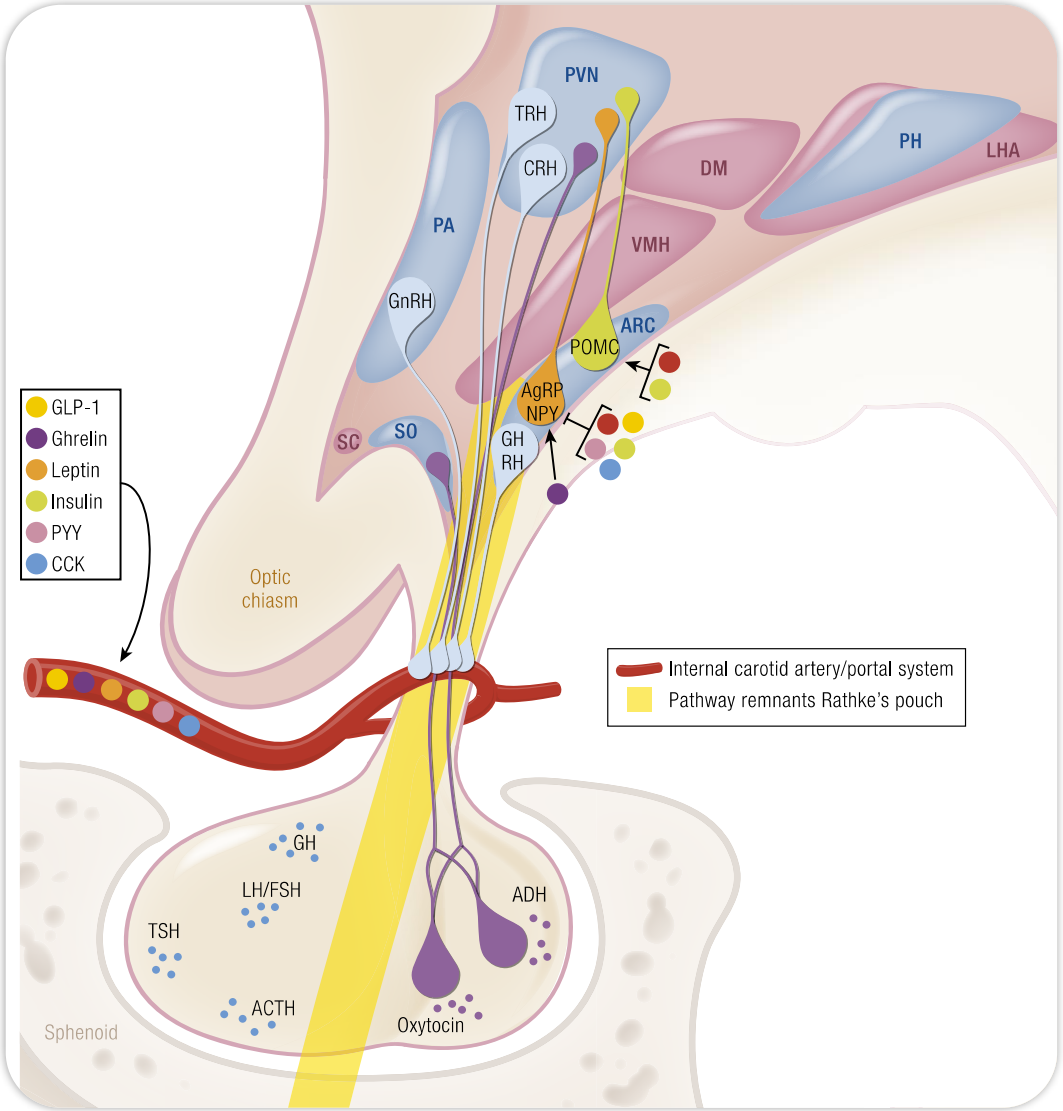
**7**
country-level distribution partnerships

# Hypothalamic Obesity: A Rare, Acquired Form of Obesity Following Injury to the Hypothalamic Region

**Craniopharyngioma** (CP) and **other suprasellar brain tumors** and treatment – tumor resection surgery and radiation – is most common cause

**MC4R pathway** deficiency following injury to hypothalamic region causes reduced energy, hyperphagia and rapid-onset, severe obesity

**No approved treatments available**




van Iersel et al. Endo Rev. 2020 (PMID: 30247642)



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# Severe, Life-long Burden for Patients with Acquired HO

**Frequent visits with multiple specialists, a complex regimen of medications, and hospitalization**

**"Treatment of patients with tumor/treatment-related hypothalamic obesity in the first two years following surgical treatment or radiotherapy"**

**Müller et al., 2025**

**scientific reports**

**3.7** average hospitalizations during the two years following index;

**23%** included ICU admission in the first year

**12** average number of general practitioner visits and

**20** specialist visits, during the two years following index

**5.5** average active prescriptions per quarter

**22.1** average number of unique medications over 2 years

**89%** were receiving ≥3 therapies for neuroendocrine dysfunction



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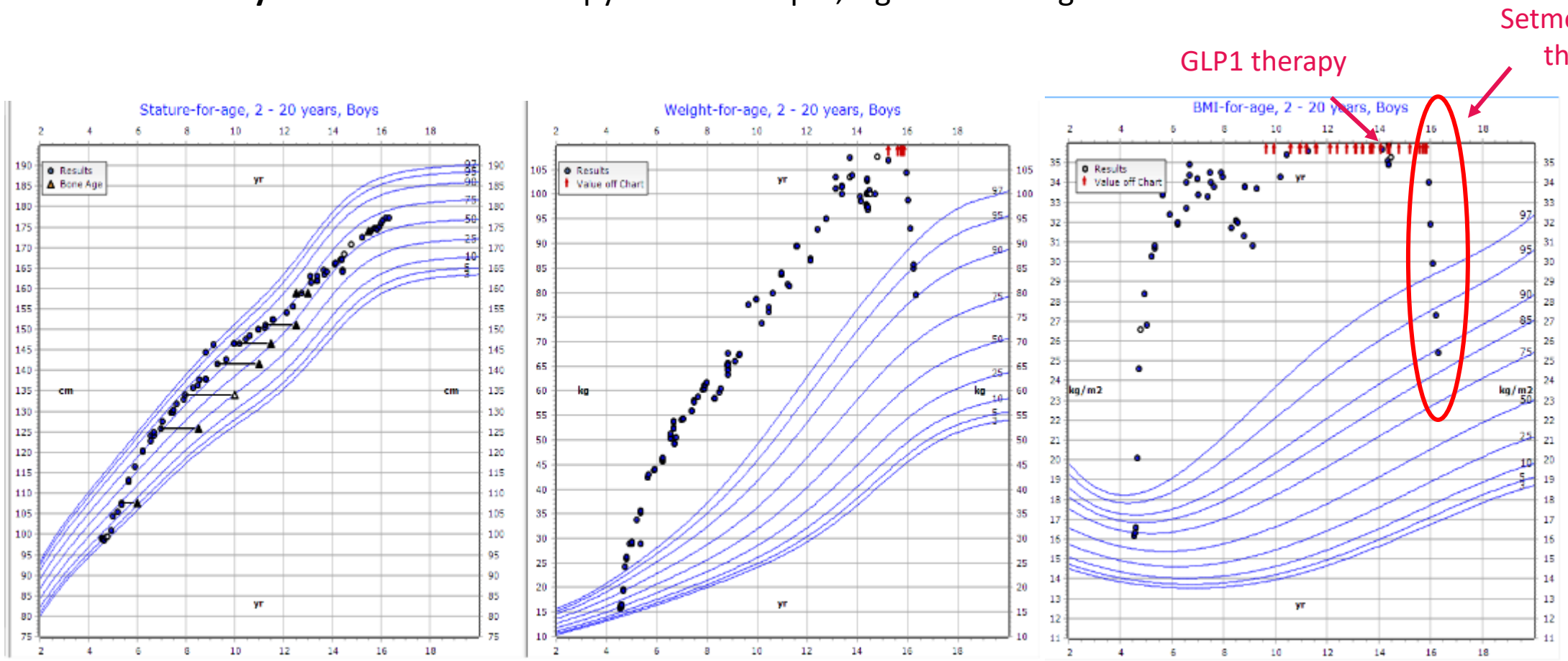
# HO: Aggressive, Rapid Weight Gain follows Therapy for CP

**Patient Case Study:** Setmelanotide therapy achieved rapid, significant weight loss




Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota



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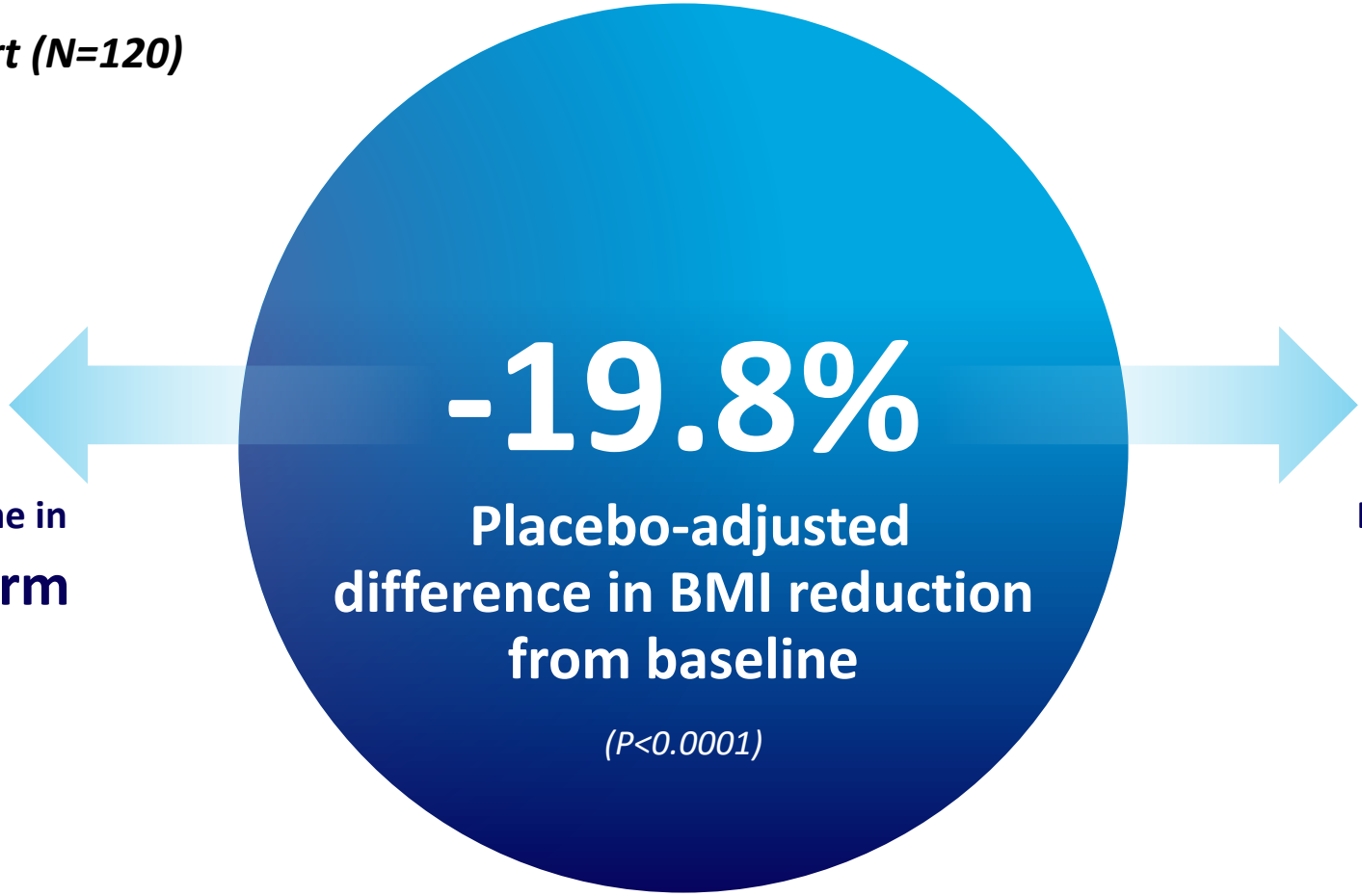
# Setmelanotide Achieved Statistically Significant and Highly Clinically Meaningful Reduction in BMI in Phase 3 Acquired HO Trial

***Primary analysis cohort (N=120)***




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.



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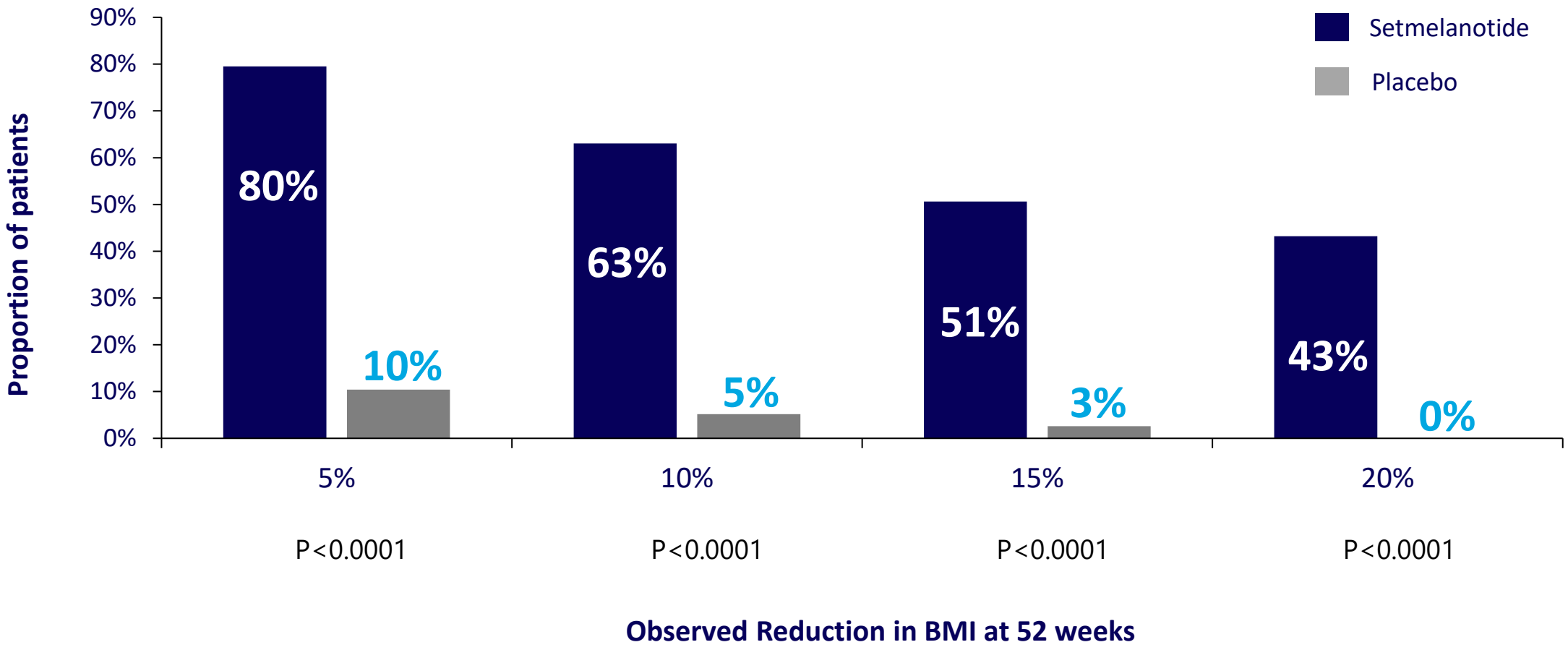
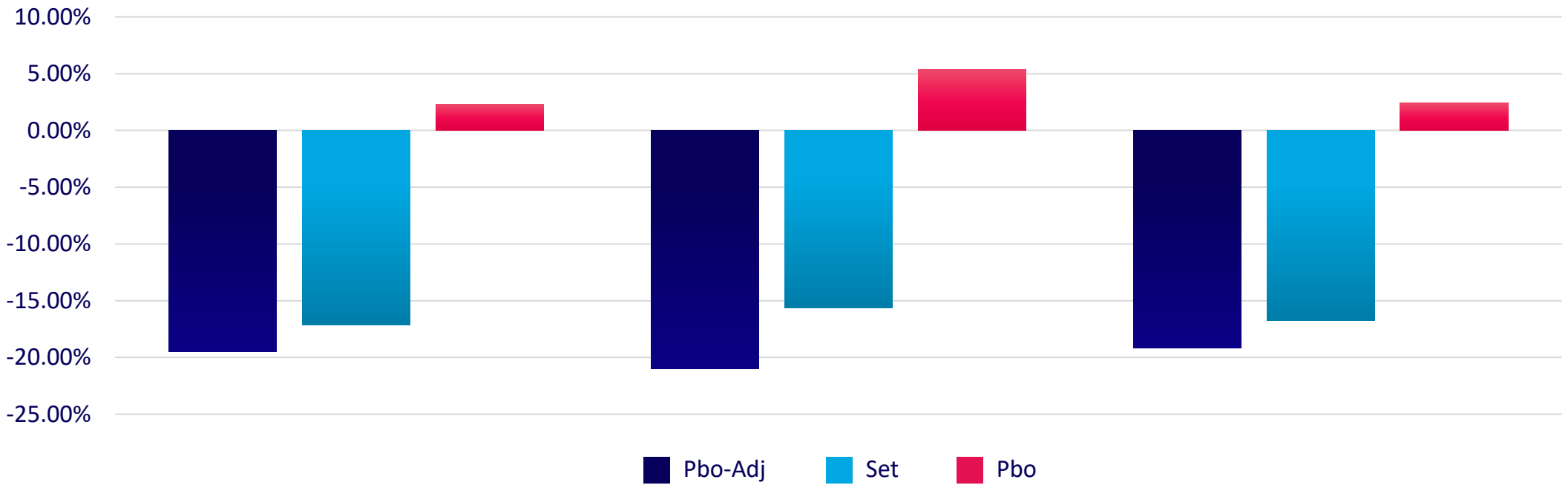
# Consistent Response to Setmelanotide Therapy Observed across Majority of Patients in Phase 3 Trial in Acquired HO

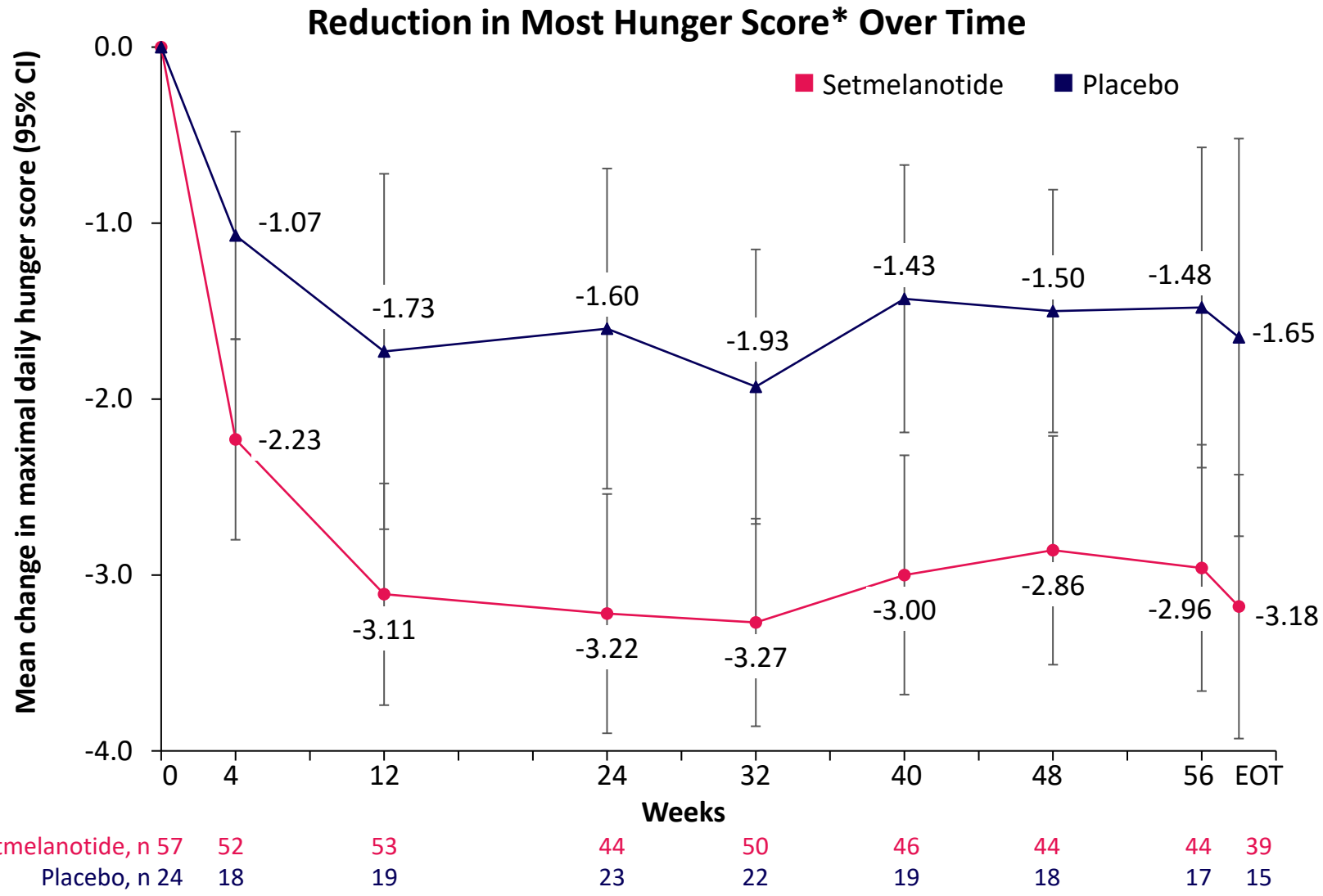


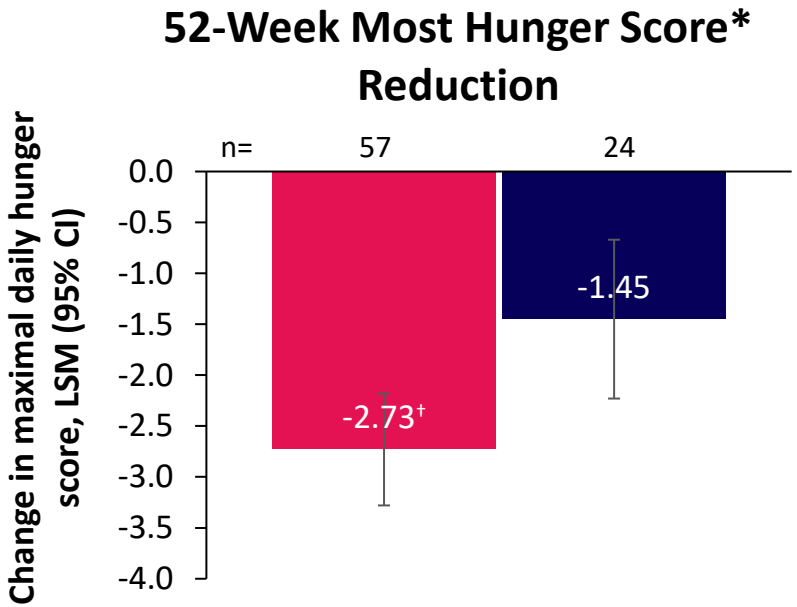
# Mean BMI Reduction Consistent Across Stratified Age Groups in Phase 3 Trial Evaluating Setmelanotide in Acquired HO

| < 12 Yrs | 12 – < 18 Yrs | ≥ 18 Yrs |
|---|---|---|
| ***-19.5%*** | ***-21.0%*** | ***-19.2%*** |
| ***p <0.0001*** | ***p <0.0001*** | ***p <0.0001*** |
| *(n=31: 20 setmelanotide, 11 placebo)* | *(n=40: 28 setmelanotide, 12 placebo)* | *(n=49: 33 setmelanotide, 16 placebo)* |



# Rapid and Statistically Significant Reduction in Most Hunger Score With Setmelanotide vs Placebo (Participants Aged ≥12 Years)



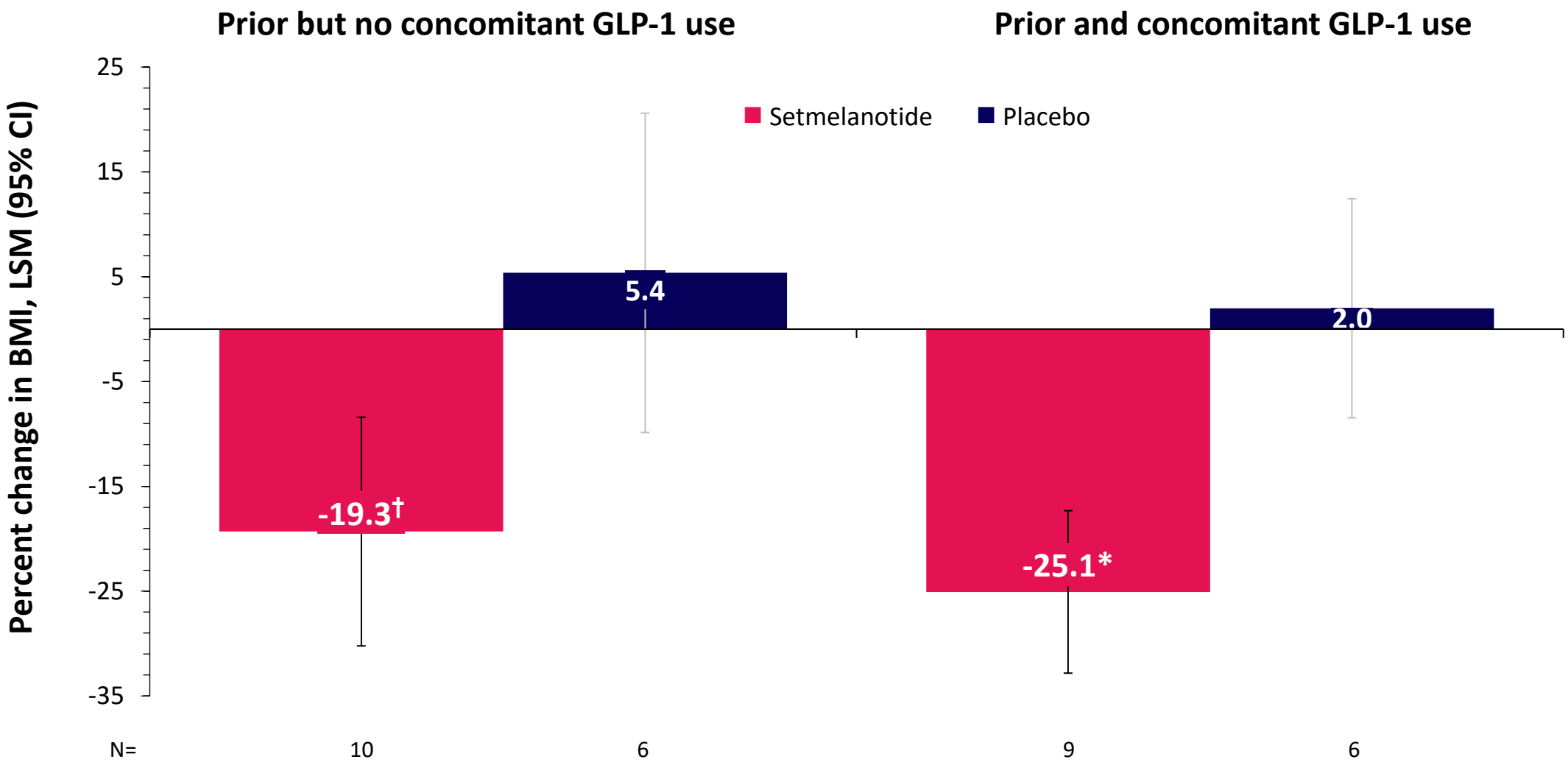

**PBO-adjusted difference** **-1.28**

†*P*=0.0086 vs placebo.

As presented at ENDO 2025

*Weekly average of daily scores. participants ≥12 years of age who were able to self-report were administered the questionnaire. Participants were asked to rate their most hunger on an 11-point numerical rating scale from 0 to 10, where 0 = not hungry at all and 10 = hungriest possible via the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" CI, confidence interval; LSM, least squares mean.

# Significant BMI Reductions Observed in Patients With Prior or Concomitant Use of GLP-1RA




†*P*=0.0046 and **P*<0.0001 vs placebo.
BMI, body mass index; CI, confidence interval; GLP-1RA, glucagon-like peptide-1 receptor agonist; LSM, least squares mean.



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# Setmelanotide Was Generally Well Tolerated With No New AE Signals

| | Setmelanotide (n=81) | Placebo (n=39) | Overall (n=120) |
|---|---|---|---|
| ≥1 AE of any cause | 81 (100.0) | 35 (89.7) | 116 (96.7) |
| ≥1 Drug-related AE | 71 (87.7) | 26 (66.7) | 97 (80.8) |
| ≥1 Serious AE | 23 (28.4) | 3 (7.7) | 26 (21.7) |
| ≥1 Drug-related serious AE | 1 (1.2)* | 0 | 1 (0.8) |
| ≥1 AE that resulted in death | 1 (1.2) | 0 | 1 (0.8) |
| ≥1 AE leading to study drug withdrawal | 6 (7.4) | 3 (7.7) | 9 (7.5) |
| ≥1 AE leading to study discontinuation | 4 (4.9) | 0 | 4 (3.3) |
| **Most common (≥20% in setmelanotide arm)** | | | |
| Skin hyperpigmentation | 45 (55.6) | 3 (7.7) | 48 (40.0) |
| Nausea | 41 (50.6) | 12 (30.8) | 53 (44.2) |
| Headache | 31 (38.3) | 12 (30.8) | 43 (35.8) |
| Vomiting | 32 (39.5) | 7 (17.9) | 39 (32.5) |
| Diarrhea | 19 (23.5) | 8 (20.5) | 27 (22.5) |
| Injection site reaction | 19 (23.5) | 9 (23.1) | 28 (23.3) |

One serious AE was considered related to the study drug (setmelanotide): hypernatremia (sodium levels 150-158 mmol/L [normal upper limit 145 mmol/L]); resolved after 2 days with treatment

One death due to seizures in a patient with a history of seizure disorder, which was not considered related to the study drug

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

*In a participant with arginine vasopressin deficiency who was unable to ingest their oral desmopressin tablet because of drug-associated nausea and vomiting, which led to increased blood sodium concentrations and subsequent hospitalization. AE, adverse event.

# Significant Global Market Opportunity in aHO

**~10,000**

estimated U.S. prevalence[1]

**~10,000**

estimated European prevalence[2]

**5,000 – 8,000**

estimated Japanese prevalence[3]

**~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.



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Karmelo
The story of a brain tumor survivor
with acquired hypothalamic obesity

# Physician Panel

**Ashley Shoemaker, MD, MSCI**
**Lewis Blevins, MD**
*Moderator:* **David Meeker, MD**

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# Break

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# U.S. Commercial Strategy

**Jennifer Lee**

***Executive Vice President, Head of North America***

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# Excitement Building for Launch in Acquired Hypothalamic Obesity

**RYTM is getting ready to launch**

**Addressing a severe unmet need**

**Transformative opportunity**

# Focus for Today

***What we've done***

**Building on success in BBS**

***What we've learned***

**Market research validates unmet need**

***What we're focused on***

**U.S. launch strategic priorities**



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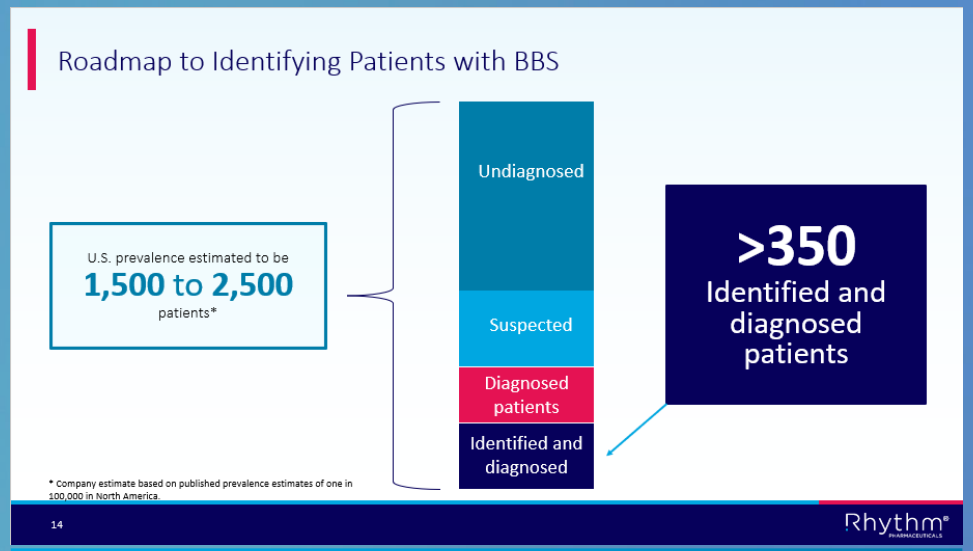
# Leveraging Data and Persistent Patient Finding Drive BBS Growth




**February 2022**

Four months before BBS launch

Steady growth over the last three years



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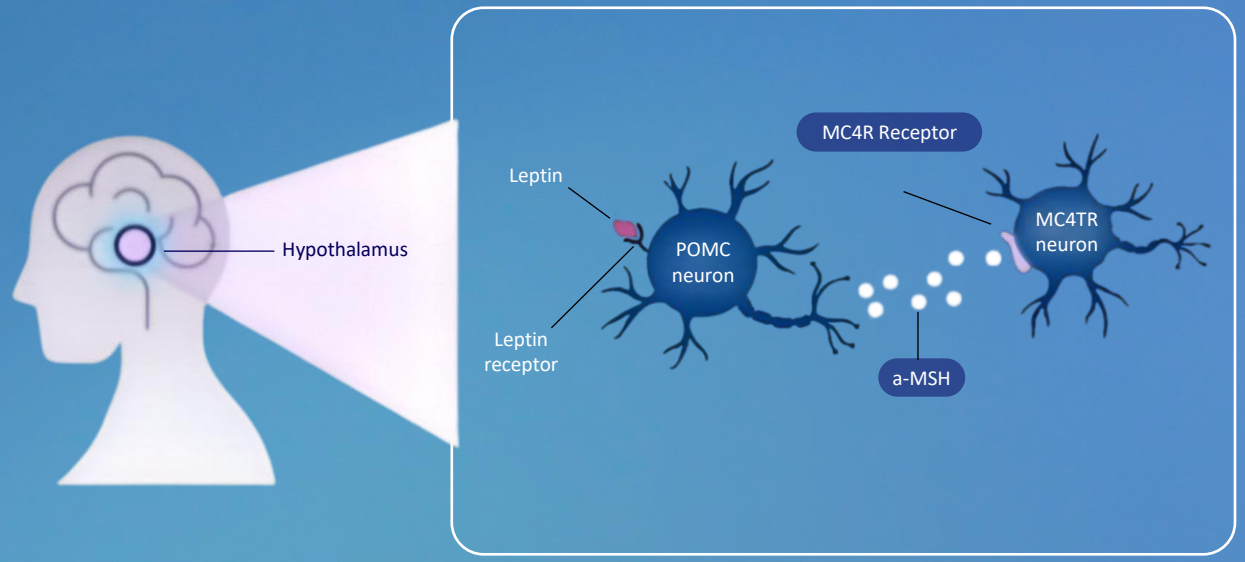
# Education and Engagement with Health Care Providers Drives Awareness

## Differentiating MC4R disease and burden of hyperphagia




THE LANCET
Diabetes & Endocrinology

Articles

### Efficacy and safety of setmelanotide, a melanocortin-4 receptor agonist, in patients with Bardet-Biedl syndrome and Alström syndrome: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial with an open-label period

Andrea M Haqq, Wendy K Chung, Hélène Dollfus, Robert M Haws, Gabriel A Martos-Moreno, Christine Poitou, Jack A Yanovski, Robert S Mittleman, Guojun Yuan, Elizabeth Forsythe, Karine Clément, Jesus Argente

**Summary**

**Background** Impaired cilial signalling in the melanocortin-4 receptor (MC4R) pathway might contribute to obesity in patients with Bardet-Biedl syndrome and Alström syndrome, rare genetic diseases associated with hyperphagia and early-onset severe obesity. We aimed to evaluate the effect of setmelanotide on bodyweight in these patients.

**Methods** This multicentre, randomised, 14-week double-blind, placebo-controlled, phase 3 trial followed by a 52-week open-label period, was performed at 12 sites (hospitals, clinics, and universities) in the USA, Canada, the UK, France, and Spain. Patients aged 6 years or older were included if they had a clinical diagnosis of Bardet-Biedl syndrome or Alström syndrome and obesity (defined as BMI >97th percentile for age and sex for those aged 6–15 years and ≥30 kg/m² for those aged ≥16 years). Patients were randomly assigned (1:1) using a numerical randomisation code to receive up to 3·0 mg of subcutaneous setmelanotide or placebo once per day during the 14-week double-blind period, followed by open-label setmelanotide for 52 weeks. The primary endpoint, measured in the full analysis set, was the proportion of patients aged 12 years or older who reached at least a 10% reduction in bodyweight from baseline after 52 weeks of setmelanotide treatment. This study is registered with ClinicalTrials.gov, NCT03746522.

**Findings** Between Dec 10, 2018, and Nov 25, 2019, 38 patients were enrolled and randomly assigned to receive setmelanotide (n=19) or placebo (n=19; 16 with Bardet-Biedl syndrome and three with Alström syndrome in each group). In terms of the primary endpoint, 32·3% (95% CI 16·7 to 51·4; p=0·0006) of patients aged 12 years or older with Bardet-Biedl syndrome reached at least a 10% reduction in bodyweight after 52 weeks of setmelanotide. The most commonly reported treatment-emergent adverse events were skin hyperpigmentation (23 [61%] of 38) and injection site erythema (18 [48%]). Two patients had four serious adverse events (blindness, anaphylactic reaction, and suicidal ideation); none were considered related to setmelanotide treatment.

**Interpretation** Setmelanotide resulted in significant bodyweight reductions in patients with Bardet-Biedl syndrome; however, these results were inconclusive in patients with Alström syndrome. These results support the use of setmelanotide and provided the necessary evidence for approval of this drug as the first treatment for obesity in patients with Bardet-Biedl syndrome.

**Funding** Rhythm Pharmaceuticals.



*Lancet Diabetes Endocrinol* 2022

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See Online/Comment https://doi.org/10.1016/S2213-8587(22)00309-6

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## Introduction

The central hypothalamic melanocortin pathway is a key regulator of energy balance.[1] Pathway disruption leading to impaired melanocortin-4 receptor (MC4R) signalling probably contributes to hyperphagia (a pathological insatiable hunger) and decreased energy expenditure, resulting in early-onset severe obesity (ie, BMI ≥35 kg/m² or ≥120% of the 95th percentile).[1] Bardet-Biedl syndrome is a rare autosomal recessive pleiotropic and genetically heterogeneous disease that arises from impaired primary cilium function.[2] This syndrome is associated with hyperphagia, early-onset severe obesity, and other clinical features (including polydactyly and retinal degeneration).[2,3] Obesity is present in 72–92% of patients with Bardet-Biedl syndrome, with frequent onset during infancy.[2,3] Obesity and hyperphagia are among the most distressing manifestations of Bardet-Biedl syndrome,[4] with a substantial burden to patients and their caregivers.[5,6] Alström syndrome, a rare genetic disease also associated with cilium dysfunction, is characterised by early-onset obesity, hyperphagia, and multisystem dysfunction (including visual and auditory impairments, renal dysfunction, and cardiomyopathy).[7]

Bardet-Biedl syndrome and Alström syndrome are associated with rare genetic variants. Variants in 27 genes have been identified and are known to cause Bardet-Biedl syndrome, and the associated proteins assist in formation or function of cilia.[2,8–11] Alström syndrome is caused by





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# Experienced Rare Disease Team in Place to Support Ongoing Growth in BBS

**Territory managers in the field**

**Access team supporting reimbursement**

Rhythm InTune
Support made personal



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# Market Insights: What we've Learned about the HO Opportunity

**Diagnosis**

**Disease management**

**Access**

# Current Challenges with Diagnosing and Treating HO

**Distinct** and **variable presentation**

**Underdiagnosed** and **treated as general obesity**

**Further education needed** on signs and symptoms

> *Immediately after the surgery, I was ravenously hungry. I gained 20 pounds in two weeks, and that was on just what the hospital was feeding me. I was hungry a lot, and I have struggled with fatigue ever since then."*
>
> ***- Brain Tumor Survivor***



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# Patient Care Highly Complex Following Hypothalamic Injury

## Shock of tumor diagnosis

Multiple interventions for hormonal insufficiencies

Transient weight changes with corticosteroids or other therapies

## Primary concerns following hypothalamic injury

Pituitary insufficiencies

Hypothalamic obesity (Hyperphagia and fatigue)

Diabetes insipidus

**Urgent need for new and effective treatment options for hypothalamic obesity**



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# Setmelanotide Product Profile Resonates with Endocrinologists

**In a hypothetical placebo-controlled trial, how compelling would you find 15% BMI reduction vs 0% for placebo?**

**94%** extremely compelling or compelling

**100%** would prescribe setmelanotide to patients with HO

(N=50)

*I love seeing that there is improvement in a patient-centered outcome – that being the change in hunger. For me, it's not all weight-centric all the time – I think we get really focused on that"*

***- Endocrinologist***



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# Anticipate Strong Commercial, Medicaid Coverage for Setmelanotide for HO

**Anticipate similar or better coverage than BBS**

Vast majority of commercial and Medicaid lives covered

Prior authorizations aligned with label

*Adjusted to include only patients <18yo in states where approvals for reimbursement are limited to EPSDT



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# Strategic Priorities for IMCIVREE Launch in Hypothalamic Obesity

**Differentiating MC4R pathway diseases**

**Expediting patient diagnosis**

**Establishing IMCIVREE as *the* foundational treatment upon approval**

**Securing market access**



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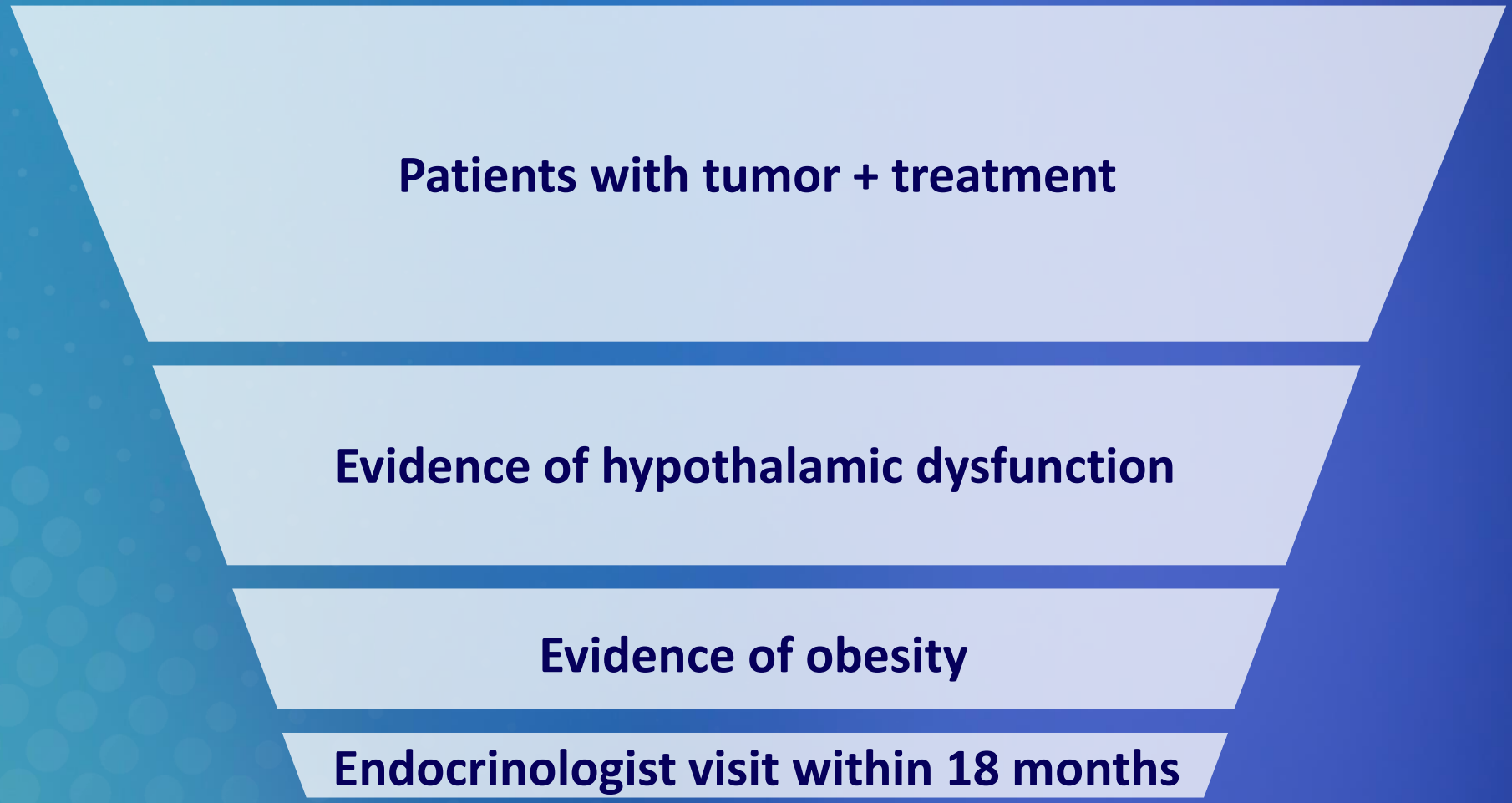
# Data-driven Approach to Identifying Patients



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# Specialty Opportunity Focused on Endocrinologists




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# Immediate Focus on Patients Diagnosed or Suspected of Having HO

**~2,000**

patients diagnosed or suspected to have acquired hypothalamic obesity

# The Right Teams are in Place

**16**
**Territory Managers for BBS**

**43**
**Territory Managers for HO**

**Area development managers and medical science liaisons remain in the field**

**Scaled access and patient support teams for launch**



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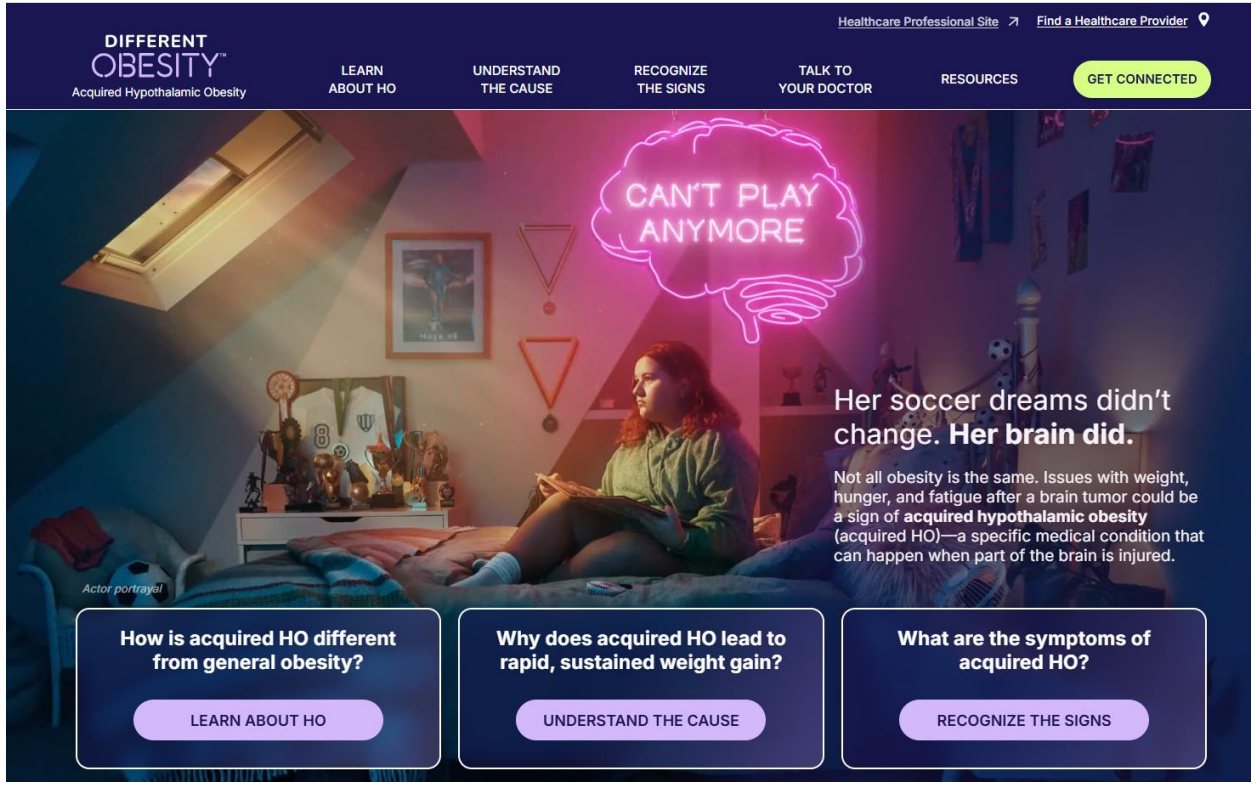
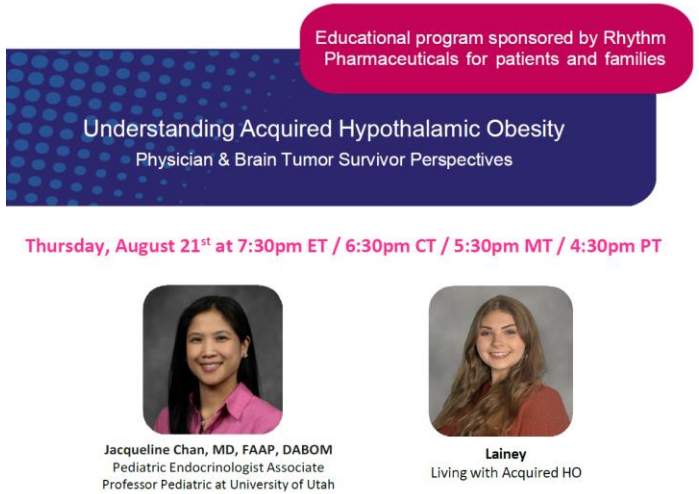
# Hypothalamic Disease Education Programming Underway




DifferentObesity.com





# PDUFA



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# Closing

**David Meeker, MD**

***Chairman, CEO and President***

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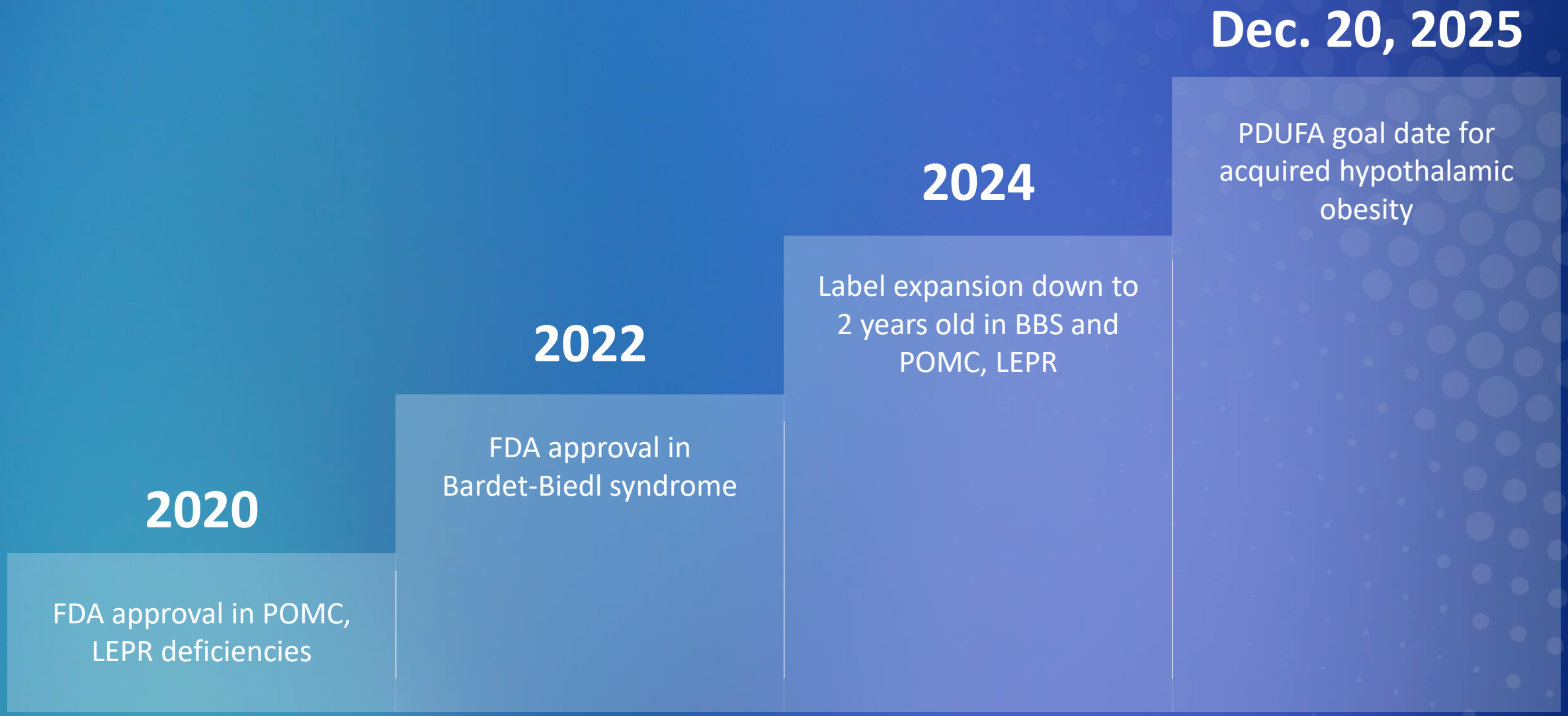
# Expanding the Opportunity for IMCIVREE (setmelanotide)



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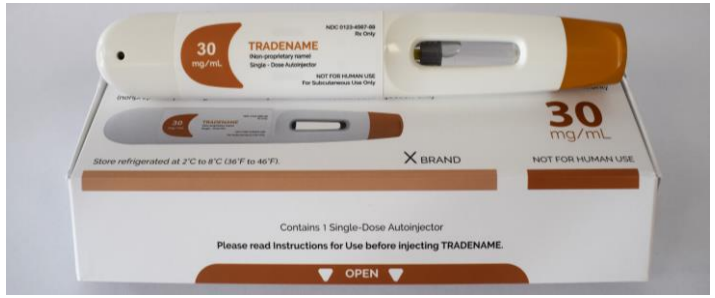
# Bivamelagon, RM718 May Extend MC4R Franchise Well into 2040s


## Bivamelagon (LB54640)

- Daily oral, highly selective MC4R agonist
- Achieved positive Ph2 results as announced in July 2025
- Phase 3 trial anticipated to begin 2026




## RM-718

- 7-amino acid peptide administered QW
- In vivo results: supportive of no off-target cardiovascular effects, like setmelanotide; No hyperpigmentation observed
- Ongoing Ph1 trial in healthy volunteers and patients with acquired hypothalamic obesity



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# Key Takeaways

1

Clear **unmet need** for an effective treatment for **acquired hypothalamic obesity**

2

Rhythm is **getting ready** to launch

3

Acquired HO is a **transformative global opportunity** for Rhythm



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# Q&A

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