# Rhythm Pharmaceuticals

## Second Quarter 2025 Financial Results and Business Update

**August 5, 2025**

# On Today's Call

- David Connolly, Executive Director of Investor Relations and Corporate Communications
- David Meeker, MD, Chair, President and Chief Executive Officer
- Jennifer Lee, Executive Vice President, Head of North America
- Yann Mazabraud, Executive Vice President, Head of International
- Hunter Smith, Chief Financial Officer

# 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 that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding 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, including, setmelanotide, bivamelagon, and RM-718; the potential use of setmelanotide in patients with acquired hypothalamic obesity; our expectations surrounding potential regulatory submissions, progress, or approvals for any of our product candidates; the announcement of data from our clinical trials, including the substudy evaluating setmelanotide for patients with congenital hypothalamic obesity, the Phase 3 EMANATE trial evaluating setmelanotide in genetically caused MC4R pathway diseases, Part C of the Phase 1 trial evaluating RM-718 and the open-label Phase 2 trial evaluating setmelanotide in patients with Prader-Willi syndrome; the ongoing enrollment in our clinical trials; existing or future collaboration agreements; our business strategy and plans; our anticipated financial performance and financial position for any period of time, including estimated Non-GAAP Operating Expenses for the quarter ending June 30, 2025; and the sufficiency of our cash, cash equivalents and short-term investments to fund our planned operations for at least 24 months; our anticipated achievement of profitability or operating cash flow break even in 2027 or any other time period; 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, 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 relating to product liability lawsuits, inability to maintain collaborations, or the failure of these collaborations, our reliance on third parties, risks relating to intellectual property, our ability to hire and retain necessary personnel, general economic conditions, risks related to internal control over financial reporting, and the other important factors discussed under the caption “Risk Factors” in our Form 10-Q for the quarter ended June 30, 2025 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.

**Non-GAAP Financial Measures**

This presentation and the accompanying oral presentation include Non-GAAP Operating Expenses, a supplemental measure of our performance that is not required by, or presented in accordance with, U.S. GAAP and should not be considered as an alternative to operating expenses or any other performance measure derived in accordance with GAAP. We define Non-GAAP Operating Expenses as GAAP operating expenses excluding stock-based compensation and fixed consideration related to in-licensing. We caution investors that amounts presented in accordance with our definition of Non-GAAP Operating Expenses may not be comparable to similar measures disclosed by our competitors because not all companies and analysts calculate this non-GAAP financial measure in the same manner. We have not provided a quantitative reconciliation of forecasted Non-GAAP Operating Expenses to forecasted GAAP operating expenses because we are unable, without making unreasonable efforts, to calculate the reconciling item, stock-based compensation expenses, with confidence. This item, which could materially affect the computation of forward-looking GAAP operating expenses, is inherently uncertain and depends on various factors, some of which are outside of our control.

# David Meeker, MD

**Chair, President and CEO**

# Long-term Growth Strategy: Advancing Multiple MC4R Agonists in Several Disease States with Significant Unmet Need

## Q2’25 Highlights

- Continued solid growth in global IMCIVREE® (setmelanotide) sales in Q2 2025
- On track to complete U.S. and EU regulatory submissions for setmelanotide in acquired hypothalamic obesity (HO) in Q3 2025
- Strong results from Ph2 trial of oral bivamelagon in acquired HO
- Well-capitalized with ~$189.2M net proceeds raised from upsized public offering of common stock

# Significant Market Opportunity for MC4R Agonists

## U.S. patent protection for next-generation assets bivamelagon and RM-718 extends into 2040s

### Approved for IMCIVREE (setmelanotide) in U.S., EU,+

**4,000 – 5,000***
Bardet-Biedl syndrome

**600 – 2,500***
POMC, PCSK1 and LEPR deficiencies

### Acquired hypothalamic obesity

**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]

### Additional potential

**~29,000****
EMANATE
Lead indications

**+DAYBREAK Ph2:**
Positive signals observed in **six new genes and gene families**

*Estimated prevalence of U.S. patients based on company estimates; does not include ex-U.S. prevalence estimates. Estimated U.S. patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results that factor in variant classifcations, as applicable, current estimated responder rates and that 1.7% of the U.S. population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018†); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017). **Estimated prevalence in United States of SH2B1 and POMC and/or PCSK1 cohorts.

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.

# Qualitative Interviews following Ph3 Trial in HO Advance Disease Understanding, Improvements with Setmelanotide Therapy

**30 patients, caregivers share experiences with HO, assessments on weight change, fatigue and physical activity**

> But the weight just came on and it came on drastically...He went **from 37 pounds to 130 pounds** in just a little over a year."
> **CAREGIVER**

> She was **waking up in the middle of the night** in her sleep crying out for food and saying she was hungry."
> **CAREGIVER**

> Tremendously changed. I was **always hungry**. My mom had to put a **lock on the kitchen**…"
> **ADOLESCENT**

> Going to a store and walking around...I remember always looking around, looking for somewhere to sit."
> **ADOLESCENT**

## Setmelanotide Therapy

> It's meaningful to me because I feel like **I'm in control of myself**...I feel like a normal person."
> **ADULT**

> I remember being so miserable and just horrible about myself...**now I feel good**."
> **ADOLESCENT**

> Not feeling starving all of the time has significantly impacted his ability to participate in the world... to see him **find joy** in other things has been a really big impact."
> **CAREGIVER**

Adapted from ENDO 2025 poster presentation: 'Experiences and Observations With Acquired Hypothalamic Obesity: A Qualitative Interview Substudy.' *Qualitative interview data analysis and reporting were completed prior to unblinding.

# Exit Interview Participants Report Weight Gain, Increased Hunger and Decreased Energy with Acquired Hyothalamic Obesity

| | PARTICIPANTS AGED ≥ 12 years to < 18 years (n = 4) | ADULT TRIAL PARTICIPANTS AGED ≥ 18 years (n = 10) | CAREGIVERS OF TRIAL PARTICIPANTS | | Total (n = 30) |
|---|---|---|---|---|---|
| | | | AGED < 12 years (n = 8) | AGED ≥ 12 years (n = 8) | |
| Weight gain | 4 | 10 | 8 | 8 | 30 |
| Increased hunger frequency | 4 | 10 | 8 | 8 | 30 |
| Increased hunger intensity | 3 | 9 | 8 | 8 | 28 |
| Changes in eating habits | | | | | |
| *Never felt full* | *2* | *3* | *6* | *4* | *15* |
| *Less likely to feel full* | *2* | *7* | *2* | *3* | *14* |
| *Decreased control of eating* | *3* | *9* | *8* | *8* | *28* |
| *Increased food eaten* | *3* | *9* | *8* | *8* | *28* |
| Decreased energy levels | 4 | 9 | 8 | 8 | 29 |
| *Fatigue* [a] | *4* | *9* | — | — | |
| Decreased physical activity | 4 | 8 | 8 | 8 | 28 |

[a] The concept of fatigue was probed only with patient participants and not with caregivers; Adapted from ENDO 2025 poster presentation: 'Experiences and Observations With Acquired Hypothalamic Obesity: A Qualitative Interview Substudy.'

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

***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.

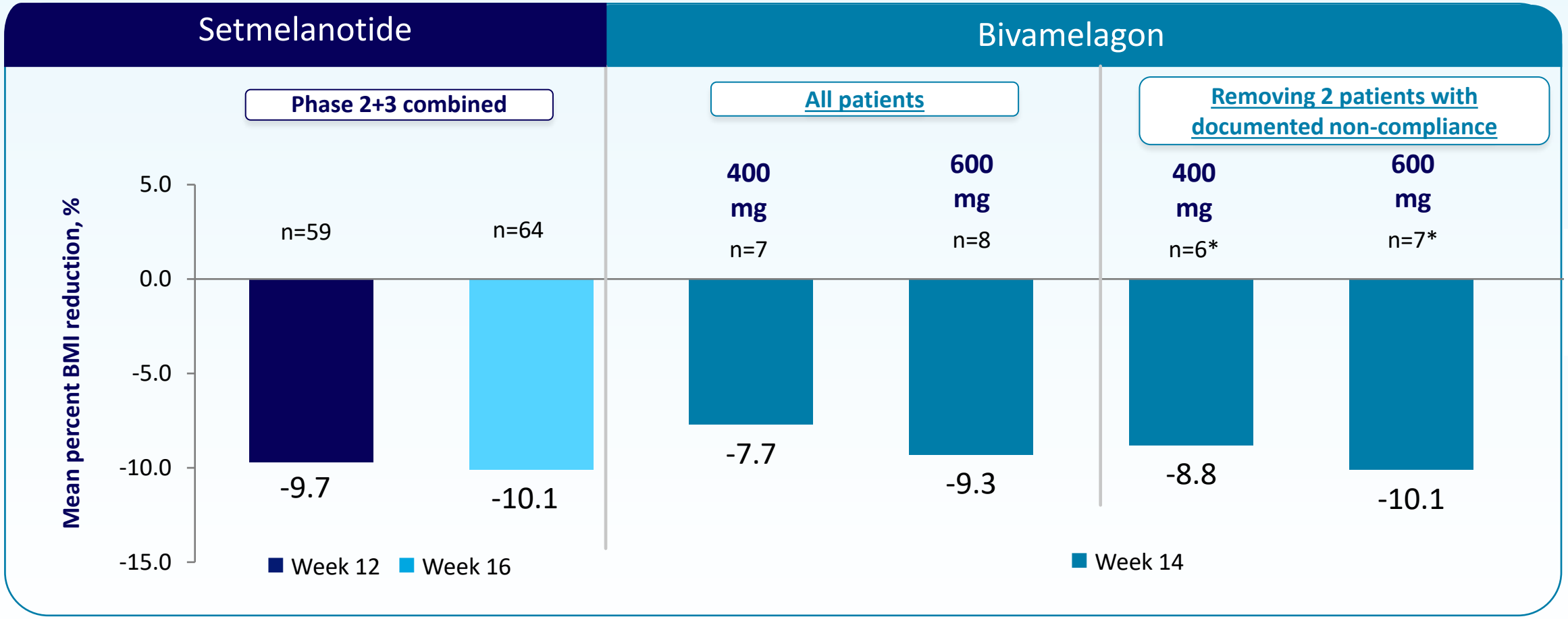
# Bivamelagon Achieved Statistically Significant BMI Reductions at All Doses in 14-week, Phase 2 Trial

| Placebo | 200 mg | 400 mg | 600 mg |
|---|---|---|---|
| **+2.18%** | **-2.68%** | **-7.69%** | **-9.31%** |
| Mean BMI increase from baseline (n=7) | Mean BMI reduction from baseline (n=6) **p-value = 0.0180** | Mean BMI reduction from baseline (n=7) **p-value = 0.0002** | Mean BMI reduction from baseline (n=8) **p-value = 0.0004** |

Note: Arithmetic means and p-values from 2-sided t-test shown above.

Post-hoc analysis:

# Bivamelagon Achieved BMI Reductions Consistent with Setmelanotide




*1 patient in 400 mg arm and 1 patient in 600 mg arm removed due to Week 1 discontinuation and documented partial compliance respectively.



Rhythm® PHARMACEUTICALS

# **IMPROVE 2025** Draws ~150 Physicians and Researchers from 19 Countries with Focus on Rare MC4R Pathway Diseases




Rhythm® PHARMACEUTICALS

# Multiple Anticipated Milestones

| | |
|---|---|
| **Q3 2025** | Complete **U.S. and EU regulatory submissions** for setmelanotide **in acquired hypothalamic obesity** |
| **H2 2025** | Disclose preliminary results from exploratory **Ph2 Prader-Willi trial** evaluating setmelanotide |
| **Q1 2026** | Complete enrollment in **Part C** of **Ph1 trial evaluating RM-718** in acquired hypothalamic obesity |
| **Q1 2026** | Topline data from **12-patient Japanese cohort** of **Ph3 acquired hypothalamic obesity trial** evaluating setmelanotide |
| **Q1 2026** | Topline data from **Ph3 EMANATE trial** evaluating setmelanotide in four genetically-defined, rare MC4R pathway diseases |
| **H1 2026** | Complete enrollment in **Ph3 congenital hypothalamic obesity substudy** evaluating setmelanotide |
| **2026** | Initiate **pivotal Ph3 trial** evaluating **oral bivamelagon** in **acquired hypothalamic obesity** |

# Jennifer Lee

**EVP, Head of North America**

# Steady Growth in BBS Commercial Performance Continued in Q2

**Consistent demand growth fueled** by productive patient finding efforts

Increased **breadth and depth** of prescribers

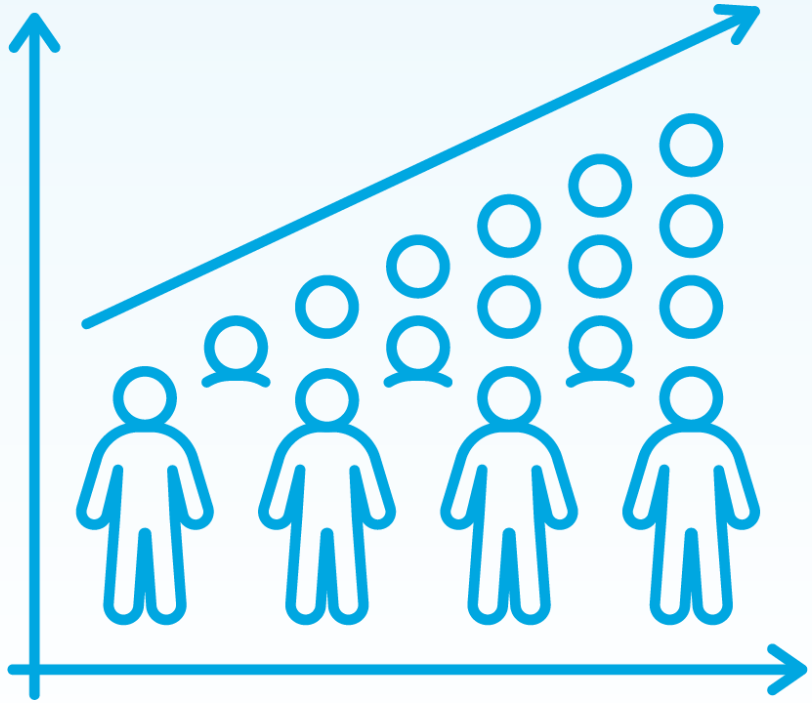
**Growth** in prescriptions **for pediatric patients <18**

Ongoing efforts to prepare for launching in **acquired HO**




Rhythm® PHARMACEUTICALS

# Consistent Growth in IMCIVREE Prescriber Base for Patients with BBS

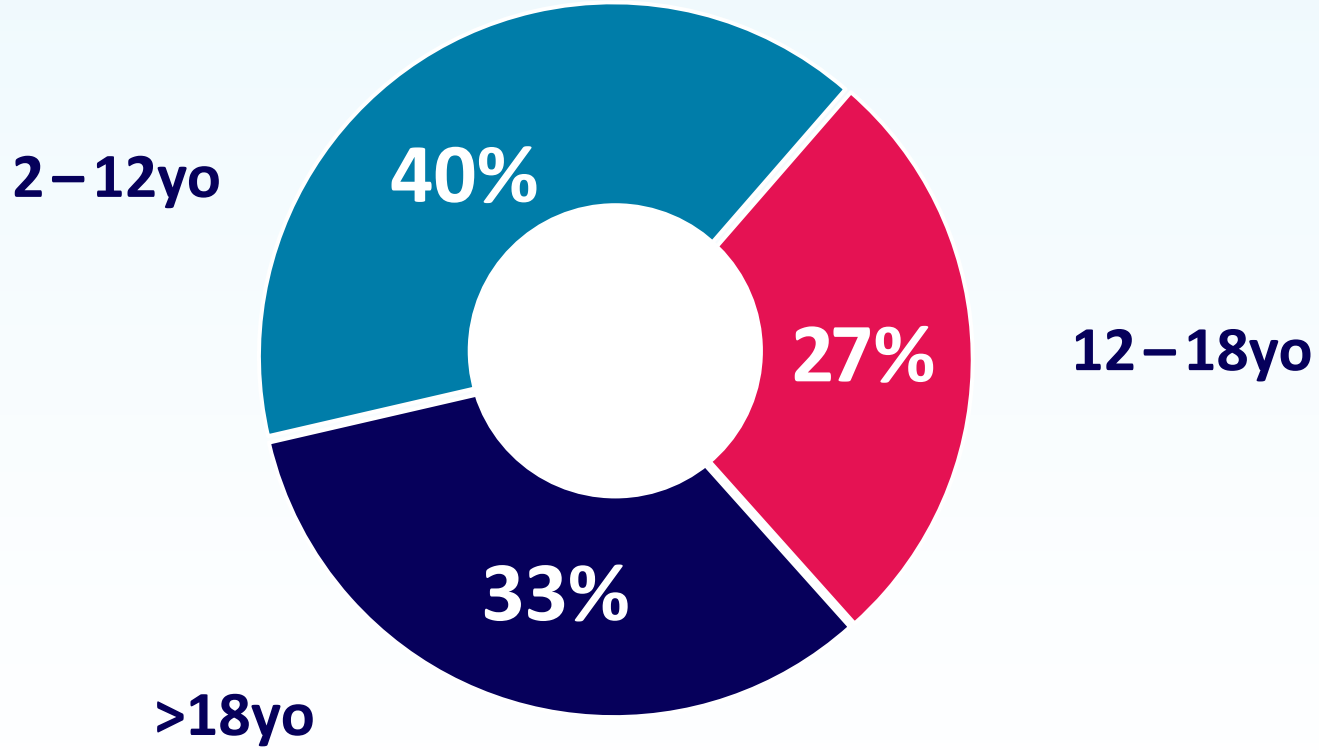


**38%** **increase in cumulative prescribers Q2 ‘24 to Q2 ‘25**

**9%** **increase in cumulative prescribers Q1 ‘25 to Q2 ‘25**

# Label Expansion down to 2yo Broadens Physician Engagement

**Q2'25 IMCIVREE prescriptions by age**



# Rhythm Update on Commercial Readiness for Acquired Hypothalamic Obesity

# Yann Mazabraud

**EVP, Head of International**

# IMCIVREE available in >20 countries outside the United States

## Drivers of Growth

**Ongoing BBS, POMC/LEPR sales**

**Early-access HO programs in France and Italy**

**Named patient sales**

# IMPROVE: Focus on Peer-to-peer Scientific Exchange and Sharing Best Practices

## Workshops

**Care for patients with rare MC4R pathway diseases**

**Erica van den Akker** *(The Netherlands)* & **Martin Wabitsch** *(Germany)*

**Multidisciplinary care and treatment perspectives for patients aged under 6 years**

**Peter Kühnen** *(Germany)* & **Jesús Argente** *(Spain)*

**How to manage the different comorbidities and comedications in patients with acquired hypothalamic obesity (aHO)**

**Hanneke van Santen** *(The Netherlands)* **& Hermann Müller** *(Germany)*

**43** poster presentations

**3** recognized as IMPROVE 2025 winners

**Stefanie Zorn,** *Germany*

Early childhood height, weight, and BMI development in children with monogenic obesity: a European multicenter, retrospective, observational study

**Belma Haliloglu,** *Türkiye*

Dykens' Hyperphagia Questionnaire as a Screening Test for Monogenic Obesity

**Jasmin Giesche,** *Germany*

Establishment of a sandwich ELISA for the detection of ASIP to identify novel patients carrying mutations in the ASIP gene

# Hunter Smith

**Chief Financial Officer**

# Well-capitalized Following Oversubscribed, Upsized Stock Offering in July

**$291M**

cash, cash equivalents and short-term investments as of June 30, 2025

Cash on-hand does not include:

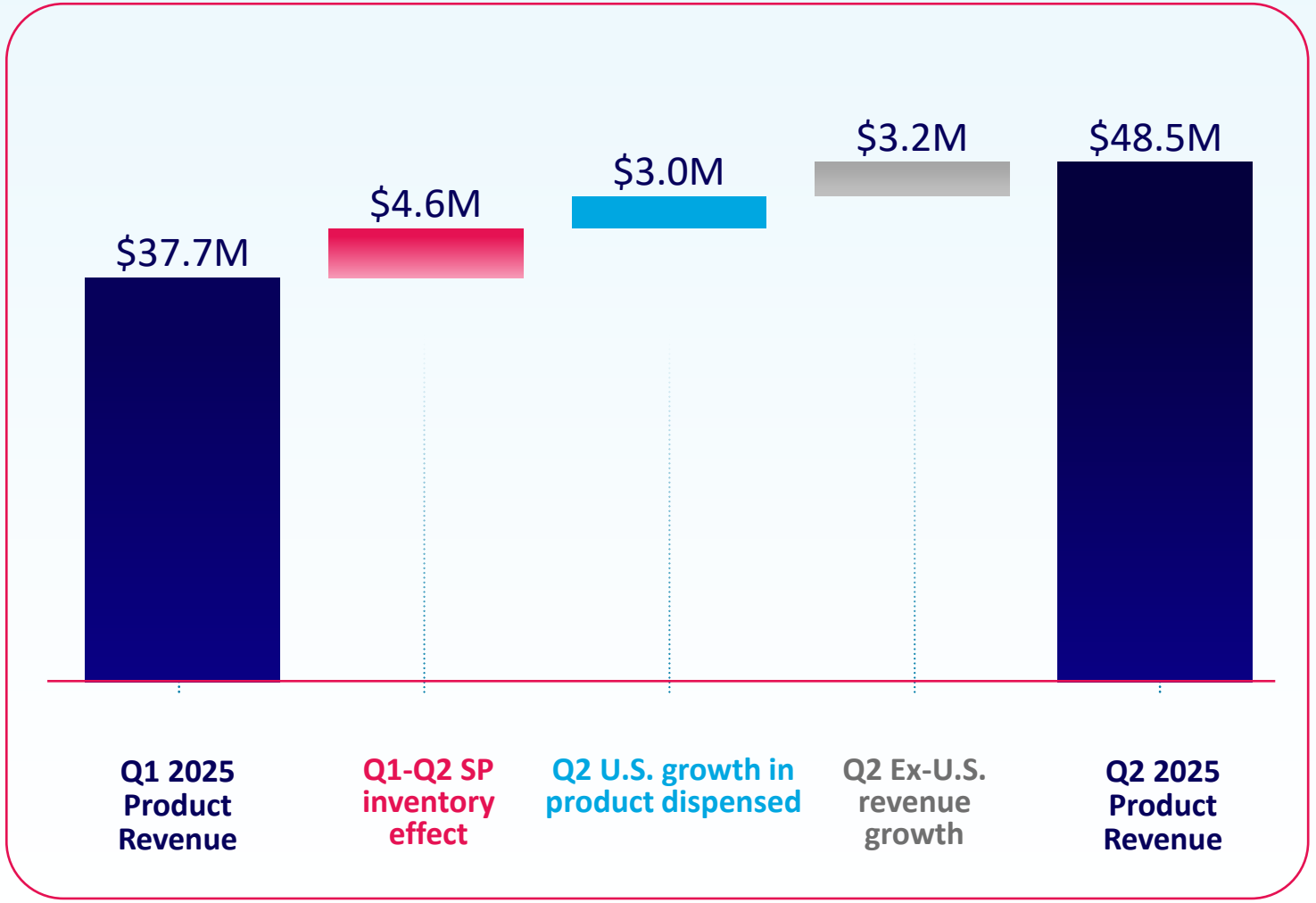
**+$189.2M** net proceeds from public offering of common stock that closed July 11, 2025

**-$40M** LGC in-license milestone paid in July 2025; R&D expense accounted for in 2024

RYTM expects cash to be sufficient to fund planned operations **for at least 24 months**

# Q2 ’25: Consistent Growth in Patient Demand Continues in U.S. and ex-U.S.

- **$48.5M** in net product revenue from global sales; 29% sequential growth
- Patients on reimbursed therapy grew by ~12% globally QoQ
- Ex-U.S. growth driven by increased numbers of BBS patients, HO early access, and named patient sales




SP= U.S. specialty pharmacy

# 2Q 2025 Financial Snapshot

| ($ in millions, except per share data and shares outstanding) | Three months ended June 30, 2025 | Three months ended June 30, 2024 |
|---|---|---|
| Product revenue, net | $48.5M | $29.1M |
| R&D expenses | $42.3M | $30.2M |
| SG&A expenses | $45.9M | $36.4M |
| Net Loss attributable to common stockholders | $(48.0)M | $(33.6)M |
| Common shares outstanding | 63,684,359 | 61,011,824 |
| Net Loss per share attributable to common stockholders – basic and diluted | ($0.75) | ($0.55) |
| Cash, cash equivalents and short-term investments position (period end) | $291.0M | $319.1M |

# Operating Expenses in Q2 ‘25; Reiterate Full-year Guidance

## Q2 ‘25 OpEx

**$88.2M**

Q2 2025 **OpEx** includes

**$15.9M**

in stock-based compensation expense

## 2025 OpEx Guidance unchanged

**$285M to $315M**

anticipated **non-GAAP Operating Expenses*** for 2025 includes:

**SG&A:** $135M to 145M

**R&D:** $150M to $170M

**$40M** LGC in-license milestone paid in July 2025 accounted for as R&D expense in 2024

* Non-GAAP Operating Expenses is a non-GAAP financial measure. We define Non-GAAP Operating Expenses as GAAP operating expenses excluding stock-based compensation and fixed consideration related to in-licensing. For more information, see slide 3 – Non-GAAP Financial Measures

# Questions