Rhythm Pharmaceuticals

First Quarter 2022 Financial Results and Business Update

May 3, 2022

Forward Looking Statements

This presentation contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including without limitations statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipated timing for initiation of clinical trials and release of clinical trial data and our expectations surrounding potential regulatory submissions, approvals and the timing thereof, our business strategy, prospects and plans, including regarding commercialization of setmelanotide, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, and the sufficiency of our cash, cash equivalents and short-term investments to fund our operations. Statements using words such as "expect", "anticipate", "believe", "may", "will" 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 impact of management departures and transitions, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our expenses, the impact of the COVID-19 pandemic on our business 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.

On Today's Call

David Meeker, MD, Chair, President and Chief Executive Officer

Jennifer Chien, Executive Vice President, Head of North America

Linda Shapiro Manning, MD, PhD, Chief Medical Officer

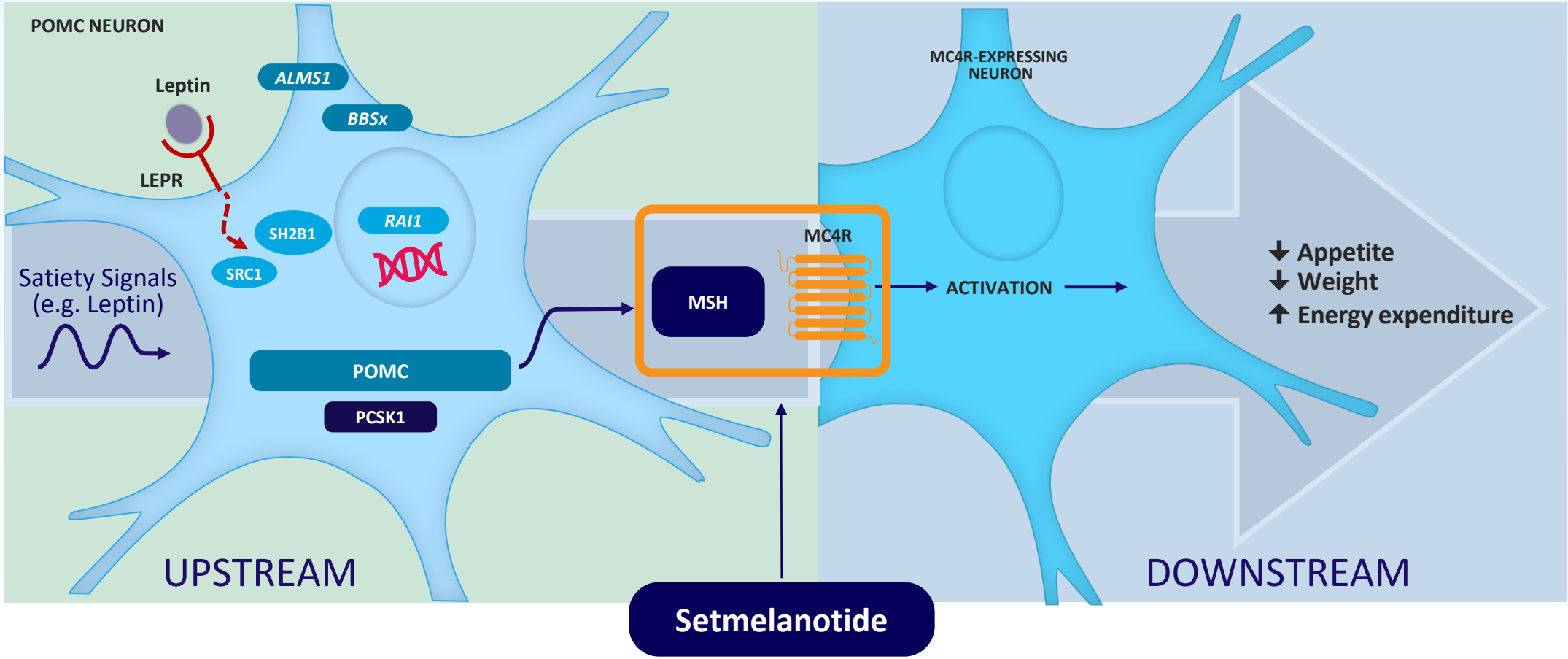
Hunter Smith, Chief Financial Officer

Yann Mazabraud, Executive Vice President, Head of International

David Meeker, MD

MC4R Pathway Biology is Clear and Strong: Regulates Hunger, Caloric Intake, Energy Expenditure and, Consequently, Body Weight

Setmelanotide can redress MC4R pathway impairment contributing to early-onset, severe obesity



On Track for U.S. BBS Launch, International Market Access and Expansion of Addressable Patient Populations through Clinical Development

U.S. Commercial Progress

- Ready for Bardet-Biedl syndrome (BBS) launch at PDUFA goal date of June 16
- BBS: Active patient identification and disease state education efforts ongoing
- IMCIVREE U.S. commercial availability lays strong foundation for BBS

Achieving Market Access in Key International Geographies

- First European commercial sales in France
- Germany sales to begin 2Q 2022
- BBS CHMP* recommendations and EC decision expected this summer and fall

Clinical Development Advancing

- EMANATE, DAYBREAK, hypothalamic obesity, pediatrics and weekly formulation trials ongoing
- Updated data readouts at PES, ENDO
- Hypothalamic, MC4R rescuable interim data expected mid 2022

*CHMP is the European Medicines Agency's Committee for Medicinal Products for Human Use (**CHMP**); EC is European Commission.

First Commercial Sales Achieved in France with Progress in Germany, UK and Additional Key Markets

- First commercial patients started in March under paid early access program
- Access achieved approximately one year ahead of standard schedule

- Exemption from Annex II (lifestyle products) confirmed and published in federal gazette
- Reimbursement dossier to be submitted in May
- Commercial launch expected Q2 2022

United Kingdom

- NICE recommendation expected June

Italy

- Final stages of price negotiations with AIFA

The Netherlands

- Reimbursement dossier submitted in October, ongoing discussion with the Zorginstituut

Spain

- Reimbursement dossier to be submitted before the end of Q2

Sweden

- Reimbursement dossier to be submitted before the end of Q2

Continued Progress in EMANATE and DAYBREAK Trials to Drive Expansion of Setmelanotide's Potential Addressable Market

Phase 3 EMANATE Trial

Four independent sub-studies

6,000†	**Heterozygous POMC/PCSK1 insufficiency**
4,000†	**Heterozygous LEPR insufficiency**
20,000†	**SRC1 insufficiency**
23,000†	**SH2B1 insufficiency**

Phase 2 DAYBREAK Trial

Exploring an additional **10 genes**

Emanate
Obesity and Hunger Clinical Trial

Daybreak
Obesity and Hunger Clinical Trial

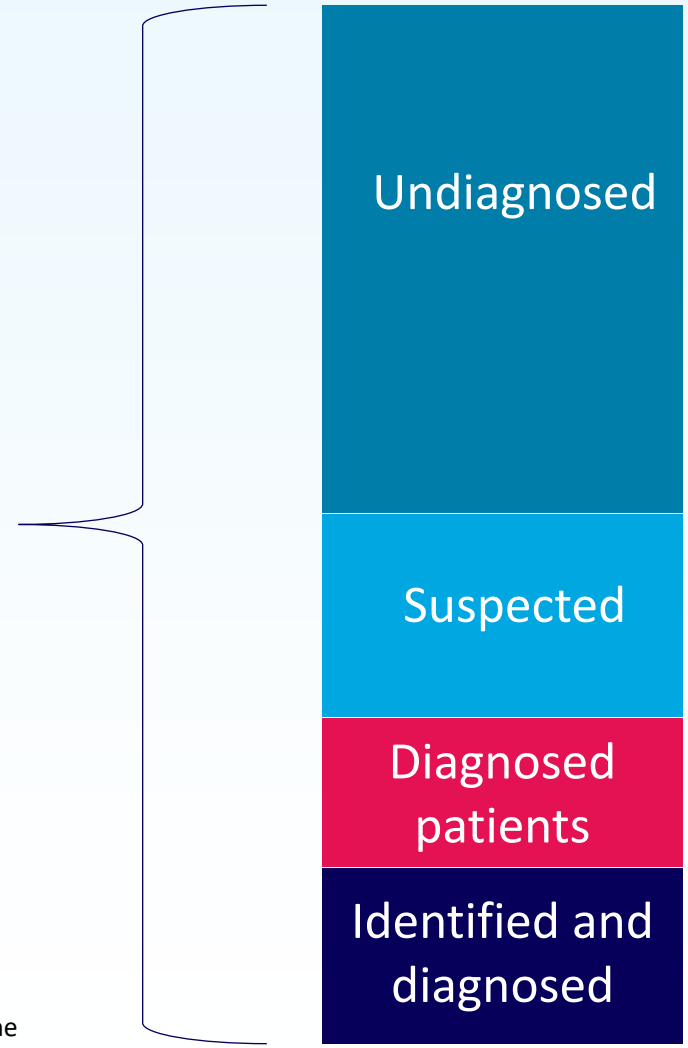
† U.S. patient estimates represent patient population with early-onset, severe obesity who may benefit from setmelanotide therapy based on sequencing results, current estimated responder rates and that 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018); ~95% of individuals with severe early onset obesity continue to have obesity into adulthood (Ward et al 2017).

Jennifer Chien

Commercial Readiness for BBS and Alström Syndrome U.S. Launch

Roadmap to Identifying Patients with BBS

U.S. prevalence estimated to be
1,500 to **2,500**
patients*



>350
Identified and diagnosed patients**

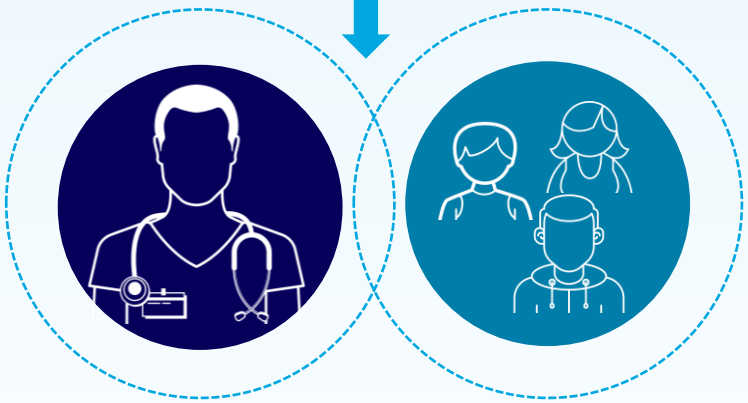
* Company estimate based on published prevalence estimates of one in 100,000 in North America.

** As announced on Feb. 16, 2022.

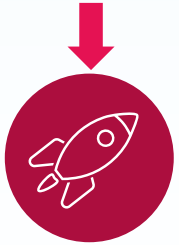
Rhythm® PHARMACEUTICALS

Pre-launch HCP Focus

ENGAGE



1 HCPs with BBS patients and support of the community



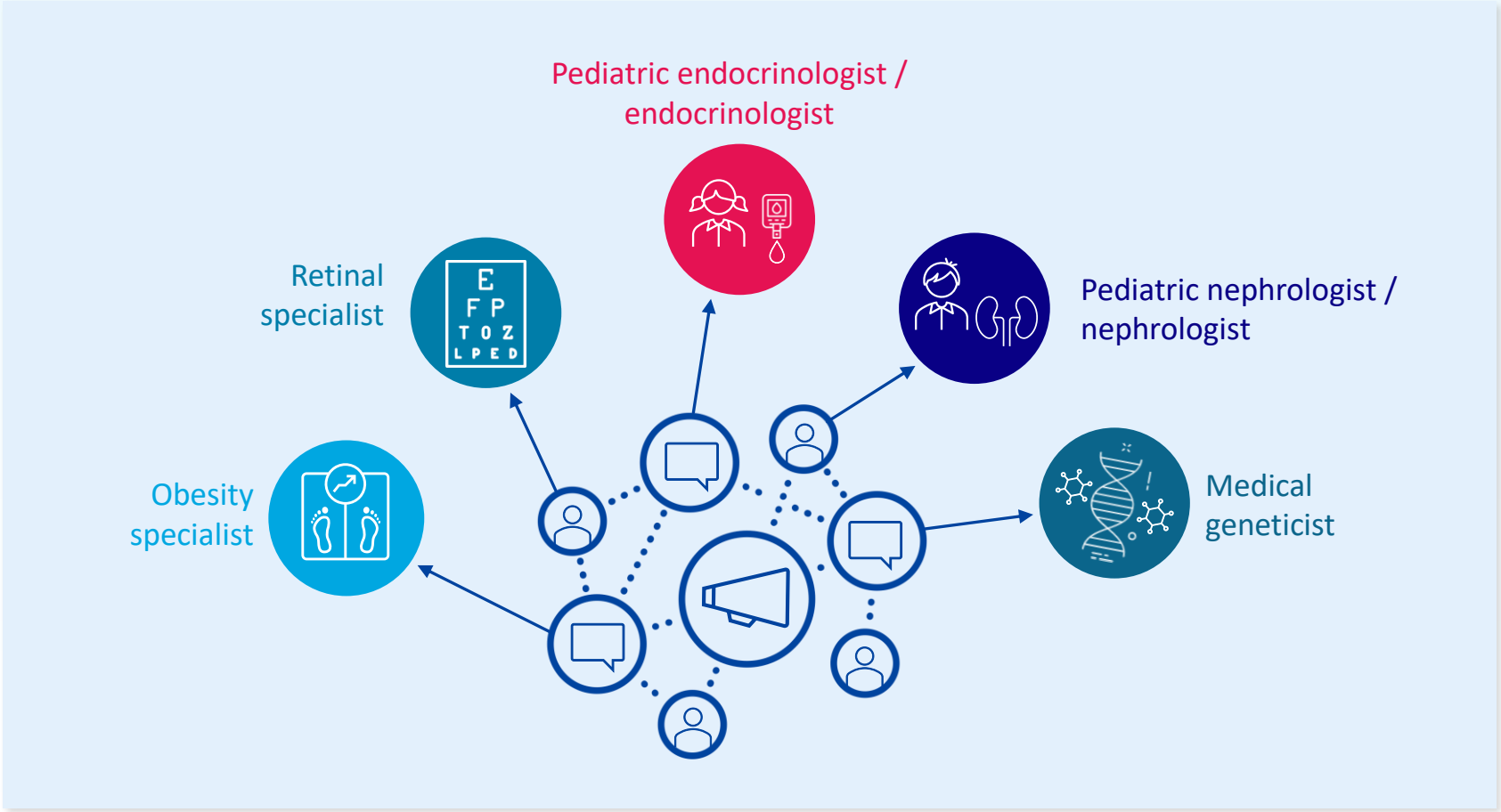
Priority targets to prepare for launch

SUPPORT DIAGNOSIS

2 Uncovering Rare Obesity genetic tests follow up

3 Machine learning HCP targets

Supporting the Build of BBS Care Networks



Rhythm InTune Support Services

Personalized program for patients and health care providers, removes barriers and supports adherence

Rhythm InTune
Support made personal

- ✓Gaining access and coverage
- ✓Ongoing support and education
- ✓Building the community

Introduce IMCIVREE | **Set expectations** | **Injection tips** | **Goal setting** | **Treatment support** | **Adherence** | **Discuss therapy with physician**

Rhythm® PHARMACEUTICALS

Commercial Team Ready to Launch in BBS on Day One

DAY 1

Direct outreach to priority physicians

Rhythm InTune: 1:1 outreach to consented BBS caregivers and patients

Marketing outreach to and programs for health care providers, patients and caregivers

Outreach with patient advocacy organizations

Linda Shapiro, MD, PhD

Regulatory, Clinical & Medical Update

BBS Regulatory Reviews Progressing in US and Europe

FDA PDUFA

June 16, 2022

EU EMA

CHMP opinion in 2H2022

CHMP Positive Opinion for patients with renal impairment announced April 22, 2022*

*The European Medicines Agency's Committee for Medicinal Products for Human Use (**CHMP**) recommended the European Commission approve a modification to the SmPC to allow for IMCIVREE to be prescribed to PPL patients with renal impairment (no dose adjustment in mild to moderate renal impairment; dose adjustment with more gradual dose titration to clinical response in patients with severe renal impairment). An EC decision is anticipated in July 2022.

Multiple Ongoing Clinical Trials Evaluating Setmelanotide

Emanate

Phase 3 Trial

Daybreak

Phase 2 Trial

Hypothalamic Obesity
Phase 2 Trial

Weekly Formulation
Phase 3
Switch Trial

Pediatrics Trial
Phase 3
Patients aged 2 to <6 years

Phase 3 EMANATE Trial to Evaluate Setmelanotide Across Four Rare Genetic Subtypes with Highest Likelihood for Success

Targeted patient populations: Patients with pathogenic, likely pathogenic or suspected pathogenic variants

- Genetic variants with highest likelihood of impairing MC4R pathway function

Primary Endpoint: Change from baseline in BMI; well suited to population including adults and children

First patient: Enrolled in April 2022

~5.1% patients with early-onset obesity test positive for eligible genetic variants with Rhythm's Uncovering Rare Obesity (URO) genetic test

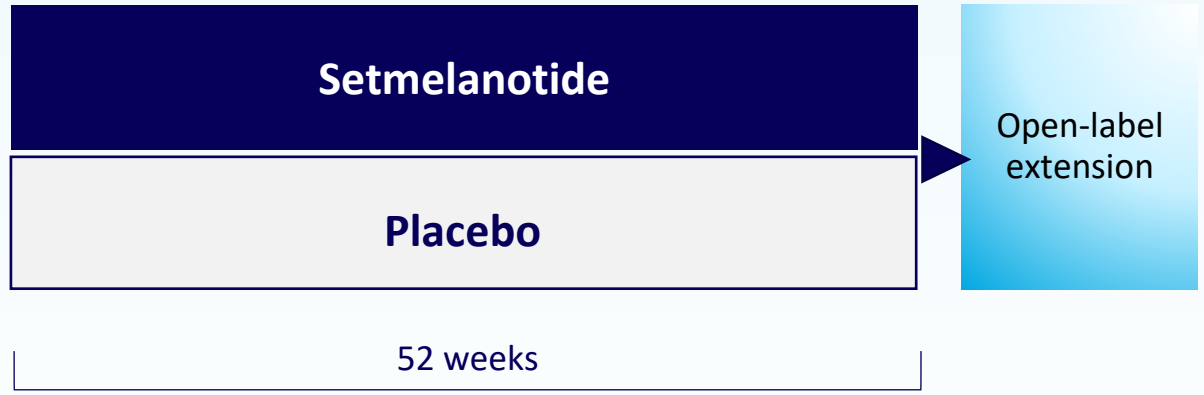
Phase 3 EMANATE Trial Comprised of Four Independent Sub-studies

Design allows for independent data readouts in each sub-study and potential registration for each gene

a.	**POMC/ PCSK1***	**86** patients	• Pathogenic • Likely pathogenic • VUS*-Suspected pathogenic
b.	**LEPR***	**86** patients	• Pathogenic • Likely pathogenic • VUS-Suspected pathogenic
c.	**SRC1**	**112** patients	• All VUS
d.	**SH2B1**	**112** patients	• Pathogenic • Likely pathogenic • VUS

Enrollment 12-18 Months

Each sub-study: Patients randomized 1:1



Endpoints

- Primary: Difference in mean percent change in BMI from baseline to 52 weeks in setmelanotide arm compared to placebo arm
- Key secondary: Additional measurements of effects on weight-related and hunger/hyperphagia endpoints

* VUS – Variant of uncertain significance.

Phase 2 DAYBREAK Trial to Evaluate Setmelanotide Across 10 Genes

Daybreak

Obesity and Hunger Clinical Trial

Relevance to MC4R Pathway: Rhythm's ClinGen-based framework suggests all 10 genes have very strong relevance to MC4R pathway

Efficient, two-stage trial design

- **Open-label run-in** allows for fast signal-seeking in individual gene cohorts
- **Placebo-controlled treatment** period enables robust proof of concept
- Each genetic cohort can read out independently

First patient: Enrolled in January 2022

Approximately 13.1% of patients with early-onset obesity test positive for DAYBREAK-eligible variants with Rhythm's URO

Hypothalamic Obesity: Acute Onset of Hyperphagia, Weight Gain and Other Endocrine-related Sequelae from Injury to Hypothalamus

Rapid onset of acute, severe obesity and hyperphagia post treatment

Most commonly caused by **craniopharyngioma,** a type of brain tumor, and its treatment of tumor resection surgery and/or radiation

No effective therapeutic options:

- Nutrition and physical activity interventions are ineffective
- Patients and families face **new disease burden**

Raymond A. Wood foundation

FDA Patient Listening Session on Hypothalamic Obesity

> He demonstrated excessive hunger upon returning home from the hospital. He foraged at night. We locked up food to avoid having to stay up all night to monitor his night eating."
>
> *-- Caregiver*

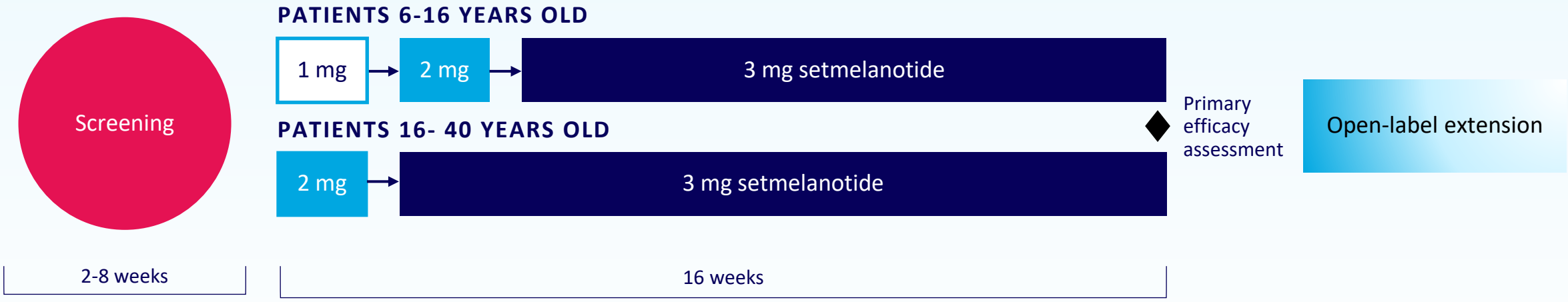
> Hyperphagia is the biggest cause of low quality of life of all the conditions from the tumor (worse than low vision, diabetes insipidus, adrenal insufficiency, etc.)"
>
> *-- Patient*

> Within 6 months I gained 30 pounds and couldn't get a doctor to even hear my concerns or issues regarding the sudden weight gain and lack of muscle tone."
>
> *-- Patient*

Excerpted from FDA Listening Session, hosted in October 2021 by the Raymond A. Wood Foundation

Phase 2 Open-label Trial Designed to Evaluate Setmelanotide's Therapeutic Effect in Patients with Hypothalamic Obesity

Enrollment completed in February 2022; Interim data expected mid-year



Enrollment criteria: Documented evidence of hypothalamic obesity, treated at least 6 months previously; Obesity, with documented change post HO treatment of BMI increase >5% and ≥35 kg/m2 in adults, or BMI Z score increase ≥0.2 and BMI ≥95th percentile for age and gender in patients <18 years old.

Primary Endpoint: Proportion of patients who achieve at least 5% reduction from baseline in BMI

Rhythm Delivers Multiple Presentations at Major Medical Meetings

Pediatric Endocrine Society (PES) Annual Meeting 2022, April 28-May 1:

Presentation Title	Presenting Author
Patient- and Caregiver-Reported Experiences of Hyperphagia in Bardet-Biedl Syndrome Before and During Setmelanotide Treatment	Claire Ervin
Setmelanotide Treatment in Pediatric and Adolescent Patients With Bardet-Biedl Syndrome and Severe Obesity	Dr. Robert Haws
Clinical Safety Summary of Setmelanotide in Healthy Volunteers With Obesity and Patients With Rare Genetic Diseases of Obesity	Dr. Jesús Argente
Impact of Setmelanotide Treatment on Lipid Parameters and Vital Signs in Patients With Bardet-Biedl Syndrome in a Phase 3 Trial	Dr. Andrea Haqq

Endocrine Society Annual Meeting & Expo (ENDO) 2022, June 11-14:

Presentation Title	Presenting Author
Body Mass Index and Weight Reductions in Patients With Obesity Due to Heterozygous Variants in POMC, PCSK1, and LEPR After 1 Year of Setmelanotide	Dr. Jesús Argente
Body Mass Index and Weight Reduction in Patients With SH2B1 Genetic Variant Obesity After One Year of Setmelanotide	Dr. Jesús Argente
Body Mass Index and Weight Reductions in Patients With SRC1 Genetic Variant Obesity After 1 Year of Setmelanotide	Dr. Gabriel Ángel Martos-Moreno
Long-term Efficacy of Setmelanotide in Patients With Bardet-Biedl Syndrome	Dr. Wendy Chung
Long-term Efficacy of Setmelanotide in Patients With Obesity Due to POMC, PCSK1, and LEPR Biallelic Deficiency	Dr. Karine Clément
Setmelanotide in Patients With Heterozygous POMC, LEPR, SRC1, or SH2B1 Obesity: Design of EMANATE – A Placebo-Controlled Phase 3 Trial	Dr. Martin Wabitsch

17
oral and poster presentations

PES Pediatric Endocrine Society
ESHG European Society of Human Genetics
ZOOM forward 22 ECO IFSO-EC Congress on Obesity Maastricht, 4-7 May 2022
ENDO 2022
ECE 2022 24th European Congress of Endocrinology

Hunter Smith
1Q 2022 Financial Results

1Q2022 Financial Snapshot

($ in millions except as noted, per share data and shares outstanding)	Three months ended March 31, 2022	Three months ended March 31, 2021
Product revenue, net	$1.5M	$0.035M
R&D expenses	$32.5M	$19.9M
SG & A expenses	$21.4M	$15.5M
Net income / (loss)	$(52.8)M	$43.8M*
Shares outstanding (basic and diluted share count)	50,326,627	47,638,565**
Net (loss)/ income per share basic and diluted	$(1.05)	$0.92**
Cash, cash equivalents and short-term investments position (period end)	$241.0M	$404.8M

Cash Expected to be Sufficient to Fund Operations into at least 4Q 2023

* Income in 1Q 2021 was primarily due to $99M million received from the sale of Rhythm's priority review voucher in February 2021; ** In the three months ending March 31, 2021, diluted shares were 48,501,697, and diluted income per share was $0.90.

David Meeker, MD
Conclusion

Continued Transformational Progress in 2022

Recently achieved milestones

- ✓ Initiated Phase 2 DAYBREAK trial
- ✓ Initiated Phase 3 “switch study” of weekly formulation
- ✓ Initiated Phase 3 trial in pediatric patients aged 2-6 years old
- ✓ Initiated Phase 3 EMANATE trial
- ✓ Achieved first European sales of IMCIVREE

Anticipated milestones in 2022

1H: PDUFA for BBS and Alström June 16, 2022

1H: Long-term data in BBS; SRC1; SH2B1, heterozygous and biallelic POMC/PCSK1/LEPR

1H: IMCIVREE launch in Germany

Mid 2022: Initial Ph 2 data from in hypothalamic obesity

Mid 2022: Initial Ph 2 data in MC4R rescuable patients

2H: CHMP decision on BBS

2H: IMCIVREE launch in UK and Italy

2H: Initiate Phase 3 “de novo study” of weekly formulation

Questions