Rhythm Pharmaceuticals

Fourth Quarter / Year End 2021 Financial Results

March 1, 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 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, 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. 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

Linda Shapiro Manning, MD, PhD, Chief Medical Officer

Yann Mazabraud, Executive Vice President, Head of International

Hunter Smith, Chief Financial Officer

David Meeker, MD

Multiple Recent Highlights and Achievements

Preparing for BBS U.S. launch

- Severe obesity and hyperphagia
- No approved therapies
- PDUFA goal date now June 16

U.S. IMCIVREE commercial availability meeting expectations

- 4Q21 net sales > $1.8M
- Continued progress with reimbursement from payers
- Patient Support Services in place

Advancing Market Access in Key International Geographies

- GB-A exemption in Germany
- Paid early access to start in France
- RareStone licensed IMCIVREE for development in China

Clinical development programs underway

- DAYBREAK, pediatrics and weekly trials initiated
- Enrollment complete in Phase 2 hypothalamic obesity trial

THE MORRIS FAMILY

Our Life with BBS

Rhythm Continues to Advance to BBS Commercial Launch

Key takeaways from our virtual BBS Commercial Event held on Feb. 16

Unmet need in BBS

- Hyperphagia
- Severe obesity
- Co-morbidities
- Current disease management strategies don't work

Solution

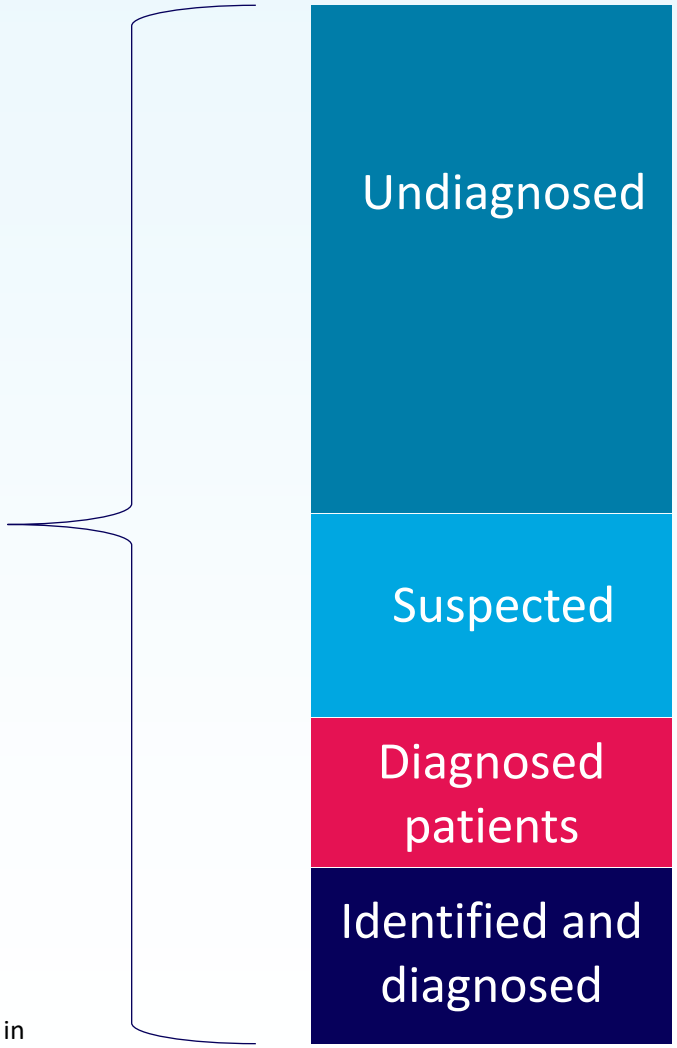
- Address root cause
- Hunger reduction
- Weight loss
- Established safety profile

Rhythm is ready to launch in BBS

- Commercial foundation established
- Experienced commercial team in place
- >350 patients already identified

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.

Rhythm® PHARMACEUTICALS

IMCIVREE Commercial Availability Met Expectations in 2021

$3.2M revenue in 2021

$1.8M revenue in 4Q21

Exclusive Licensing Agreement with RareStone Expected to Expand Reach into Asia

RARESTONE 珑钰集团

In December 2021, RareStone was granted an exclusive license to develop and commercialize IMCIVREE in China, including mainland China, Hong Kong and Macau

RareStone agreed to:

- Seek local approvals to commercialize IMCIVREE for the treatment of obesity and hyperphagia due to POMC, PCSK1 and LEPR deficiency, as well as BBS and Alström syndrome
- Fund efforts to identify and enroll patients from China in EMANATE trial

Under the terms of the agreement:

- RareStone made an upfront payment of $7M and issued $5M in equity to Rhythm
- Rhythm eligible to receive development and commercialization milestones of up to $63.5M, as well as tiered royalty payments on annual net sales of IMCIVREE

Linda Shapiro, MD, PhD

Regulatory and Clinical Update

Rare Disease Day, World Obesity Day and Obesity Care Week

Multiple Trials Evaluating Setmelanotide

Weekly Switch Trial
Phase 3

Pediatrics Trial
(patients aged 2 to <6 years)
Phase 3

Daybreak

Phase 2 Trial

Emanate

Phase 3 Trial

Anticipated Clinical Data Readouts coming in 1H2022

Long-term Extension Trial

- 12-month data for SRC1 deficiency obesity
- 12-month data for SH2B1 deficiency obesity
- 24-month data for Bardet-Biedl syndrome
- 24-month data for biallelic POMC, PCSK1 or LEPR deficiency obesity

Phase 2 Hypothalamic Obesity Study

- Preliminary data

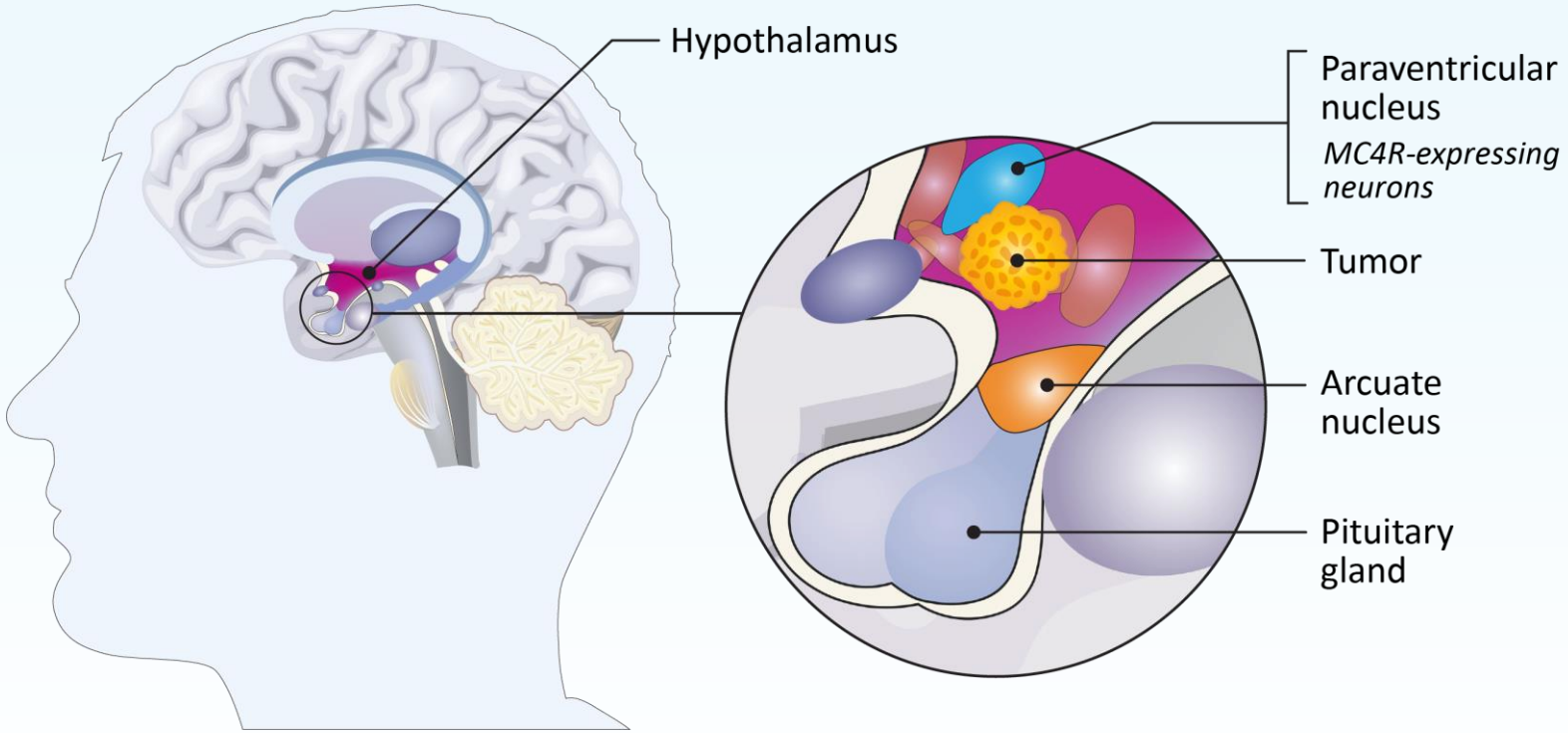
Exploratory Phase 2 Basket Study

- Preliminary data from MC4R deficiency obesity cohorts

Hypothalamic Obesity: An Acquired Form of Obesity Following Injury to the Hypothalamic Region

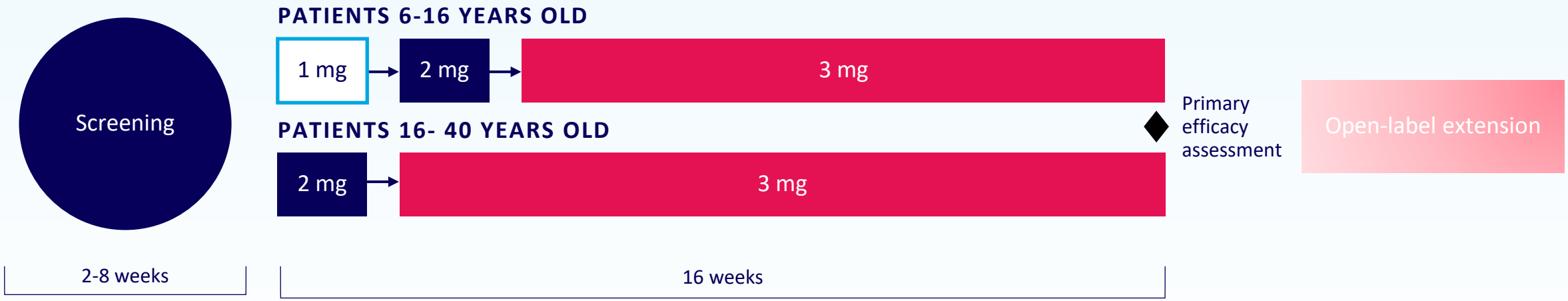
Craniopharyngioma and its treatment - tumor resection surgery and radiation - is considered the most common cause

Clinical and pre-clinical data suggest **MC4R pathway** deficiency following injury to hypothalamic region causes severe obesity



Phase 2 Open-label Study Designed to Evaluate Setmelanotide's Effect on Body Mass Index in Patients with Hypothalamic Obesity

Primary Endpoint: Proportion of patients who achieve at least 5% reduction from baseline in BMI at ~16 weeks of treatment



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.

Yann Mazabraud
International Update

Rhythm's International Organization Designed to Achieve Market Access in Key Markets

>100

identified patients with biallelic POMC, PCSK1 or LEPR in EU4 + UK

Experienced team across EU4 + UK

+ the Netherlands, the Nordics, Turkey and Argentina

EU Rare Diseases community better organized

- KOLs and Centers of Excellence
- Rare diseases national plans and National Centers of Reference
- European Rare Diseases Networks

Rare Genetic Diseases of Obesity better understood and diagnosed in the EU4 + UK

- 30+ years of academic and medical research in rare genetic diseases of obesity

Advancing Access to IMCIVREE in Europe and UK

July 2020
Submission of Marketing Authorization Application to the European Medicines Agency for Setmelanotide in POMC and LEPR Deficiency Obesities

October 2020
Initial hire in the International organization

July 2021
European Commission Authorization of IMCIVREE® for the Treatment of Obesity and Control of Hunger Associated with POMC, PCSK1 and LEPR Deficiency

September 2021
Marketing Authorization of IMCIVREE® in the United Kingdom

October 2021
Submission of Type II Variation Application to EMA for IMCIVREE® for Bardet-Biedl syndrome

2022
First commercial sales expected in Germany and France

2020 | 2021 | 2022

IMCIVREE Featured in EMA's *Human Medicines Highlights of 2021*

- **92 positive EMA opinions in 2021**

- **8 "outstanding contributions to public health"**
  - Cancer: Abecma, Trodelvy
  - Gastroenterology/Hepatology: Bylvay
  - Immunology/Rheumatology/Transplantation: Tavneos, Voxzogo
  - **Metabolism: Imcivree**
  - Neurology: Evrysdi
  - Ophthalmology: Enspryng

First Commercial Sales Expected in Germany in Second Quarter 2022

- KOL support
- Ongoing exclusion from Annex II (list of “lifestyle” indications and products –not reimbursed by health insurances)
- German Federal Joint Committee (GB-A) plenary session on January 20th, 2022
  - Strong vote in favor of IMCIVREE’s exemption
  - First-ever drug designed to affect weight loss to be exempted
- First sales expected to happen in Q2 in Germany

First Commercial Sales Expected in France in Second Quarter of 2022

- KOL support
- French Haute Autorité de Santé (HAS) granted paid early access for IMCIVREE
  - "AP2" granted for POMC & LEPR on January 19th, 2022
- Patients within label (> 6 years old) can be treated with IMCIVREE without limitations and without prior authorization
- First sales expected to happen in Q2 in France

Additional Progress in Key International Markets on Track

United Kingdom

- Selected for Highly Specialized Technology evaluation; Positive discussion at initial NICE Committee meeting in December 2021

Italy

- Reimbursement dossier submitted to Italian Medicines Agency (AIFA) in July 2021

Spain

- Reimbursement dossier ready for submission; Agency of Medicines and Medical Devices (AEMPS) issued positive Therapeutic Positioning Report with no restriction to label

The Netherlands

- Reimbursement dossier submitted

Israel

- Patients identified for named patient sales; Reimbursement dossier ongoing

Advancing Submissions and Market Access Efforts for BBS in Europe

CHMP decision expected 2H2022

Estimated European prevalence estimated to be

~2,500*

patients with BBS

More than

1,500

individuals identified in

EU4 + UK

at ~20 academic medical centers each with

>40 BBS patients

* Based on company estimates.

Hunter Smith
4Q/YE 2021 Financial Results

Q4 and FY 2021 Financial Highlights Cash Expected to be Sufficient to Fund Operations into 2H 2023

($ in millions except as noted, per share data and shares outstanding)	Three months ended December 31, 2021	Twelve months ended December 31, 2021
Product revenue, net	$1.8	$3.2
R&D expenses	$31.6	$104.1
SG & A expenses	$21.0	$68.5
Net loss	$(42.9)	$(69.6)
Shares outstanding (basic and diluted share count)	50,270,801	49,600,294
Net loss per share basic and diluted	$(0.85)	$(1.40)
Cash, cash equivalents and short-term investments position as of 12/31/21		$294.9
Cash expected to be sufficient to fund operations into 2H 2023		

David Meeker, MD
Conclusion

Progress Expected 2022

	1H 2022
✓	Initiate Phase 2 DAYBREAK trial
✓	Initiate Phase 3 “switch study” of weekly formulation
✓	Initiate Phase 3 trial in pediatric patients aged 2-6 years old
	Initiate Phase 3 EMANATE trial
	PDUFA for BBS and Alström syndrome June 16, 2022
	Initial data from Phase 2 in MC4R patients
	Initial data from Phase 2 trial in hypothalamic obesity
	Long-term data in BBS; biallelic POMC/PCSK1/LEPR
	2H 2022
	Initiate Phase 3 “*de novo* study” of weekly formulation
	CHMP decision on BBS

Questions