Rhythm Pharmaceuticals

First Quarter 2023 Financial Results and Business Update

May 2, 2023

On Today's Call

David Connolly, Executive Director of Investor Relations and Corporate Communications

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

Jennifer Chien, Executive Vice President, Head of North America

Yann Mazabraud, Executive Vice President, Head of International

Hunter Smith, Chief Financial Officer

Important Notice

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, the potential financial impact, growth prospects, benefits of and research and development efforts following our acquisition of Xinvento B.V., our anticipated financial performance and financial position, including estimated Non-GAAP Operating Expenses for the year ending December 31, 2023, 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.

This presentation and the accompanying oral presentation includes 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. 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

Building a Global Company Focused on Rare MC4R Pathway Diseases

Strong BBS commercial execution

- Strong start to U.S. BBS launch continues
- Launched for BBS in Germany with federal reimbursement

IMCIVREE® (setmelanotide) injection

Phase 3 trial in hypothalamic obesity underway

- First patients enrolled and dosed in pivotal, Ph3 trial
- Enrollment completion anticipated in 1Q 2024
- Multiple Ph2 and LTE data presentations planned

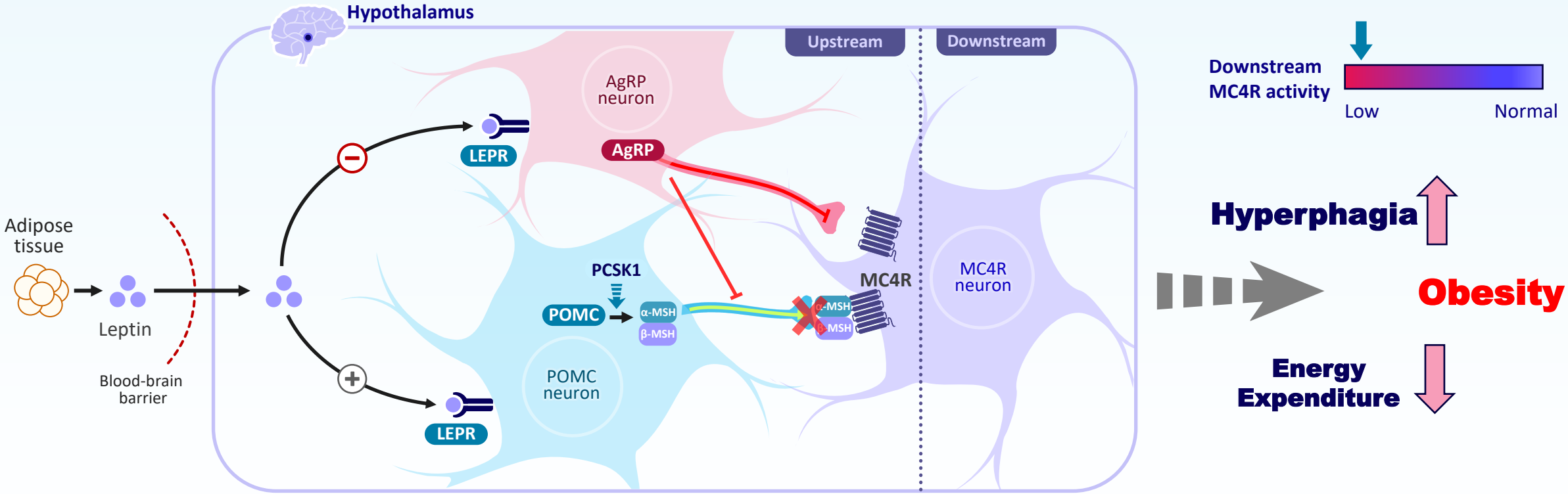
Meaningful expansion opportunity

- Executing on six active clinical trials
- Additional 2H 2023 data readouts:
  - Ph3 pediatrics
  - Ph3 switch
  - Preliminary data from Ph2 DAYBREAK trial
- Advancing towards candidate selection and IND in 2024 following Xinvento acquisition

Cash expected to fund operations into 2025

MC4R Pathway Regulates Hyperphagia, Energy Expenditure and Body Weight

Hyperphagia: ***Insatiable, pathological hunger that leads to abnormal food-seeking behaviors***



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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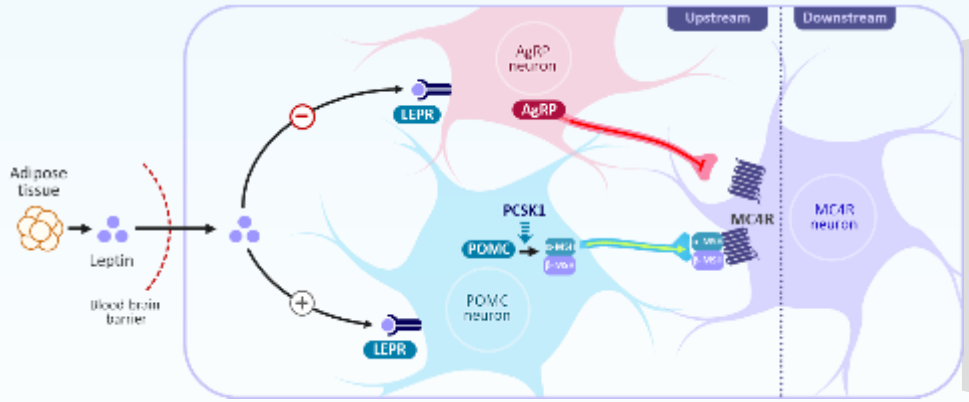
Rare MC4R Pathway Diseases Combine for Significant Opportunity



Approved in U.S. and Europe

Bardet-Biedl syndrome and
POMC, PCSK1 and LEPR deficiencies

4,600 – 7,500 patients in the U.S.*

Phase 3 Trial Initiated

Hypothalamic obesity

5,000 – 10,000 patients in the U.S.*

Phase 3 EMANATE Trial

Heterozygous POMC/PCSK1 insufficiency

Heterozygous LEPR insufficiency

SRC1 deficiency

SH2B1 deficiency

53,000 patients in the U.S.*

*Estimated prevalence of U.S. patients based on company estimates.

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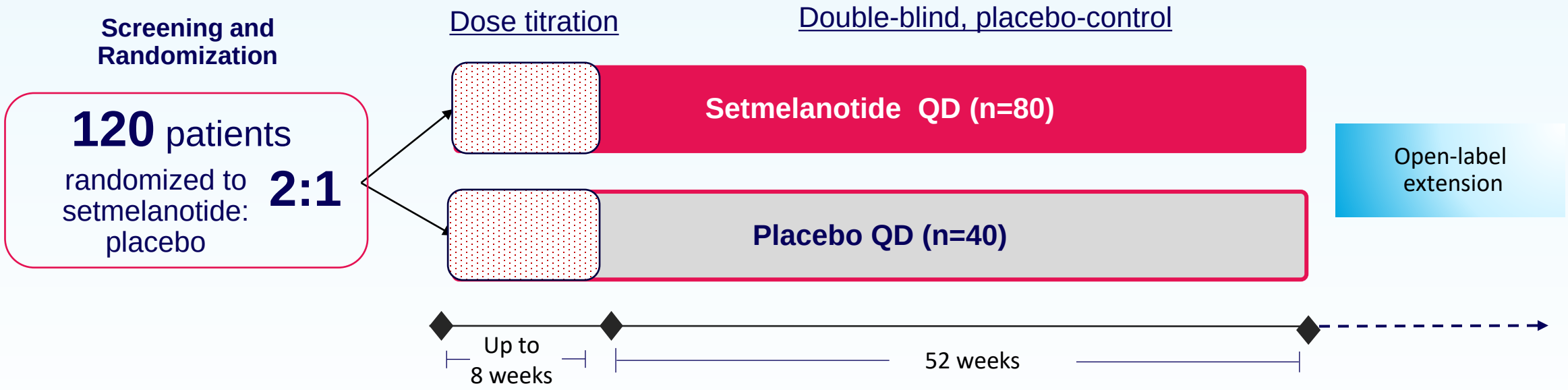
Hypothalamic Obesity: First Patients Dosed in Phase 3 Trial

Trial designed with FDA feedback under Breakthrough Designation; Enrollment expected to be complete in 1Q 2024



Starting dose for all patients is 0.5mg QD; Maximum dose for patients<6yo is between 1.5mg QD and 3.0mg QD based on body weight; maximum dose for patients >6yo with a body weight of 30 kgs or more is 3.0mg QD.

Primary endpoint: Mean % change in BMI from baseline to after approximately 52 weeks on a therapeutic regimen of setmelanotide compared with placebo.

BMI, body mass index; QD, once daily.

Clinical Programs Designed to Achieve Label and Pipeline Expansion

Product/Program	Patient Population	Phase 2	Phase 3	Commercially Approved
IMCIVREE™ (setmelanotide) injection	POMC, PCSK1 or LEPR (PPL) deficiency			
	Bardet-Biedl syndrome (BBS)			
Setmelanotide *daily formulation*	Hypothalamic Obesity			
	Emanate Obesity and Hunger Clinical Trial			
	Pediatrics (age 2 to <6 years, POMC or LEPR deficiency obesity or BBS)			
	Daybreak Obesity and Hunger Clinical Trial			
Setmelanotide *weekly formulation*	Switch study with patients previously on setmelanotide			
	Patients with BBS naïve to setmelanotide therapy (ex-U.S.)			
Undisclosed	Congenital Hyperinsulinism (CHI)	Lead candidate optimization underway; IND anticipated in 2024		

Complete Denotes study underway Denotes planned study

Jennifer Chien

BBS U.S. Launch

Strong Demand for IMCIVREE for BBS Continues

>300*

New BBS prescriptions

>100

received during 1Q 2023

>160*

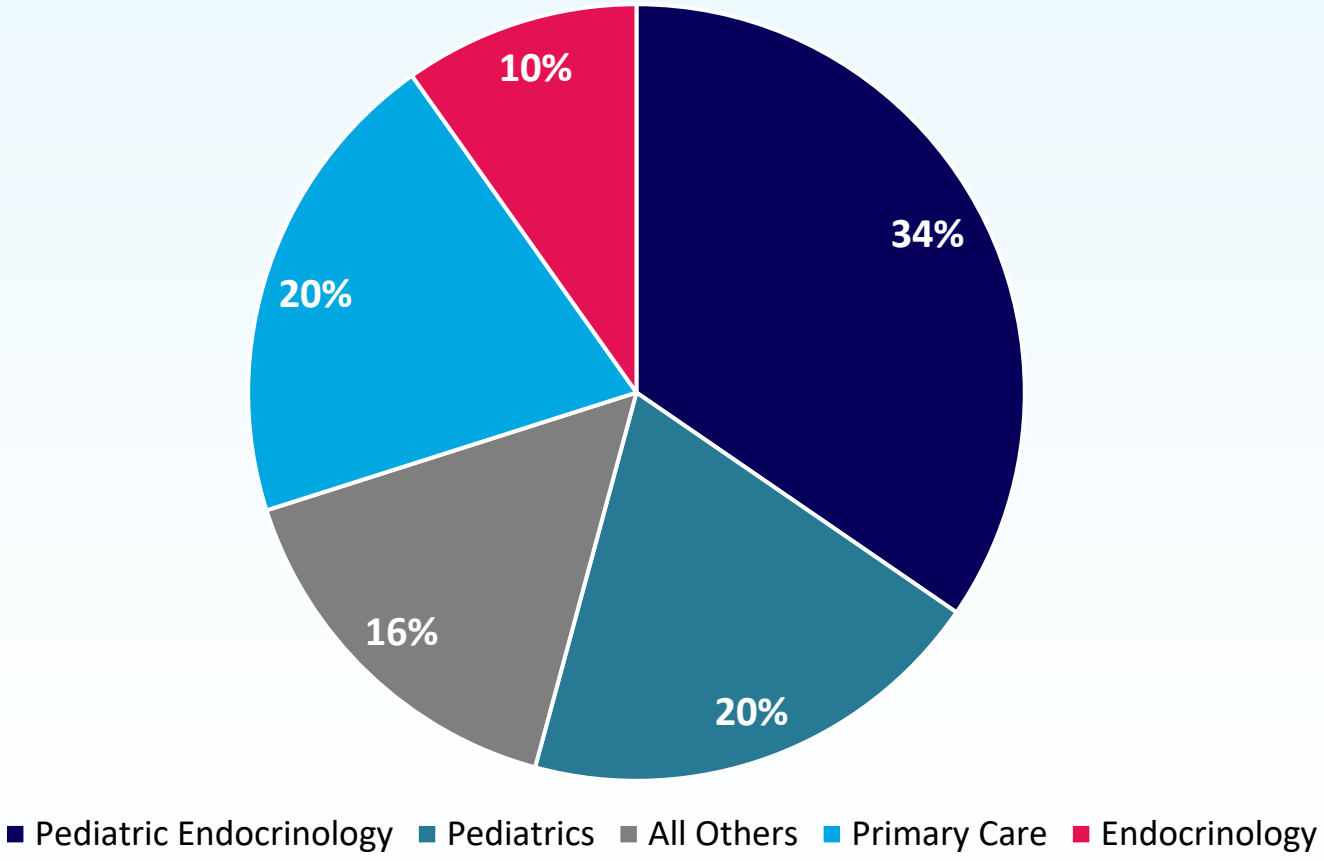
reimbursement approvals

>175*

unique prescribers

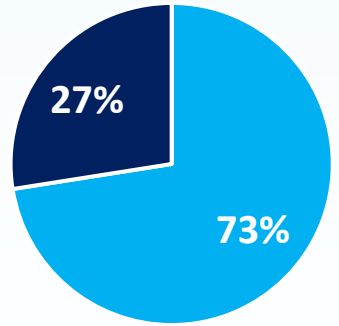
* As of March 31, 2023. IMCIVREE was approved by the U.S. FDA on June 16, 2022.

BBS IMCIVREE Prescribers by Specialty Since Launch



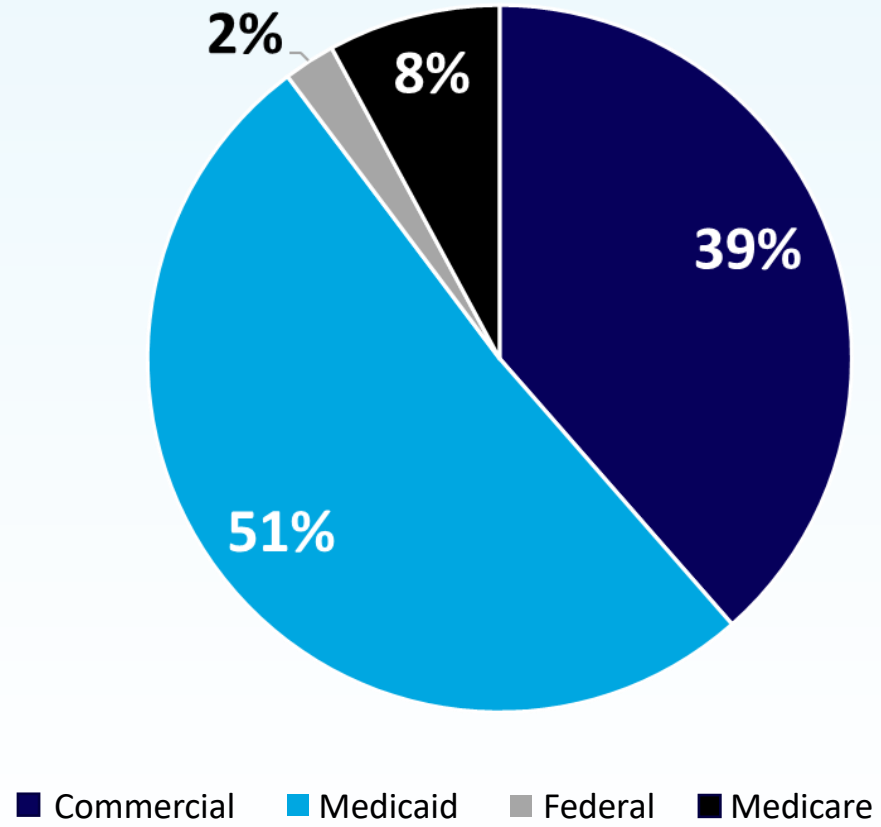
>175*

Prescribers
as of 3/31/2023



*As of March 31, 2023

Almost 90% of BBS Prescriptions Since Launch Fall Under Commercial and Medicaid Plans



>160

Reimbursement approvals

*As of March 31, 2023

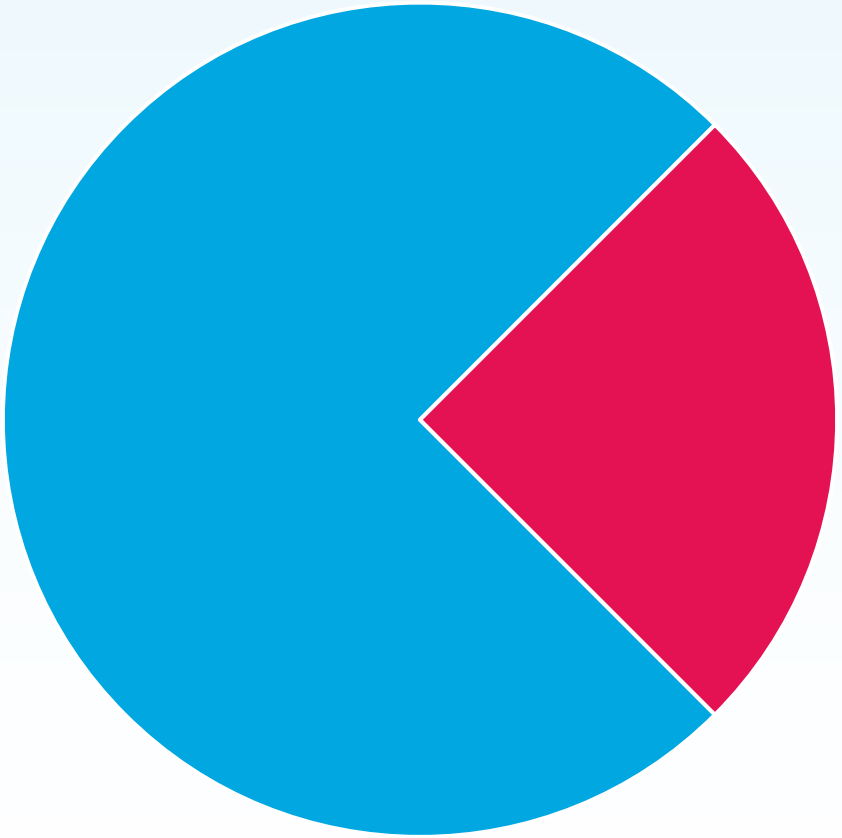
~75% of Medicaid Covered Lives in States with Positive Coverage Policies or Positive Coverage Decisions for IMCIVREE

Medicaid Covered Lives = ~85 million

~75%

of covered lives split between states with:

- an IMCIVREE policy in place; or
- or a positive coverage decision in the absence of an IMCIVREE policy**



~25%

of covered lives in states with:

- no IMCIVREE prescription received;
- or IMCIVREE prescription being processed;
- or no access by policy **

* According to Medicaid, there were approximately 85 million individuals enrolled in Medicaid in all fifty states, Puerto Rico and the District of Columbia, as of December 2022; ** As of March 31, 2023

Snapshot of Patient Prescriptions

Age Range	Since Launch
Adult (18+)	~50%
Adolescent (12-17)	~27%
Pediatric (6-11)	~23%

Rhythm InTune
Support made personal

97%

of BBS prescriptions are written for patients who are consented to **InTune**

*As of March 31, 2023

Results of Patient Identification Efforts Support Opportunity for Continued Growth

Successful Patient Identification Efforts

- Genetic testing with Uncovering Rare Obesity
- Machine learning using ICD-10 codes
- Non-personal, digital promotion

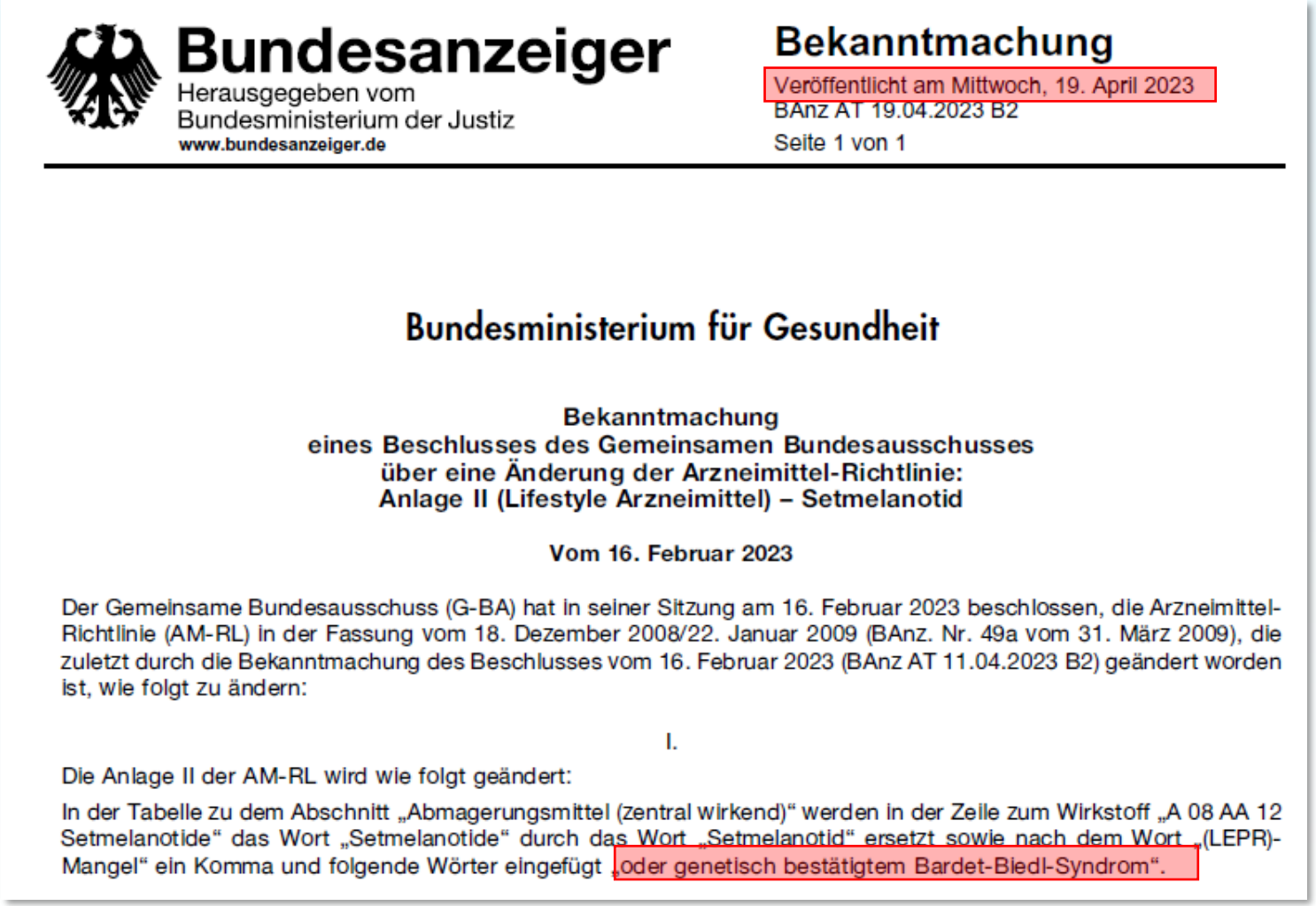
Opportunities Ahead

- Prescribers of IMCIVREE with additional BBS patients
- Physicians who have not yet prescribed IMCIVREE, but are ready to treat existing BBS patients
- Physicians with BBS patients, not ready to begin treatment

Yann Mazabraud

EVP, Head of International

IMCIVREE Approved for BBS in Germany and Made Eligible for Full Reimbursement by Federal Joint Committee (G-BA)



Bundesanzeiger
Herausgegeben vom
Bundesministerium der Justiz
www.bundesanzeiger.de

Bekanntmachung
Veröffentlicht am Mittwoch, 19. April 2023
BAnz AT 19.04.2023 B2
Seite 1 von 1

Bundesministerium für Gesundheit

Bekanntmachung
eines Beschlusses des Gemeinsamen Bundesausschusses
über eine Änderung der Arzneimittel-Richtlinie:
Anlage II (Lifestyle Arzneimittel) – Setmelanotid

Vom 16. Februar 2023

Der Gemeinsame Bundesausschuss (G-BA) hat in seiner Sitzung am 16. Februar 2023 beschlossen, die Arzneimittel-Richtlinie (AM-RL) in der Fassung vom 18. Dezember 2008/22. Januar 2009 (BAnz. Nr. 49a vom 31. März 2009), die zuletzt durch die Bekanntmachung des Beschlusses vom 16. Februar 2023 (BAnz AT 11.04.2023 B2) geändert worden ist, wie folgt zu ändern:

I.

Die Anlage II der AM-RL wird wie folgt geändert:

In der Tabelle zu dem Abschnitt „Abmagerungsmittel (zentral wirkend)“ werden in der Zeile zum Wirkstoff „A 08 AA 12 Setmelanotide“ das Wort „Setmelanotide“ durch das Wort „Setmelanotid“ ersetzt sowie nach dem Wort „(LEPR)-Mangel“ ein Komma und folgende Wörter eingefügt „oder genetisch bestätigtem Bardet-Biedl-Syndrom“.

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IMCIVREE Launched for BBS in Germany with Experienced Team

- Setmelanotide has strong legacy in Germany
- Strong team in place engaging with physicians and centers of excellence
  - German General Manager has led multiple launches
  - 6 people dedicated to IMCIVREE launch
- Genetic confirmation
  - ~50% of BBS patients diagnosed in Germany have been genotyped
- BBS treatment landscape
  - Treatment guidelines in development by German experts
  - Well-organized patient advocacy group
  - Existing registries for rare renal and rare ophtalmogical diseases

First-ever setmelanotide clinical trial patient treated at Charité Hospital in Berlin in 2012

Significant Opportunity for IMCIVREE and BBS in Germany

Team engaging with BBS sites and focused on patient identification and medical education activities

18

BBS sites

~1,200 Estimated German prevalence*

~800 Patients diagnosed with BBS*

>250 Patients with BBS identified*

*Internal company estimates.

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Europe is an Important Market for BBS, POMC and LEPR Deficiencies

IMCIVREE available in 9 ex-U.S. countries through full reimbursement, named patients sales or early access programs

POMC, PCSK1 and LEPR Deficiency Obesities

~100

individuals identified in **EU4 + UK**

Estimated European prevalence

600 - 2,500

Bardet-Biedl Syndrome

>1,500

individuals identified in **EU4 + UK**
(~20 academic medical centers with >40 BBS patients)

Estimated European prevalence

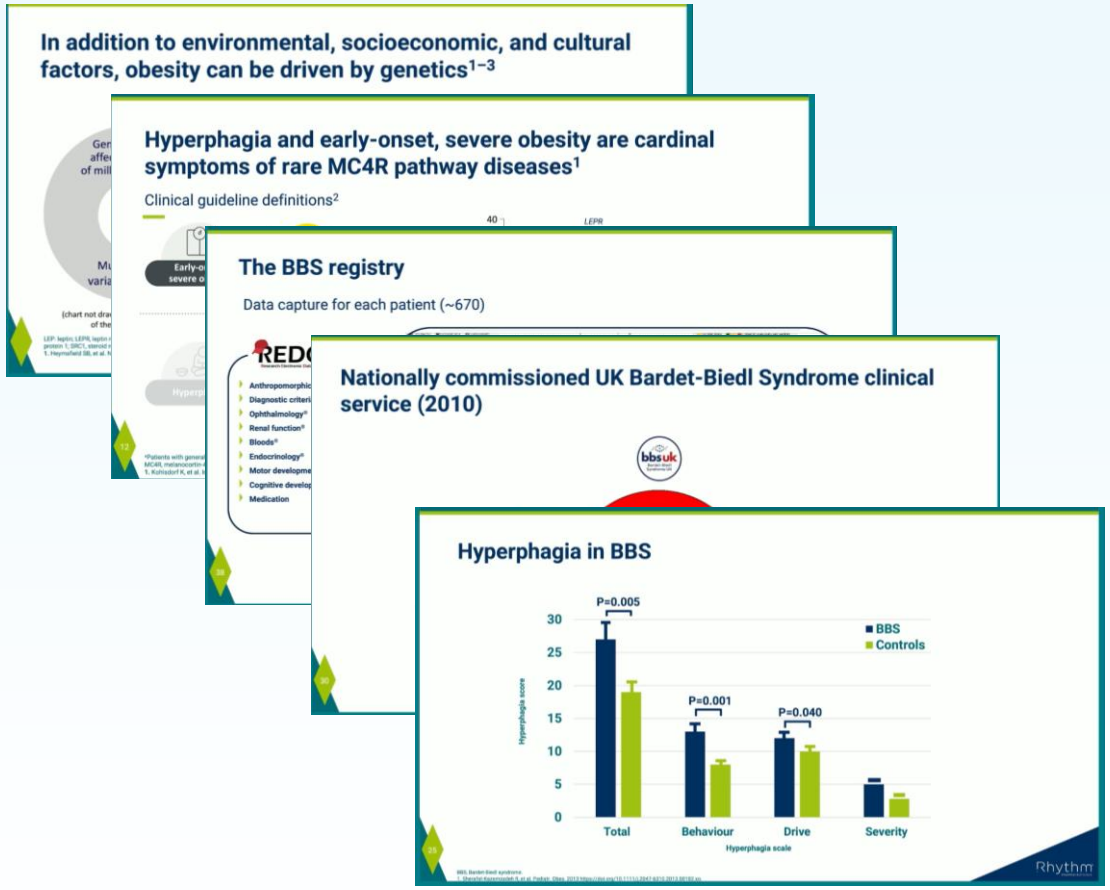
4,000 – 5,000

First International Webinar on Genetic Causes of Obesity Draws >125 Healthcare Providers from 17 Countries

Angela Scudder
Mother of a person living with BBS; Staff member at BBS UK and Patient Liaison Officer at BBS UK Clinics

Philip Beales, M.D., Ph.D.
University College London, UCL Great Ormond Street Institute of Child Health

Sadaf Farooqi, M.D., Ph.D.
Wellcome-MRC Institute of Metabolic Science and NIHR Cambridge Biomedical Research Centre



Hunter Smith
1Q 2023 Financial Results

1Q 2023 Financial Snapshot

($ in millions, except per share data and shares outstanding)	Three months ended March 31, 2023	Three months ended March 31, 2022
Product revenue, net	$11.5M	$1.5M
R&D expenses	$37.9M	$32.5M
SG&A expenses	$24.6M	$21.4M
Net Loss	$(52.2)M	$(52.8)M
Shares outstanding (basic and diluted share count)	56,708,975	50,326,627
Net Loss per share - basic and diluted	$(0.92)	$(1.05)
Cash, cash equivalents and short-term investments position (period end)	$294.6M	$241.0M

1Q 2023 Financial Highlights

~83%
of 1Q 23023 revenue from U.S. sales of IMCIVREE vs. 85% in 4Q 2022

1Q 2023
R&D costs include
$5.4M
associated with Xinvento acquisition

1Q 2023
OpEx includes
$6.4M
in stock-based compensation vs. $5.3M in 4Q 2022

Non-GAAP OpEx Guidance for 2023:
$200M to $220M

$294.6M cash, cash equivalents and short-term investments as of March 31, 2023

Cash expected to be sufficient to fund planned operations **into 2025**

David Meeker, MD
Conclusion

Plans for Continued Execution: Anticipated Upcoming Milestones and Data Readouts

Anticipated clinical milestones

- ✓ Early 2023: Initiate Ph 3 hypothalamic obesity trial
- ○ 2H2023: Present data analyses from Ph2 and LTE trials in hypothalamic obesity at medical conferences
- ○ 2H23: Initiate a Ph 3 weekly “de novo’ study
- ○ 2H23: Announce preliminary data from Phase 2 DAYBREAK trial in 2H2023
- ○ 2H23: Announce topline data Ph3 open-label pediatrics trial in patients between 2 and 6 years old
- ○ 2H23: Announce PK and tolerability data Ph3 weekly switch trial
- ○ 1Q24: Complete enrollment in Phase 3 hypothalamic obesity trial

Ex-US Market Access:

- ✓ 2Q23: Germany for BBS
- ○ 2H23: The Netherlands for BBS
- ○ 2H23: Launch in Canada for both BBS and POMC, PCSK1 or LEPR, pending Health Canada approval

Rhythm's Strategic Priorities for 2023

Execute on global commercial strategy with **BBS launches**

Enroll and execute **Phase 3** trial to evaluate setmelanotide in **hypothalamic obesity**

Expand IMCIVREE opportunity and clinical development **pipeline with Xinvento assets**

Questions