Rhythm Pharmaceuticals

Fourth Quarter / Full Year 2022 Financial Results and Business Update

March 1, 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 and benefits of 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 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.

David Meeker, MD

Rare Disease Day, World Obesity Day and Obesity Care Week

Rhythm® PHARMACEUTICALS

Building a Global Company: The Next Chapter

Global commercial strategy execution

- Strong start to U.S. BBS launch*
  - >200 new prescriptions
  - >125 prescribers
  - >100 reimbursement approvals
- IMCIVREE available in 8 ex-US markets for BBS and/or POMC and LEPR deficiencies

Hypothalamic obesity leads setmelanotide expansion

- Actively engaged patient community
- Screening patients for pivotal, Ph3 trial following strong Ph2 data
- Anticipated 2H 2023 readouts:
  - Ph3 pediatrics
  - Ph3 switch
  - Preliminary data from Ph2 DAYBREAK trial

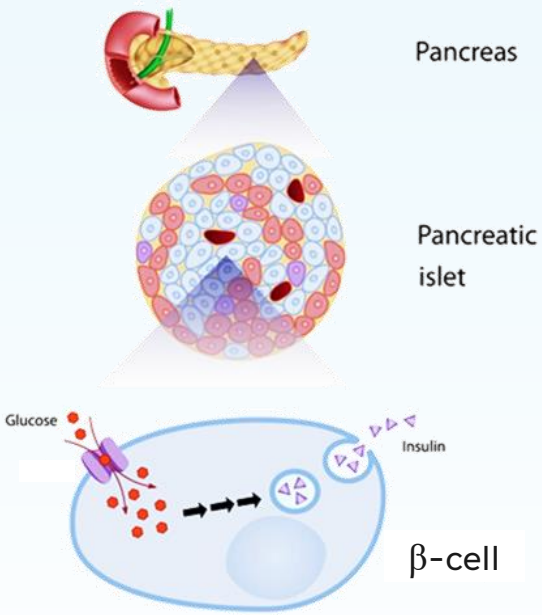
Meaningful new opportunity with acquisition of Xinvento

- Congenital hyperinsulinism
- Strong strategic fit with Rhythm's rare endocrinology focus
- Anticipate initiating clinical development in 2024

Cash expected to fund operations into 2025

*U.S. commercial metrics account for the period between FDA approval on June 16, 2022, and Dec. 31, 2022.

Clear Unmet Medical Need for Improved Treatment Options for Patients with Congenital Hyperinsulinism



- Chronic dysregulation of insulin from pancreatic β-cells, resulting in hypoglycemias
- Can cause brain damage with neuro-developmental deficits in ~50% of patients; without proper and immediate treatment, can result in seizures, coma, permanent brain damage or death
- Most frequent cause of severe, persistent hypoglycemias in newborns and children

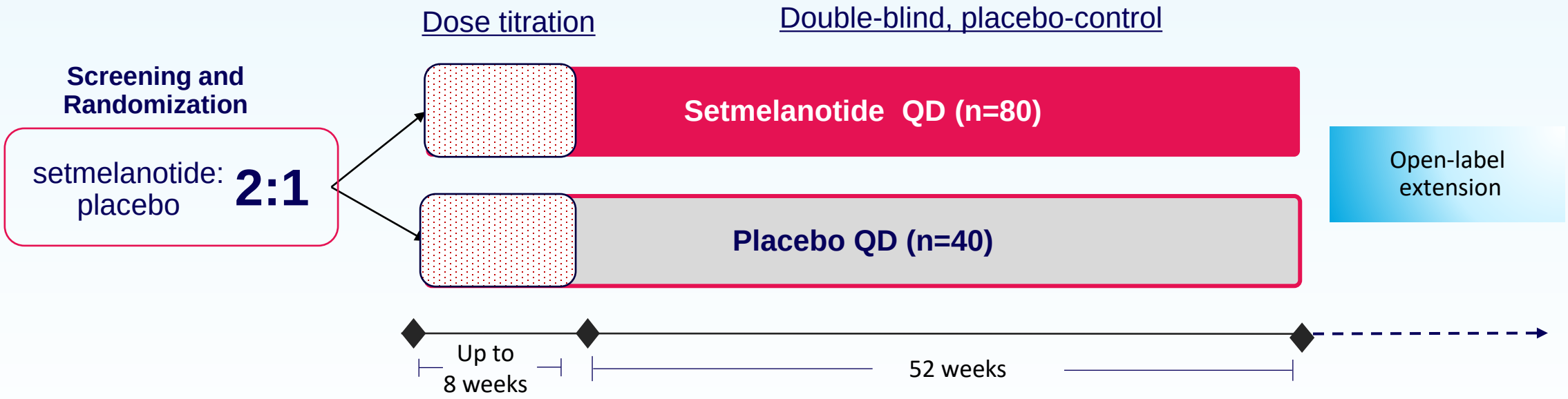
1:29,000 - 31,000*

incidence in EU, U.S., UK and Japan

*Incidence based on recent studies (Yau et al 2020, Yamada et al 2020, and Chen et al, 2021.

Hypothalamic Obesity: Sites Initiated, Patients Being Screened for Phase 3 Double-blind, Randomized Controlled Trial

Enrollment Expected to be Complete in 6-12 Months



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.

Hypothalamic Obesity: A Transformative Opportunity for Rhythm

5,000 – 10,000*

patients

Estimated U.S. prevalence

~500* additional cases diagnosed in U.S. each year

- ✓ Unmet medical need is high; no approved therapies
- ✓ MC4R pathway deficiency following injury to hypothalamic region
- ✓ Compelling Phase 2 efficacy data with consistent, durable weight loss
- ✓ Patients are identified and engaged with the system receiving specialist care for pituitary complications

*To estimate the number of patients with incident and prevalent craniopharyngioma and astrocytoma with obesity, Rhythm analyzed the literature and used the number of new cases of each per year in the United States, overall survival rates after a diagnosis of each brain tumor type and obesity rates among those patients at diagnosis or post-diagnosis. See appendix for details.

Multiple Clinical Trials Ongoing to Expand IMCIVREE Label and Overall Opportunity

Pediatrics Trial
Phase 3
Patients aged 2 to <6 years

Weekly Formulation
Phase 3
Switch Trial

Emanate
Phase 3 Trial

Daybreak
Phase 2 Trial

Hypothalamic obesity
Phase 3 Trial initiated

Updated

Bardet-Biedl Community is Established and Patients are Identified

U.S. prevalence estimated to be

4,000 to **5,000*** patients

More than **600** individuals with BBS are enrolled in **CRIBBS registry**

European prevalence estimated to be

4,000 – 5,000* patients

>1,500 individuals identified in **EU4 + UK** (~20 academic medical centers with >40 BBS patients)

* Estimates are based on field work and patient identification efforts in both the United States and Europe and our proprietary genetic sequencing data.

Jennifer Chien

BBS U.S. Launch

Journey for Patients, Prescribers and Payers

Consistent focus since FDA approval for BBS in June 2022

Results Show Strong Demand and Commercial Execution since FDA Approval for IMCIVREE through December 31,2022

>200*

New BBS prescriptions

6/16/22 to 12/31/22

>120

received as of Sept. 30, 2022

>80

received during 4Q2022

>100*

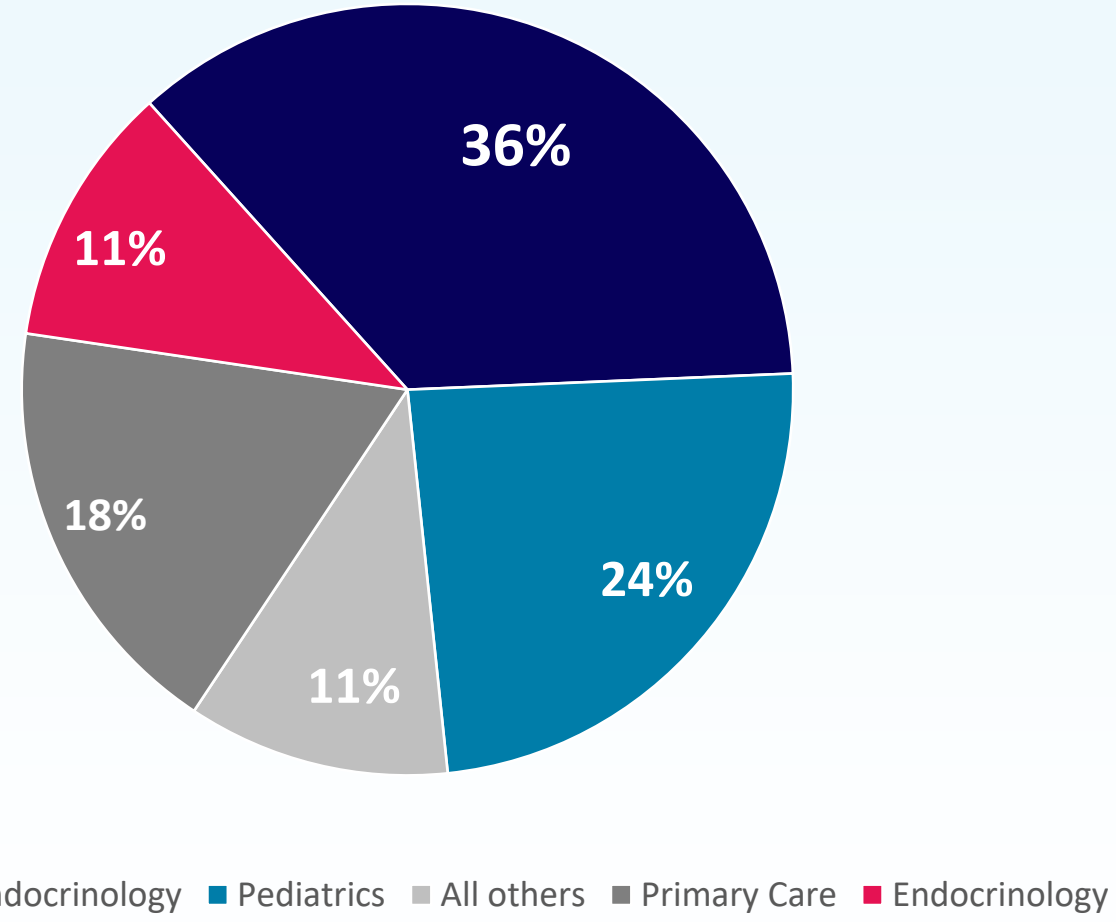
reimbursement approvals

>125*

unique prescribers

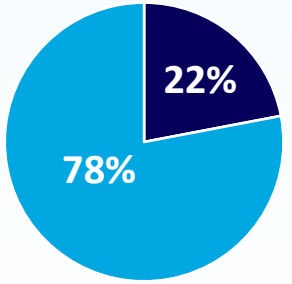
* As of December 31, 2022. IMCIVREE was approved by the U.S. FDA on June 16, 2022.

BBS IMCIVREE Prescribers by Specialty Since Launch



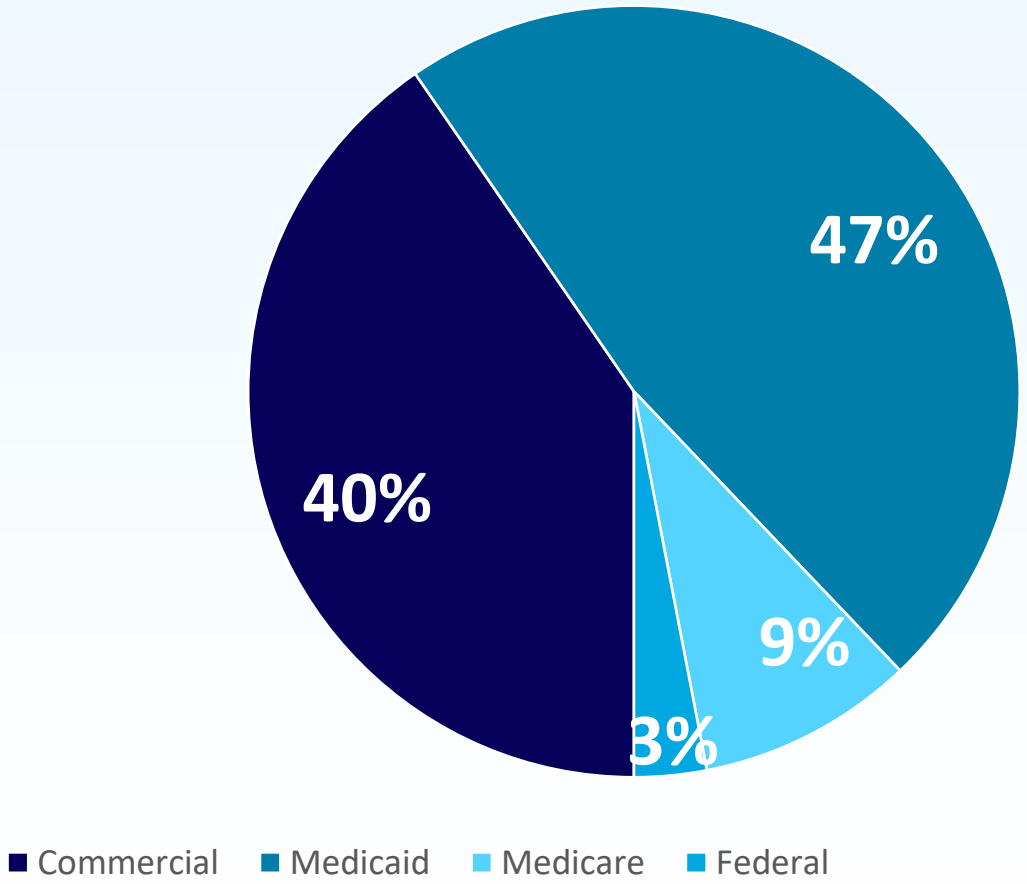
>125*

Prescribers
as of 12/31/2022



*As of December 31, 2022

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



*As of December 31, 2022

>100 Reimbursement approvals

- Typically payer approval process takes between **one and three months**
- Following initial approvals, subsequent approvals are faster for that payer

Snapshot of Patient Prescriptions

Age Range	Since Launch
Adult (18+)	~46%
Adolescent (12-17)	~28%
Pediatric (6-11)	~26%

Rhythm InTune
Support made personal

95%

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

*As of December 31, 2022

Accelerating Hope: Rhythm North America Kick Off Meeting to Align on 2023 Strategy

Priorities for 2023

- Solidify the need to treat MC4R pathway driven hyperphagia and obesity
- Establish IMCIVREE as the preferred treatment for BBS patients
- Cultivate a positive Rhythm and IMCIVREE experience for customers
- Identify more BBS patients and treaters

Yann Mazabraud

EVP, Head of International

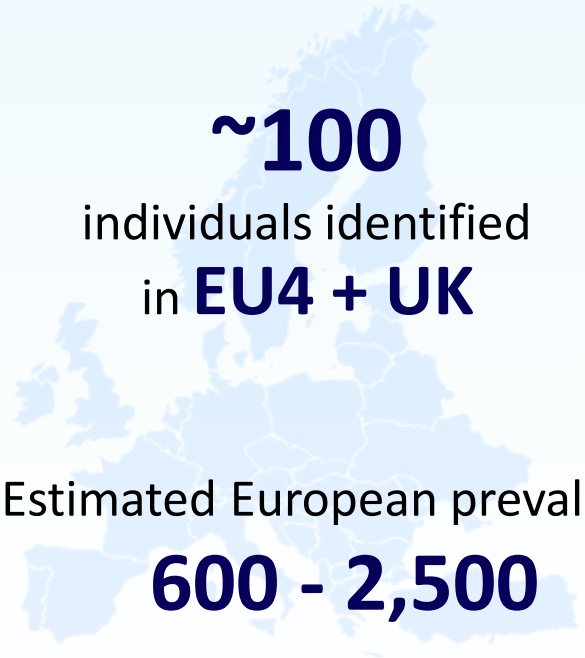
International Team in Place in Nine Ex-U.S. Countries

2023 International Priorities

- Best practices in market access, patient identification and omnichannel approach
- Execution of integrated, aligned & simple launch plans
- Operational excellence

Market Access for Patients with POMC, PCSK1 and LEPR Achieved in Eight Countries

POMC, PCSK1 and LEPR Deficiency Obesities



~100
individuals identified
in **EU4 + UK**

Estimated European prevalence
600 - 2,500

- ✓ **United Kingdom:** Launched
- ✓ **Germany:** Launched
- ✓ **France:** Paid early access
- ✓ **Italy:** Launched
- ✓ **The Netherlands:** Launched
- ✓ **Austria:** Named patient sales
- ✓ **Turkey:** Named patient sales
- ✓ **Argentina:** Early access

Making Significant Progress towards Access for BBS since September 2022 EC Marketing Authorization

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

- ✓ **France:** Paid early access

Anticipated Launches:

- **Germany:** G-BA exemption status progressing and launch in 2Q 2023
- **The Netherlands:** Launch in 4Q2023
- **Italy:** Launch 1H2024
- **Spain:** Launch in 1H2024
- **United Kingdom:** NICE HST evaluation ongoing with launch in 2H2024

Initiated reimbursement activities in several additional EU countries

Hunter Smith
4Q/YE 2022 Financial Results

4Q 2022 Financial Snapshot

$333.3M* cash on hand expected to be sufficient to fund operations into 2025

($ in millions except as noted, per share data and shares outstanding)	Three months ended December 31, 2022	Three months ended December 31, 2021	Year ended December 31, 2022	Year ended December 31, 2021
Product revenue, net	$8.8M	$1.8M	$16.9M	$3.2M
Collaboration revenue	--		$6.8M	_
R&D expenses	$23.5M	$31.6M	$108.6M	$104.1M
SG & A expenses	$26.3M	$21.0M	$92.0M	$68.5M
Net (loss) from operations	$(42.1)M	$(51.0)M	$(179.2)M	$(170.1)M
Shares outstanding (basic and diluted share count, weighted average)	56,299,525	50,270,801	52,120,701	49,600,294
Net (loss) per share basic and diluted	($0.75)	($0.85)	($3.47)	($1.40)
Cash, cash equivalents and short-term investments position (period end)	$333.3M	$294.9M	$333.3M	$294.9M

* As of December 31, 2022.

Efficient Execution to Maximize Shareholder Value

Anticipated Non-GAAP Operating Expenses[1] for 2023:
$200M to $220M

- R&D: $120 million to $130 million
- SG&A: $80 million to $90 million
- Does not include stock-based compensation

Acquisition of Xinvento*

- $5 million upfront payment; $6 million in preclinical development milestones
- Up to additional $50 million upon certain U.S. or EU regulatory approvals.
- Additional $150 million in commercial net sales milestones related to lead candidate or second molecule, if second molecule is selected, developed and approved

*As announced on February 27, 2023.

[1]Non-GAAP Operating Expenses is a non-GAAP financial measure. We define Non-GAAP Operating Expenses as GAAP operating expenses excluding stock-based compensation. 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
Conclusion

Plans for Continued Execution: Anticipated Upcoming Milestones and Data Readouts

Anticipated clinical milestones

- ✓ Early 2023: Initiate Ph 3 hypothalamic obesity trial
- 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 topline data Ph3 weekly switch trial

Ex-US Market Access:

- 2Q23: Germany for BBS
- 2H23: The Netherlands for BBS
- 2H23: 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