Rhythm Pharmaceuticals

Positive Topline Results from Pivotal Phase 3 Clinical Trial Evaluating Setmelanotide in Patients with Bardet-Biedl and Alström Syndromes

December 2020

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 Rhythm's expectations for 2020, the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, anticipated timing for enrollment and release of our clinical trial results, the timing for submission of NDA, MAA or other similar filings, our goal of changing the paradigm for the treatment of rare genetic disorders of obesity, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, and expectations regarding our sufficiency of cash and financial position, strategy, prospects and plans. 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.

Agenda

- David Meeker, MD

  Chair, Chief Executive Officer and President

- Murray Stewart, MD

  Chief Medical Officer

- Q&A

David Meeker, M.D.

Chair, Chief Executive Officer and President

Working Toward Changing the Paradigm for the Treatment of Rare Genetic Diseases of Obesity

Validation

FDA approved

for chronic weight management for obesity due to **POMC, PCSK1** or **LEPR** deficiency[1]

\+ **Meaningful Opportunity**

Positive topline results in **Bardet-Biedl syndrome**

Growth Potential

Establish proof-of-concept in new indications in Phase 2 Basket Study

Drive COMMUNITY BUILDING and GENETIC SEQUENCING

[1]In adult and pediatric patients ages 6 and older, confirmed by genetic testing.

Phase 3 Clinical Trial Met Primary and All Key Secondary Endpoints

Setmelanotide achieved statistical significance and delivered clinically meaningful weight loss and hunger reduction

Phase 3 Topline Data (n=31[a])

34.5%[b]	**-6.2%**	**-30.8%**	**60.2%**
p=0.0024	**p<0.0001**	**p<0.0001**	**p<0.0001**
≥10% weight loss	mean weight reduction	mean hunger score reduction	≥25% reduction in worst hunger

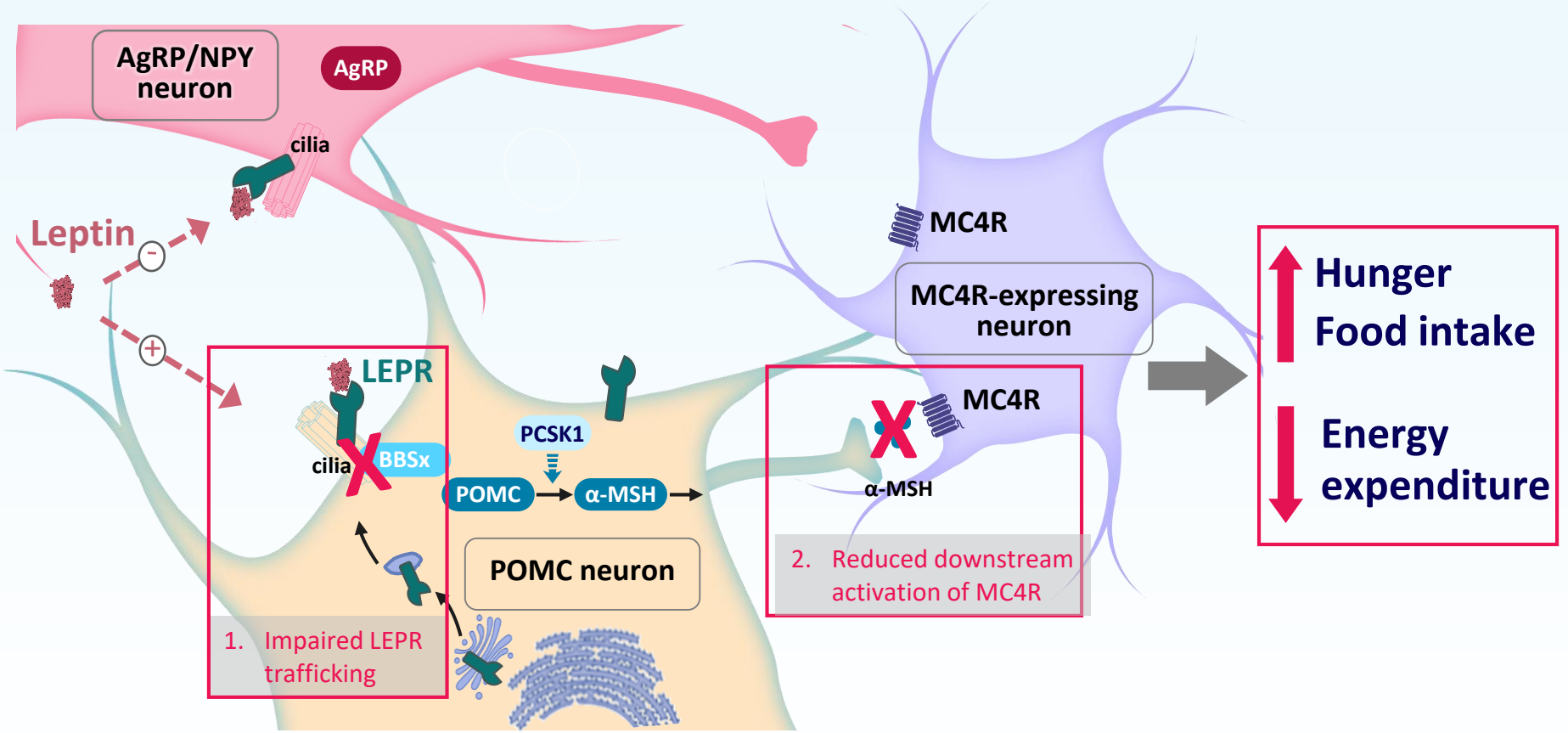
All primary endpoint responders were BBS patients.

[a]Study participants older than 12 counted in full analysis set for primary and key secondary endpoints; Five participants were younger than 12, and two participants older than 12 discontinued during placebo-controlled period prior to receiving active therapy. [b]Response rate was estimated based on imputation methodology discussed with FDA.

Murray Stewart, M.D.

Chief Medical Officer

In Patients With BBS, Cilia Dysfunction May Reduce Downstream Activation of MC4R, Which Can Lead to Hyperphagia and Obesity[1-3]



- Loss of functional BBS proteins may disrupt LEPR trafficking to the cell membrane, thus impairing its signaling[4-5]
  - Patients with BBS have higher circulating leptin, suggesting greater leptin resistance, compared with individuals with general obesity[6]

AgRP, agouti-related protein; BBS, Bardet-Biedl syndrome; BBSx, proteins associated with BBS; LEPR, leptin receptor; MC4R, melanocortin 4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Yazdi FT, et al. *PeerJ.* 2015;3:e8561. **2.** Davenport JR, et al. Curr Biol. 2007;17:1586. **3.** Vaisse C, et al. Cold Spring Harb Perspect Biol. 2017;9:a028217. **4.** Seo S, et al. *Hum Mol Genet*. 2009;18:1323-1331 **5.** Guo DF, et al. *PLoS Genet.* 2016;12:e1005890. **6.** Feuillan PP, et al. *J Clin Endocrinol Metab*. 2011;96:E528-E535.

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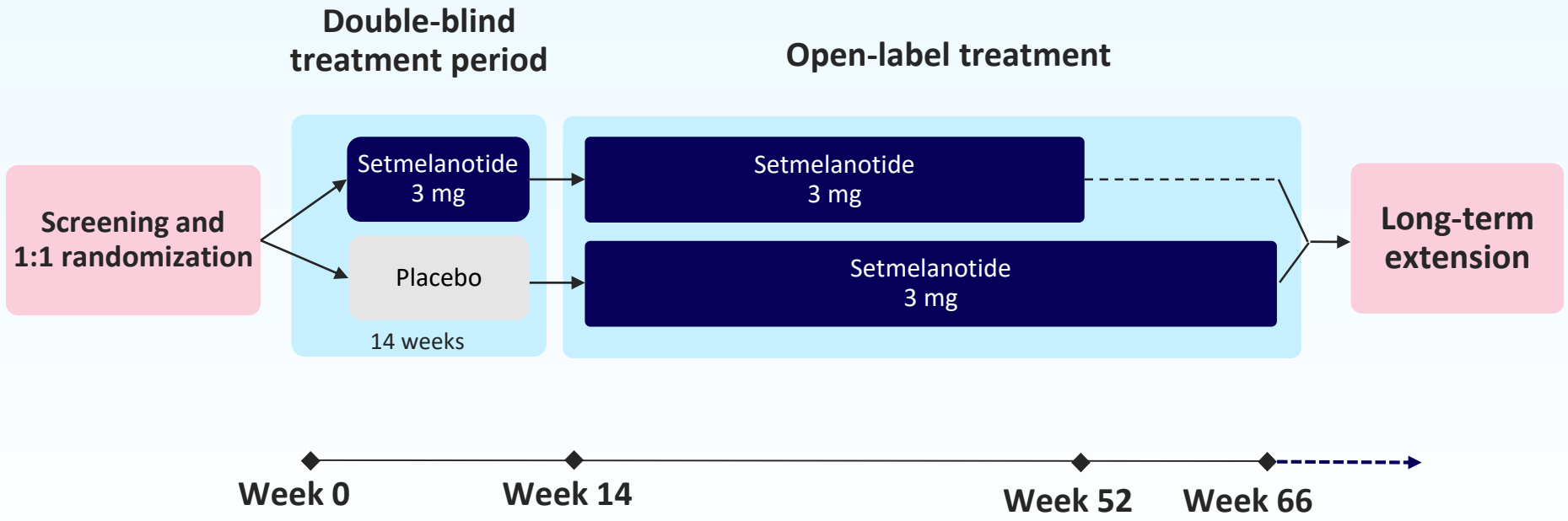
Bardet-Biedl and Alström Syndromes Phase 3 Trial Design

Pivotal cohort
- 32 BBS patients
- 6 Alström syndrome patients



Primary Endpoint: proportion of patients (≥12 years of age) who have at least a 10% reduction in body weight.

BBS, Bardet-Biedl syndrome.

Baseline Characteristics and Demographics in Evaluable Patients

Baseline Characteristics (N=31)	
Diagnosis, n (%)	
BBS	**28 (90)**
Alström syndrome	**3 (10)**
Age, mean (range), years	**21 (12-44)[b]**
Overall age, mean (range) years	**14 (45)**
Adolescents (12-17 years old), n (%)	
Male, n (%)	**14 (45)**
Weight, mean (range), kg / lbs	**117 (62-192) / 258 (136-423)**
BMI, mean (range), kg/m^2	**44 (24, 83)**
"Most hunger" score, mean (range)[a]	**7 (4-10)**
Cognitive impairment, n (%)	**15 (48)**

[a]Weekly average at active treatment baseline for participants ≥12 years of age assessed daily using a numeric rating score from 0-10, with 0 = not hungry at all and 10 = hungriest possible. BBS, Bardet-Biedl syndrome. [b]14 adolescents, 11 of whom are still growing.

Primary Endpoint Met: Setmelanotide Achieved Statistically Significant and Clinically Meaningful Weight Reductions at ~1 Year on Therapy

34.5%[a] of participants (95% CI, 17.5 to 51.6; *P*=0.0024) achieved the primary endpoint threshold of ≥10% weight loss from baseline at Week 52

	Baseline	~1 year at target dose	Percent change from baseline
Mean (SD) body weight (n=31)	**117.0 kg** (29.4)	**109.9 kg** (30.6)	**-6.2%** (8.3) *P*<0.0001

[a] Response rate was estimated based on imputation methodology discussed with FDA. All 11 responders were BBS patients; of the 11, 2 were initially randomized to placebo and had not reached 52 weeks of treatment at data cut.
CI, confidence interval.

Setmelanotide Achieved Statistically Significant Reduction in “Most” Hunger Score at ~1 Year on Therapy

60.2%[a] of participants (95% CI, 35.3 to 85.1 *P*<0.0001) achieved ≥25% reduction from baseline in daily hunger score at Week 52

	Baseline	~1 year at target dose	Percent change from baseline
“Most” hunger[b] (n=16)	**7.3** (2.0)	**5.1** (2.4)	**-30.8%** (25.1) *P*<0.0001

[a] Response rate was estimated based on imputation methodology discussed with FDA.
[b]Weekly average of scores reported for participants ≥12 years of age assessed daily using a numeric rating score from 0-10, with 0 = not hungry at all and 10 = hungriest possible.
CI, confidence interval.

A Closer Look at Patients with Alström Syndrome

3 Evaluable patients with Alström syndrome **≥12** years old

- 1 discontinued
- 2 gained weight (mean change was +8.9 kg)

2 Patients **< 12** years old not included in primary endpoint

- 1 patient lost approximately 8% body weight
- 1 patient discontinued

Hunger reduction in Alström patients observed to be between 20% and 30%.

* One of six enrolled patients withdrew while receiving placebo.

A Closer Look at Patients with Bardet-Biedl Syndrome

28 patients with **BBS ≥12** years old in primary analysis

- **13 adolescent** patients < 18

11 BBS
patients achieved primary endpoint of **≥10%** weight loss:

- Mean actual weight loss: **-17.2 kg**
- Mean percentage weight loss: **- 14.7%**
- 8 of 11 were adults

5 BBS
patients (3 adults, 2 adolescents) **had 5-9%** weight loss reduction at week 52

Setmelanotide Was Generally Well Tolerated in Individuals With BBS or Alström Syndrome

Parameter	n (%)
Any treatment-emergent adverse event (TEAE)	38 (100)
Serious TEAEs[a]	2 (5.3)
Serious treatment-related TEAEs	1 (2.6)
TEAEs leading to discontinuation	5 (13.2)
TEAEs leading to death	0 (0.0)

- Treatment-emergent adverse events (TEAEs) included mild injection site reactions and nausea with infrequent vomiting
- There was one serious TEAE considered related to treatment: anaphylactic reaction during placebo treatment
- Five participants had TEAEs leading to discontinuation
- There were no setmelanotide-related cardiovascular TEAEs

[a]3 serious AEs occurred in 2 participants, including blindness, suicidal ideation, and anaphylactic reaction; 1 serious AE was considered treatment-related (anaphylactic reaction).
AE, adverse event; BBS, Bardet-Biedl syndrome.

David Meeker, M.D.

Chair, Chief Executive Officer and President

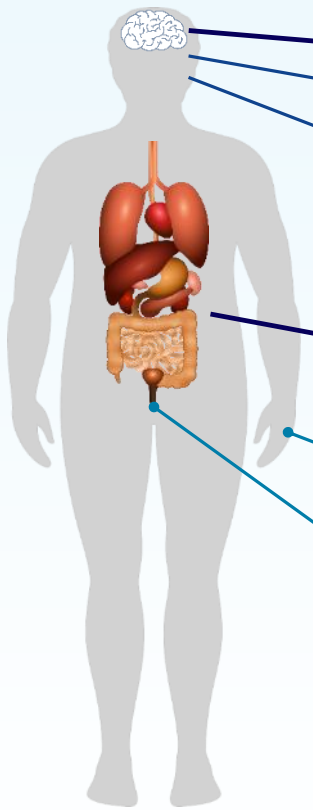
Early-onset, Severe Obesity and Hunger Prominent Among Clinical Characteristics of BBS and Alström Syndrome

Bardet-Biedl syndrome[1]

Rare ciliopathy disease resulting from genetic variants within **BBS family of genes**

U.S. prevalence estimated to be approximately

1,500 to **2,500** patients[2]



Hyperphagia

Cognitive impairment

Progressive vision impairment/loss

Early-onset, severe obesity

Polydactyly (extra finger or toe)

Renal disease

1. Forsyth RL, Gunay-Aygun M. Bardet-Biedl Syndrome Overview. 2003 Jul 14 [Updated 2020 Jul 23]. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2020. https://www.ncbi.nlm.nih.gov/books/NBK1363/. **2.** Rhythm Pharmaceuticals. https://www.rhythmtx.com/our-focus/. Accessed December 10, 2020.

Hunger and Obesity Post a Major Burden to Families and Physicians with No Approved Therapies

Adalissa and Solomon with their siblings (unaffected)

"They are constantly, all day long saying they are hungry and asking what's for the next meal and what are we eating the next day."

"We have had to put locks on our cupboards and fridge and freezer to protect them from themselves!"

– Olivia, Mother of Adalissa and Solomon, siblings diagnosed with ***BBS***

"Greatest frustration is lack of efficacious treatment for hyperphagia and the obesity…"

- ***Endocrinologist***

"There are no treatments for obesity. If we can help with this, it helps combat the co-morbidities that come along with it…."

-Cardiologist

"People say that you dig your grave with your fork and knife. It is extremely critical to treat it."

-Primary Care Physician

Setmelanotide's Path Forward for Bardet-Biedl and Alström Syndromes

1H21 Additional Analyses to Come

- Further analysis of data specific to BBS and Alström syndrome
- Analyses on BMI and BMI-Z scores
- Data from 14-week placebo-controlled period

2H21 Supplemental New Drug Application to U.S. FDA for BBS

- Breakthrough Therapy designation
- Orphan Drug designation
- Approved for chronic weight management for obesity due to POMC, PCSK1 and LEPR deficiency[1]

2H21 Marketing Authorization Application to EMA for BBS

- EMA PRIME designation
- Orphan Drug designation
- MAA under review for obesity due to POMC, PCSK1 and LEPR

[1]In adult and pediatric patients ages 6 and older, confirmed by genetic testing.

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