Rhythm Pharmaceuticals

Targeting MC4 receptor pathway and transforming the care of patients with rare genetic diseases of obesity

November 27, 2020

US-SET-2000084 11/2020

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 the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide and RM-853, anticipated timing for enrollment and release of our clinical trial results, the timing for filing 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 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.

Agenda

- David Meeker, MD
  Chairman, CEO and President
- Murray Stewart, MD
  Chief Medical Officer
- Jennifer Chien
  EVP, Head of North America
- Q&A

David Meeker, MD

Chairman, CEO 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

Meaningful Opportunity

Deliver Bardet-Biedl and Alström syndromes pivotal Phase 3 data

Growth Potential

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

Drive COMMUNITY BUILDING and GENETIC SEQUENCING

Now Approved in the United States

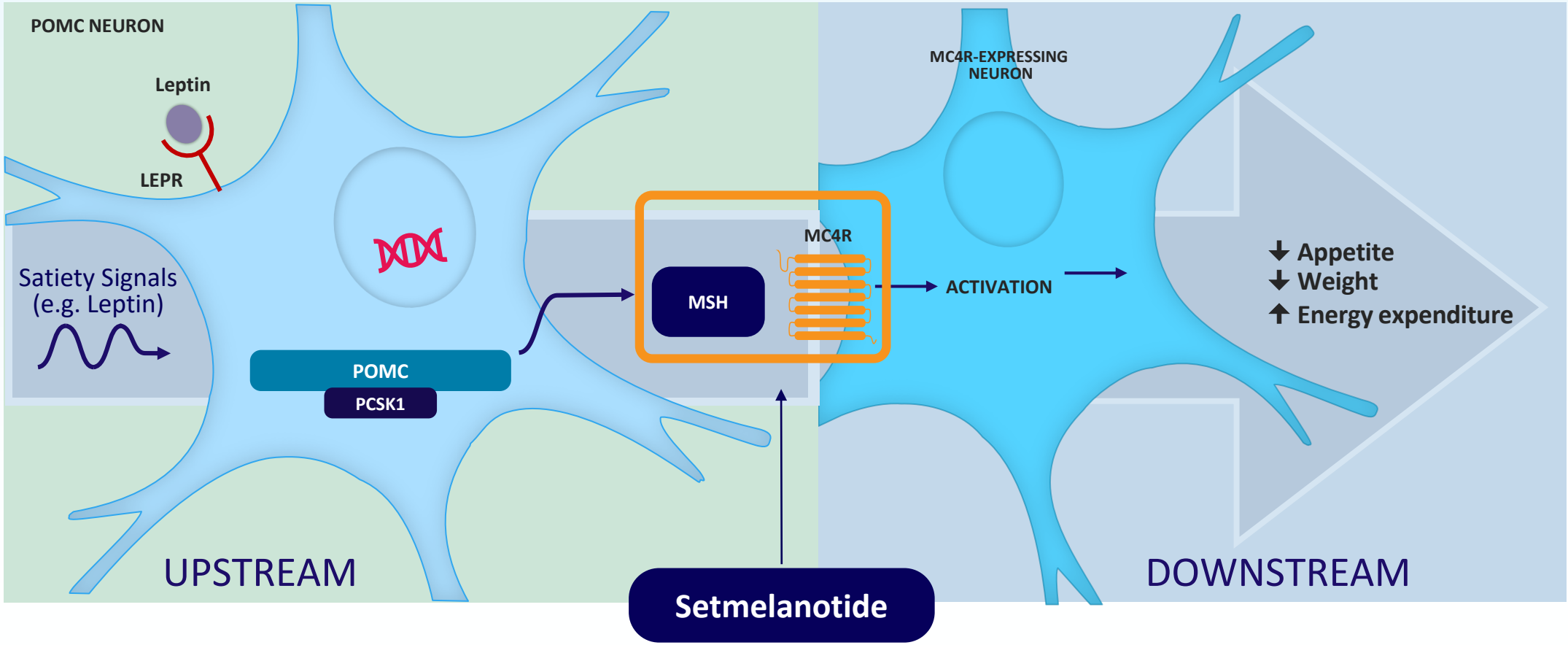
IMCIVREE™
(setmelanotide) injection

Murray Stewart, MD

Chief Medical Officer

MC4R Pathway Regulates Hunger, Caloric Intake, and Energy Expenditure, and, Consequently, Body Weight

When signaling cascade is impaired, setmelanotide may restore function by replacing MSH stimulating hormone

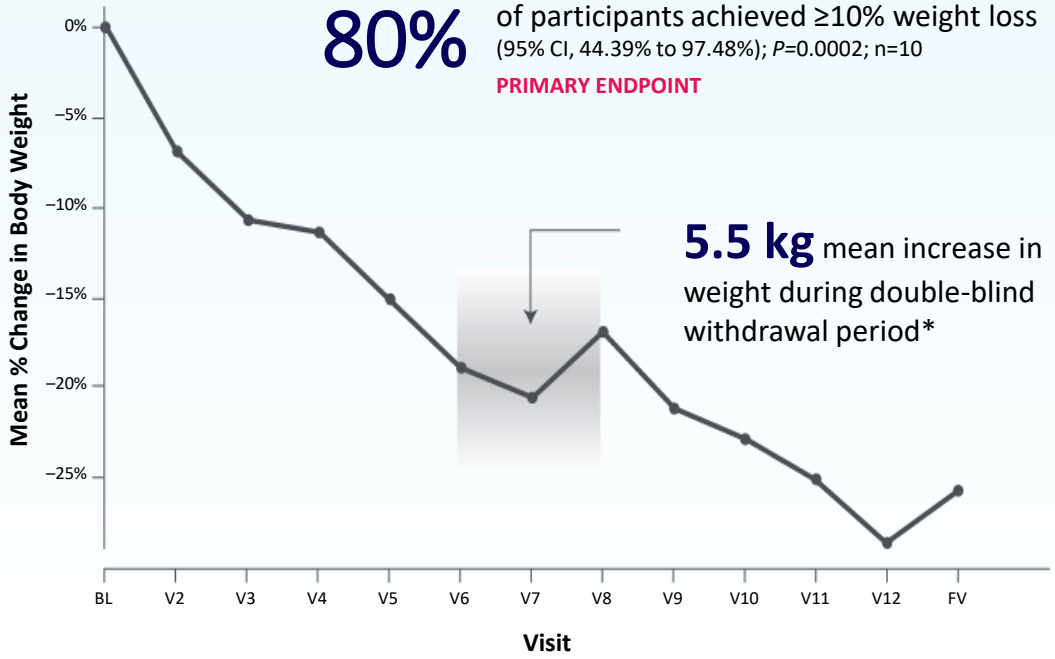


Approval of IMCIVREE Based on Phase 3 Data from Largest Studies Conducted in Obesity due to POMC, PCSK1 or LEPR Deficiency

POMC/PCSK1

80% of participants achieved ≥10% weight loss
(95% CI, 44.39% to 97.48%); *P*=0.0002; n=10
PRIMARY ENDPOINT

5.5 kg mean increase in weight during double-blind withdrawal period*

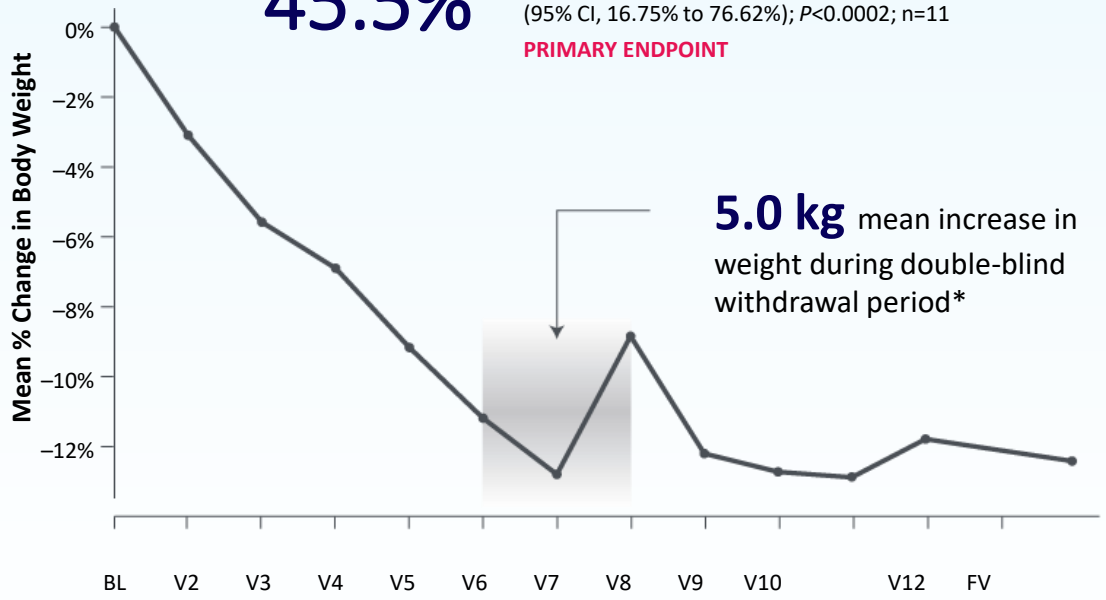


BL, baseline; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; FV, final visit; V, visit.
The withdrawal period lasted 8 weeks, which included 4 weeks of setmelanotide followed by 4 weeks of placebo.
†N=9 participants who achieved weight loss threshold (5 kg or 5% if <100 kg) after the first open-label active treatment phase. **Reference:** IMCIVREE Prescribing Information

LEPR

45.5% of participants achieved ≥10% weight loss
(95% CI, 16.75% to 76.62%); *P*<0.0002; n=11
PRIMARY ENDPOINT

5.0 kg mean increase in weight during double-blind withdrawal period*



BL, baseline; FV, final visit; LEPR, leptin receptor; V, visit.
The withdrawal period lasted 8 weeks, which included 4 weeks of setmelanotide followed by 4 weeks of placebo;
†N=7 participants who achieved weight loss threshold (5 kg or 5% if <100 kg) after the first open-label active treatment phase. **Reference:** IMCIVREE Prescribing Information.

IMCIVREE Reduced Hunger Over 1 Year in Phase 3 Trials

Worst hunger in last 24 hours*		Study 1 (POMC/PCSK1) (N=8)	Study 2 (LEPR) (N=11**)
Baseline	Median	7.9	7.0
	Min, Max	7, 9	5, 8
1 year	Median	5.5	4.4
	Min, Max	3, 8	2, 8
Change from baseline to 1 year	Median	-2.0	-3.0
	Min, Max	-7, -0	-5, -1

Hunger scores generally worsened during the double-blind, placebo withdrawal period among those patients who had experienced an improvement from baseline, and scores improved when IMCIVREE was reinitiated.

Note: This analysis includes patients aged 12 years and older who received at least 1 dose of study drug and had available data.
* Hunger score was captured in a daily diary and was averaged to calculate a weekly score for analysis. Hunger ranged from 0 to 10 on an 11-point scale where 0 = “not hungry at all” and 10 = “hungriest possible.”
** One patient in Study 2 had missing hunger data at Week 52.

Overview of U.S. Prescribing Information for IMCIVREE

Indications and Usage

IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to proopiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency confirmed by genetic testing demonstrating variants in *POMC, PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

Limitations of Use

IMCIVREE is not indicated for the treatment of patients with the following conditions as IMCIVREE would not be expected to be effective:

- Obesity due to suspected POMC, PCSK1, or LEPR deficiency with POMC, PCSK1, or LEPR variants classified as benign or likely benign
- Other types of obesity not related to POMC, PCSK1 or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity.

Warnings and Precautions

Warnings and precautions include disturbance in sexual arousal, skin pigmentation and darkening of pre-existing nevi. Depression and suicidal ideation ideation have occurred with IMCIVREE. Monitor patients for new onset or worsening depression and consider discontinuing if patients experience suicidal thoughts or behaviors. There may be a risk of serious adverse reactions due to benzyl alcohol preservative in neonates and low birth weight infants. IMCIVREE is not approved for use in neonates or infants.

Administration

Select patients for treatment who have genetically confirmed or suspected deficiency of POMC, PCSK1, or LEPR; Treat patients with variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS) in the clinical context of the patient; Evaluate weight loss after 12-16 weeks of treatment. If a patient has not lost at least 5% of baseline body weight, or 5% of baseline BMI for patients with continued growth potential discontinue IMCIVREE

No black box warning and no contraindications

Overview of U.S. Prescribing Information for IMCIVREE

Dosage in Adults and Pediatric Patients 12 Years of Age and Older

- The starting dose of IMCIVREE is 2 mg (0.2 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for gastrointestinal (GI) adverse reactions.
- If the starting dose is not tolerated, reduce to 1 mg (0.1 mL) once daily. If the 1 mg (0.1 mL) once daily dose is tolerated, and additional weight loss is desired, titrate to the 2 mg (0.2 mL) once daily dose
- If the 2 mg daily dose is tolerated, increase the dose to 3 mg (0.3 mL) once daily. If the 3 mg once daily dose is not tolerated, maintain administration of 2 mg (0.2 mL) once daily.

Dosage in Pediatric Patients 6 to less than 12 Years of Age

- The starting dose is 1 mg (0.1 mL) injected subcutaneously once daily for 2 weeks. Monitor patients for GI adverse reactions. Monitor patients for GI adverse reactions
- If the 1 mg dose is tolerated, increase the dose to 2 mg (0.2 mL) once daily.
- If the starting dose is not tolerated, reduce to 0.5 mg (0.05 mL) once daily dose. If the 0.5 mg (0.05 mL) once daily dose is tolerated, and additional weight loss is desired, titrate to the 1 mg (0.1 mL) once daily dose
- If the 2 mg once daily dose is not tolerated, reduce to 1 mg (0.1 mL) once daily dose
- If the 2 mg once daily dose is tolerated, and additional weight loss is desired, the dose may be increased to 3 mg (0.3 mL) once daily

Monitoring

- Periodically assess response to IMCIVREE therapy. In pediatric patients, evaluate the impact of weight loss on growth and maturation
- Evaluate weight loss after 12-16 weeks of treatment. If a patient has not lost at least 5% of baseline body weight, or 5% of baseline BMI for patients with continued growth potential, discontinue IMCIVREE as it is unlikely that the patient will achieve and sustain clinically meaningful weight loss with continued treatment

Adverse Events Reported in Open-Label Trials of Setmelanotide for Obesity due to POMC/PCSK1 or LEPR Deficiency

Adverse events occurring ≥20% of patients treated with setmelanotide in open-label clinical studies of 52-week duration

Adverse event	Setmelanotide-treated patients (N=27)
Injection site reaction[a]	96%
Skin hyperpigmentation[b]	78%
Nausea	56%
Headache	41%
Diarrhea	37%
Abdominal pain [c]	33%
Back pain	33%
Fatigue	30%
Vomiting	30%
Depression[d]	26%
Upper respiratory tract infection	26%
Spontaneous penile erection[e]	23%

[a] Includes injection site erythema, pruritus, edema, pain, induration, bruising, hypersensitivity, hematoma, nodule, and discoloration.
[b] Includes skin hyperpigmentation, pigmentation disorders, skin discoloration.
[c] Includes abdominal pain and upper abdominal pain.
[d] Includes depressed mood.
[e] n = 13 male subjects.

Reference: IMCIVREE Prescribing Information

Jennifer Chien

EVP, Head of North America

Unmet Needs may be Addressed with Effective Therapy

Patient, caregiver interviews on challenges of obesity due to POMC or LEPR deficiency without treatment

> ***It became overwhelming*** *…. planning meals, limiting access to food, instilling self-worth and confidence…"*

> *"**We've worked so hard** at trying to manage this condition. We've done everything…..* ***and we still feel powerless"***

Strategic Imperatives for IMCIVREE's Successful Debut in U.S. Market

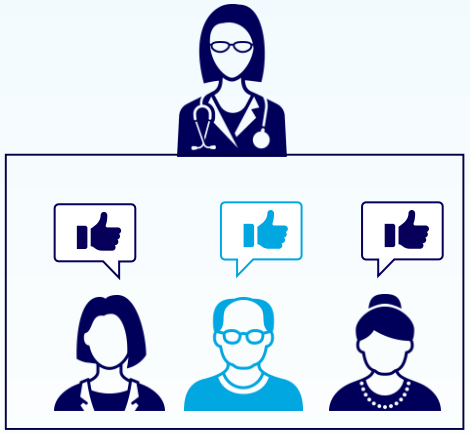
Ensure positive experience for patients, caregivers and prescribing physicians

Establish efficient and scalable model to meet the needs of identified and future patients

Education and awareness

Genetic testing

Access, reimbursement and patient assistance

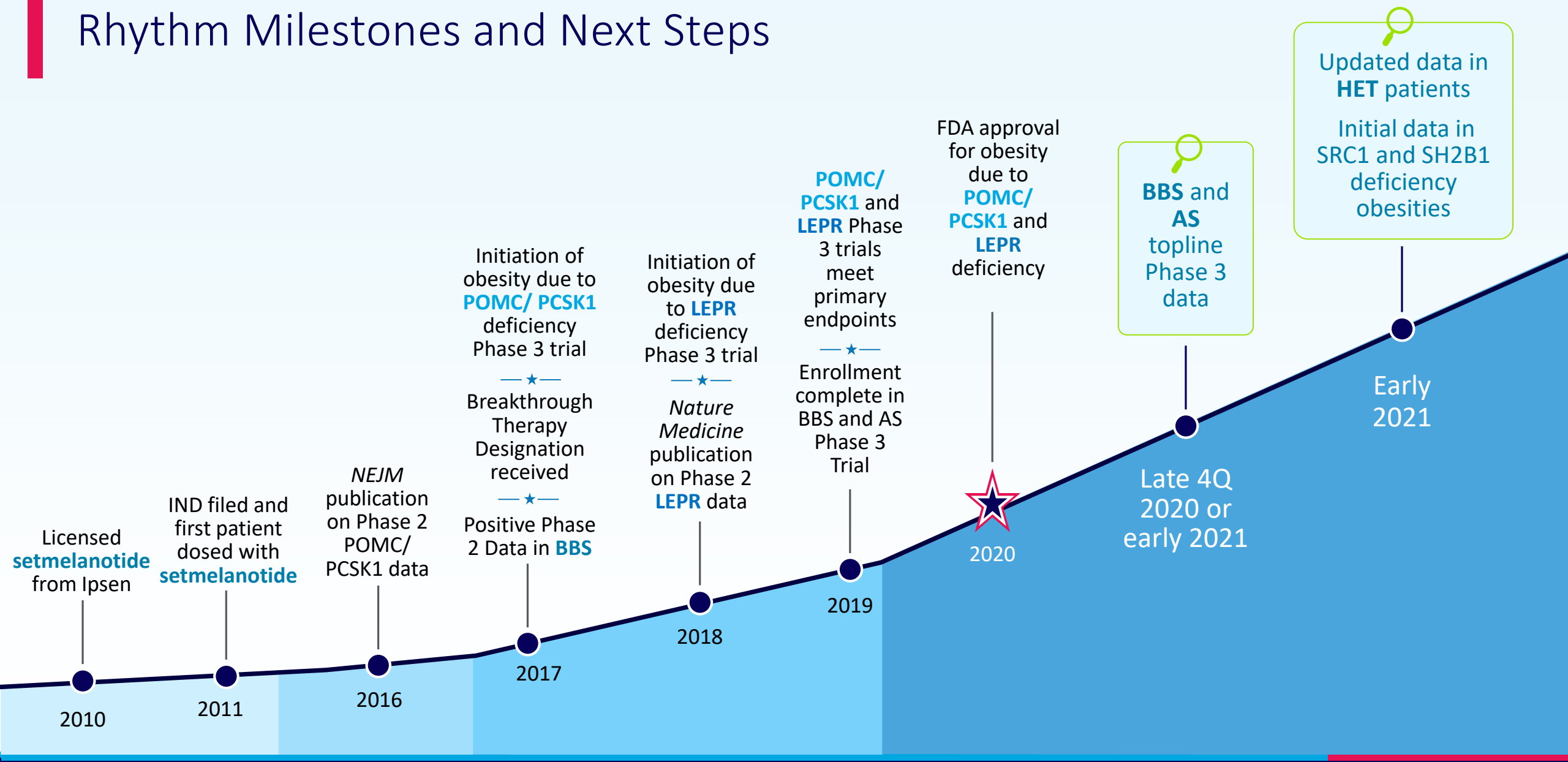


Positive experience

David Meeker, MD

Chairman, CEO and President

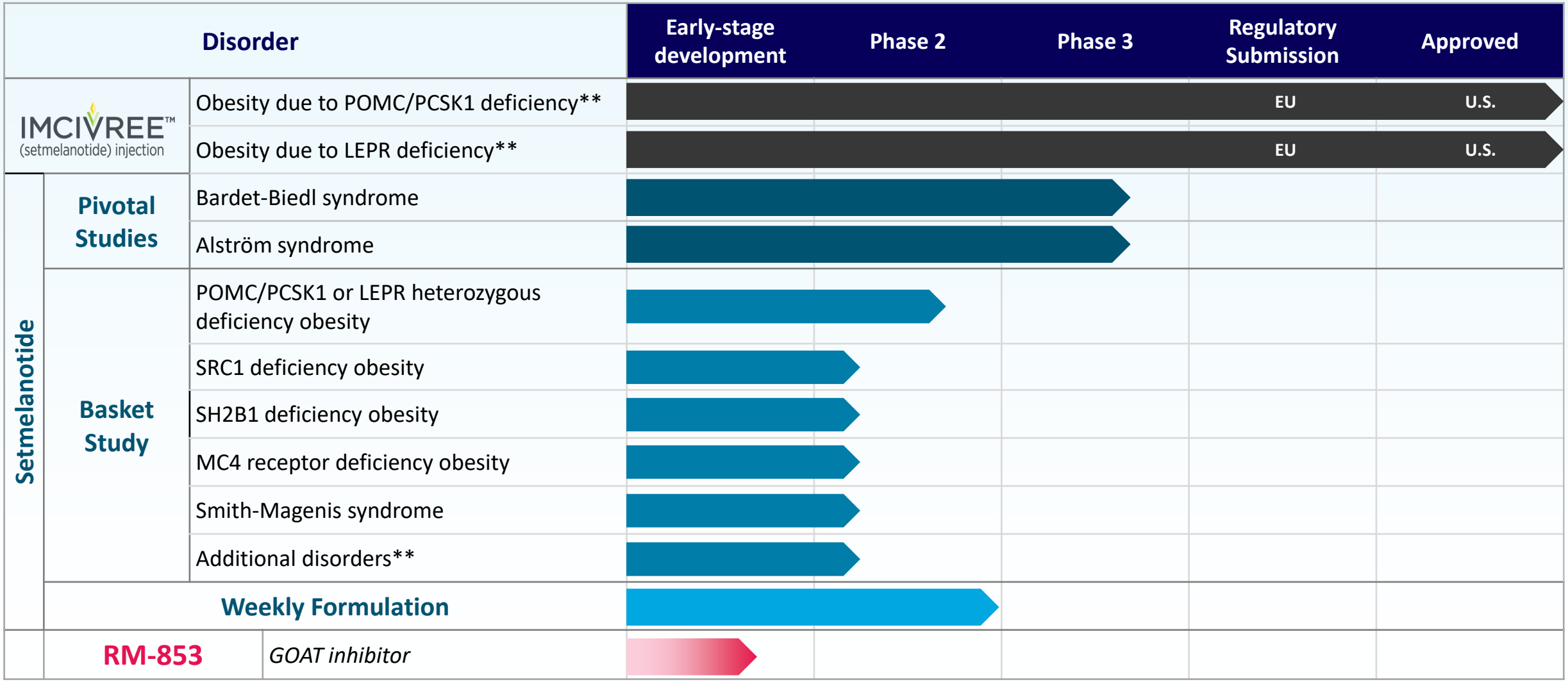
Rhythm Milestones and Next Steps



Rhythm® PHARMACEUTICALS


Rhythm®
PHARMACEUTICALS

Rhythm Pipeline Focused on MC4R Pathway Diseases



* Indicated for chronic weight management in adult and pediatric patients 6 years of age and older with obesity due to POMC, PCSK1 or LEPR deficiency confirmed by genetic testing demonstrating variants in *POMC*, *PCSK1*, or *LEPR* genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance ; *** Rhythm is currently assessing setmelanotide in additional diseases of obesity, as part of investigator-initiated protocols within the basket study. Given the recent discovery of these rare disorders of the MC4R pathway, there is currently limited or no genetic sequencing or epidemiology data that defines prevalence. However, Rhythm believes that these are rare disorders which may be setmelanotide-responsive.*

Rhythm® PHARMACEUTICALS