Targeting upstream MC4 pathway defects that result in life-threatening obesity

Company Presentation
March 2018

Forward-Looking Statements

This presentation contains forward-looking statements that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words “anticipate,” “believe,” “estimate,” “expect,” “intend,” “may,” “plan,” “predict,” “project,” “target,” “potential,” “will,” “would,” “could,” “should,” “continue,” and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect Rhythm’s current views with respect to future events, and Rhythm assumes no obligation to update any forward-looking statements except as required by applicable law.

Forward-looking statements represent our management’s beliefs and assumptions only as of the date hereof. You should read our filings with the Securities and Exchange Commission, including the prospectus for our initial public offering, as well as our Form 10-Q, including the Risk Factors set forth therein, and the documents that we have filed as exhibits to the registration statement for our initial public offering, and the Form 10-Q, completely and with the understanding that our actual future results may be materially different from what we expect. We have included important factors in the cautionary statements included in such documents, particularly in the Risk Factors sections, that we believe could cause actual results or events to differ materially from the forward-looking statements that we make.

Executive Summary

Targeting MC4 Pathway Defects that Result in Life-Threatening Obesity

Orphan Focus

Compelling data in MC4 pathway deficiencies; basis for multiple rare genetic disorders of obesity

- Focus on rare genetic deficiencies targeting MC4 pathway disorders, where setmelanotide has potential to serve as replacement therapy
- Demonstrated proof-of-concept (POC) in POMC deficiency obesity (POMC), LepR deficiency obesity (LepR) and Bardet-Biedl syndrome (BBS)
  - **Dramatic reductions in both weight and hunger**
  - **FDA awarded "Breakthrough Therapy Designation" for POMC and LepR**

Opportunity

Significant potential opportunity across multiple indications

- Phase 3 trials underway in POMC and LepR deficiency obesity; BBS expected to initiate in 2018
- Additional MC4 pathway POC trials initiated in BBS, Alström Syndrome, POMC Heterozygous (Hetz), and POMC Epigenetic disorders
- Focused development program with rapid paths expected to approval
- Significant newsflow expected in the near-term

Team

Experienced management team with proven capabilities

- Delivered Allergan Ghrelin acquisition in 4Q16
- Recently appointed Hunter Smith as Chief Financial Officer (previously at Celgene) and Nithya Desikan as Chief Commercial Officer (previously at Biogen)
- Strong financial position
  - Successful IPO – 8 million shares at $17 per share in Oct. 2017
  - $148.1 million cash at Dec. 31, 2017

Experienced Leadership Team and Blue-Chip Investors

Management Team

Keith Gottesdiener, MD	Chief Executive Officer	MERCK
Hunter Smith	Chief Financial Officer	Celgene
Fred Fiedorek, MD	Chief Medical Officer	Bristol-Myers Squibb, GlaxoSmithKline
Lex Van der Ploeg, PhD	Chief Scientific Officer	Abraxis BioScience, MERCK
Nithya Desikan	Chief Commercial Officer	Biogen, Johnson & Johnson

Board of Directors*

David Meeker, MD	Genzyme, Harvard
Neil Exter	Third Rock Ventures
Todd Foley	MPM Capital
Keith Gottesdiener, MD	Rhythm, CEO
Christophe Jean	Ipsen Group
Ed Mathers	NEA, MedImmune
David McGirr	Relypsa, Cubist

Scientific Advisory Board

Lee Kaplan, MD, PhD *(Chair)*	MGH, Harvard
John Amatruda, MD	Merck, Yale
Michael Camilleri, MD	Mayo Clinic
William Chin, MD	PhRMA, Harvard, Lilly
Liz Stoner, MD	MPM, Merck, Rhythm Founder

Pre-IPO Investors

DEERFIELD · IPSEN Innovation for patient care · MPM CAPITAL Investing in Healthcare Innovation · NEA · OrbiMed Healthcare Fund Management · Pfizer Ventures · THIRD ROCK VENTURES

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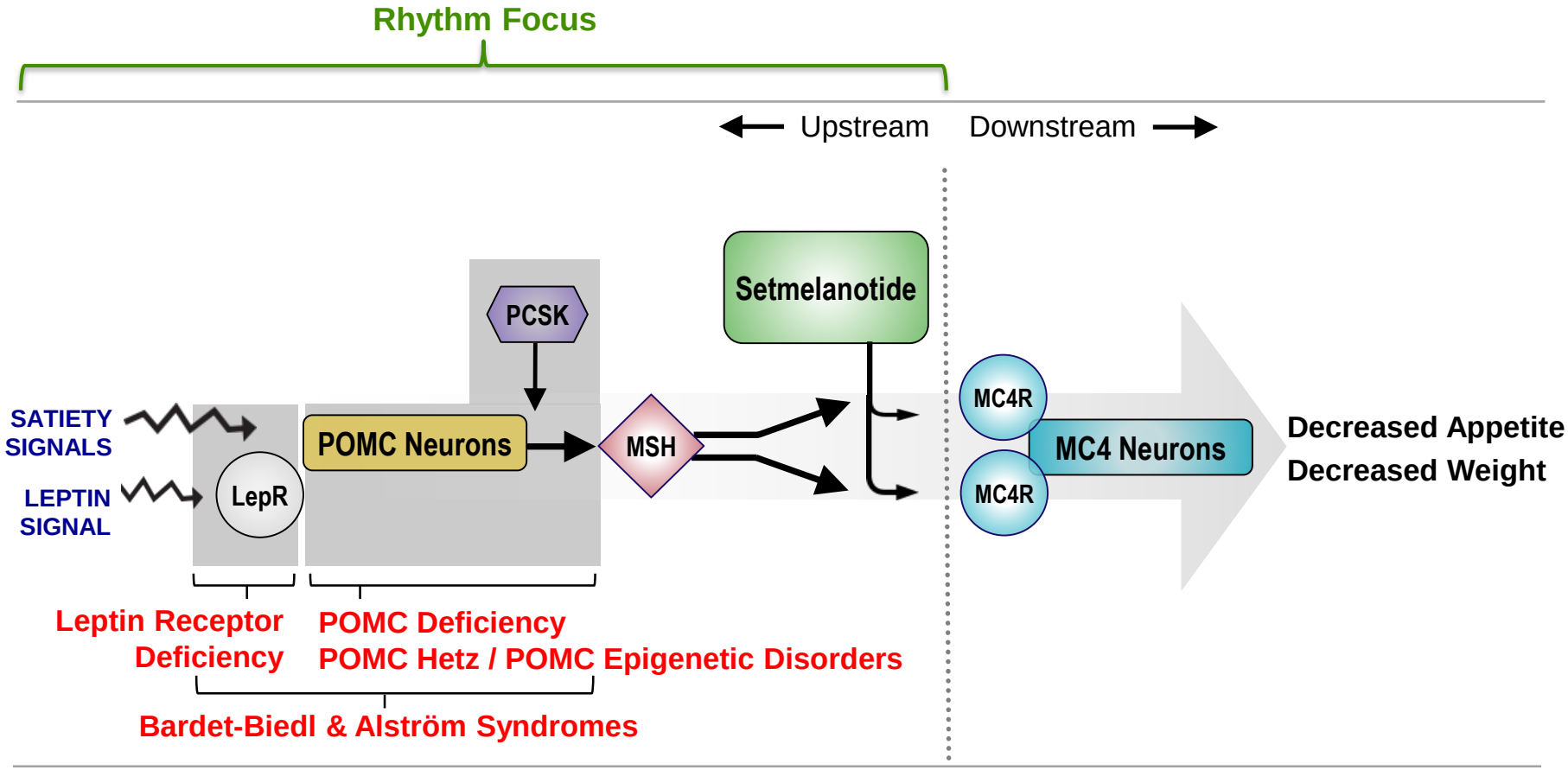
Targeting Upstream MC4 Pathway Defects

- These genetic defects result in severe obesity and hyperphagia
- Setmelanotide, an MC4R agonist, has potential to serve as “replacement therapy”

MC4 Pathway



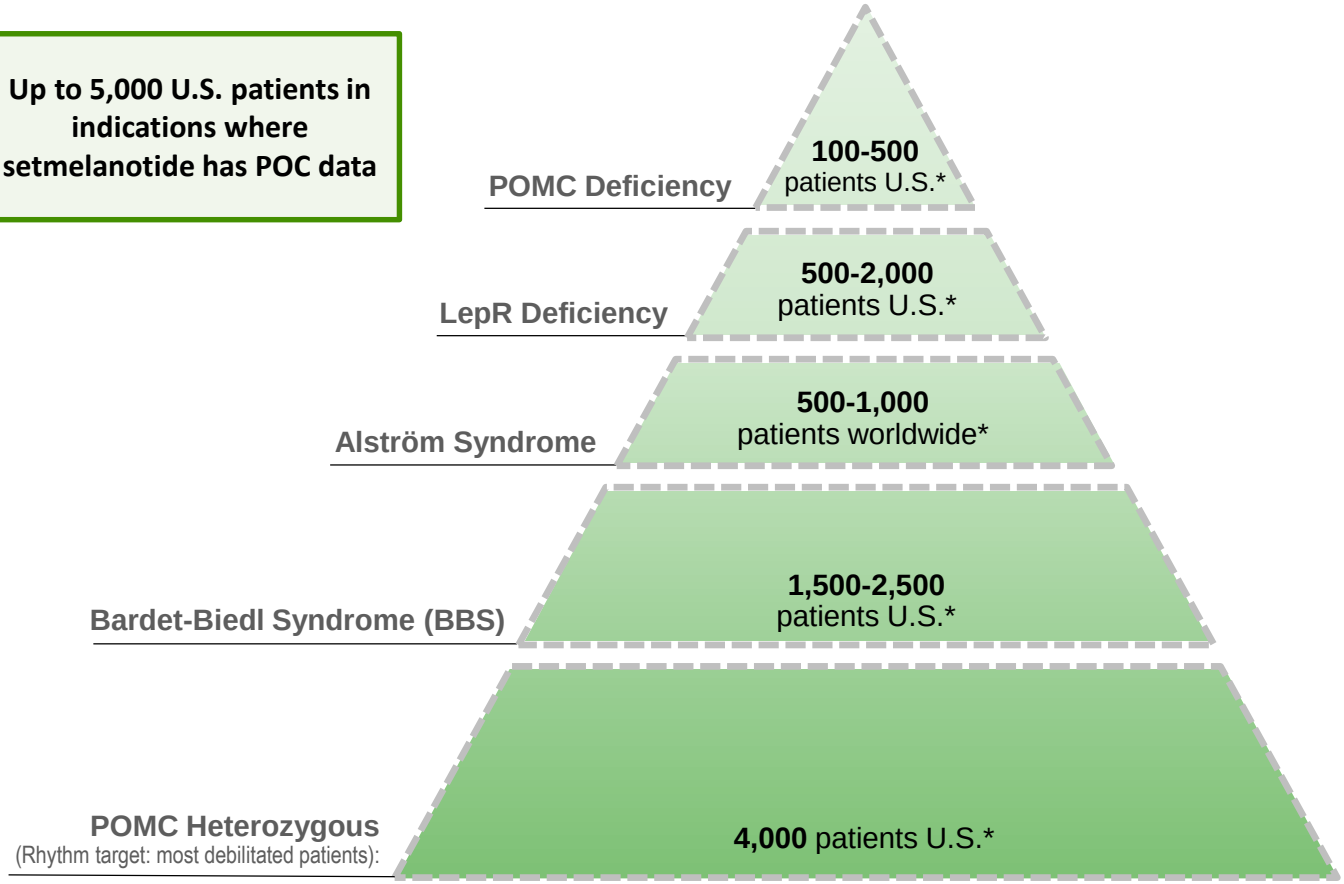
Creemers et al. *Diabetes* 2012; 61:383. Challis et al. Human Molecular Genetics 2002; 11: 1997. Buono et al. *Clinical Chemistry* 2005; 51: 1358. Farooqi. Genetics of Obesity Study (GOOS), unpublished data

Setmelanotide Development Pipeline – MC4 Pathway Deficiencies

Indication	PHASE 1	PHASE 2	PHASE 3	Proof-of-Concept	Last Event	Next Expected Event
POMC Deficiency Obesity				✓	Positive Phase 2; Phase 3 initiated	Complete enrollment of 10 patients 1H 2018 Phase 3 results 1H 2019
Leptin Receptor Deficiency Obesity				✓	Positive Phase 2; Phase 3 initiated	Phase 3 enrollment complete 2018
Bardet-Biedl Syndrome				✓	Positive Phase 2	Initiate Phase 3 2018
POMC Heterozygous Deficiency Obesity					Initiated Phase 2	Phase 2 results 1H 2018
Alström Syndrome					Initiated Phase 2	Phase 2 results 1H 2018
POMC Epigenetic Disorders					Initiated Phase 2	Phase 2 results 1H 2018

Setmelanotide Addresses Significant Market Opportunity †

Up to 5,000 U.S. patients in indications where setmelanotide has POC data



European patient populations believed to be at least as large as those in the U.S. (1)
Potentially a total of 10,000 U.S. and E.U. patients in POMC, LepR and BBS indications

* The patient numbers above are based on company estimates
† Epidemiological estimates not yet available for POMC epigenetic disorders
(1) Rhythm believes that the addressable patient population in Europe is at least as large as in the U.S. However, Rhythm does not have a comparable epidemiological data from the European Union and these estimates are therefore based solely on applying relative population percentages to the Company-derived estimates

A 2nd Approach to Patient Numbers: Genetic Epidemiology

Genetic Epidemiology for U.S. Patients:

- Uses large genomic databases with full genome or exome sequencing
- Rhythm analysis of ~140,000 genomes, representative of U.S. population
- Supports estimates that POMC and LepR patients are at least as large, if not larger, than our current estimates
  - PCSK1, one of the defects in POMC deficiency, itself might be more than 1,000 patients in the US
- Work underway to expand this preliminary information
- New genetic epidemiological analyses to be presented in late-breaking poster presentation on March 19, 2018 at ENDO

Overview of Setmelanotide

Potent First-in-Class MC4R agonist in development for the treatment of Rare Genetic Disorders of Obesity

- Setmelanotide: an 8 amino acid peptide with high potency (EC_{50} 0.27nM)
  - Retains specificity and functionality of the naturally occurring hormone that activates MC4R
  - Administered by once daily subcutaneous injection
- POC achieved for long-acting setmelanotide formulation
  - Profile consistent with once weekly dosing: half life ~123 hours
- Previous clinical trials with approximately 300 obese patients demonstrated statistically significant weight loss with good tolerability
  - Setmelanotide showed statistically significant 6.85% increases in resting energy expenditure in obese humans
- Toxicology Studies: Large margins at the NOAEL* (>300 fold)
- IP: Composition of matter in all major markets
  - US patent expires in 2027; possible extension to 2032 under Hatch-Waxman
- Highly competitive cost of goods sold

* NOAEL: No-observed-effect-level

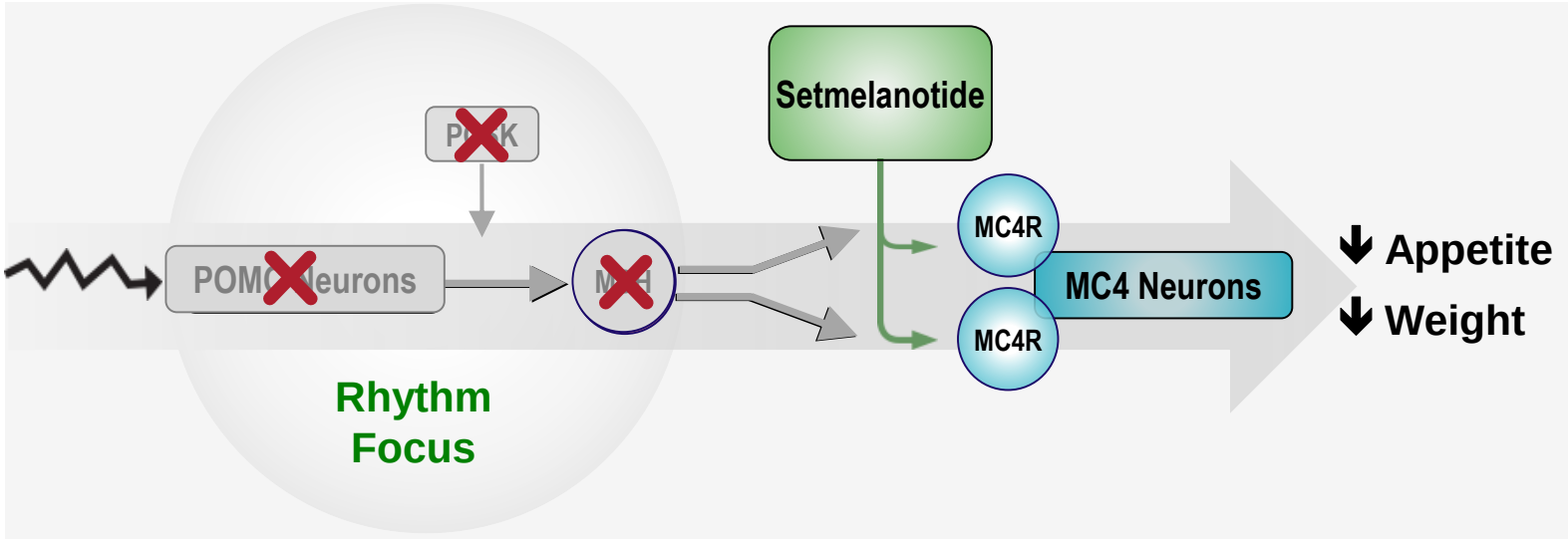
Setmelanotide Clinical Development

POMC Deficiency Obesity

POMC Homozygous Patients

- Ultra-rare disorder caused by two different homozygous genetic defects
- Causes severe, early-onset obesity and profound hyperphagia
- 50 patients reported to date; Company estimates U.S. addressable population of 100–500 patients
  - Ongoing Rhythm genetic epidemiology study suggests significant potential upside to these patient numbers

MC4 Pathway



Clinical Status

- FDA Breakthrough Designation; EMA scientific advice also expressed general support
- Phase 3 ongoing
  - n=10, ~1-year duration
  - 1º endpoint: categorical analysis of responders; 2º endpoint: percent weight change from baseline
  - FDA supported enrolling add'l (e.g., pediatric) patients, with less than 1-year data at filing, to better understand the benefits of setmelanotide treatment in a broader population
  - Expect to complete pivotal enrollment in first half of 2018; results expected in 1H19

POMC Deficiency Obesity Phase 2 Study

NEJM Publication July 21, 2016

The NEW ENGLAND JOURNAL of MEDICINE

Original Article

Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist

Peter Kühnen, M.D., Karine Clément, M.D., Susanna Wiegand, M.D., Oliver Blankenstein, M.D., Keith Gottesdiener, M.D., Lea L. Martini, M.D., Knut Mai, M.D., Ulrike Blume-Peytavi, M.D., Annette Grüters, M.D., and Heiko Krude, M.D.

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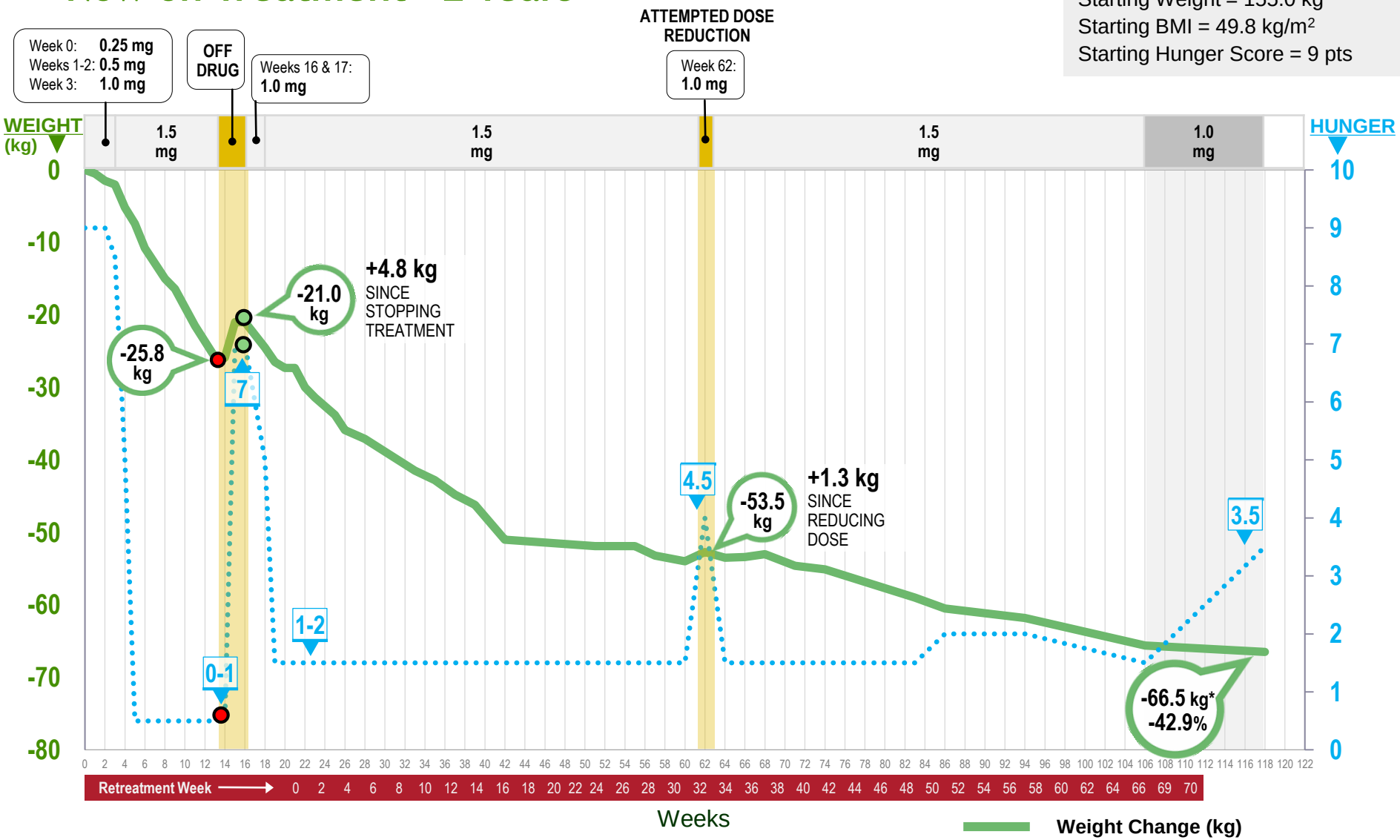
POMC Deficiency Obesity Phase 2 Study: Patient #1

Now on Treatment >2 Years

20 yr old female
Starting Weight = 155.0 kg
Starting BMI = 49.8 kg/m^2
Starting Hunger Score = 9 pts



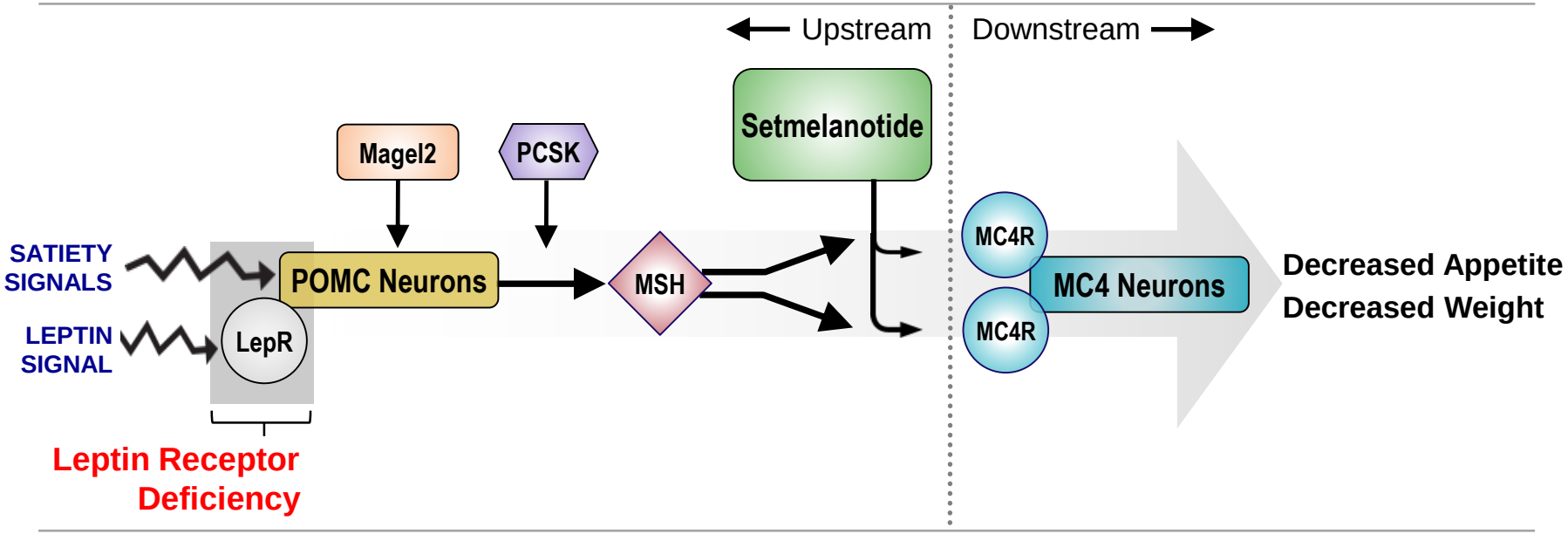
* Figures represent cumulative weight lost in kgs

Leptin Receptor Deficiency Overview

Leptin Receptor Deficiency (LepR)

- Like other upstream MC4 pathway deficiencies, causes severe, early onset obesity and hyperphagia
- Company estimates 500-2,000 addressable patients in the U.S.

MC4 Pathway



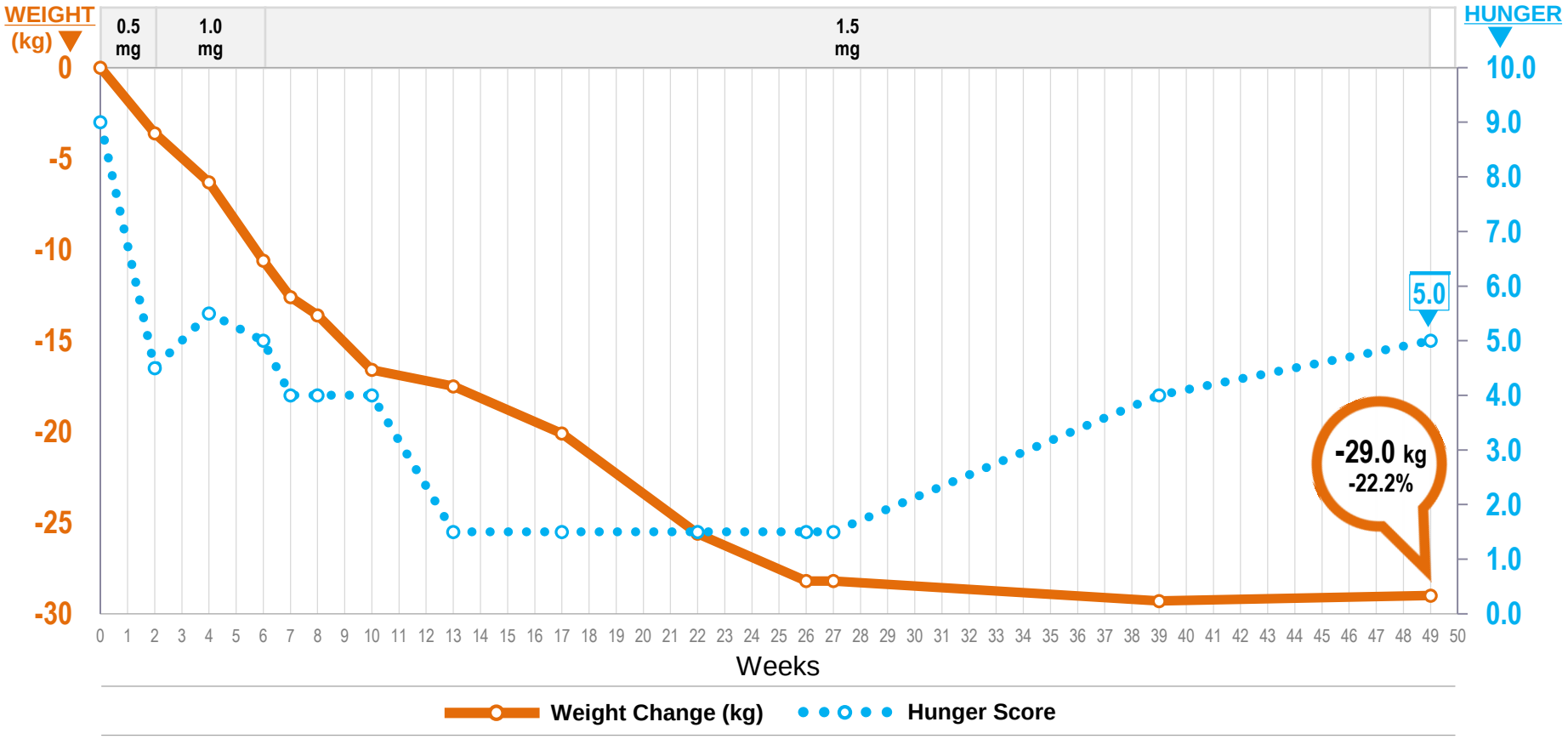
Clinical Status

- FDA Breakthrough Designation
- Phase 3 initiated
  - n=10, ~1-year duration
  - 1º endpoint: categorical analysis of responders; 2º endpoint: percent weight change from baseline
  - First patient enrolled; expect to complete enrollment in 2018

LepR Deficiency Obesity Phase 2 Study: Patient #1

LepR Patient #1

23 yr old male – LepR Mutation
Starting Weight = 130.6 kg
Starting BMI = 39.9 kg/m^2
Starting Hunger Score = 9.0 pts



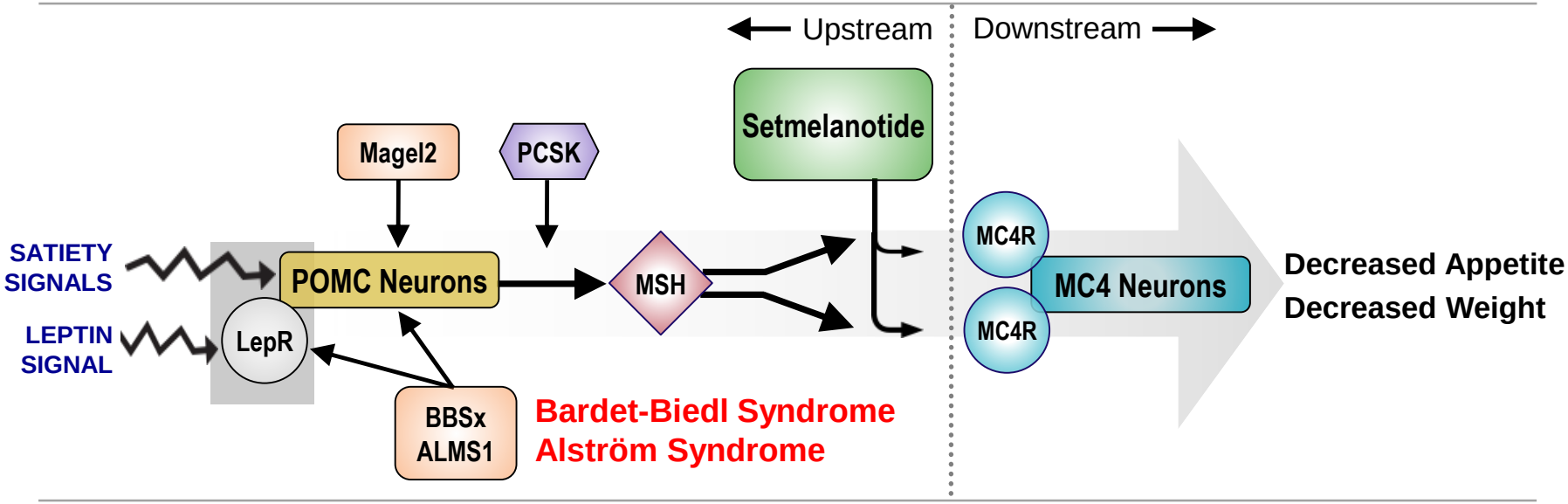
* Figures represent cumulative weight lost in kgs

Bardet-Biedl & Alström Syndromes

Two Related Rare-Genetic Obesities

- Like other upstream MC4 pathway deficiencies: severe, early onset obesity and hyperphagia
- Other findings very prominent: progressive vision loss, kidney abnormalities, polydactyly (BBS), congestive heart failure (Alström), hyperinsulinemia and Type 2 diabetes (Alström), and others
- Genetic defects in ciliary proteins: BBS 1-21 in Bardet-Biedl and ALMS1 in Alström Syndrome
  - Defects result in leptin resistance and impaired POMC signaling in MC4 pathway
- Company estimates 2,000-3,500 addressable patients in the U.S. across both indications

MC4 Pathway



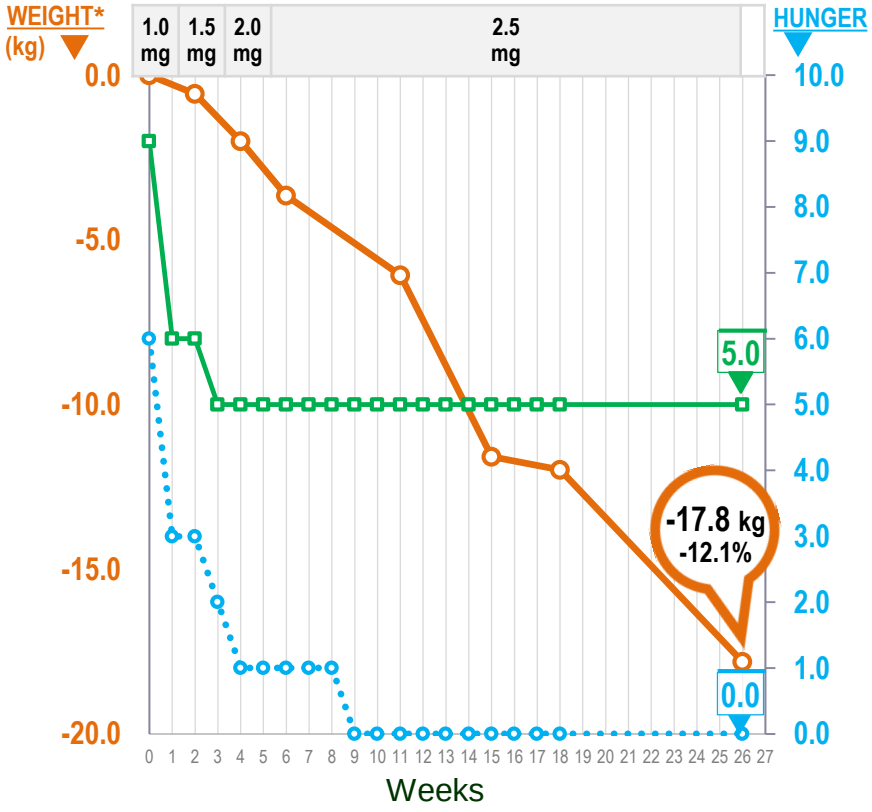
Clinical Status

- Phase 2 initiated for both BBS and Alström Syndrome
- POC achieved for BBS in 5 pts; Phase 2 results reported 4Q17; plan to initiate BBS Phase 3 trial in 2018
- First Alström patient enrolled; preliminary results expected in 1H18

BBS Obesity Phase 2 Study: Patients #1 & #2

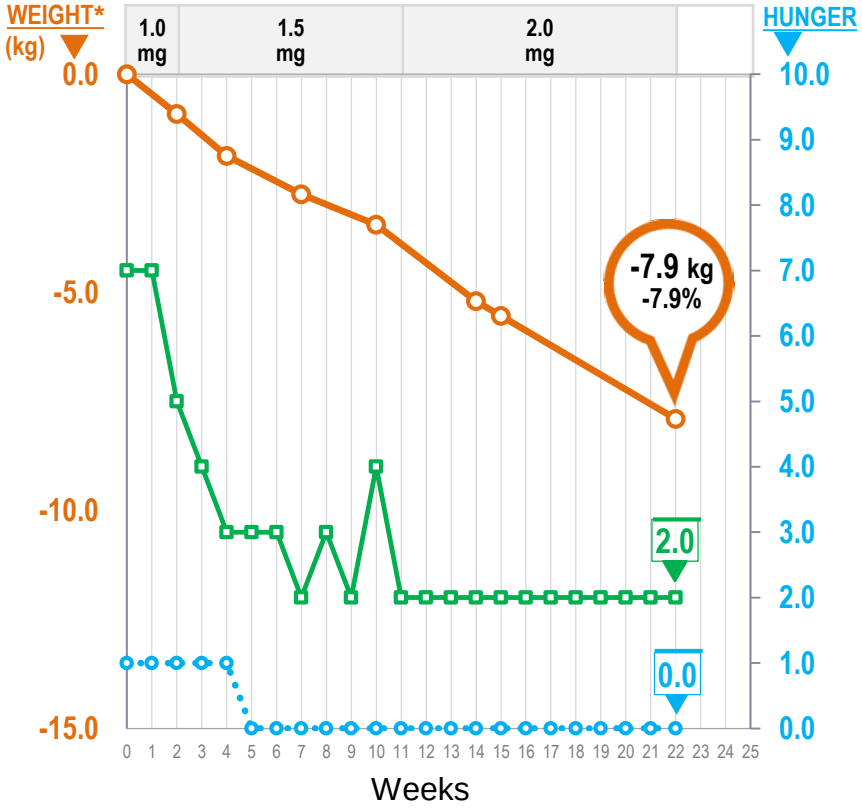
BBS Patient #1

25 yr old male - BBS1 Mutation
Starting Weight = 147.5 kg
Starting BMI = 44 kg/m^2
Starting Hunger Score = 9.0 pts



BBS Patient #2

61 yr old female - BBS2 Mutation
Starting Weight = 99.4 kg
Starting BMI = 44 kg/m^2
Starting Hunger Score = 7.0 pts



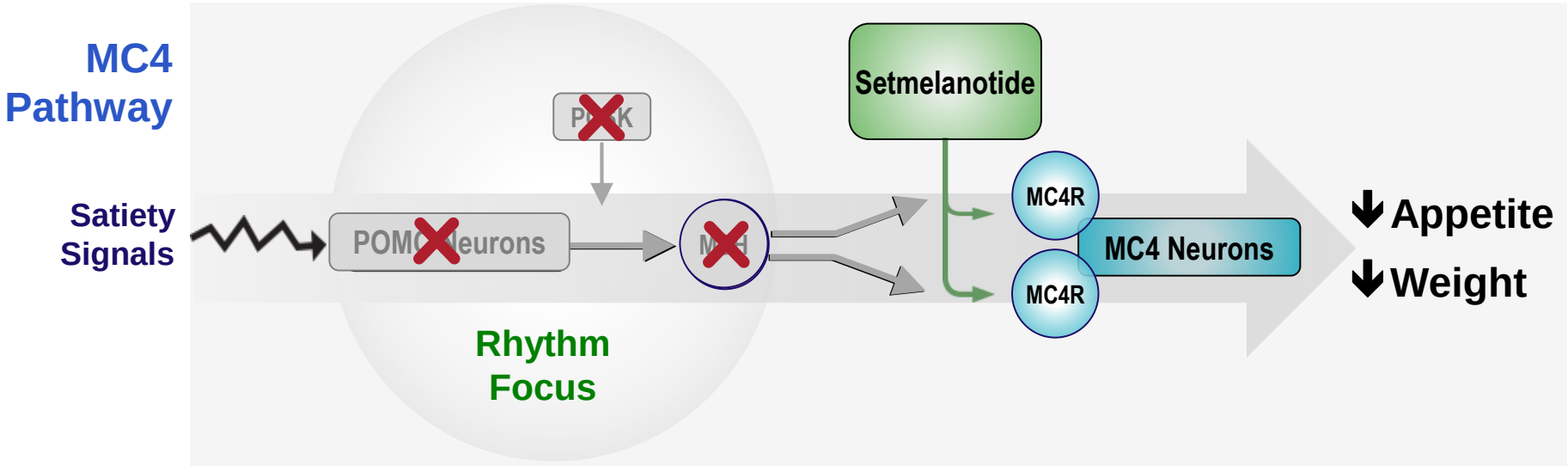
Weight Change (kg) | Morning Hunger Score | Worst Hunger Score

* Figures represent cumulative weight lost in kgs

Expansion Indications: POMC Heterozygous & Epigenetic

POMC Heterozygous and Epigenetic Patients

- POMC Heterozygous (Hetz): Caused by the loss of one of the two genetic copies in two different genetic defects
- POMC Epigenetic Disorder: DNA modifications (methylation) that can change gene expression without altering the DNA
- Both POMC Hetz and POMC Epigenetic variants also correlate with increased body weight in children and adults
- Both result in a strong predisposition to obesity, though epidemiology and clinical characterization is less well known
- Focus on most debilitated patients, with the hypothesis that POMC Hetz and Epigenetic patients may be highly responsive to setmelanotide
- First POMC Heterozygous and Epigenetic patients enrolled; preliminary results expected in 1H18

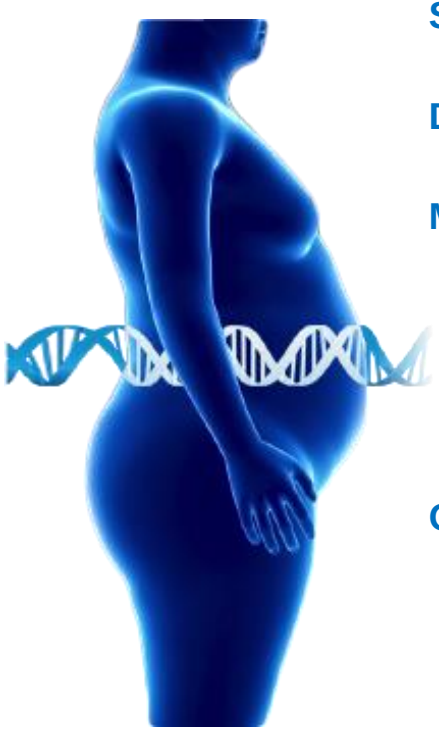


Prader-Willi Phase 2 Study (n=40)

- We completed a Phase 2, proof of concept study in PWS
  - Doses placebo, 0.5 mg, 1.5 mg and 2.5 mg
  - Primary evaluations after 4 weeks of treatment
- Only modest changes in hyperphagia without changes in weight
  - Small evidence of weight loss in small group randomized to highest dose
- Good safety and tolerability up to 2.5 mg/day
- Results do not support moving directly to Phase 3
- A future Phase 2 study may address potential factors, such as longer duration, younger age, higher doses, and operational limitations
  - Plan to reassess in 2018

Setmelanotide Was Generally Well-Tolerated

Approximately 300 Obese Subjects and Patients Exposed to Drug



Single doses up to 10 mg

Discontinuations due to Adverse Events (AEs) were uncommon

Most AEs were due to mechanism-based effects

- Little, if any, change in heart rate or blood pressure
- Occasional increase in male erections / female arousal
- Some nausea and / or vomiting: rare, mild and short-lived
- Reduced appetite

Other, non-mechanism based AEs

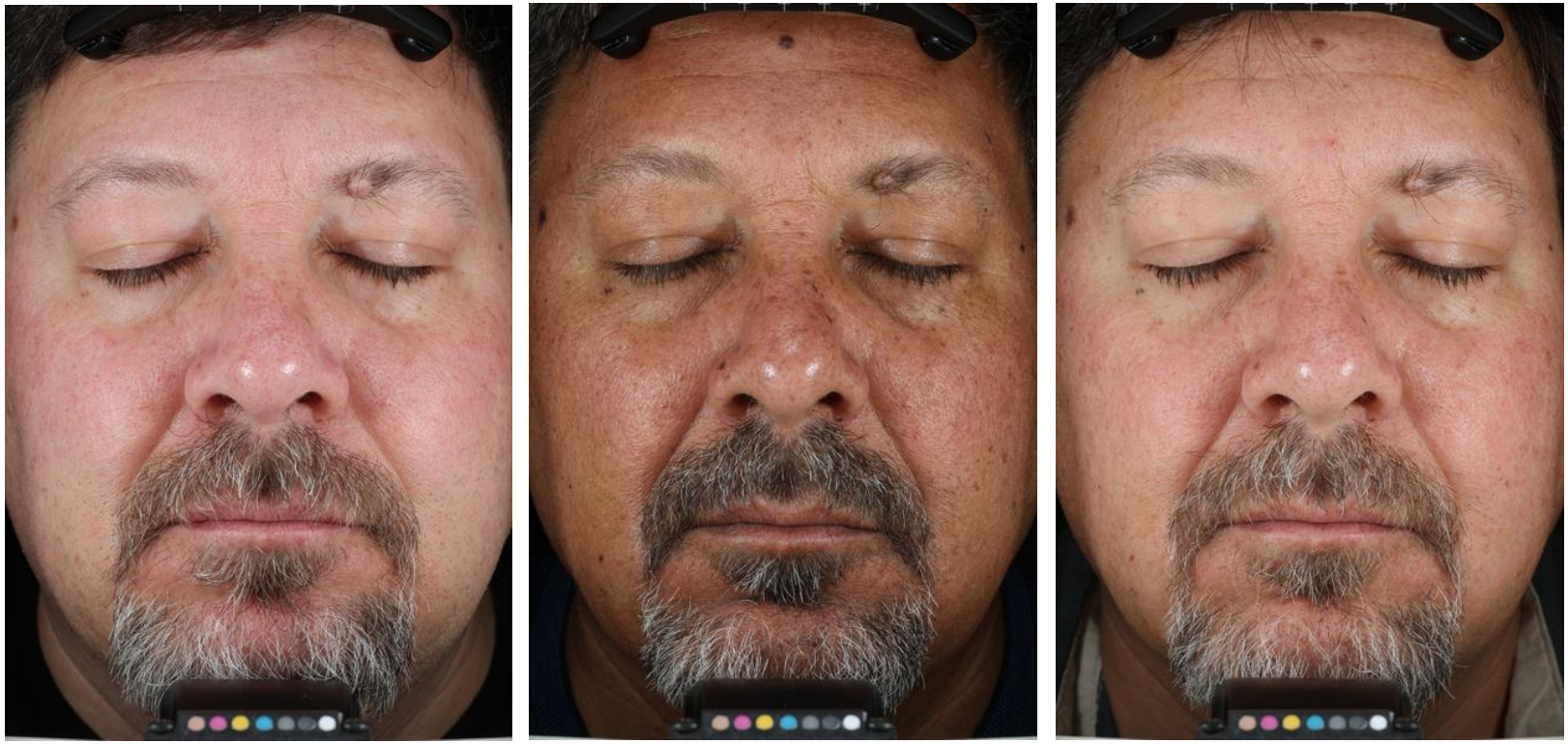
- Some injection site reactions: seen in both active and placebo
- Darkening of skin (tanning) and skin lesions
- Back pain, headaches, fatigue, diarrhea and joint pain: slightly more in active vs. placebo groups

No concerns for labs, ECGs, physical exam

Effects Mediated by the Closely Related MC1 Receptor

MC1 Mediates Skin Tanning

- Occurs after one to two weeks of treatment
- Most often plateaus by two to four weeks of treatment
- Like sun-related tanning, generally returns to baseline after treatment



Baseline **On Treatment** **Recovery**

Commercial Opportunity

Rhythm Commercial Strategy & Priorities

Rhythm's Commercial Priorities For Setmelanotide Launch:

- Improve methods of **evaluation and diagnosis** of rare genetic obesity patients through:
  - Enhanced diagnostic capabilities
  - Partnership with KOLs and pediatric endocrinologists
- Facilitate an **integrated genetic obesity community** through:
  - Services that support patient awareness, education, advocacy and treatment
- Communicate the **burden of rare genetic obesity** syndromes to:
  - Promote advocacy for patient sequencing, and
  - Support pricing and reimbursement of setmelanotide
- Build a global **commercial organization** to:
  - Drive patient identification
  - Enable a successful launch of setmelanotide

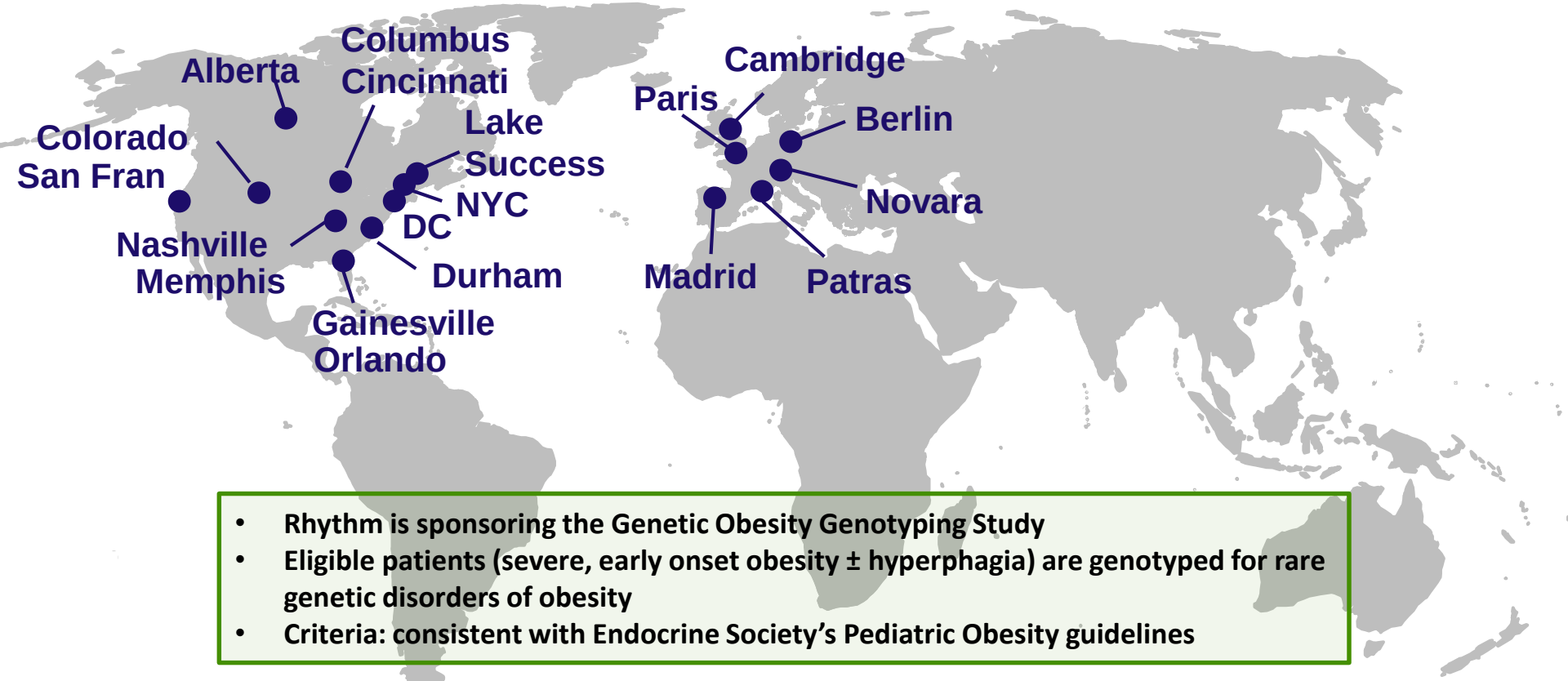
Rhythm's Commercial Strategy

- Establish a commercial and marketing organization in the U.S. and in other core strategic markets
- Target physicians treating rare genetic disorders of obesity (pediatric and adult endocrinologists)
- Establish partnerships selectively in markets outside of the U.S. for sales, marketing and distribution

Genotyping Study: Sites in North America and Europe*

Goal of the Genotyping Study

To develop a screening algorithm for selecting patients to be genotyped and diagnosed with rare genetic obesities



- Rhythm is sponsoring the Genetic Obesity Genotyping Study
- Eligible patients (severe, early onset obesity ± hyperphagia) are genotyped for rare genetic disorders of obesity
- Criteria: consistent with Endocrine Society's Pediatric Obesity guidelines

* Representative sites participating are indicated on the map

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The Genetic Obesity Project ID/Genotyping Study

Genotyping Study: initial results

- Initial results in first 560 genotyped patients in this study:
  - 2 (0.36%) POMC deficiency obesity (PCSK gene) patients
  - 3 (0.54%) LepR deficiency obesity patients
  - 59 (10.5%) Heterozygous deficiency patients
    - 5 (0.89%) R236G Heterozygous deficiency patients

Drive Significant Diagnosis Prior to Product Launch

Assert screening guidelines and support KOL advocacy for systematic genetic obesity testing

Leverage Endocrine Society guidelines just published

JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

Pediatric Obesity—Assessment, Treatment, and Prevention: An Endocrine Society Clinical Practice Guideline

Guidelines recommend:

"Genetic testing for extreme early onset obesity (before 5 years of age) with clinical features of genetic obesity syndromes (in particular extreme hyperphagia) and/or a family history of extreme obesity"

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Recent and Upcoming Milestones

Significant News Flow Expected in the Near-Term

- ✓ **3Q17:** Preliminary Bardet-Biedl proof-of-concept data
- ✓ **3Q17:** Expansion of Rhythm Executive Leadership Team
- ✓ **4Q17:** Phase 2 results reported for Bardet-Biedl Syndrome
- ✓ **Early '18:** First patient treated in LepR Phase 3 study
- ▪ **1H18:** Phase 3 enrollment complete POMC Phase 3 study
- ▪ **1H18:** Phase 2 results for each of Alström Syndrome, POMC Heterozygous, and POMC Epigenetic disorders
- ▪ **2018:** Complete enrollment of LepR Phase 3 study
- ▪ **2018:** Initiate Phase 3 study in Bardet-Biedl Syndrome
- ▪ **1H19:** Phase 3 results for POMC deficiency obesity

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