Rhythm Pharmaceuticals

Targeting MC4R pathway and transforming the care of patients with rare genetic disorders of obesity

November 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 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 and anticipated PDUFA date, 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.

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

Setmelanotide, an investigational drug, has demonstrated potential to dramatically reduce weight and hunger

Validation

Secure FDA and EMA approvals for POMC or LEPR deficiency obesities

Meaningful Opportunity

Deliver Bardet-Biedl and Alström syndromes pivotal Phase 3 data

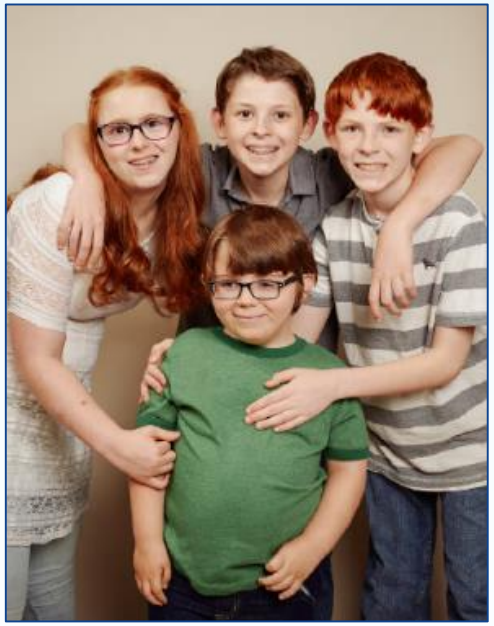
Growth Potential

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

Drive COMMUNITY BUILDING and GENETIC SEQUENCING

Living with Early-onset, Severe Obesity and Hyperphagia

Hallmark Symptoms of Rare Genetic Disorders of Obesity

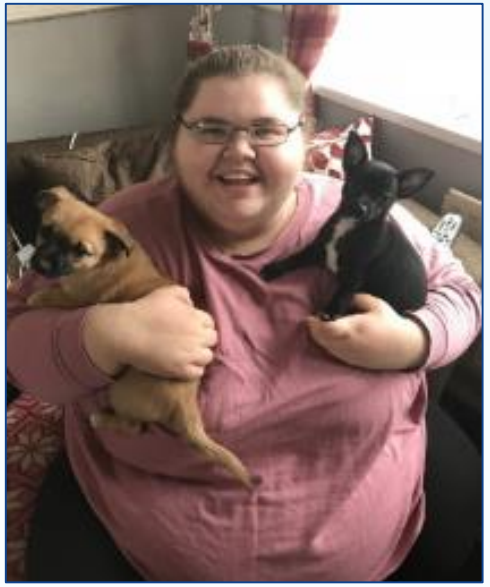


Adalissa and Solomon with their siblings (unaffected)

"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 keep a menu planned and if we deviate from that menu it's a disaster."

"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***



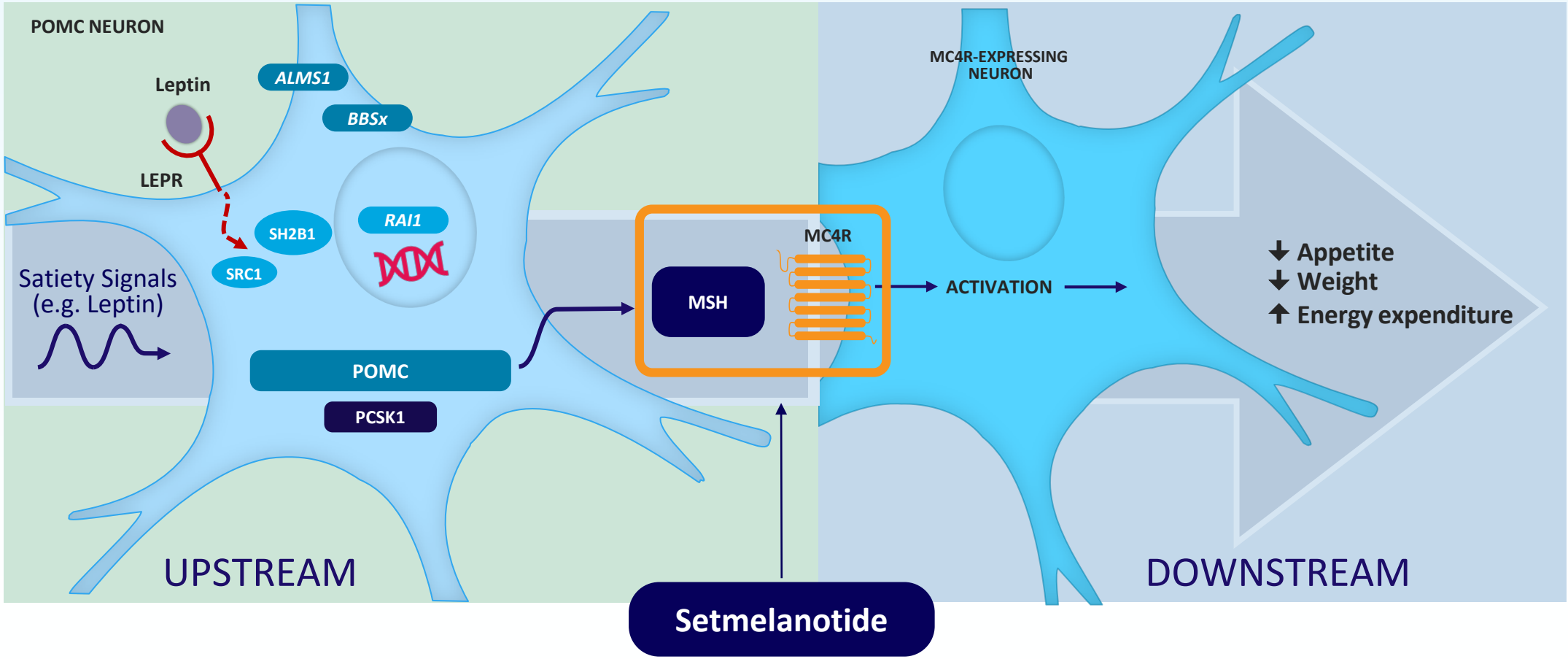
Katy, at 23 years old, 450 pounds

"It causes extreme unrelenting hunger and excessive eating. As a child…the fridge and food was controlled massively…but nobody could understand that I was desperately hungry and just wanted to stop that feeling."

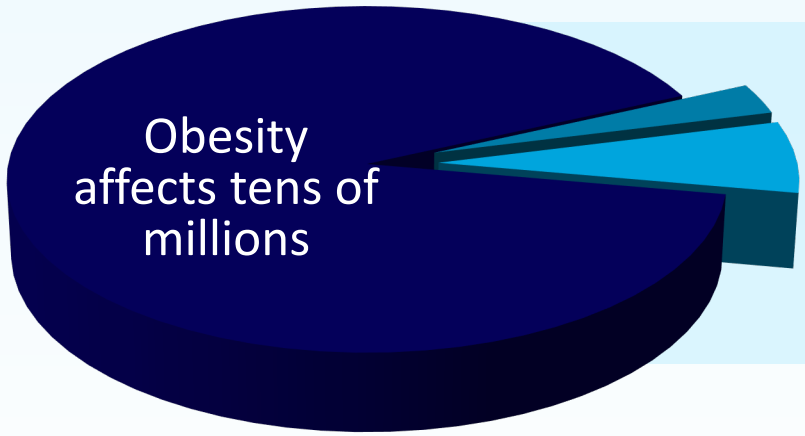
*- Katy, diagnosed with **POMC heterozygous deficiency obesity***

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

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



Rare Genetic Disorders of Obesity Associated with the MC4R Pathway Comprise a Significant Opportunity Distinct from General Obesity



Rhythm is focused on rare genetic disorders of obesity:

POMC deficiency obesity		~100-500*
LEPR deficiency obesity		~500-2,000*
Bardet-Biedl syndrome		~1,500-2,500 *
Alström syndrome		~500-1,000†
HETs	POMC or LEPR heterozygous deficiency obesity	>20,000 *
SRC1 deficiency obesity		>23,000 *
SH2B1 deficiency obesity		>24,000 *
MC4R deficiency obesity		~10,000 **
Smith-Magenis syndrome		~1,500-2,500*

Pivotal Indications Phase 2 indications

LEPR, leptin receptor, POMC, pro-opiomelanocortin; MC4R, melanocortin-4 receptor.

* Estimated prevalence of U.S. patients based on company estimates; ** Estimated prevalence of U.S. patients with addressable variants of the MC4R; † Prevalence estimate for Alström syndrome is worldwide.

Rhythm® PHARMACEUTICALS

Validation

Secure **FDA and EMA approval** for
POMC and LEPR deficiency obesities

Setmelanotide Demonstrated Statistically Significant, Clinically Meaningful Reductions in Weight and Hunger in Phase 3 Trials for POMC and LEPR

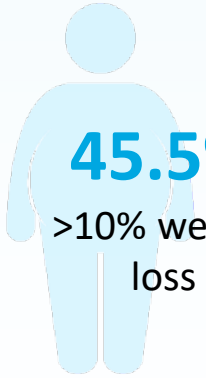
POMC Phase 3 Topline Data* (n=10)

80%
>10% weight loss

-25.4%
mean weight reduction

-27.8%
mean hunger score reduction

31.9kg / 70.2lbs
mean weight loss in 1 year



LEPR Phase 3 Topline Data* (n=11)

45.5%
>10% weight loss

-12.5%
mean weight reduction

-41.9%
mean hunger score reduction

16.7kg / 36.8lbs
mean weight loss in 1 year

Validation

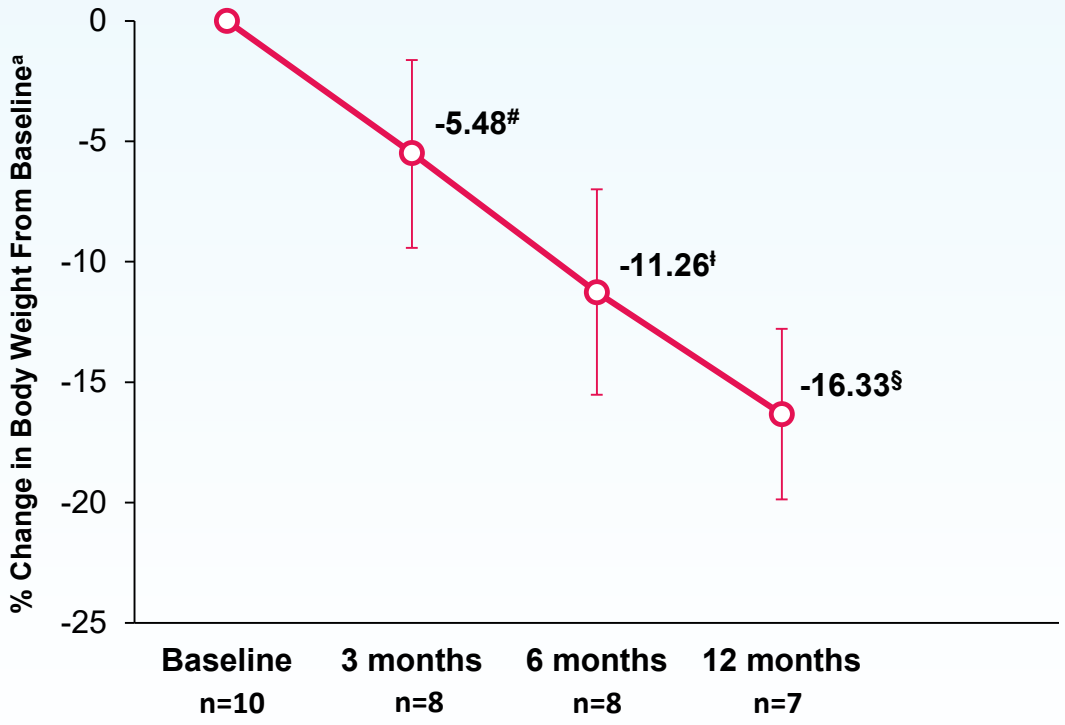
- **PDUFA date** set for Nov. 27, 2020 with priority review
- **Rare pediatric disease designations** awarded by FDA
- **MAA submitted** to EMA in 2Q2020
- Additional supporting data
  - 100% of POMC (4) and LEPR (4) **supplemental patients** achieve >10% weight loss
  - 15 patients in **LTE study** maintained durable weight loss and stable hunger scores with treatment up to 155 weeks**

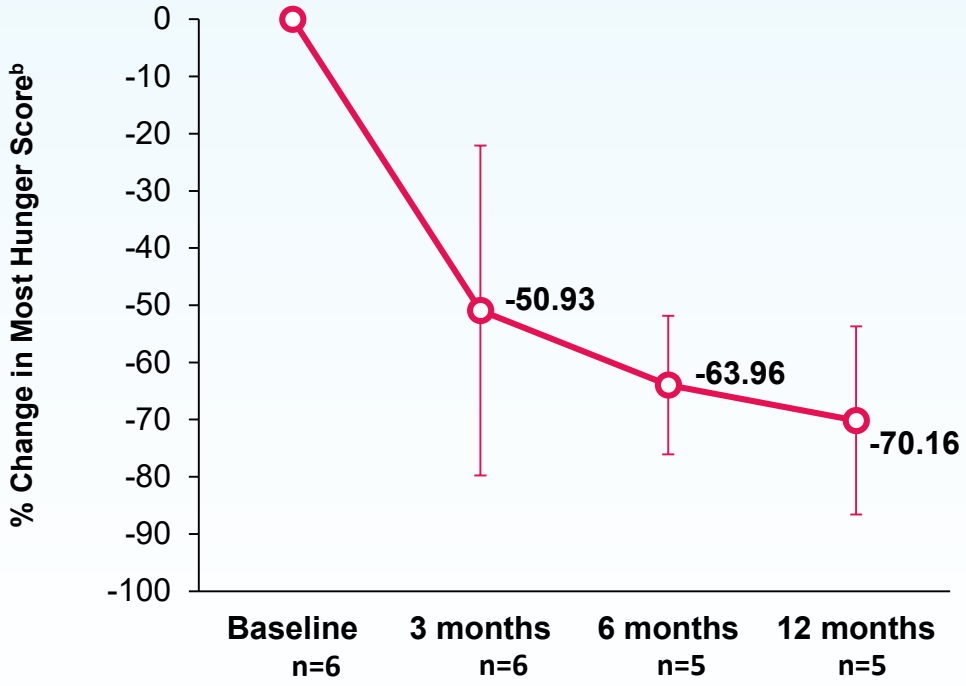
*Data announced by Rhythm in August 2019 and presented at The Obesity Society annual meeting during ObesityWeek in November 2019. ** Data as of April 16, 2020; LTE study is ongoing; two additional LEPR patients expected to enroll pending local regulatory approval. One POMC patient did not continue in LTE study.
*** All patients in the supplemental cohorts, as well as most patients in the pivotal cohorts, were enrolled by European investigators.

Meaningful Opportunity

Deliver on the potential of setmelanotide to patients with Bardet-Biedl and Alström syndromes and advance disease understanding ahead of pivotal Phase 3 data

Phase 2 Data in BBS Illustrate Sustained Weight Loss and Hunger Reduction





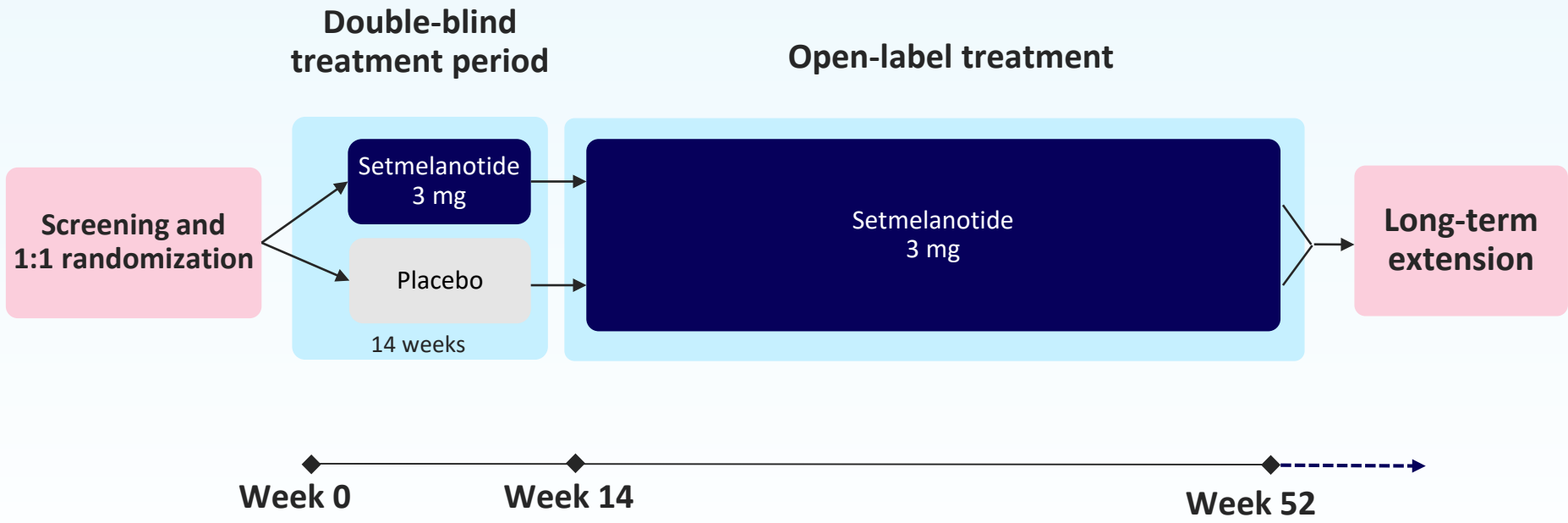
Per protocol: statistical analysis was performed via a 1-sample t test at a 1-sided 0.05 significance level. Haws RM, et al. *Diabetes Obes Metab* 2020. [a] Error bars are 90% CI. #*P*=0.02; ‡*P*<0.001, §*P*<0.0001.; [b] Three participants were unable to complete the self-reported hunger questionnaires at all timepoints because of cognitive impairment and autism with mild cognitive impairment . For these participants, hunger was evaluated by caregivers using the FPD and SEQ. Error bars are 90% CI. *P*<0.05.

Bardet Biedl & Alström Syndromes Phase 3 Trial: Enrollment in Pivotal Cohort Completed in December 2019

Topline pivotal data expected in 4Q2020 or early 1Q2021

Pivotal cohort:
- 32 BBS patients
- 6 Alström syndrome patients

Enrolling patients in supplemental cohort



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

Opportunity with Established Communities and Unmet Need for Bardet-Biedl and Alström Syndromes

Rhythm has ongoing relationships with patient advocacy groups to drive awareness, disease understanding and build support for regulatory pathway

Bardet-Biedl Syndrome Foundation	BBS UK	Alström Syndrome International (ASI)	Alström Syndrome UK

Market research points to unmet need in treatment for BBS and Alström syndrome patients

> *"Critical to treat obesity, absolutely critical!"*
>
> *"The thing is the hyperphagia is the most difficult and painful to deal with because you're always hungry."*

PCPs

Growth Potential

Establish proof-of-concept in new indications with Rhythm Engine & Basket Study

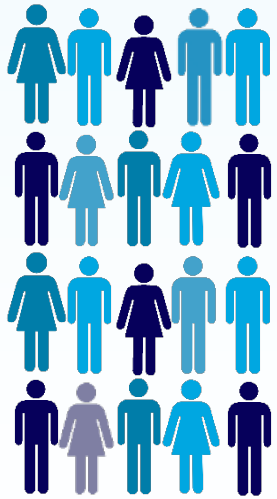
Genetic Testing Expected to Drive Future Growth through Clinical Development

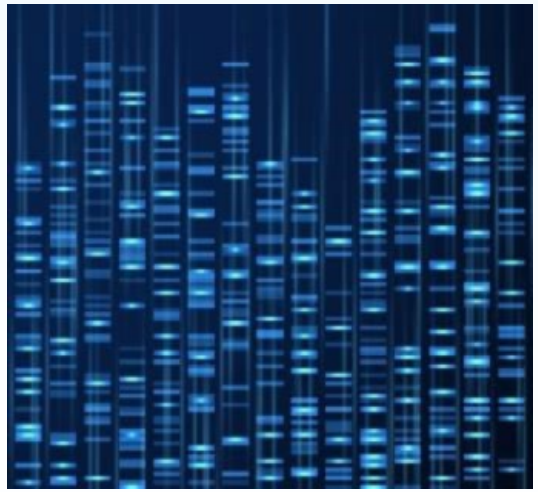
UNCOVERING RARE OBESITY

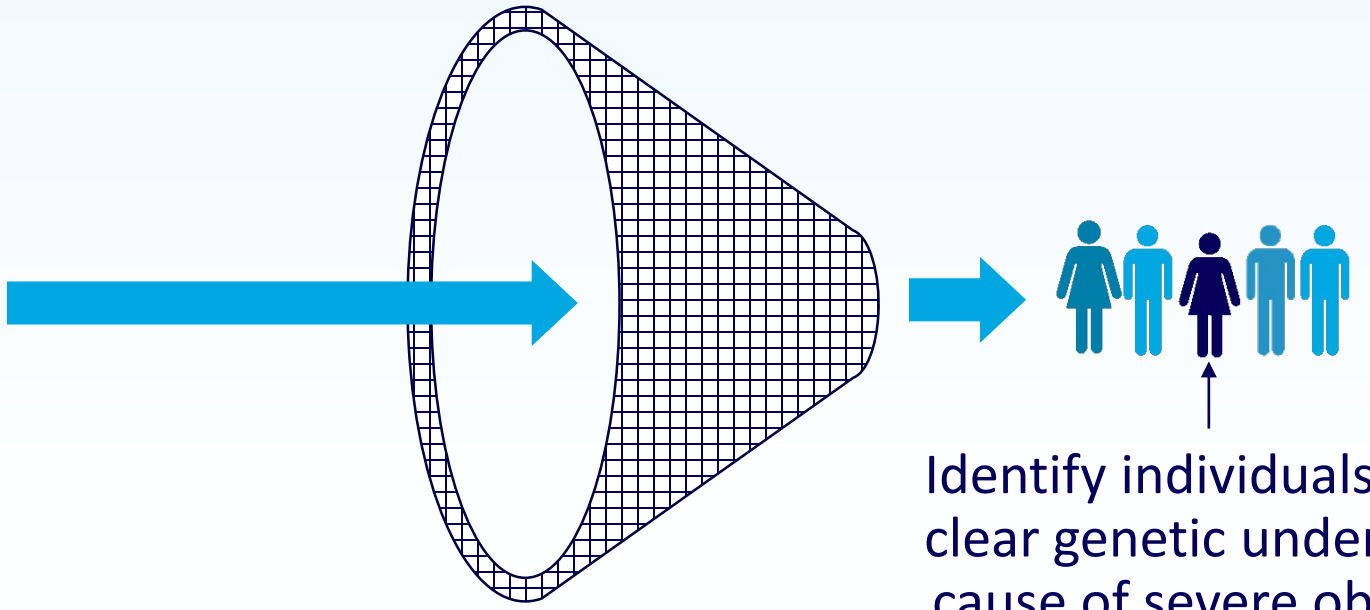
GO ID genotyping

Biobanks

101-Gene Panel





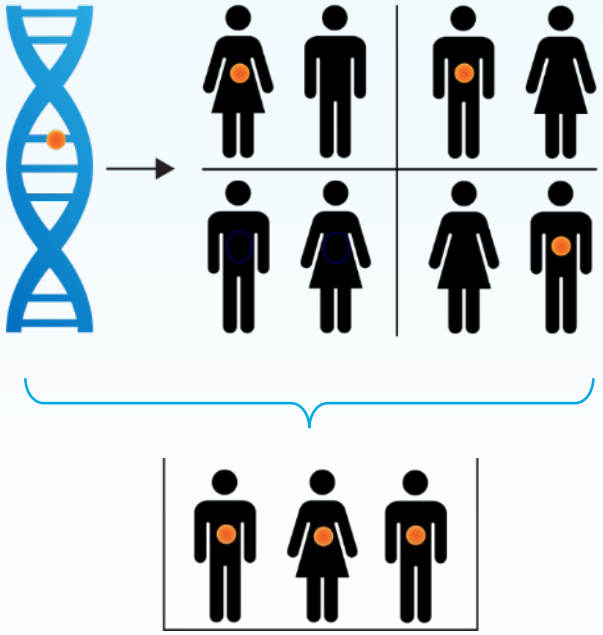


Identify individuals with clear genetic underlying cause of severe obesity

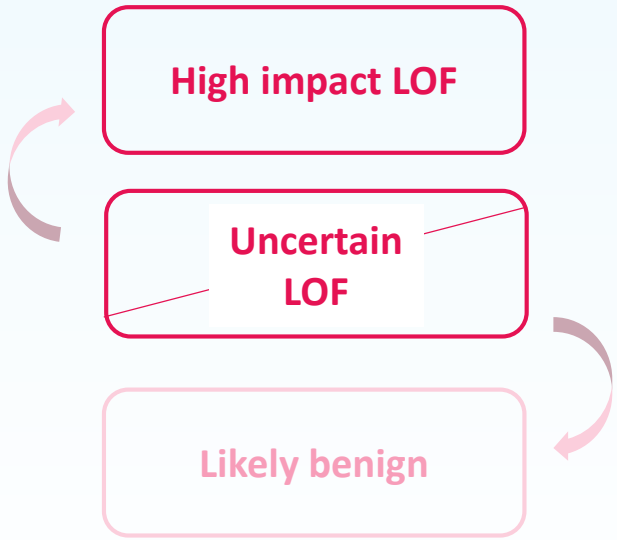
Phase 2 Basket Study Key to Advancing to MC4R Pathway Obesity Indication

Enrolling Multiple Cohorts with Genetic Variants

- Seamless integration with sequencing efforts
- Rapid understanding of setmelanotide responsiveness
- Efficient path to registration

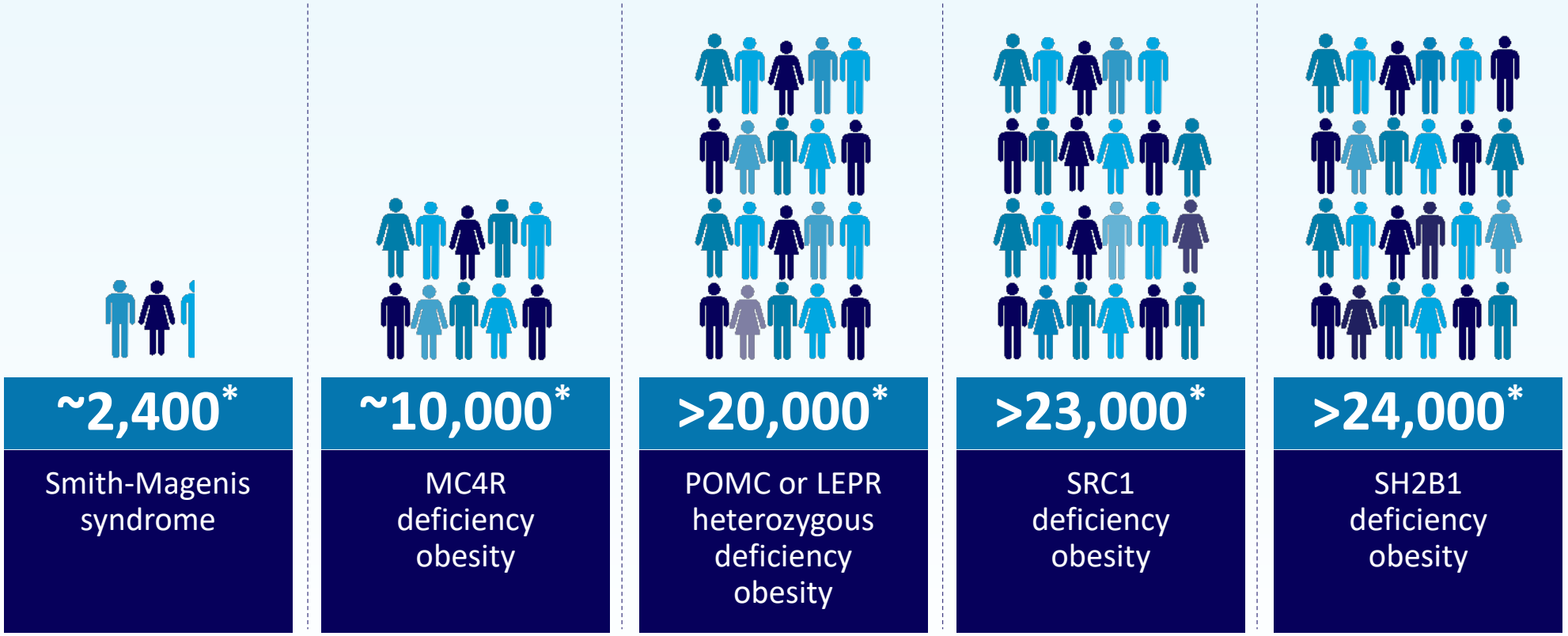


Cohort stratification



Images are for illustrative purposes only and not intended to imply or suggest actual prevalence estimates or patient identification yields.

Significant Opportunity with MC4R Pathway Disorders Now Enrolling on Phase 2 Basket Study



* Company estimates calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity (Hales et al in JAMA – April 2018: Trends in Obesity and Severe Obesity Prevalence in US Youth and Adults by Sex and Age, 2007-2008 to 2015-2016); Allele frequency based on Rhythm genetic sequencing (June 2019)

Rhythm® PHARMACEUTICALS

Setmelanotide Generally Well-tolerated Across Development Program

Setmelanotide has been evaluated in more than 400 patients with obesity, with individual patient treatment duration now exceeding four years

Setmelanotide has been generally well-tolerated

Most AEs are mild:

- Mild injection site reactions
- Hyperpigmentation and skin lesions, mediated by the closely related MC1 receptor
- Nausea/vomiting: mild and early in treatment

Discontinuations are rare; no increase in CV parameters

- In POMC and LEPR pivotal trials, setmelanotide was not associated with significant changes to blood pressure or heart rate

Patient experience with setmelanotide*

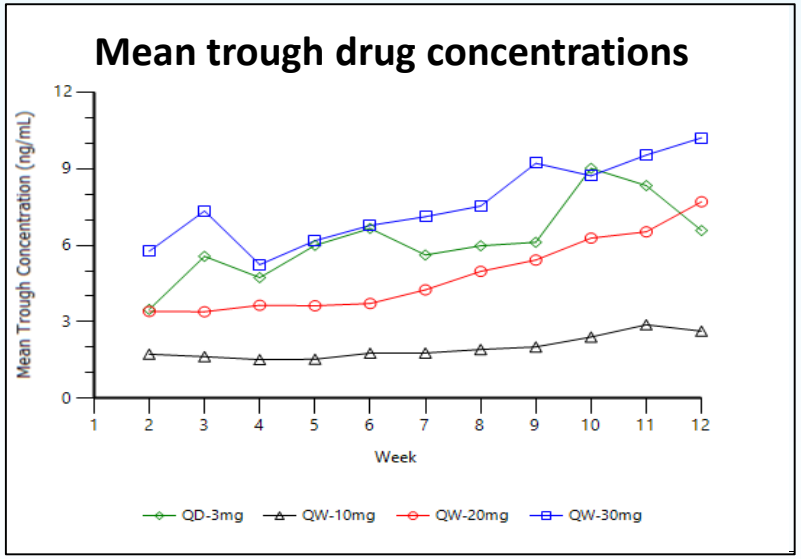
Duration on therapy	# of patients
< 1 year	**> 440**
> 1 year	**44**
> 2 years	**20**
> 3 years	**3**
> 4 years	**2**

* Estimates as of April 2020, inclusive of patients likely randomized to treatment in certain double-blinded clinical studies.

Interim Data Showed Once-weekly Formulation of Setmelanotide Achieved Safety and Efficacy Results Comparable to Daily in Phase 2 Study with 85 Healthy Obese Participants

Gel-like depot with slow diffusion, designed to be more patient-friendly and convenient and less burdensome

	Weekly					Daily	
	10mg	20mg	30mg	10mg/ 20mg	20mg/ 30mg	2mg/3mg	Placebo
Weight Change from Baseline at Week 12 (kg)*	-2.6	-3.3	-3.0	-1.1	-3.6	-2.1	0.5
Percent Change from Baseline in Most Hungry Score at Week 12 (%)*	-44.6	-39.8	45.51	83.51[1]	-50.2	-35.6	10.1



- ✓ As of data cutoff of April 17, 2020, weekly setmelanotide was well-tolerated, with no serious treatment-emergent AEs, similar to daily administration and consistent with prior clinical experience.
- ✓ PK: Mean trough drug concentrations for 20mg and 30mg doses of weekly formulation similar to 3mg daily dose

<u>Next step:</u> Discuss registration path forward with FDA

1. Increased percent change from baseline due to missing data values and outliers.
Data presented at The Obesity Society's ObesityWeek® 2020, held November 2-6, 2020. *Data presented as of a cutoff date of April 17, 2020.

Rhythm Executing with Transformational Progress

1 Validation with first potential approval for setmelanotide in POMC or LEPR deficiency obesities

✓ **1Q:** NDA submitted; *Priority Review with no Advisory Committee; PDUFA date is Nov. 27, 2020; rare pediatric disease designations granted for setmelanotide to treat POMC and LEPR deficiency obesities*

✓ **2Q:** MAA under review by the European Medicines Agency (EMA)

2 Meaningful opportunity with Bardet-Biedl and Alström syndromes in Phase 3

Late 4Q or Early 1Q21: Topline data from Phase 3 trial

3 Growth potential

1Q21: Proof-of-concept data in HET patients, initial data in SRC1 and SH2B1 deficiency obesity with update on genetic sequencing and epidemiology data

2021: Clinical development update for once-weekly formulation

Appendix

Strong Leadership Team with Broad Biopharma Experience

David Meeker, MD
Chair, President and Chief Executive Officer

SANOFI GENZYME

25-plus years; focus on rare genetic disease treatments, including Aldurazyme®, Fabrazyme® and Myozyme®

Hunter Smith
Chief Financial Officer

Celgene

Financial leadership for Otezla®; 20-plus years in finance, M&A, capital markets

Yann Mazabraud
Executive Vice President, Head of International

SANOFI GENZYME
trevi THERAPEUTICS

20 years leading global commercial strategy in rare diseases

Jennifer Chien
Executive Vice President, Head of North America

SANOFI GENZYME
Krystal

More than 20 years leading global commercial strategy in rare diseases

Murray Stewart, MD
Chief Medical Officer

novelion THERAPEUTICS
gsk

20-plus marketed products and NDAs 10-plus INDs

Simon Kelner
Chief Human Resources Officer

MERCK
teva

25-plus years global HR leadership experience in biopharma

Setmelanotide: Investigational MC4R agonist

FDA Breakthrough Therapy Designation

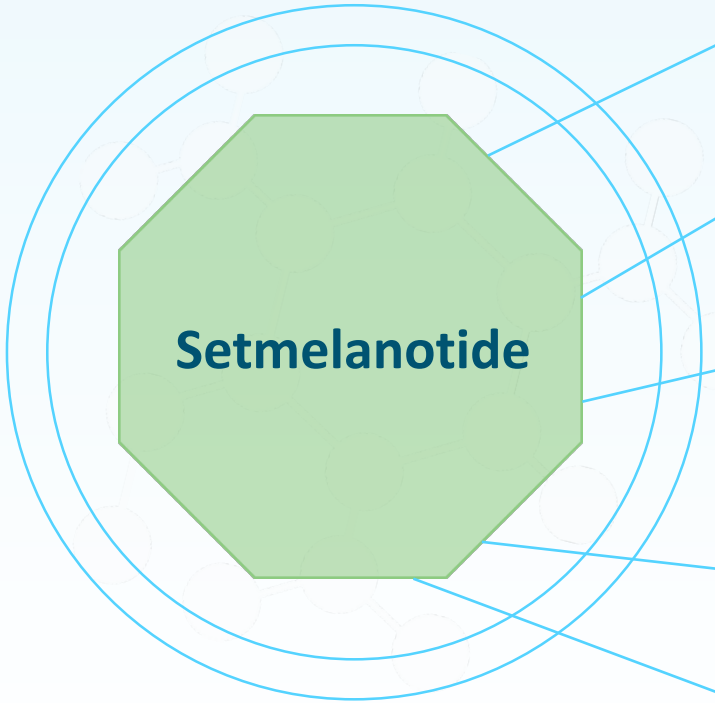
- POMC deficiency obesity
- LEPR deficiency obesity
- Bardet-Biedl syndrome
- Alström syndrome

FDA Orphan Drug Designation

- POMC deficiency obesity
- LEPR deficiency obesity
- Bardet-Biedl syndrome
- Alström syndrome

EMA PRIME Designation

- For treatment of obesity and control of hunger associated with deficiency disorders of the MC4R pathway



Eight-amino-acid cyclic peptide

Daily subcutaneous injection; once-weekly formulation in development

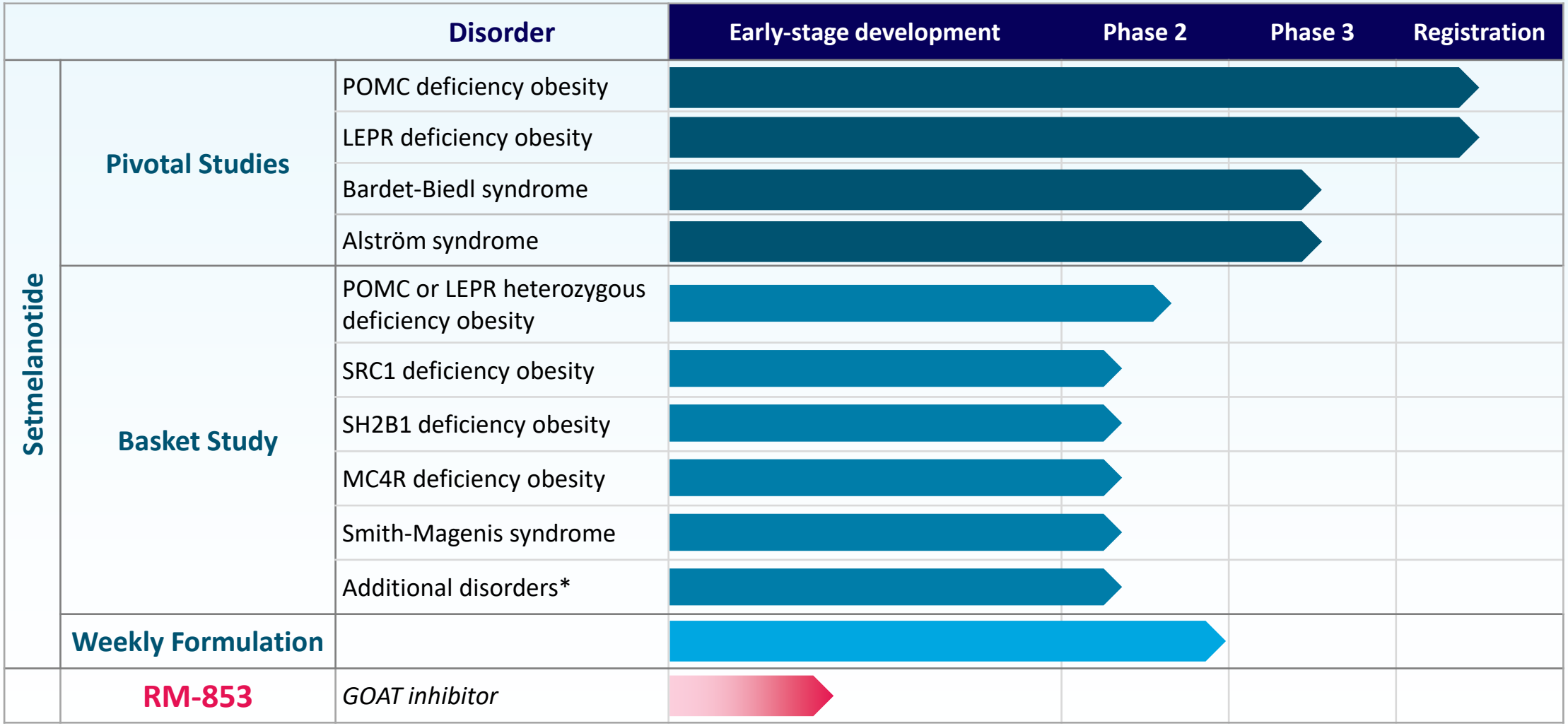
Retains specificity, functionality of naturally occurring hormone that activates MC4R

Composition of matter patents in all major markets

Highly competitive cost of goods

POMC, pro-opiomelanocortin; LEPR, leptin receptor

Rhythm Pipeline Focused on MC4R Pathway Disorders



** Rhythm is currently assessing setmelanotide in additional disorders, including POMC epigenetic disorders and LEP and CPE deficiency 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.*

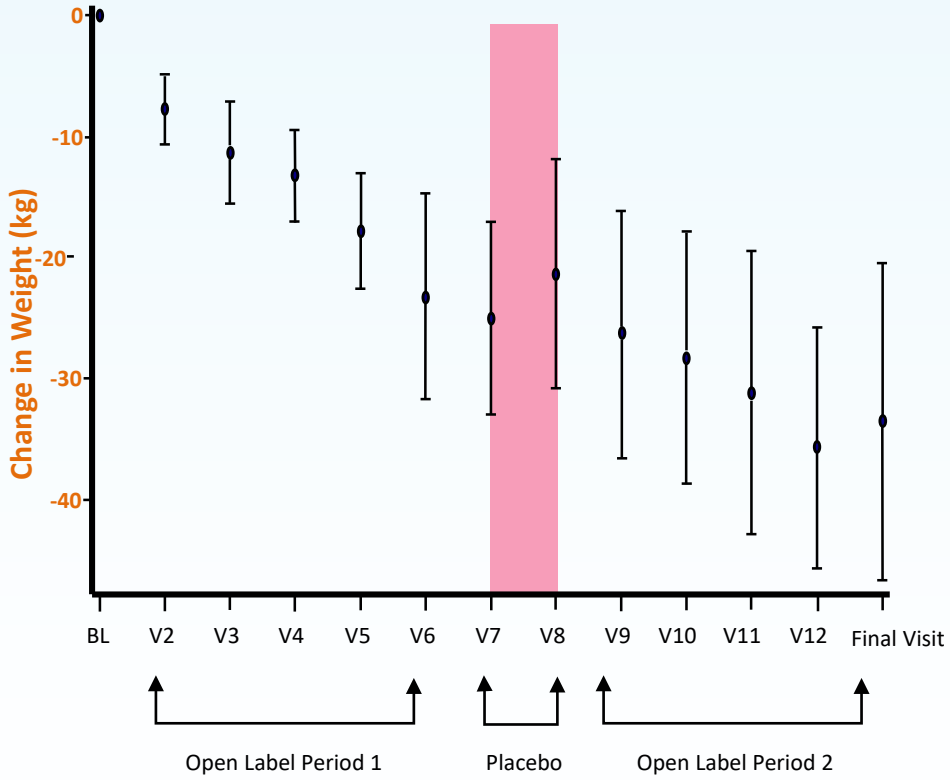
*** Rhythm is currently assessing opportunities to further evaluate setmelanotide in PWS and plans to pursue these in parallel with the development of RM-853.*

Cash Expected to be Sufficient to Fund Operations Through at Least End of 2021

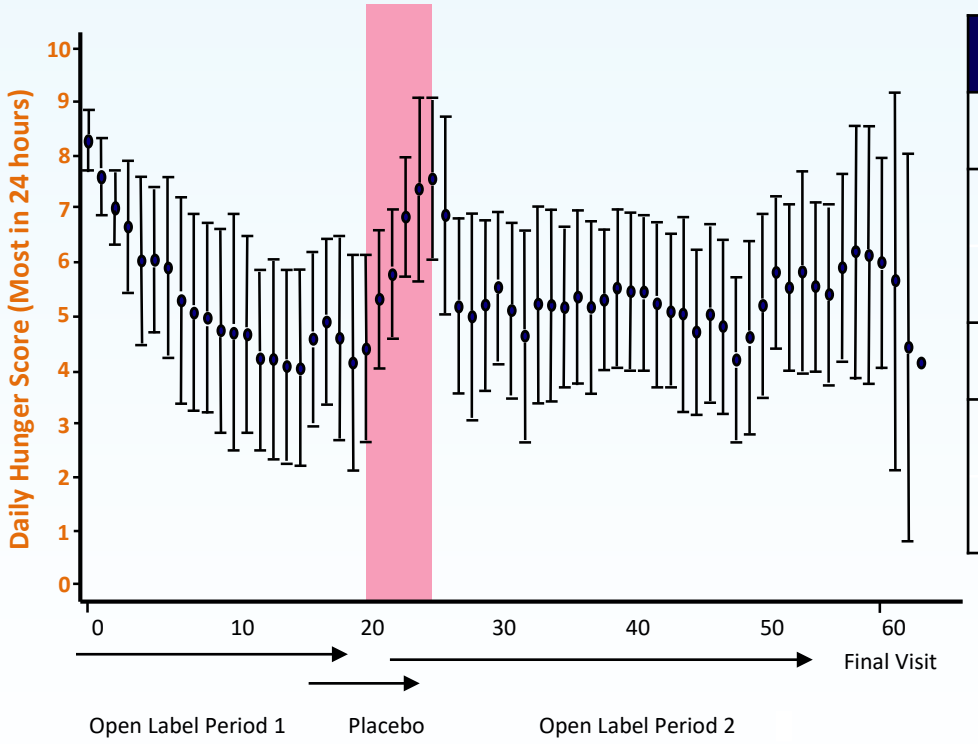
SHARES OUTSTANDING *as of 10/23/2020*	*44,204,745 (basic share count)*
CASH, CASH EQUIVALENTS AND SHORT-TERM INVESTMENTS *as of 09/30/2020*	$ 201.8 million

POMC Phase 3 Trial – Change in Weight and Hunger Over 1 Year with Substantial Weight Gain and Hunger Increase During Placebo Withdrawal

Change in Weight*



Change in Hunger Score*†



During Placebo Period:	
Change in weight (kg)	
Mean	+5.5
Range	1.5-10.5
Change in hunger score	
Mean	+2.2
Range	2.0 to 9.86

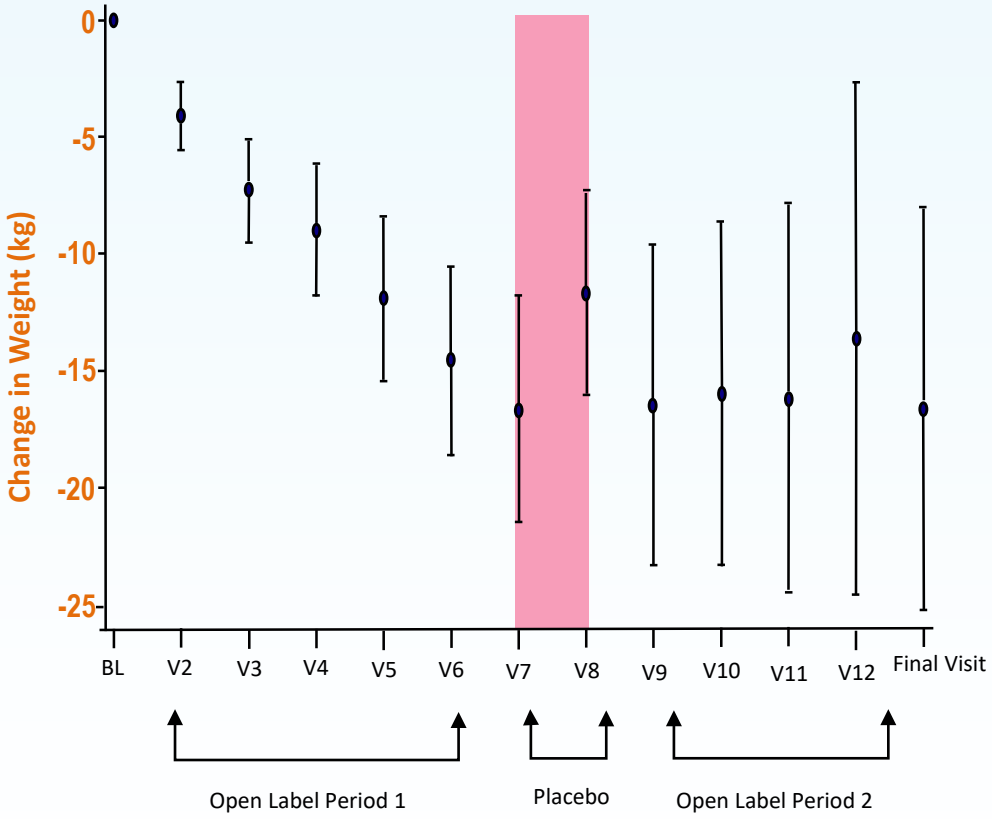
These data were presented as part of the Company's topline data disclosure on Aug. 7, 2019.

BL, baseline; V, nominal visit; N, number; error bars are confidence intervals (90%)
*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;
†, score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for participants at least 12 years of age
** This was the final nominal visit for all participants, except for one

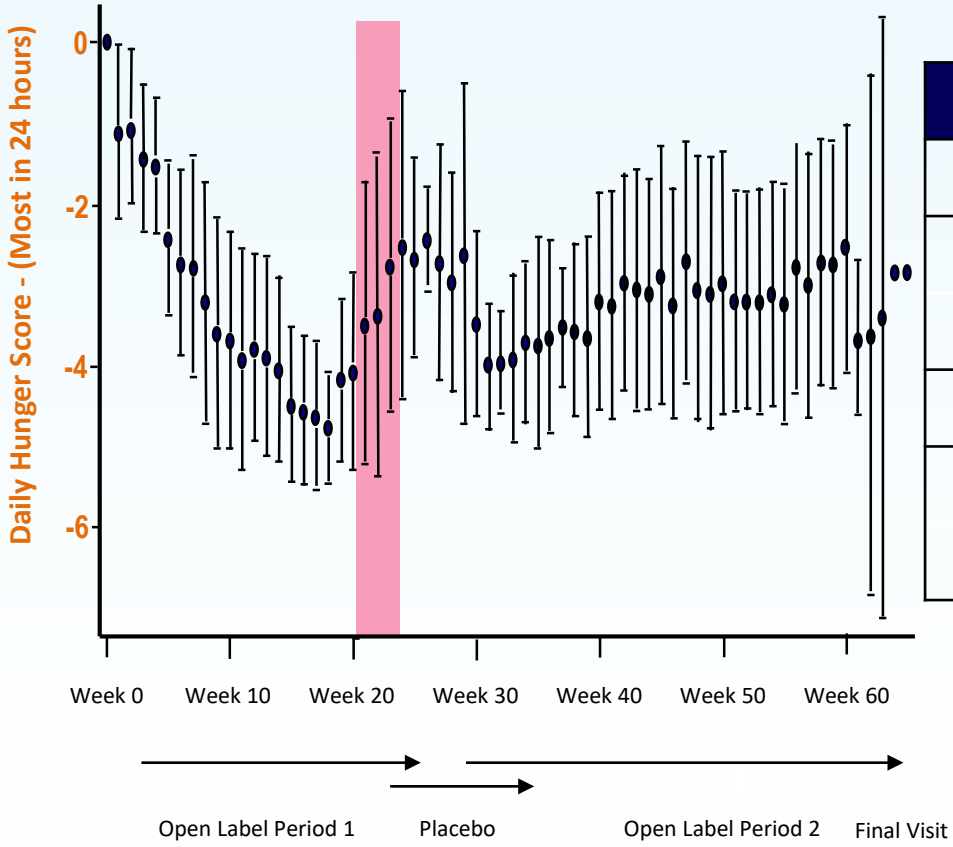
Rhythm® PHARMACEUTICALS

LEPR Phase 3 Trial – Change in Weight and Hunger Over 1 Year with Substantial Weight Gain and Hunger Increase During Placebo Withdrawal

Change in Weight*



Change in Hunger Score *†



During Placebo Period:	
Change in weight (kg)	
Mean	+4.9
Range	2.9-9.3
Change in hunger score	
Mean	+3.1
Range	4.0 to 10.0

These data were presented as part of the Company's topline data disclosure on Aug. 7, 2019.

BL, baseline; V, nominal visit; N, number; error bars are confidence intervals (90%)
*, endpoint analyzed on evaluable population, which includes participants who achieved weight loss threshold (5kg or 5% if <100 kg) after open label period 1;
†, score is based on 0-10 Likert scale from question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" for participants at least 12 years of age

Strong Phase 2 Data in BBS Showed Substantial Weight Loss and Hunger Control, Supporting Advancement into Phase 3

Published in *Diabetes Obesity and Metabolism* 2020*

Duration	Weight Change from Baseline	BMI change from baseline	Hunger Score Change from Baseline**
3 months (n=8)	**-5.5%** 90% CI, −9.3% to −1.6% *P*=0.02	**–5.5%** *P*=0.01	**-50.9%** *P*=0.01
6 months (n=8)	**-11.3%** 90% CI, −15.5% to −7.0% *P*<0.001	**–11.1%** *P*<0.001	**-64%** *P*=0.001
12 months (n=7)	**-16.3%** 90% CI, −19.9% to −12.8% *P*<0.0001	**–16.2%** *P*<0.0001	**-70.2%** *P*<0.001

* Haws RM, et al. *Diabetes Obes Metab* 2020; Per protocol: statistical analysis was performed via a 1-sample t test at a 1-sided 0.05 significance level; Ten patients enrolled in this study. One patient (pediatric patient with BBS1 variant and type 1 diabetes) experienced 53.3% reduction in hunger and reduction in hemoglobin A1c (10.1% to 7.6%) before withdrawing. Patient subsequently entered long-term extension study. Two patients (one non-genetically confirmed) withdrew due to lack of weight loss.
** 3 participants were unable to complete the self-reported hunger questionnaire because of cognitive impairment (n=2) and autism with mild cognitive impairment (n=1). For these participants, hunger was evaluated by caregivers.

Phase 2 Data in Alström Syndrome*

Age at enrollment/ Sex	Baseline Weight (kg)	Treatment, weeks	% Weight Change from Baseline	% Hunger Score Change from Baseline†
12/M	78.6	95	**-20%**	-25%
15/F	70.7	84	**1%**	-38%
16/F	91.6	68	**-6%**	0%

- Patient 1 has reached healthy body weight
- Patient 3 maintaining weight and reduced hunger – HbA1c decreased by 3% from 11% to 8%
- All 3 continuing patients plan to enter long-term extension trial

*As previously disclosed, patient 2 (data not shown) discontinued at ~14 weeks; **Updated data announced by Rhythm in September 2019.**

BBS and Alström Syndrome Pivotal Trial Statistical Approach

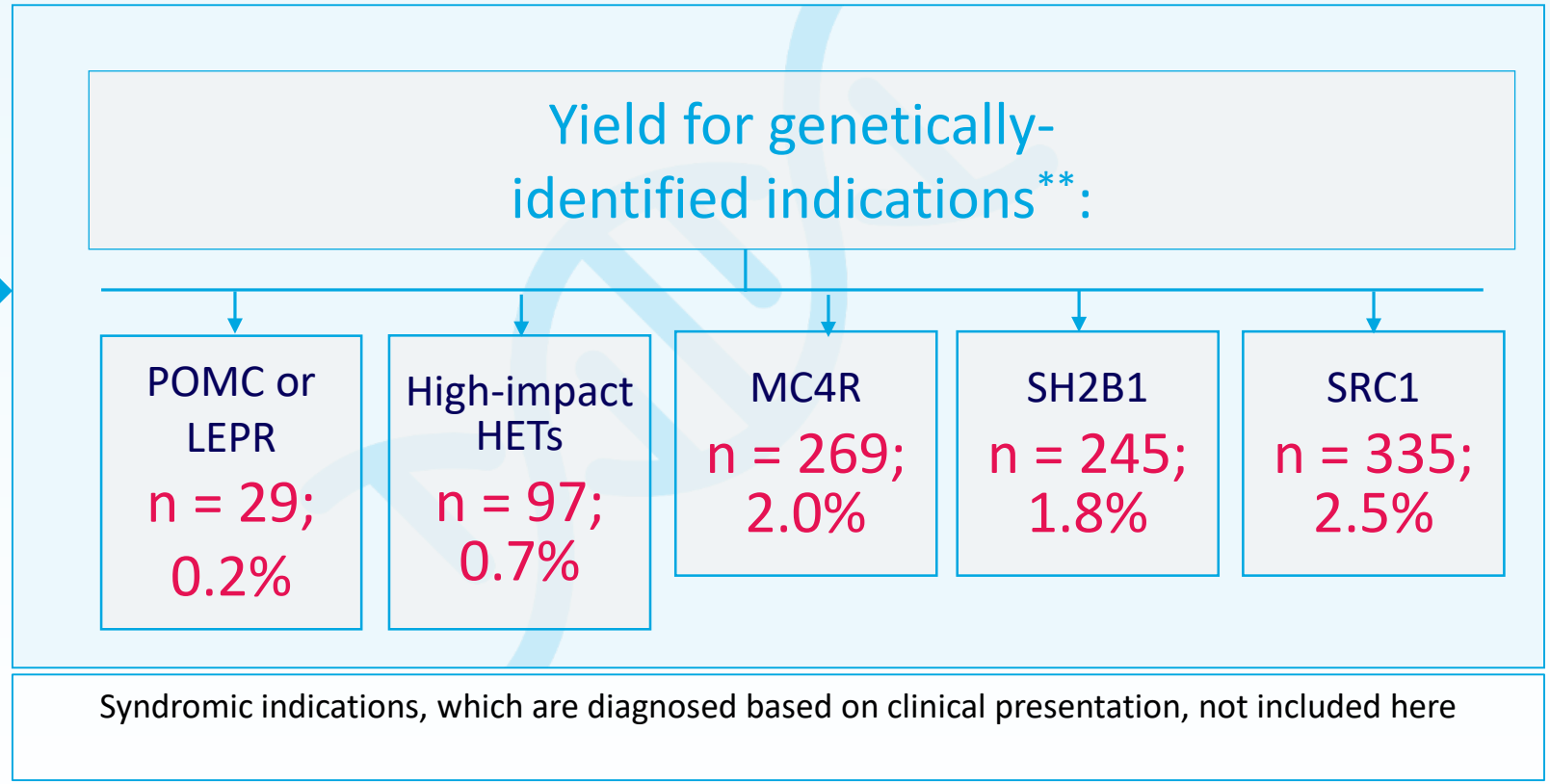
Primary endpoint	Three key secondary endpoints (after ~52 weeks of treatment)		
Proportion of patients (≥12 years old) who achieve ≥10% reduction in body weight after ~52 weeks of treatment	Proportion of patients (≥12 years old) who achieve a ≥25% improvement in daily hunger score	Body weight percent change from baseline in patients ≥ 12 years old	Daily hunger score percent change from baseline in patients ≥ 12 years old
• Primary: Based on an exact binomial test, at a 1-sided 0.05 significance level; A 2-sided 90% CI will be calculated using the exact Clopper-Pearson method. The statistical criterion corresponds to the 2-sided 90% CI for setmelanotide of the response rate excluding 10% (i.e., lower bound of the CI >0.10)		• Based on a one-sample t-test with assumed mean percent change from baseline of zero, at a 1-sided 0.05 significance level. • As in the POMC/LEPR pivotal trials, these percent change analyses to be conducted on pivotal patients who achieve at least 5 kg (or 5% if <100 kg) weight loss after 14 weeks of active setmelanotide treatment	

- Historical control response rate of 10% responders is used as a comparator for primary endpoint and responder key secondary endpoint, in the Full Analysis Set
- All prespecified primary and key secondary analyses are performed on the pooled BBS and Alström syndrome pivotal patient population
- Power Statement: A sample size of 7 patients provides ~95% power at 1-sided alpha of 0.05 and ~91% power at 1-sided alpha of 0.025, to yield a statistically significant difference, assuming the Phase 2 Basket Study 66% response for weight loss
- Although these data suggest that powering the study for the primary endpoint will require a minimal number of patients (N<10), the size of the trial is also a function of the rarity of BBS and Alström syndrome and a desire to better understand the effect of setmelanotide in these patient populations. Hence, at least 20 BBS and at least 6 Alström syndrome patients were planned to be enrolled in the study (N=38 were actually enrolled in the pivotal cohort)
- Rhythm proposed Statistical Analysis Plan; not all elements reviewed by FDA

Sequencing Yield for Genetically-identified Indications Points to Significant Opportunity

Individuals with severe obesity sequenced

13,567*

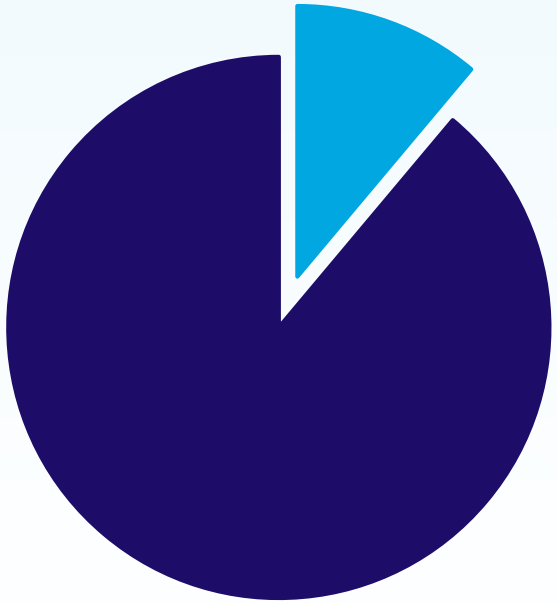


* As of June 30, 2019; sequencing efforts are ongoing.

**Basket yield includes 683 individuals with other variants; some patients have more than one variant.

Stratifying Patients Based on Loss of Function (LOF) Variant – HET Example

U.S. prevalence approximately **1 million** for individuals with heterozygous POMC or LEPR variants, and **>20,000** high-impact LOF patients in U.S.*



graph not drawn to scale

- Patients present with severe, early-onset obesity and hyperphagia
- Basket Study cohorts stratified by impact of variant on pathway function
- High-impact LOF variants expected to be most responsive to setmelanotide
- Other cohorts will clarify potential setmelanotide treatable populations
- Data update expected in 2020

* Calculated based on the following assumptions: US pop 327 million; 1.7% has early onset, severe obesity; High impact HET allele frequency based on Rhythm genetic sequencing (Feb 2019)

Phase 2 Data in HET Patients Based on LOF Variant

All high-impact LOF patients appear setmelanotide-responsive; other subgroups have more variable responses

	Total treatment duration[2] (weeks)	Baseline Weight (kg/(lbs))	Weight Loss (kg/(lbs))	Weight loss	Change in Hunger Score (10 pt scale)	Hunger score reduction
High-Impact LOF Group	37	204 (451)	18.4 (40.5)	9.0%	-9	90.0%
	29	129 (284)	22.3 (49.0)	17.3%	-5	71.4%
	4	187 (412)	7.1 (15.6)	3.8%	-4	40.0%
Other Subgroups	74	150 (330)	12.1 (26.6)	8.0%	-7	78.0%
	66	147 (323)	7.5 (16.5)	5.1%	-1	20.0%
	20	118 (259)	15.0 (33.0)	12.8%	-6	75.0%
	16	106 (232)	7.2 (15.8)	6.9%	-7	70.0%
	7	150 (330)	4.6 (10.1)	3.0%	NA	NA

High-Impact LOF Group:

- All patients ongoing; fourth patient, still very early in dose titration, showing promising weight loss and hunger score decreases.

Other Subgroups:

- Five patients ongoing[1]
- Four patients discontinued treatment:
  - One patient due to lack of efficacy at 14 weeks[3]. Three patients with ≤ 4 weeks of total therapy, so efficacy not able to be assessed: two patients due to AE (hyperpigmentation, muscle cramps)[3] and one patient withdrawn by site for patient non-compliance.

[1]Two of these patients were reported in June 2018. [2] Total treatment duration including any titration period, which can last 6-12 weeks. [3]These three patients were reported in June 2018. AE = adverse event

These data were presented in March 2019.

Rhythm's Approach Enables Deep Understanding of Rare Genetic Disorders of Obesity and Optimizes Registration/Commercial Strategy

Rhythm's Sequencing Database

U.S. Prevalence Estimate

Conservative projection of individuals whose obesity is likely due to genetic variants in the MC4R pathway

Phase 2 Basket Study

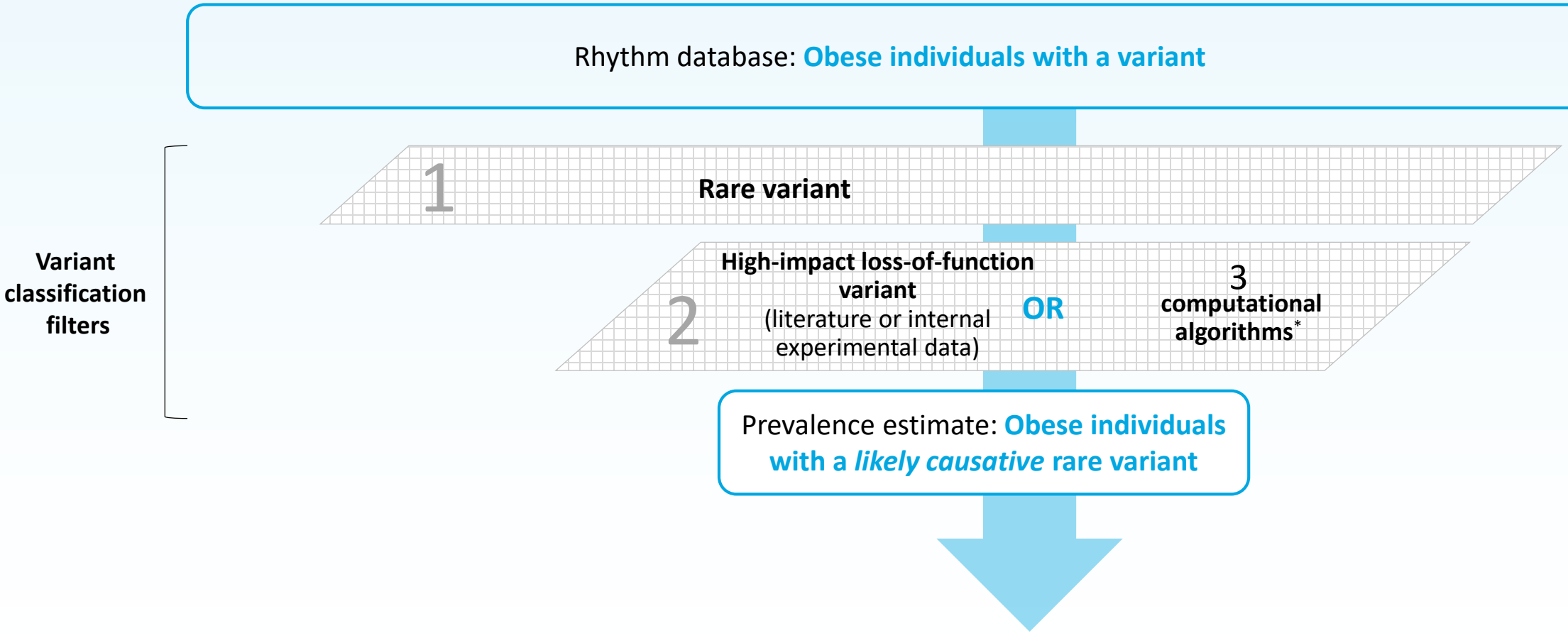
Facilitates understanding of phenotype-genotype relationship and setmelanotide responsiveness

Translational research informs classification of genetic variants and interpretation of clinical data

Optimized strategy for clinical development, registration and commercialization

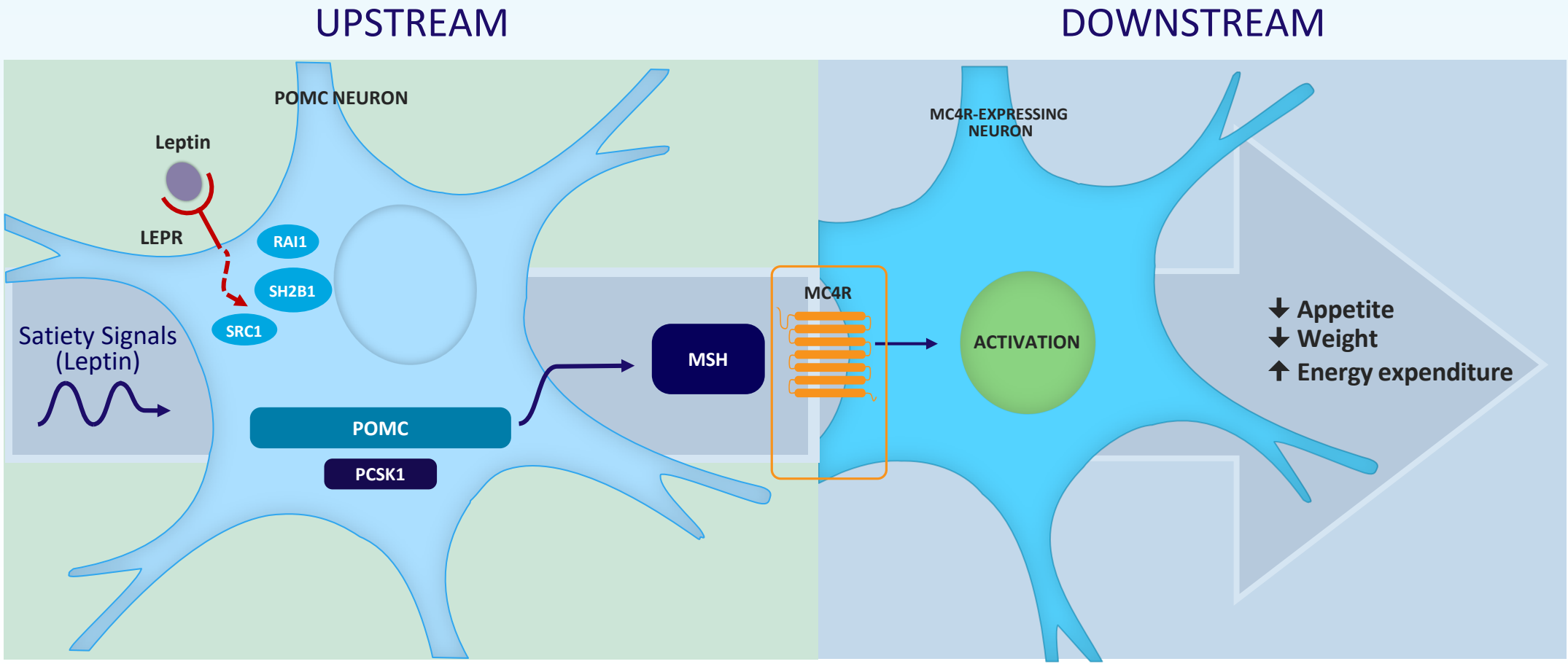
Translating Rhythm Sequencing Data to U.S. Prevalence Estimates

Most stringent criteria for variant classification to establish baseline estimates of US prevalence

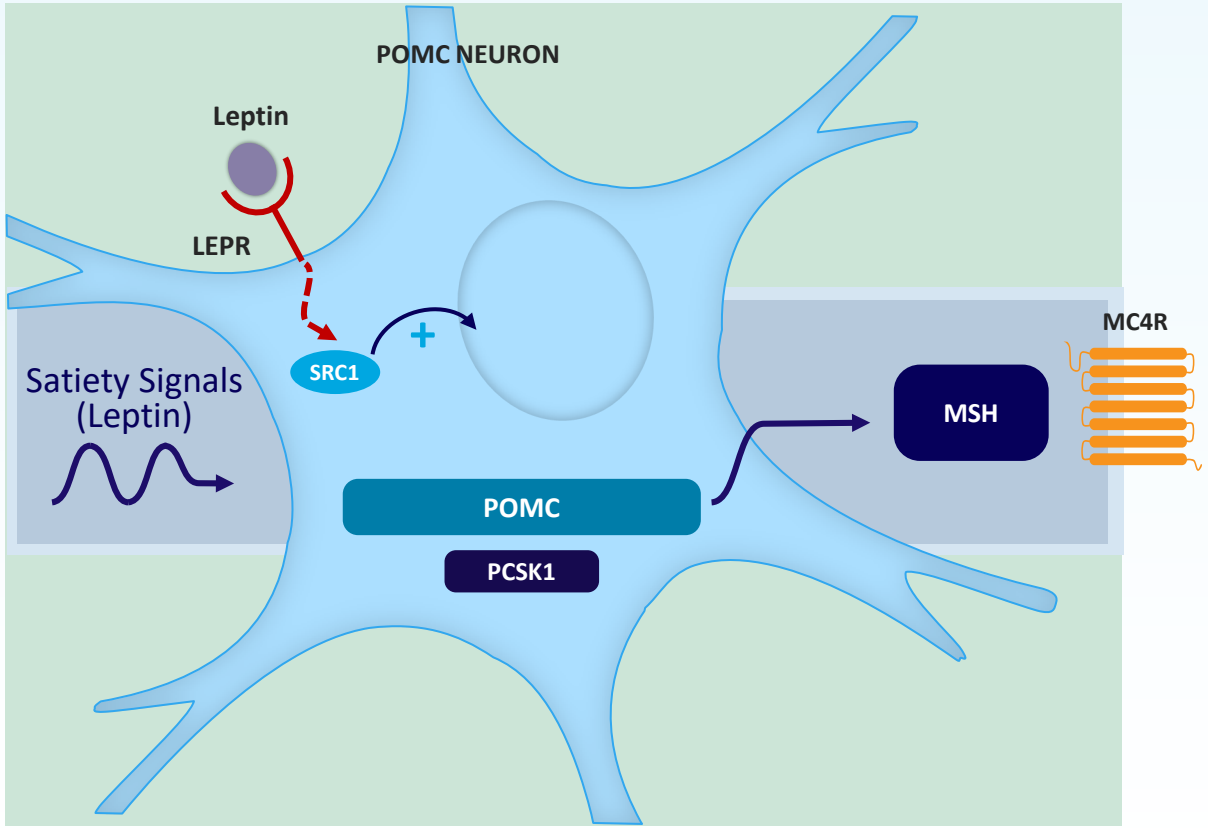


*PolyPhen: Adzhubei IA, et al. Nat Methods 7(4):248-249 (2010); SIFT: Vaser R, et al. Nat Protocol 4:1073-1081 (2009); Mutation Taster: Schwarz J.M., et al. Nat. Methods 11(4):361-362 (2014)

New MC4R Pathway Indications Based on Supported Scientific Rationale



SRC1 is a Transcriptional Coactivator that Drives POMC Expression



Pathway Relevance: **Drives POMC Expression**

- Transcriptional coactivator activated downstream of LEPR
- Found in POMC neurons

Autosomal Dominant

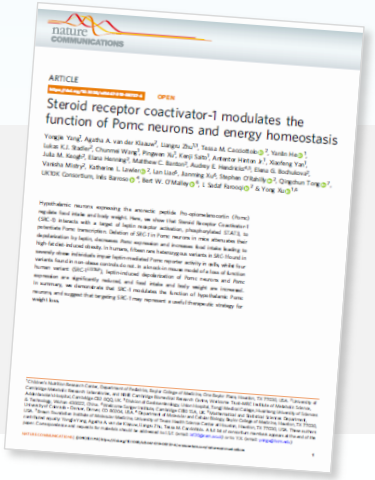
- Obesity arises due to heterozygous gene variants

Clinical Presentation

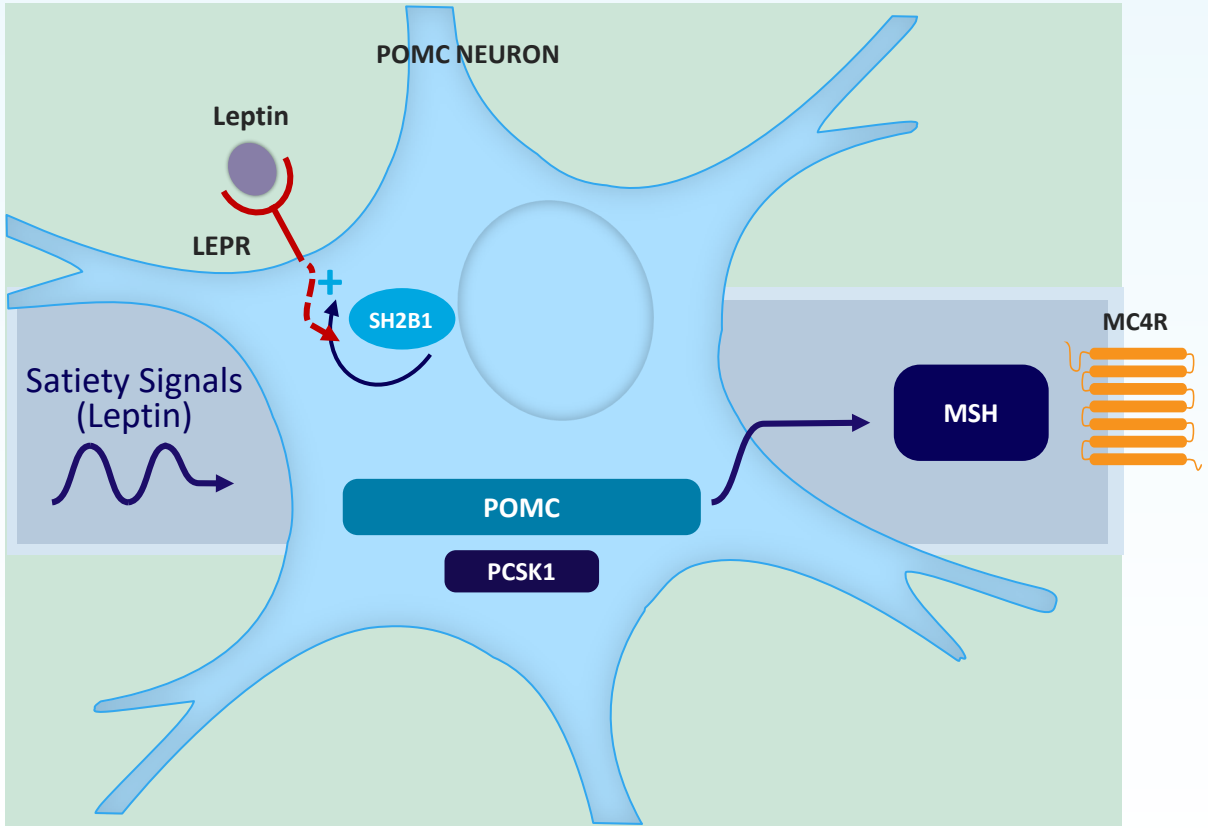
- Early onset obesity and hyperphagia
- Hyperleptinemia

Citations

- Yang et al 2019, Nat Comm. 10, Article 1718



SH2B1 is an Adapter Protein that Regulates LEPR Activity



Pathway Relevance: **Regulates LEPR activity**

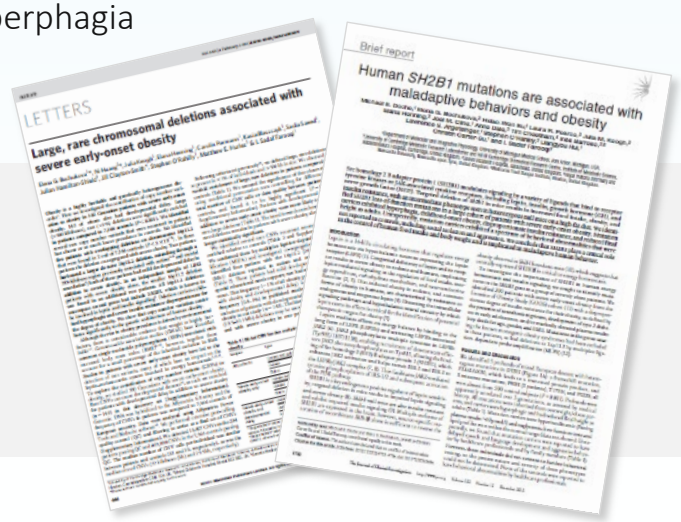
- Adapter protein
- Found in POMC neurons

Autosomal Dominant

- Obesity arises due to heterozygous gene variants or chromosomal deletions

Clinical Presentation

- Early onset obesity and hyperphagia
- Hyperinsulinemia



Citations

- Doche et al 2011, JCI, 122; 4732
- Ockukova et al 2010, Nature, 463; 666

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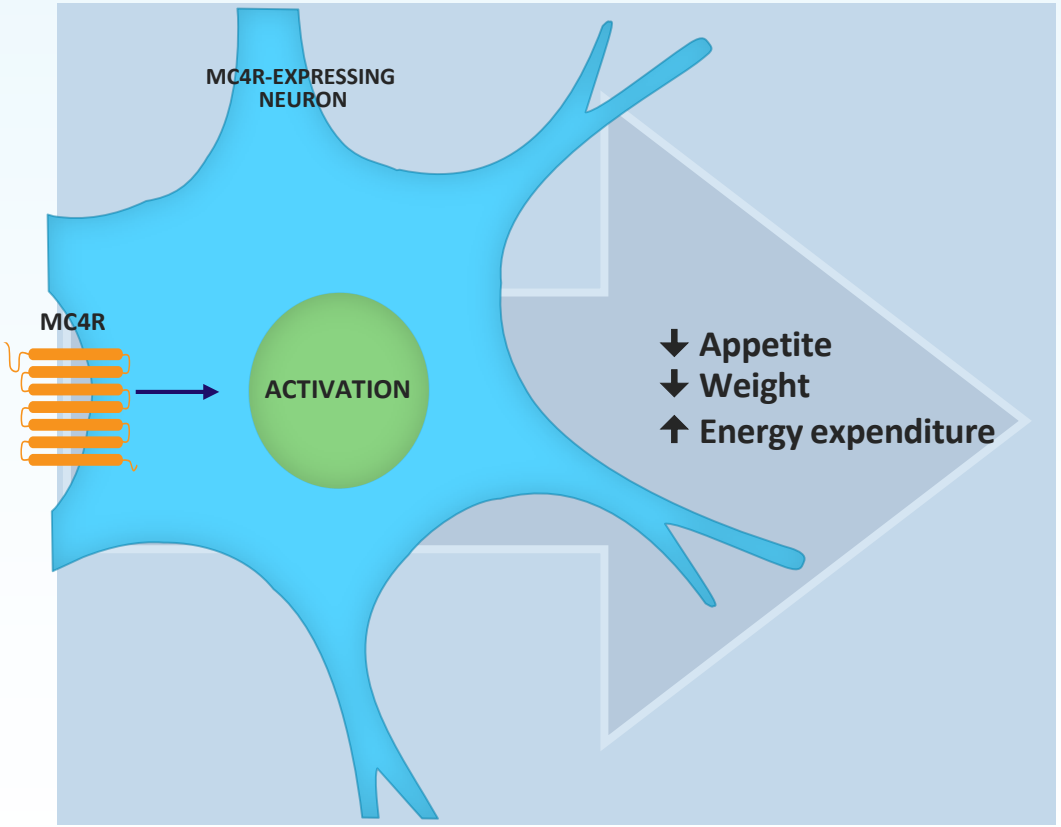
MC4R: Receptor for POMC Ligand MSH



Pathway Relevance: **Receptor for POMC ligands**

- Required for satiety effects of α/β-MSH

Autosomal Dominant

- Obesity arises due to heterozygous gene variants

Clinical Presentation

- Early onset obesity and hyperphagia

Setmelanotide

- Pharmacological target for setmelanotide
- Rhythm conducted small, 4-week PhIb study in MC4R deficiency obesity
- Rhythm biochemical studies indicate that setmelanotide can address specific MC4R variants
- Current indication is focused on addressable MC4R variant carriers

Citations

- Farooqi et al 2003, NEJM, 348; 1085
- Collett et al 2017, Molecular Metabolism, 6; 1321

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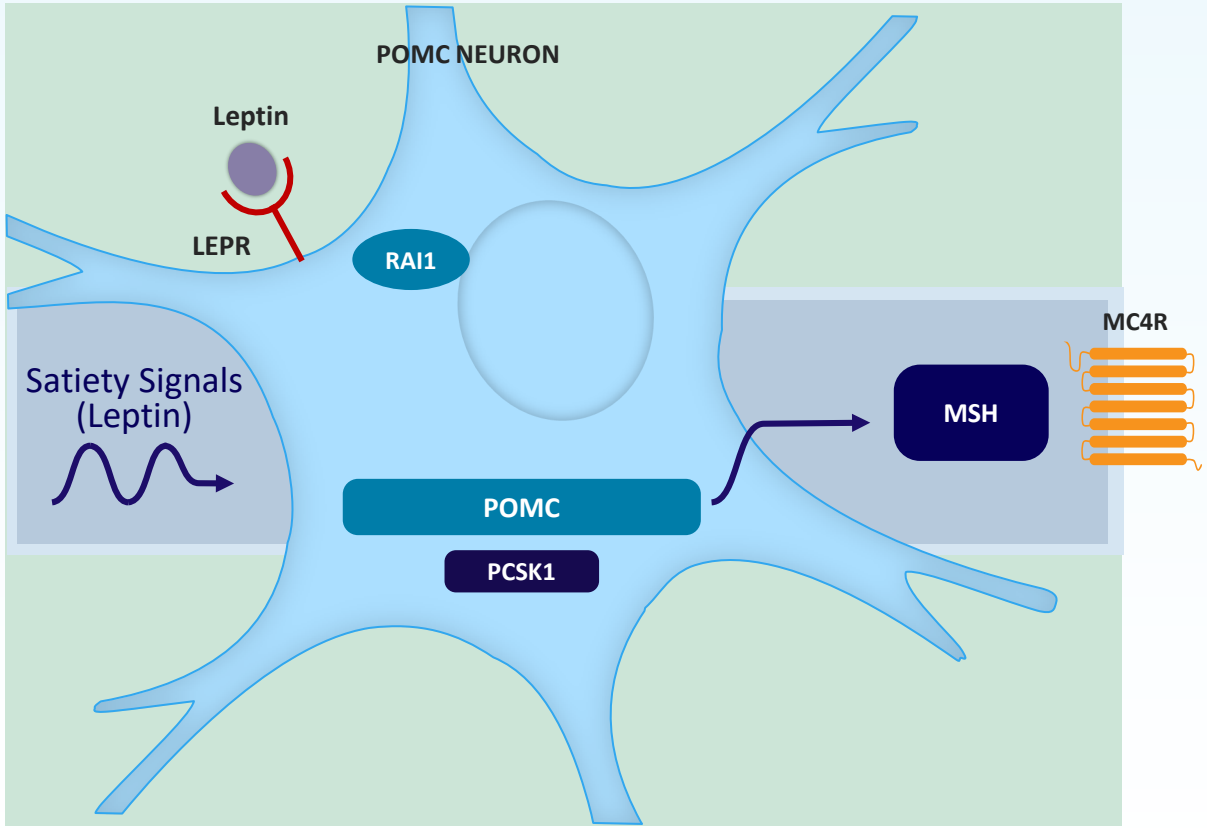
Smith-Magenis Syndrome: RAI1 Affects POMC Expression



Pathway Relevance: Decreased Pathway Function Upstream of MC4R

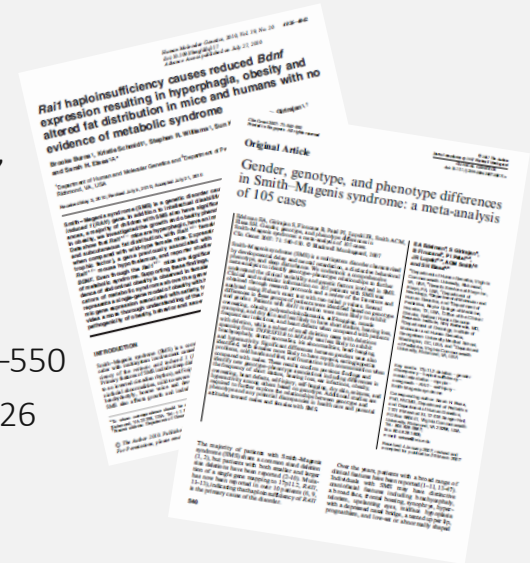
- Causal gene is RAI1
- Transcription factor for a number of pathway genes

Autosomal Dominant

- Gene variants and chromosomal deletions

Clinical Presentation

- Adolescent obesity and hyperphagia
- Sleep disturbance, cognitive impairment, craniofacial anomalies, low energy expenditure


Rai1 haploinsufficiency causes reduced Bdnf expression resulting in hyperphagia, obesity and altered fat distribution in mice and humans with no evidence of metabolic syndrome

Original Article

Gender, genotype, and phenotype differences in Smith–Magenis syndrome: a meta-analysis of 105 cases

Citations

- Edelman et al 2007, Clin Genet; 71: 540–550
- Burns et al 2010, Hum. Mol. Gen; 19; 4026

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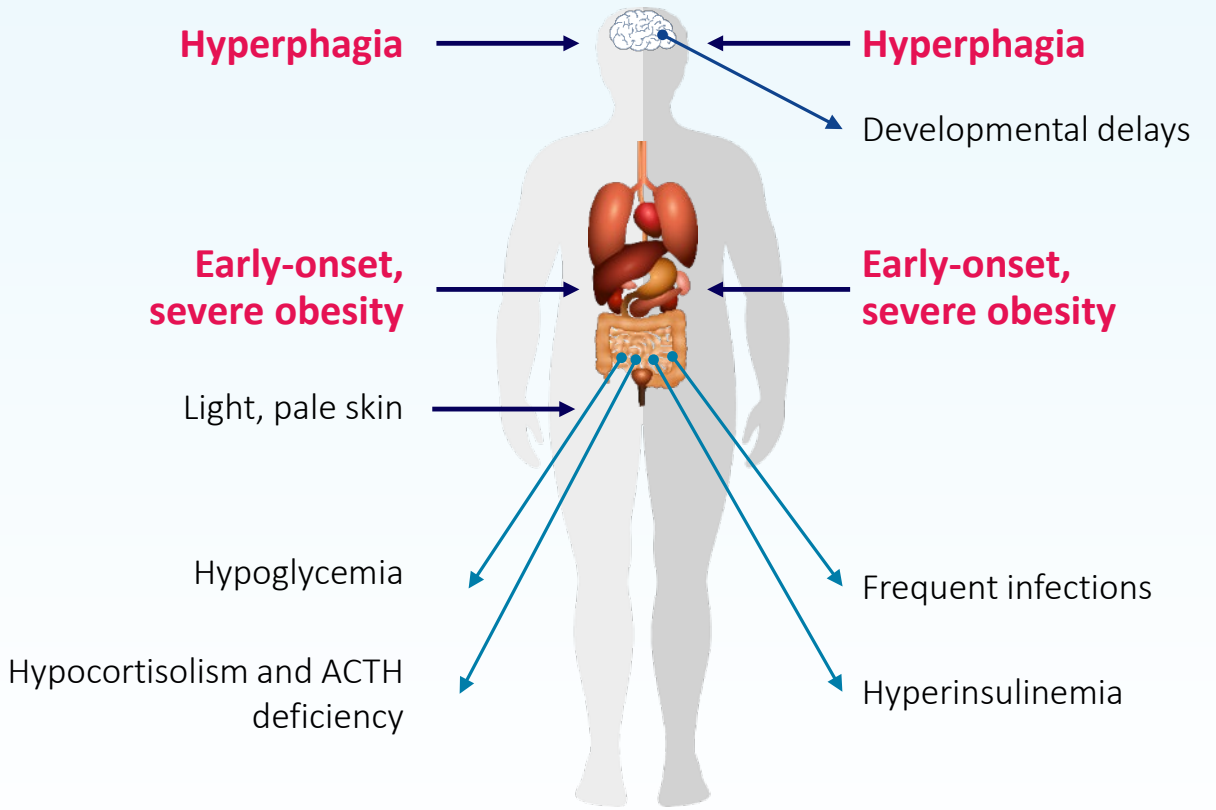
POMC and LEPR Deficiency Obesities Characterized by Early-onset Obesity, Unrelenting Hunger

POMC Deficiency Obesity

Results from loss-of-function homozygous or biallelic variants in the POMC gene

U.S. prevalence estimated to be **100** to **500 patients**



LEPR Deficiency Obesity

Results from loss-of-function homozygous or biallelic variants in the LEPR gene

U.S. prevalence estimated to be **500** to **2,000 patients**

No approved therapies

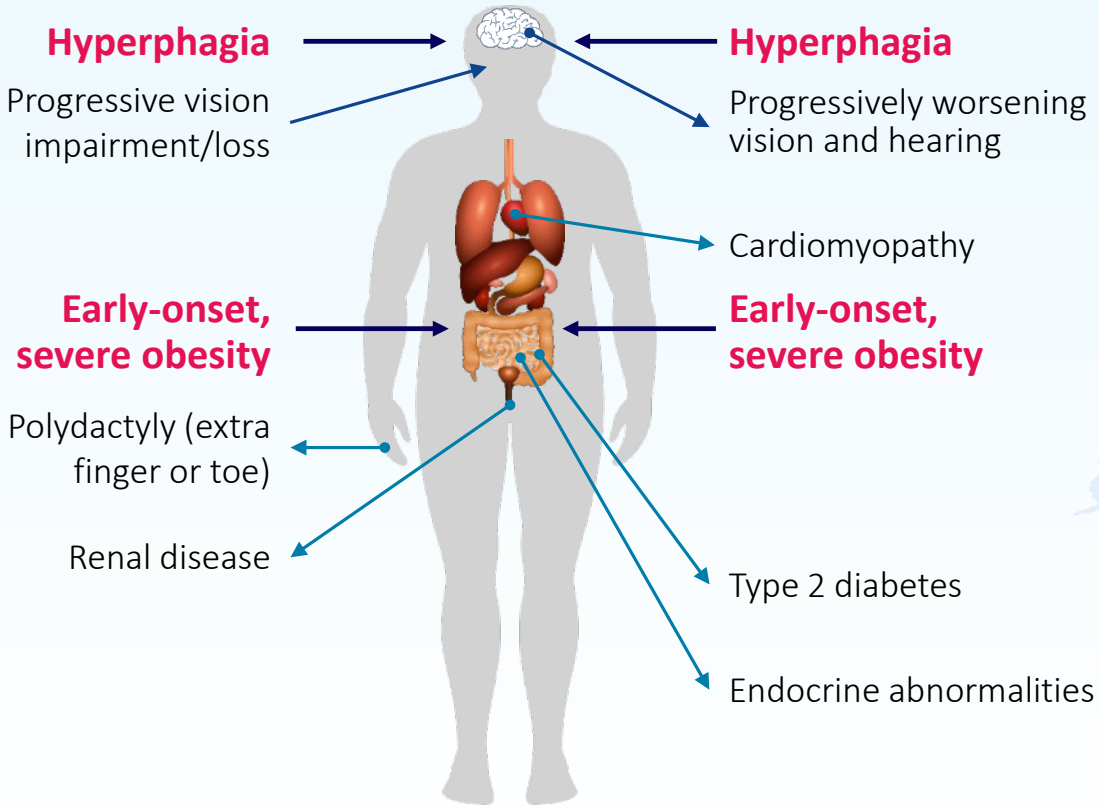
Bardet-Biedl and Alström Syndromes Associated with Severe Obesity and Hunger

Bardet-Biedl syndrome[1]

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

U.S. prevalence estimated to be

1,500 to **2,500** patients



Alström syndrome[2,3]

Rare ciliopathy disorder associated with **ALMS1 mutation**

Worldwide prevalence estimated to be

500 to **1,000** patients

References: 1. Forsythe E, Beales PL. Bardet-Biedl Syndrome. 2003 Jul 14 [Updated 2015 Apr 23]. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1363/. **2.** Marshall JD et al. *Curr Genomics*. 2011;12(3):225-235. **3.** Marshall JD et al. Alström Syndrome. 2003 Feb 7 [Updated 2012 May 31]. In: Adam MP et al, eds. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. https://www.ncbi.nlm.nih.gov/books/NBK1267/.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