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PHARMACEUTICALS

Update on MC4R Pathway Programs

An R&D event for investors and analysts

Dec. 6, 2023

Forward Looking Statements

This presentation contains certain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, and that involve risks and uncertainties, including without limitation 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 timing thereof, including for our Phase 2 DAYBREAK trial, the anticipated development plan for RM-718 and regulatory submissions for our pediatrics program; our business strategy and plans, including regarding commercialization of setmelanotide, the application of genetic testing and related growth potential, and expectations surrounding the potential market opportunity for our product candidates. Statements using words such as "expect", "anticipate", "believe", "may" 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 ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our liquidity and expenses, the impact of the COVID-19 pandemic on our business and 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.

Today's Speakers

David Meeker, MD
Chairman, President & Chief Executive Officer,

Rhythm Pharmaceuticals

Jennifer Miller, MD
Professor of Pediatric Endocrinology
University of Florida

Amy Wood
Executive Director / Co- Founder of the Raymond A. Wood Foundation

Dorit Koren, MD, MTR
Medical Director, Clinical Development, Rhythm Pharmaceuticals

Patrick Sleiman, PhD
Director, Genetics, Translational Research & Development, Rhythm Pharmaceuticals

Danica Grujic, PhD
Senior Director, Non-Clinical Development, Translational Research & Development, Rhythm Pharmaceuticals

Rhythm Update on MC4R Pathway Programs

Welcome and what you'll hear today: David Meeker, MD

Hypothalamic Obesity: Jennifer Miller, MD, and Amy Wood

Rhythm Update on MC4R Programs: David Meeker, MD

Exploratory Phase 2 DAYBREAK Trial Update

- Dorit Koren, MD, MTR
- Patrick Sleiman, PhD

Introduction to RM-718

- Danica Grujic, PhD

Topline Data from Phase 3 Pediatrics Trial

Q&A and Conclusion

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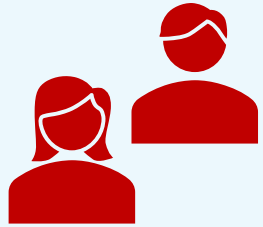
Welcome and What You'll Hear Today

David Meeker

Rhythm is Focused on Expanding the MC4R Pathway Opportunity

Science is leading to more patients and additional indications than originally thought

Increasing understanding of underlying genetics and importance of MC4R agonism



Developing additional potential treatment options to benefit more patients

Continued High-level Execution on a Global Level

Strong BBS commercial execution

- Strong growth with $22.5M in global net revenue for 3Q2023
- IMCIVREE now commercially available in Canada, Gulf Cooperation Council countries; German BBS launch underway

IMCIVREE® (setmelanotide) injection

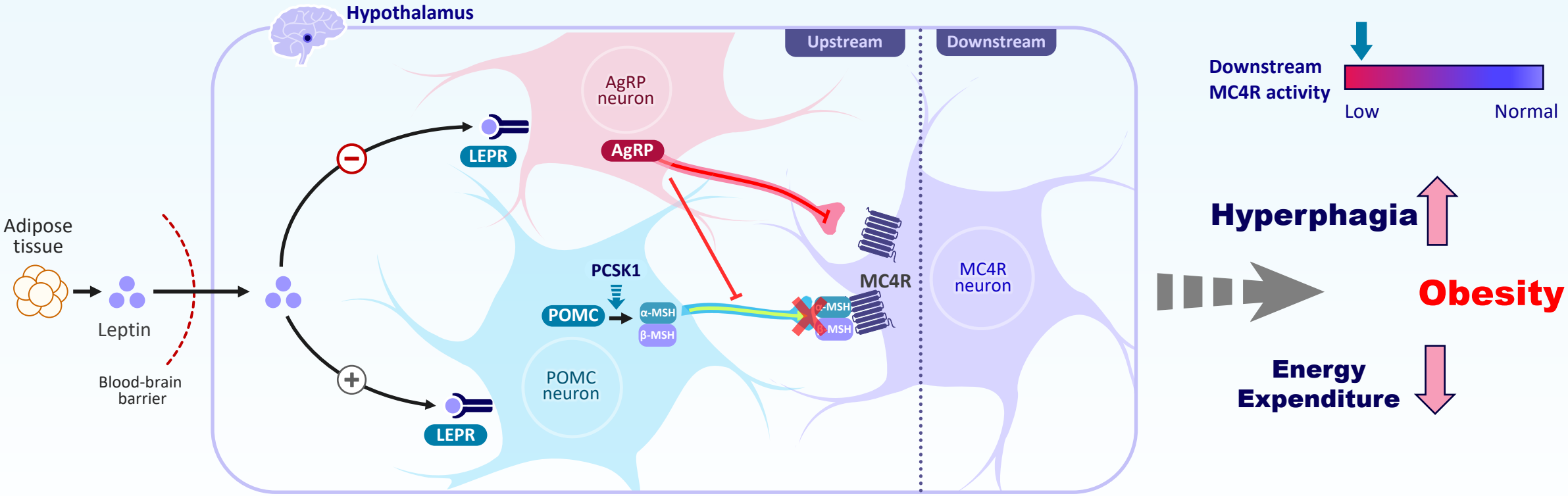
Hypothalamic obesity programs progressing

- Ph3 trial enrollment on track for completion by the end of 2023
- 12-month LTE data demonstrates sustained and deepening reductions in BMI

Multiple development programs advancing

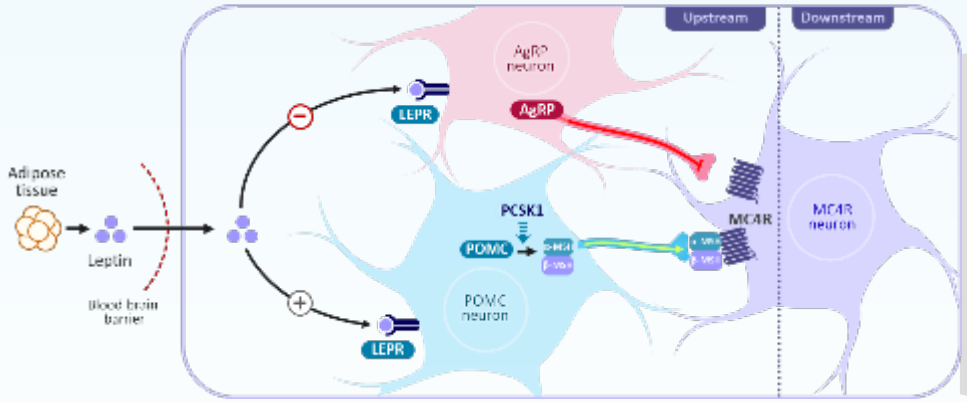
- Stage 2 of Phase 2 DAYBREAK trial ongoing
- Phase 3 EMANATE trial ongoing
- RM-718: First in-human study initiation expected 1H 2024

RYTM is Uniquely Focused on Rare MC4R Pathway Diseases



AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

Clinical Development Programs Designed to Expand IMCIVREE Label and Overall MC4R Pathway Opportunity



Approved for:€	
Bardet-Biedl syndrome	POMC, PCSK1 and LEPR deficiencies
4,000 - 5,000 patients in the U.S.*	**600 – 2,500 patients in the U.S.***

Phase 3 Trial ongoing
Hypothalamic obesity
5,000 – 10,000 patients in the U.S.*

Phase 3 EMANATE Trial**
Heterozygous POMC/PCSK1 insufficiency
Heterozygous LEPR insufficiency
SRC1 deficiency
SH2B1 deficiency
53,000 patients in the U.S.*

*Estimated prevalence of U.S. patients based on company estimates; does not include ex-U.S. prevalence estimates.

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What You'll Hear Today

Update on Hypothalamic Obesity

Dr. Jenn Miller on treating patients with hypothalamic obesity

Patient and family perspective from Amy Wood, founder of RA Wood Foundation

On track to complete enrollment in Phase 3 trial by end of 2023

Exploratory Phase 2 DAYBREAK Trial

Rationale for gene selection

Preliminary BMI data from the open label part 1 of study on 6 gene cohorts

U.S. prevalence estimates

Official Introduction of RM-718

A more selective MC4R agonist, designed to not cause hyperpigmentation

Weekly administration

Phase 1 studies to begin in 1H2023

Phase 3 Pediatrics Trial

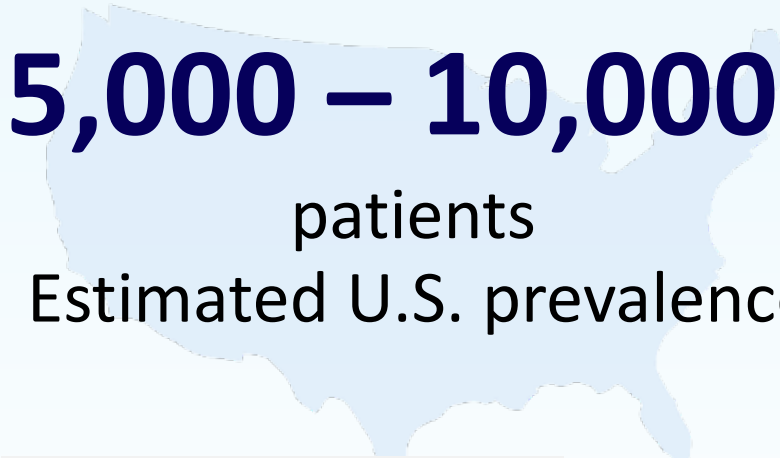
Evaluating setmelanotide in patients with BBS or POMC/LEPR deficiency obesity between the ages of 2 and younger than 6

EU regulatory path forward

U.S. regulatory path forward

Hypothalamic Obesity

Setmelanotide and Hypothalamic Obesity: A Transformative Opportunity for Rhythm



5,000 – 10,000*

patients

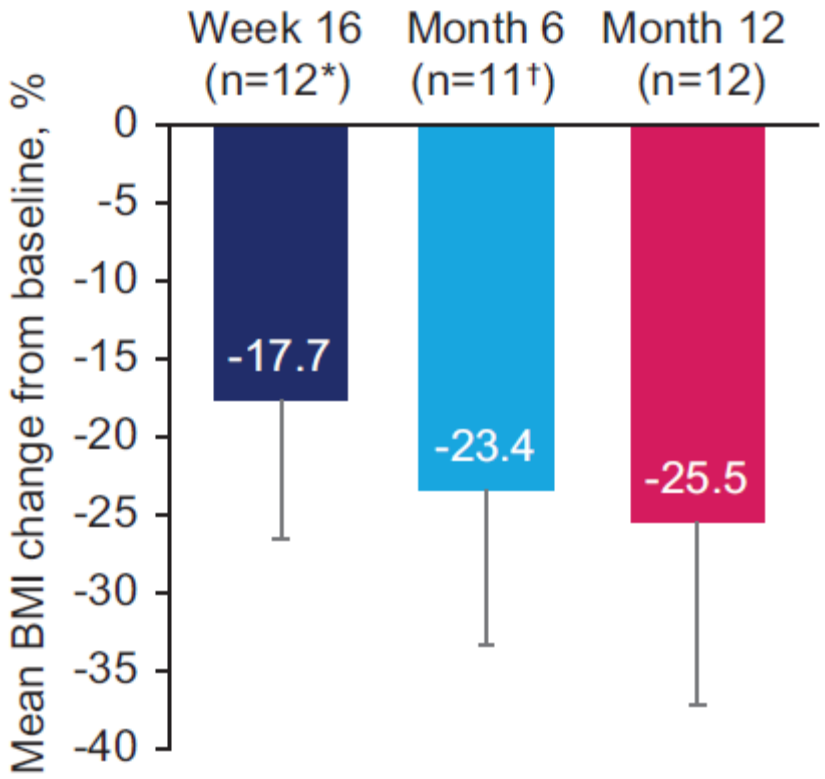
Estimated U.S. prevalence

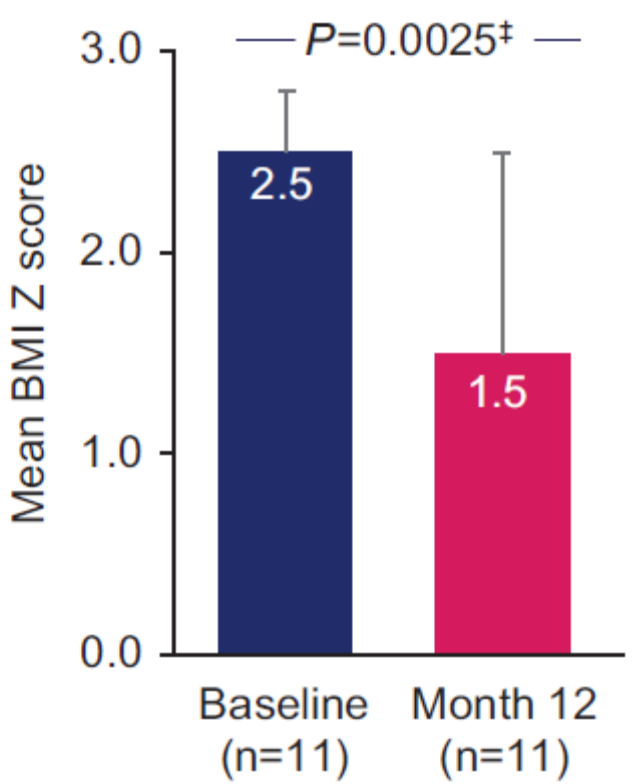
~500* additional cases diagnosed in U.S. each year

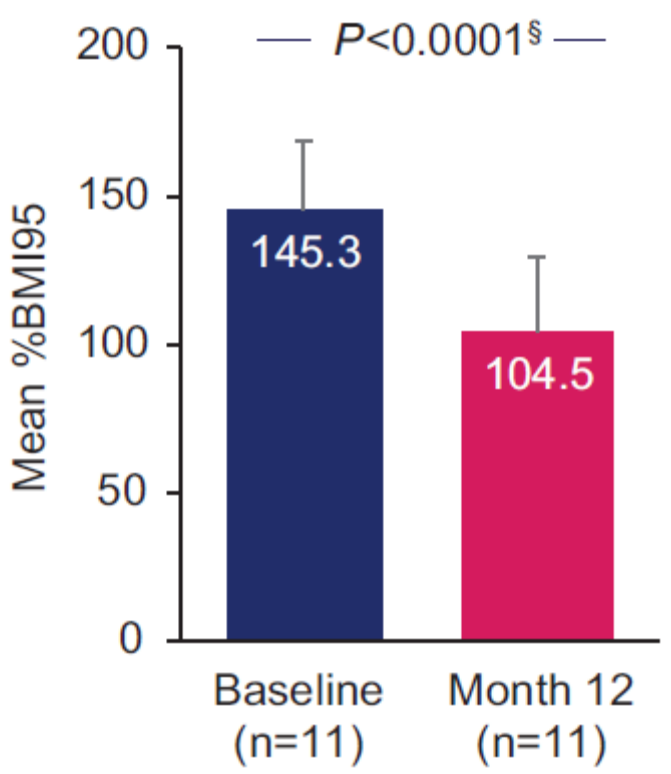
- ✓ Unmet medical need is high; no approved therapies
- ✓ MC4R pathway deficiency following injury to hypothalamic region
- ✓ Large majority of patients are identified; no genetic testing required
- ✓ Patients are engaged with the system receiving specialist care for pituitary complications

*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.

Setmelanotide Achieved Progressive, Deepening BMI Reduction at 16 Weeks, 6 and 12 Months in Patients with Hypothalamic Obesity

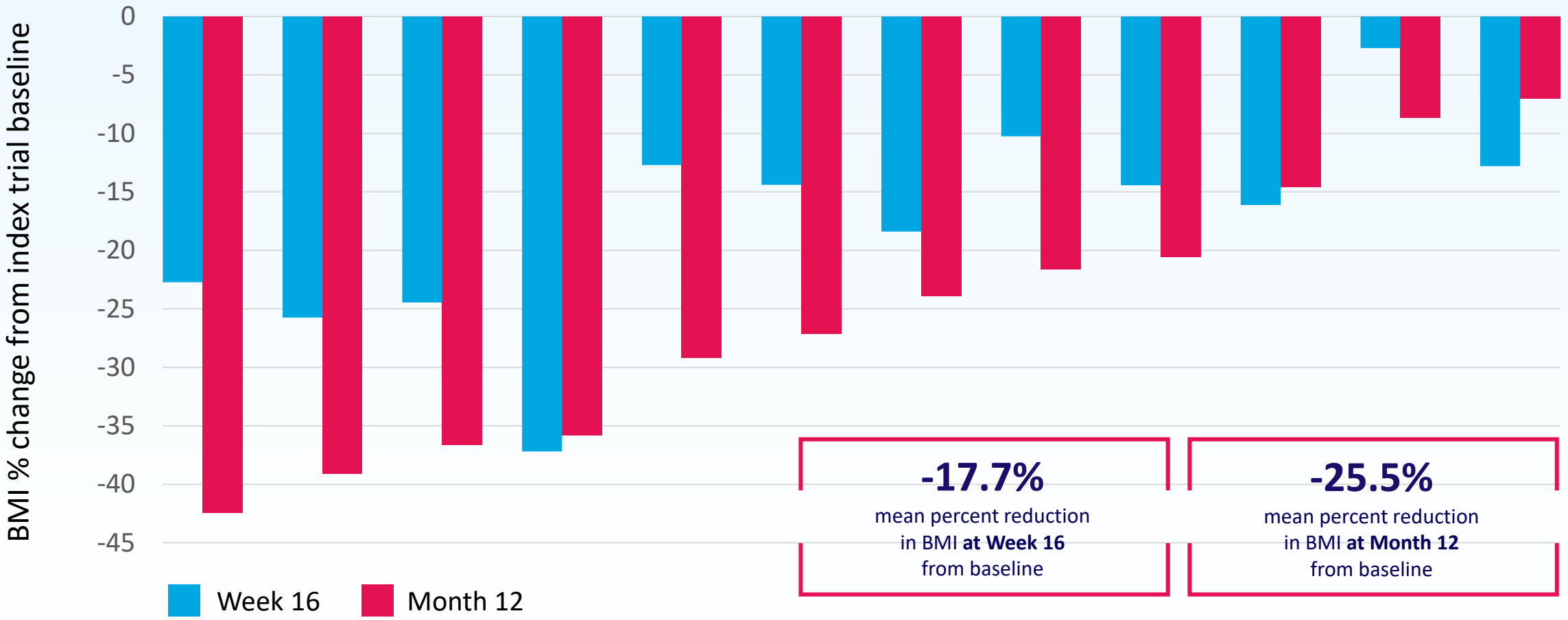






Error bars are the standard deviation. *Includes all patients who received 16 weeks of setmelanotide in the index trial and ≥12 months of treatment in the long-term extension. †One patient did not complete a Month-6 visit. ‡One sample *t*-test with 2-tailed *P*-values. §Paired *t*-test with 2-tailed *P*-values. BMI, body mass index; %BMI95, percent of the 95th percentile for BMI.

Setmelanotide Achieved Sustained and Deepened BMI Reduction in Patients with Hypothalamic Obesity at One Year



Adapted from data presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.

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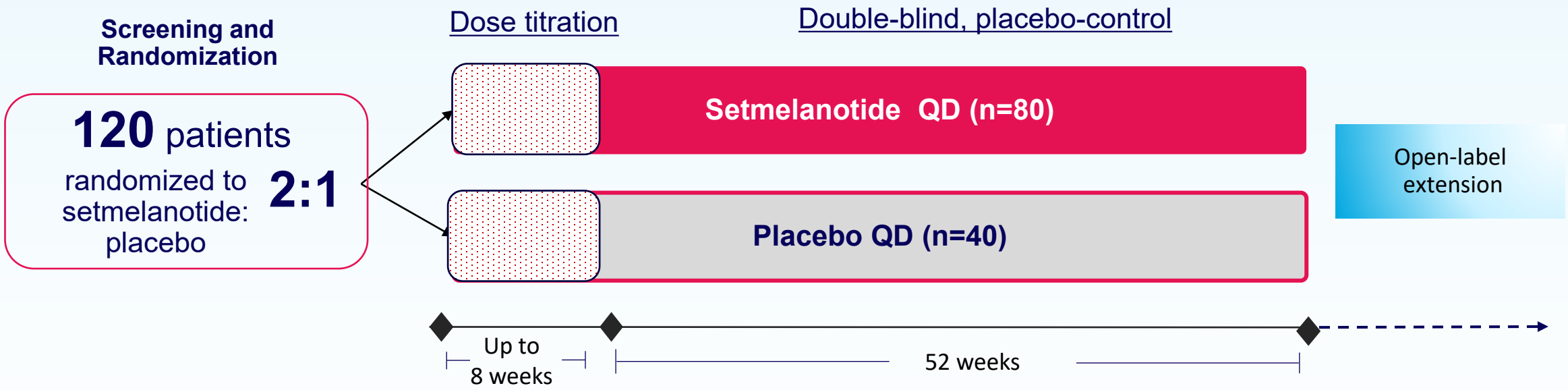
Phase 3 Hypothalamic Obesity Trial: Enrollment Completion on Track for end of 2023



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.

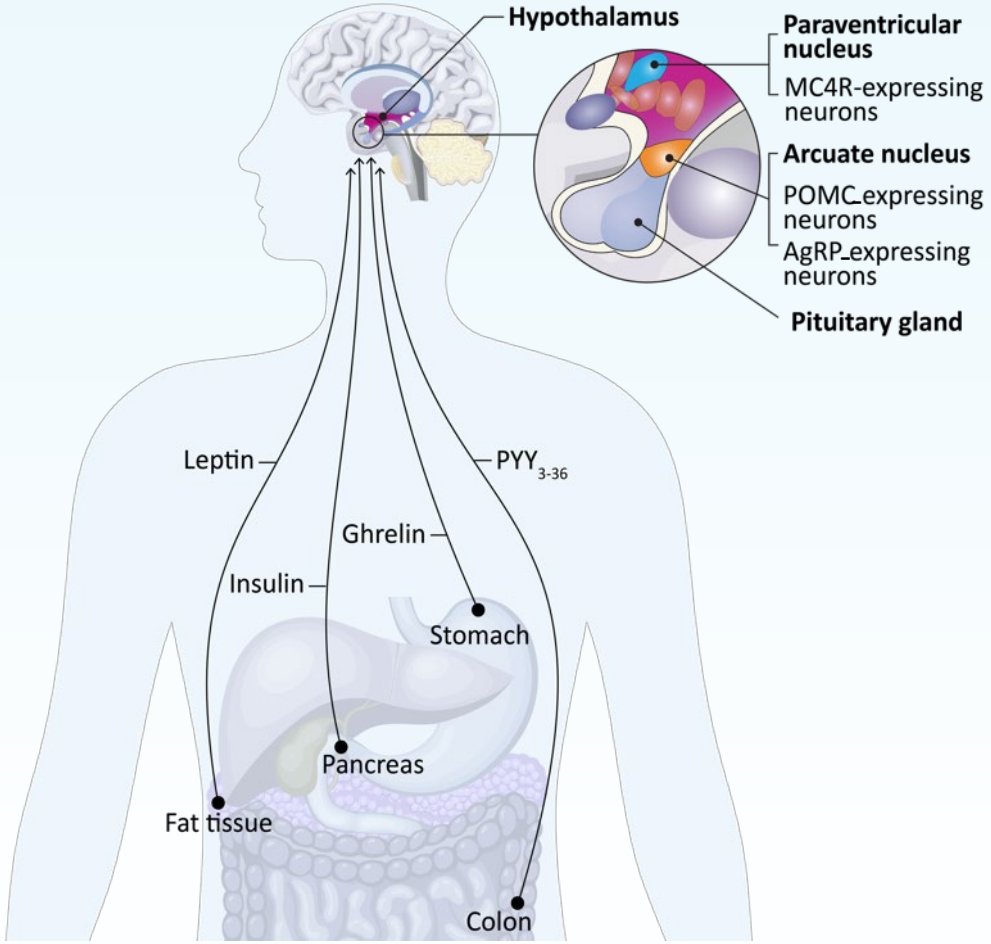
Jenn Miller

Hypothalamic Obesity and Relation to the MC4R Pathway

Craniopharyngioma and **other suprasellar brain tumors** and treatment – tumor resection surgery and radiation – is most common cause

MC4R pathway deficiency following injury to hypothalamic region causes reduced energy, hyperphagia and rapid-onset, severe obesity

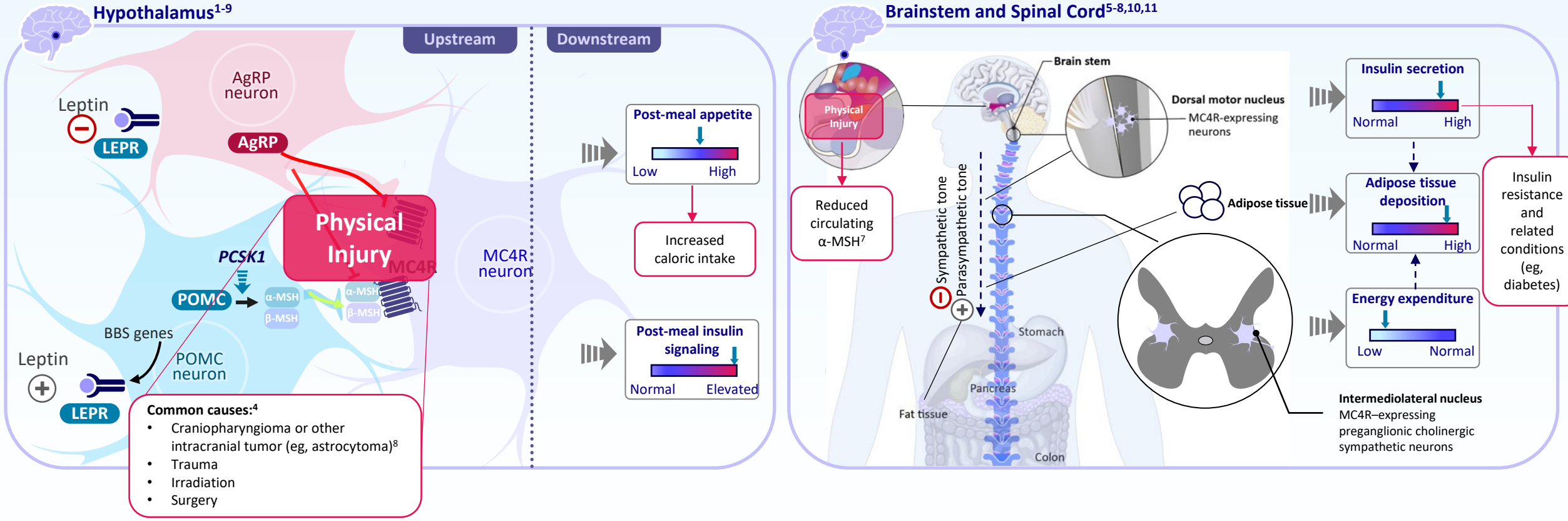
No approved treatments available



AgRP, agouti-related peptide; HO, hypothalamic obesity; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin; PYY, peptide YY.

Damage to the MC4R Pathway Can Lead to Hypothalamic Obesity

Damage to the hypothalamic region might impair downstream MC4R pathway signaling in the brainstem and spinal cord, leading to hyperphagia, severe obesity, and increased risk for comorbidities (eg, diabetes)[1-10]



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1. da Fonseca et al. *J Diabetes Complications.* 2017;31:1549-1561. **2.** Yazdi et al. *PeerJ.* 2015;3:e856. **3.** Farooqi and O'Rahilly. *Nat Clin Pract Endocrinol Metab.* 2008;4:569-577. **4.** Abuzzahab et al. *Horm Res Paediatr*. 2019;91:128-136. **5.** Erfurth. *Neuroendocrinology*. 2020;110:767-779. **6.** Roth. *Front Endocrinol (Lausanne)*. 2011;2:49. **7.** Baldini et al. *J Endocrinol.* 2019;241:R1-R33. **8.** Rose et al. *Obesity (Silver Spring)*. 2018;26:1727-1732. **9.** Seo et al. *Hum Mol Genet.* 2009;18:1323-1331. **10.** Sohn et al. *Cell.* 2013;52:612-619. **11.** Rossi et al. *Cell Metab*. 2011;13:195-204.

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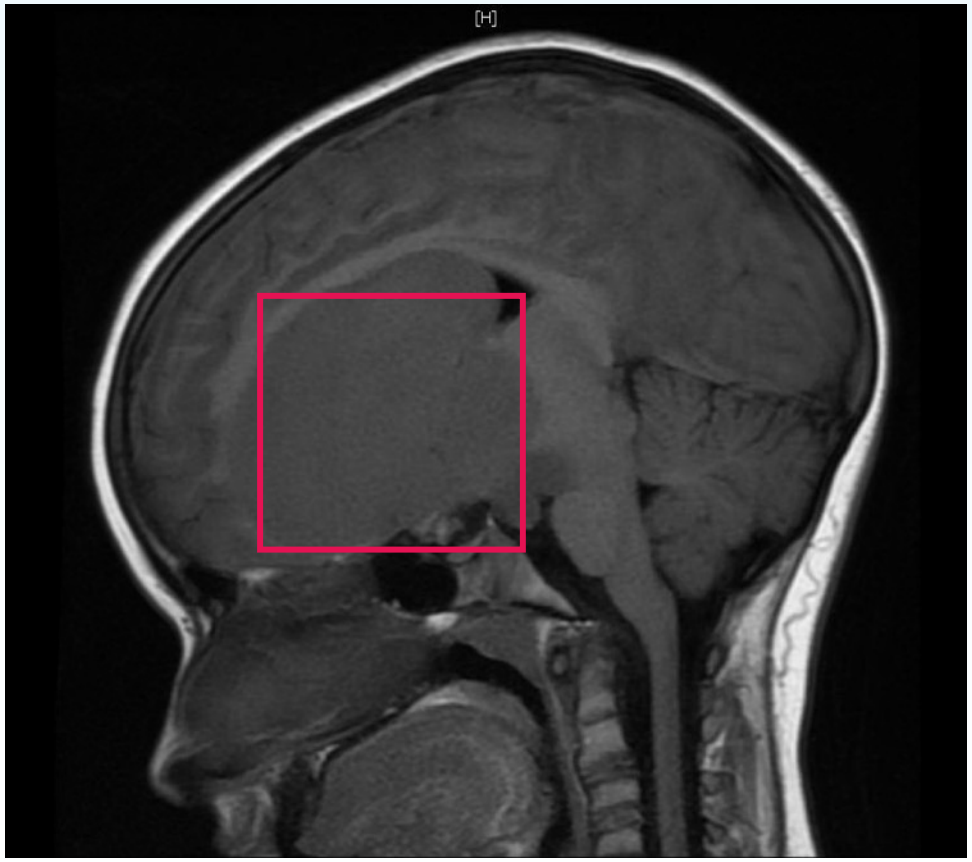
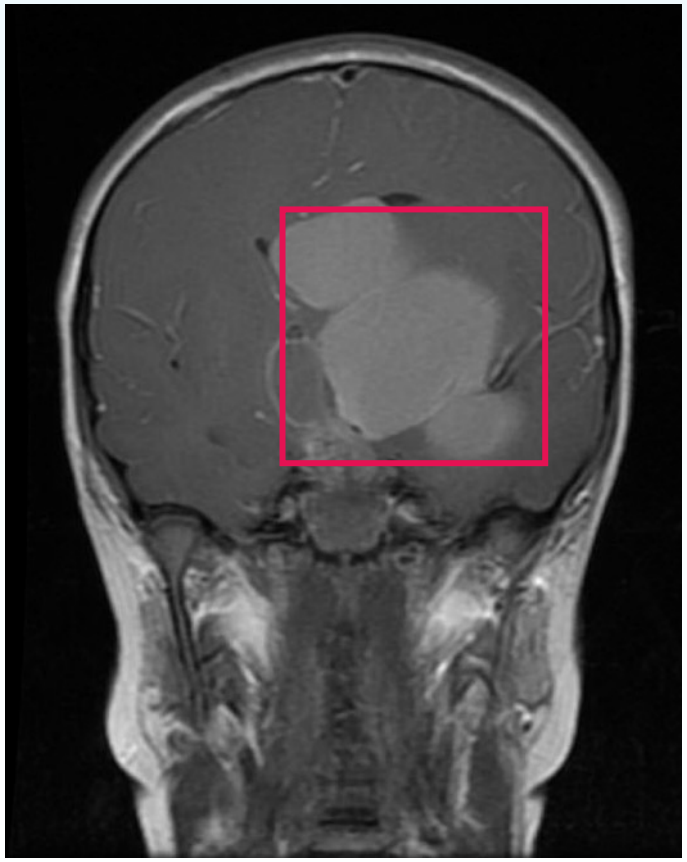
Example of Hypothalamic Injury Resulting in Hypothalamic Obesity: Craniopharyngioma

Imaging of patient with craniopharyngioma diagnosed at 4 years of age





Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota.

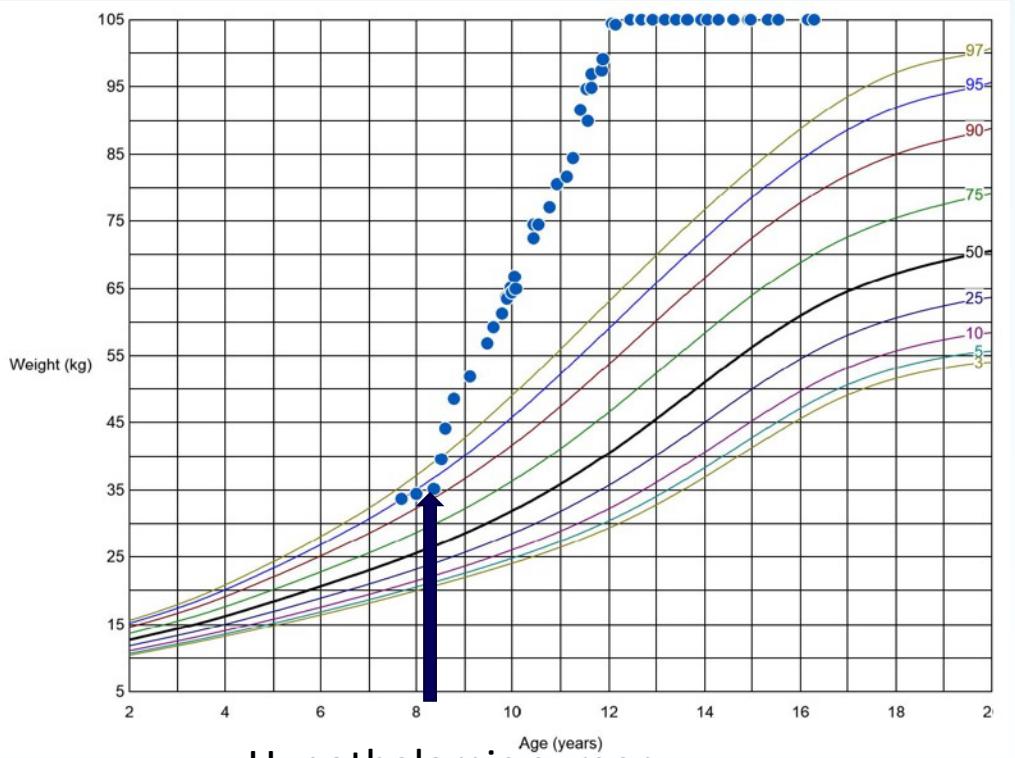
Acquired Hypothalamic Obesity Leads to Rapid Weight Gain

Most frequently occurring following surgical resection or radiation of brain tumors[1]

Most hypothalamic obesity cases follow craniopharyngioma[1,2]

- Histologically benign neoplasms located centrally within the brain2
- Frequently impact hypothalamus, pituitary gland, and optic nerve[2]
- Treatment of the tumor includes complete or incomplete resection, radiotherapy, and hormone replacement therapy to treat hypopituitarism2

~50% of patients who receive treatment for craniopharyngioma develop hypothalamic obesity[3]



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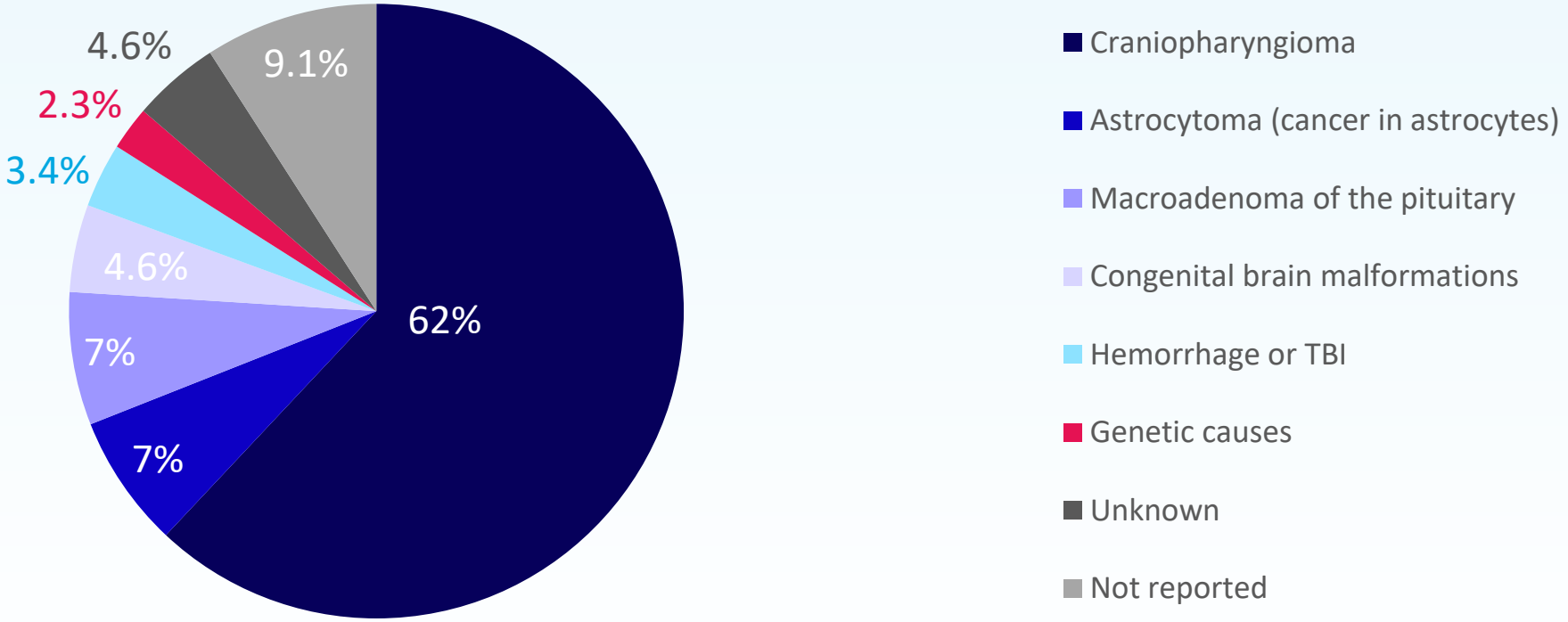
Multiple Conditions Can Lead to Hypothalamic Obesity



HO, hypothalamic obesity; TBI, traumatic brain injury.

1. Rose et al. *Obesity (Silver Spring)*. 2018;26:1727-1732. **2.** Bereket. *Horm Res Paediatr*. 2020;93:497-509. **3.** Abuzzahab et al. *Horm Res Paediatr*. 2019;91:128-136.

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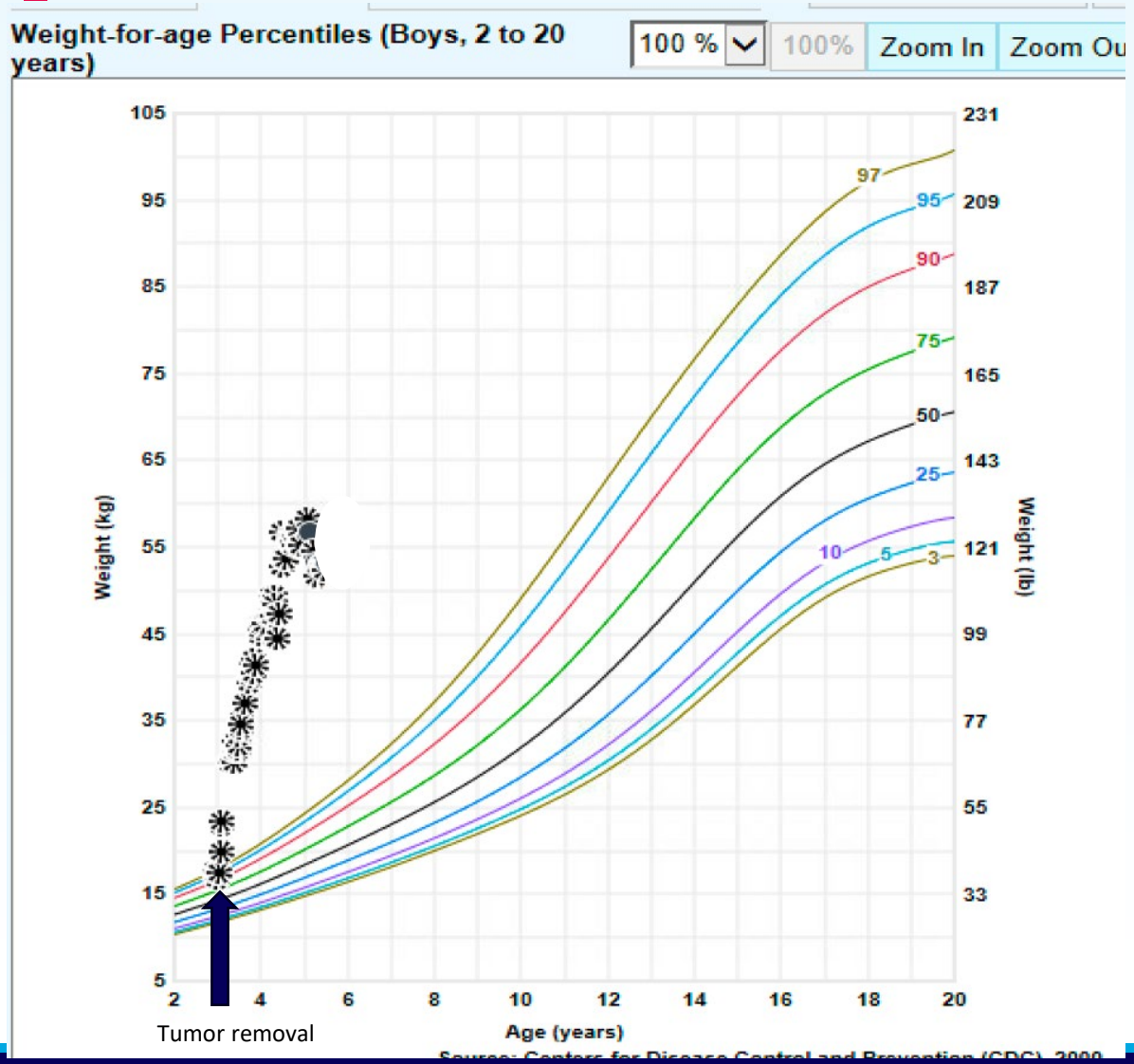
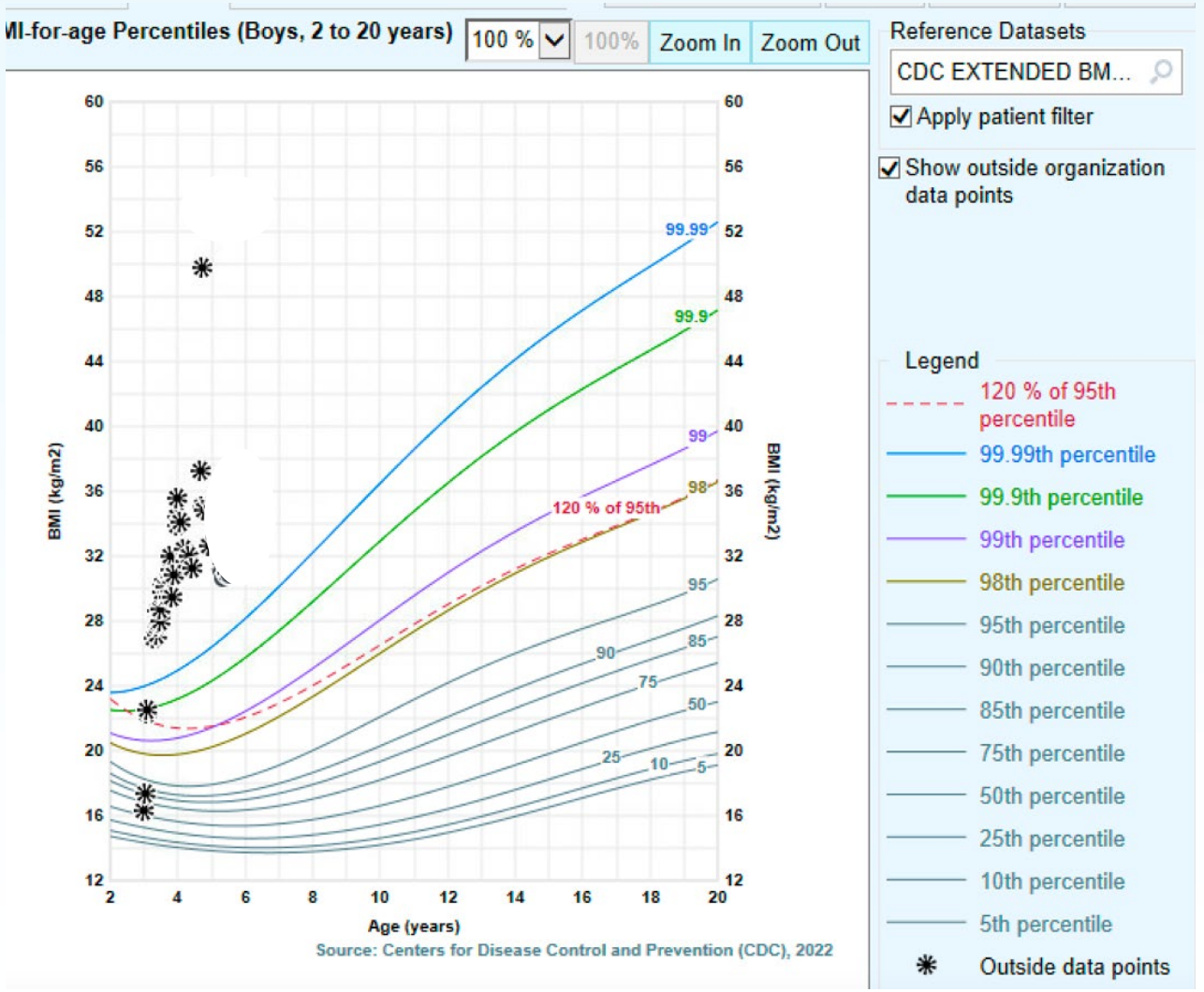
Growth Patterns in Hypothalamic Obesity





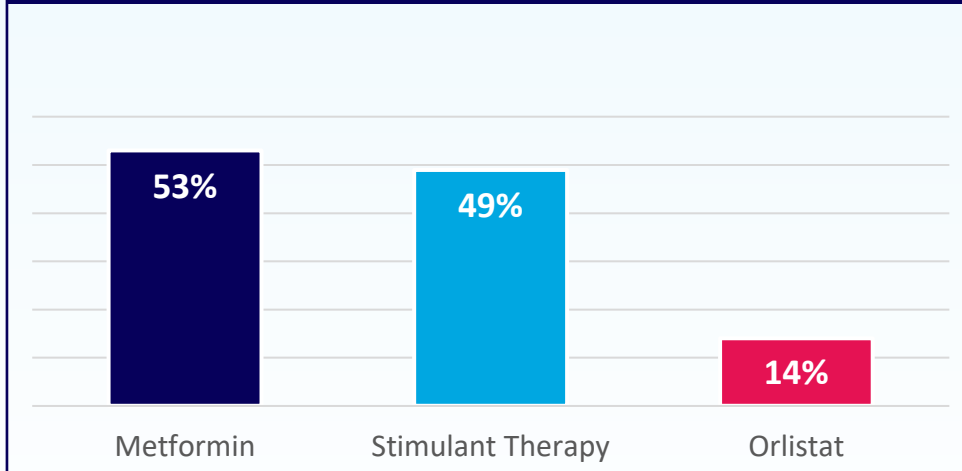
Pharmacologic Treatment Options

Pharmacologic Treatments

- There is a lack of clear treatment algorithms for HO, and there are no therapies specifically indicated for HO[1]
- Many pharmacologic treatments indicated for general weight loss have been explored in patients with HO[1-3]
- A range of case studies, observational studies, as well as a limited number of randomized control trials have assessed the impact of pharmacotherapies on HO[1-3]
- 59% of patients reported using pharmacotherapy (and ~26% reported multidrug therapy)[4]

In part because of the unique pathophysiology of HO compared with general forms of obesity, conventional pharmacologic approaches have shown limited to no benefit in patients with HO, and there are currently no FDA-approved treatments available for these patients[1,4,5]

Commonly Used Pharmacologic Treatments[4]



- Recent studies have also examined GLP-1 analogues for the treatment of HO with varying outcomes[6-9]

FDA, US Food and Drug Administration; GLP-1, glucagon-like peptide-1; HO, hypothalamic obesity.

1. Singhal et al. *Curr Opin Endocrinol Diabetes Obes.* 2021;28:55-63. **2.** Müller et al. *Endocrinol Metab Clin North Am*. 2020;49:533-552. **3.** Roth et al. *Diabetes Obes Metab*. 2021;23:363–373. **4.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732. **5.** Dimitri. *Front Endocrinol (Lausanne).* 2022;13:846880. **6.** van Schaik et al. *Obes Facts*. 2020;13:361-370. **7.** Zoicas et al. *Eur J Endocrinol*. 2013;168:699-706. **8.** Roth et al. *Diabetes Obes Metab*. 2021;23:363-373. **9.** Shoemaker et al. *Int J Obes (Lond)*. 2022;46:623-629.

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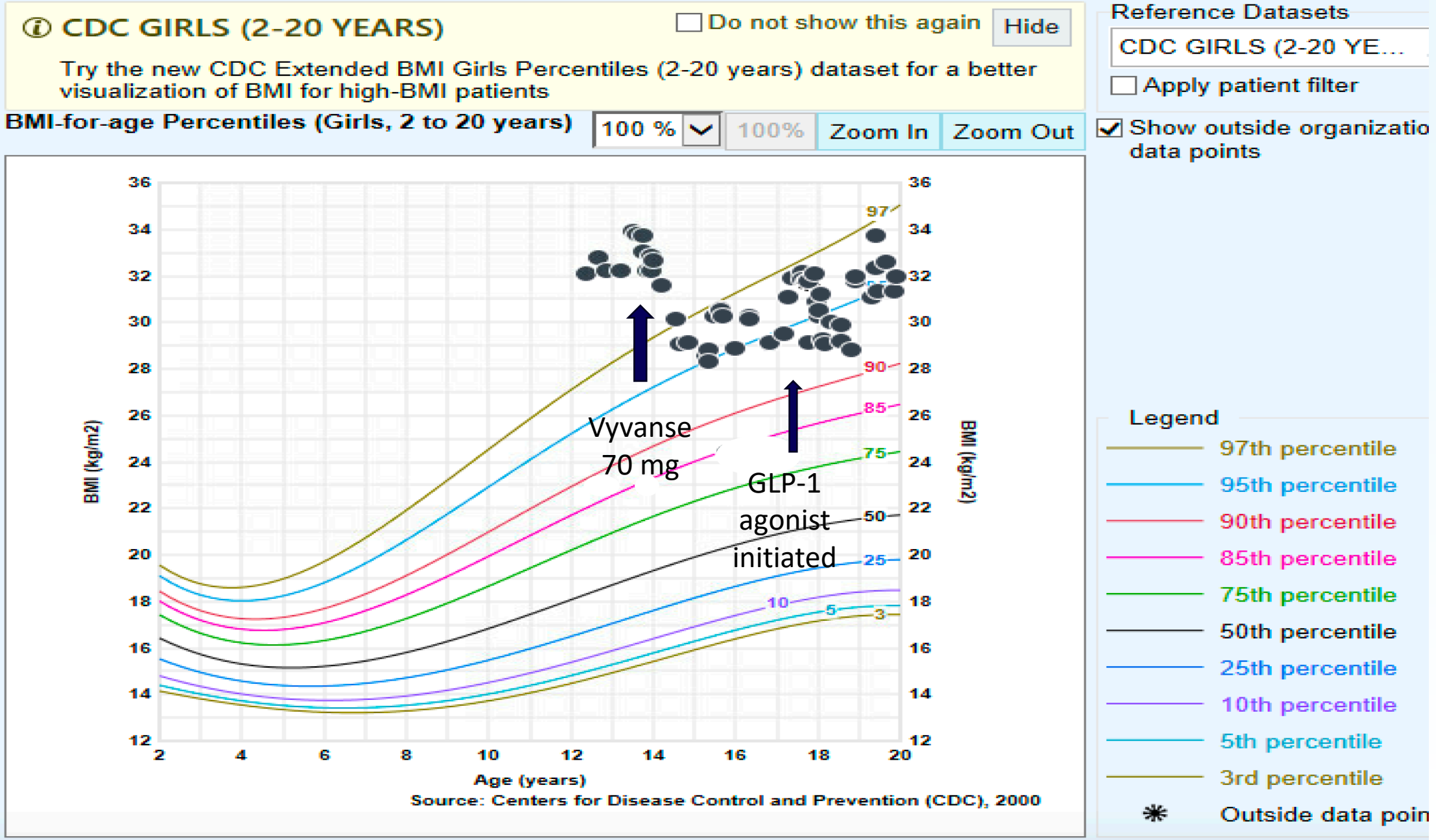
CDC GIRLS (2-20 YEARS)
Do not show this again
Hide
Try the new CDC Extended BMI Girls Percentiles (2-20 years) dataset for a better visualization of BMI for high-BMI patients
BMI-for-age Percentiles (Girls, 2 to 20 years)
100 %
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Zoom In
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Reference Datasets
CDC GIRLS (2-20 YE...
Apply patient filter
Show outside organizatio data points
Vyvanse 70 mg
GLP-1 agonist initiated
BMI (kg/m2)
Age (years)
Source: Centers for Disease Control and Prevention (CDC), 2000
Legend
97th percentile
95th percentile
90th percentile
85th percentile
75th percentile
50th percentile
25th percentile
10th percentile
5th percentile
3rd percentile
Outside data poin

Amy Wood

Hypothalamic Obesity: The Patient Perspective

Amy Wood
Caregiver, Executive Director

Raymond A. Wood foundation

Alex's Journey

Alex was healthy 4 year-old until May 21, 2015, when he woke up with his left eye drifting inward. He arrived at Johns Hopkins ED and underwent an MRI where it was determined that he has a mass in the middle of his brain.

Early the next morning, he underwent emergency brain surgery.

Two Days Before Surgery

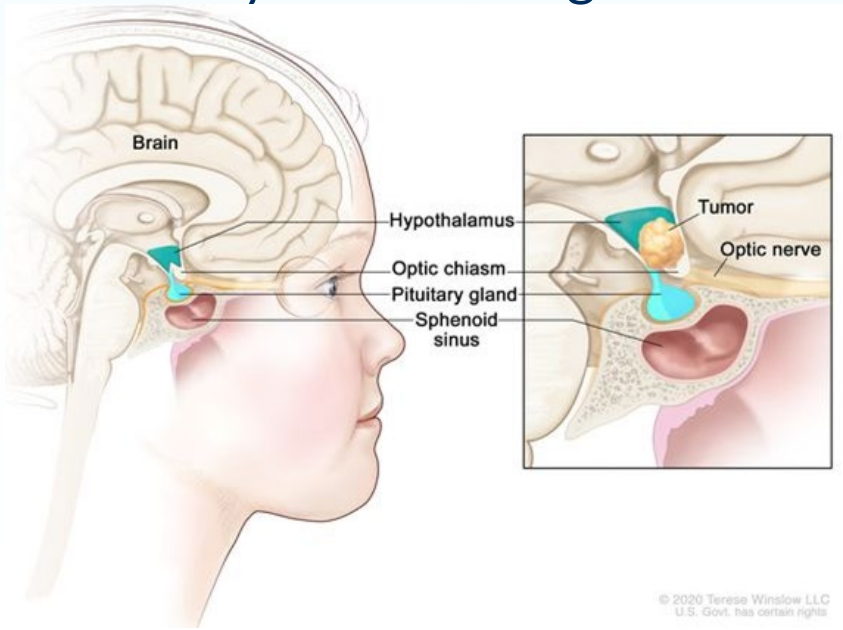
Day After Surgery

One Week After Surgery

Two Weeks After Surgery

Alex's Diagnosis: Craniopharyngioma (CP)

- Approximately 620 new cases per year in the U.S.
- Treatment: full resection via right frontal lobe craniotomy
- Spent 4 weeks in Hopkins PICU and 3 weeks inpatient rehab at the Kennedy Krieger Institute
- Had multiple ER visits, medflights and admittances for seizures and hypothermia in the year following treatment.



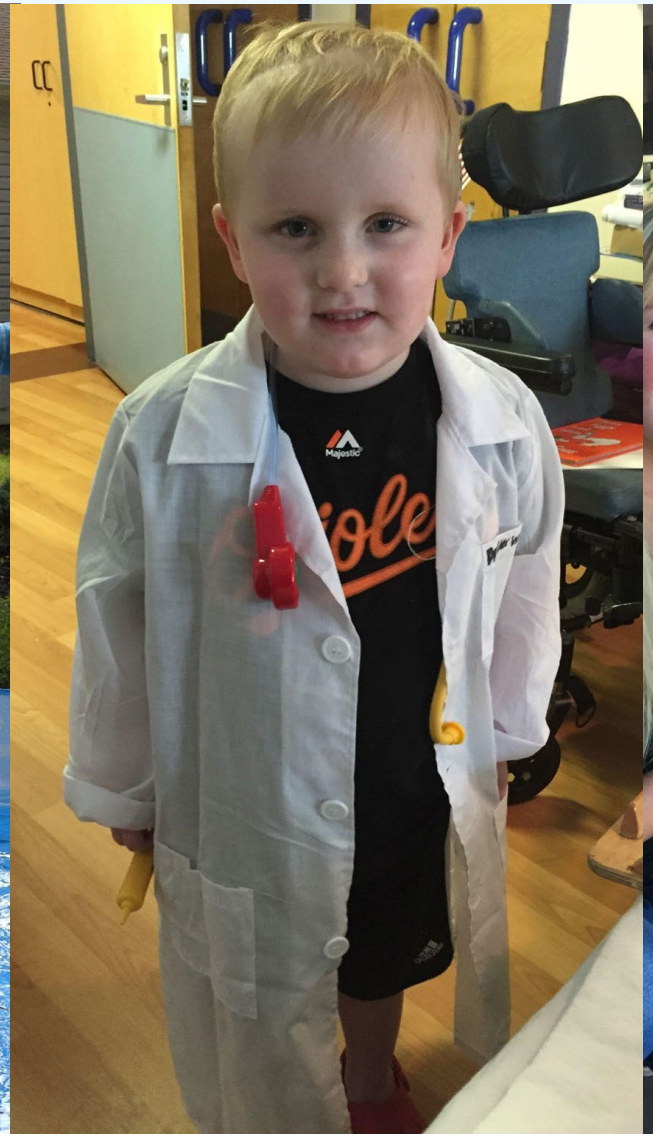
Almost 80 years ago, the father of modern neurosurgery,
Dr. Harvey Cushing,
declared craniopharyngioma **"the most formidable of intracranial tumors."**

Benign is Not Fine

Alex developed the following medical conditions:

- Panhypopituitarism
- Adipsic Diabetes Insipidus / Hypo & Hypernatremia
- Adrenal Insufficiency
- Growth Hormone Deficiency

He began to gain weight immediately after surgery. **He went into the hospital at 40 lbs and left the hospital 6 weeks later at 60 lbs.** His weight continued to climb at a rapid pace and he was later diagnosed with hypothalamic obesity (HO).



Alex was gaining at about 1-2lbs a week during the first year post surgery.

Health Issues with HO

Fears he may develop obesity-related issues on top of his long list of medical conditions like sleep apnea, hypertension, diabetes and fatty liver disease.

Developed aspiration pneumonia from eating too fast.

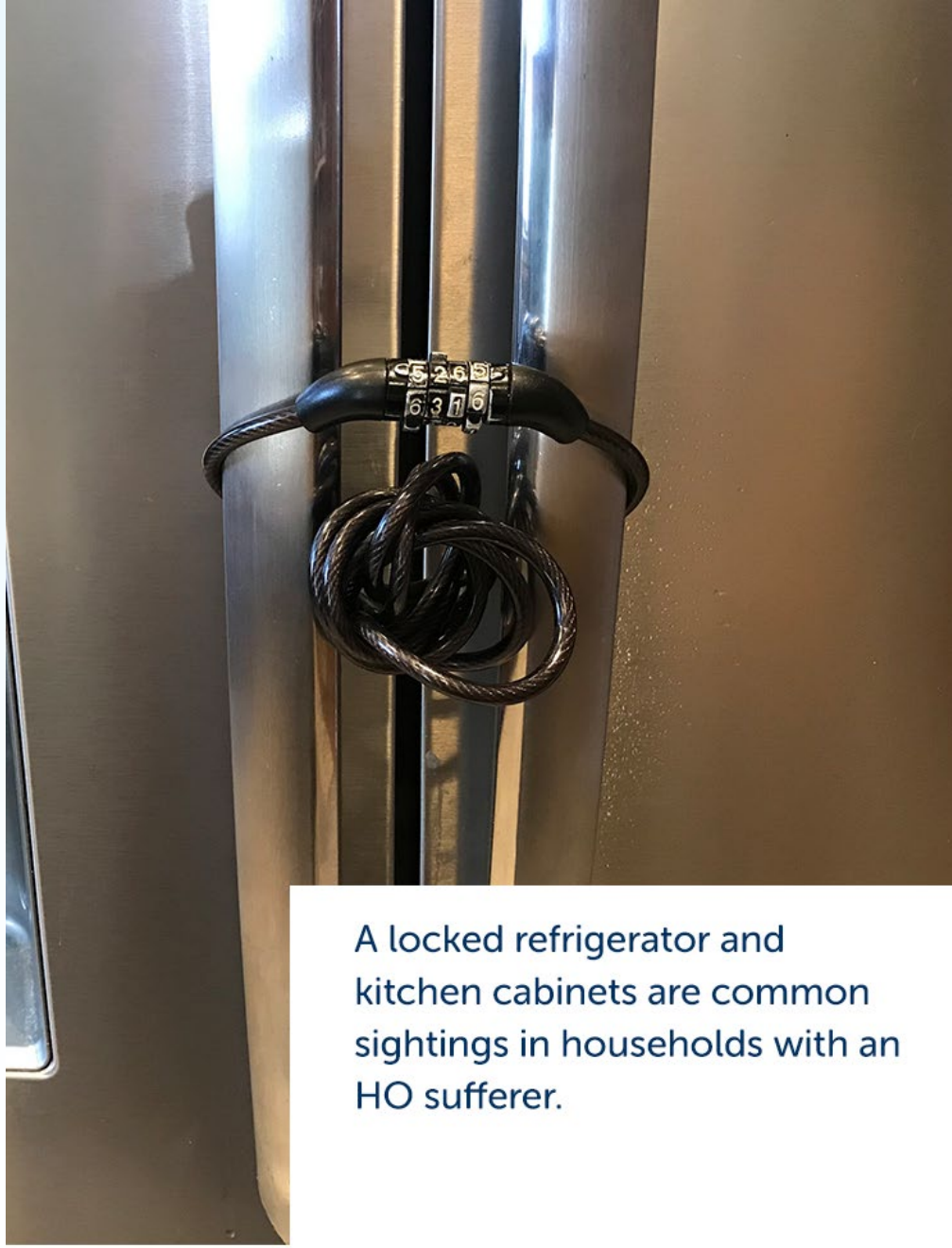
Concern for risk for choking.

He has a tree nut allergy so constant supervision outside of the home is required.

Food seeking during the night causes sleep disruption for the entire family. Wakes very early so he doesn't miss breakfast.

Constant stress and anxiety on the family and social isolation. Constantly asking about food, every minute of the day.

Orthopedic issues, low energy and exercise intolerance.



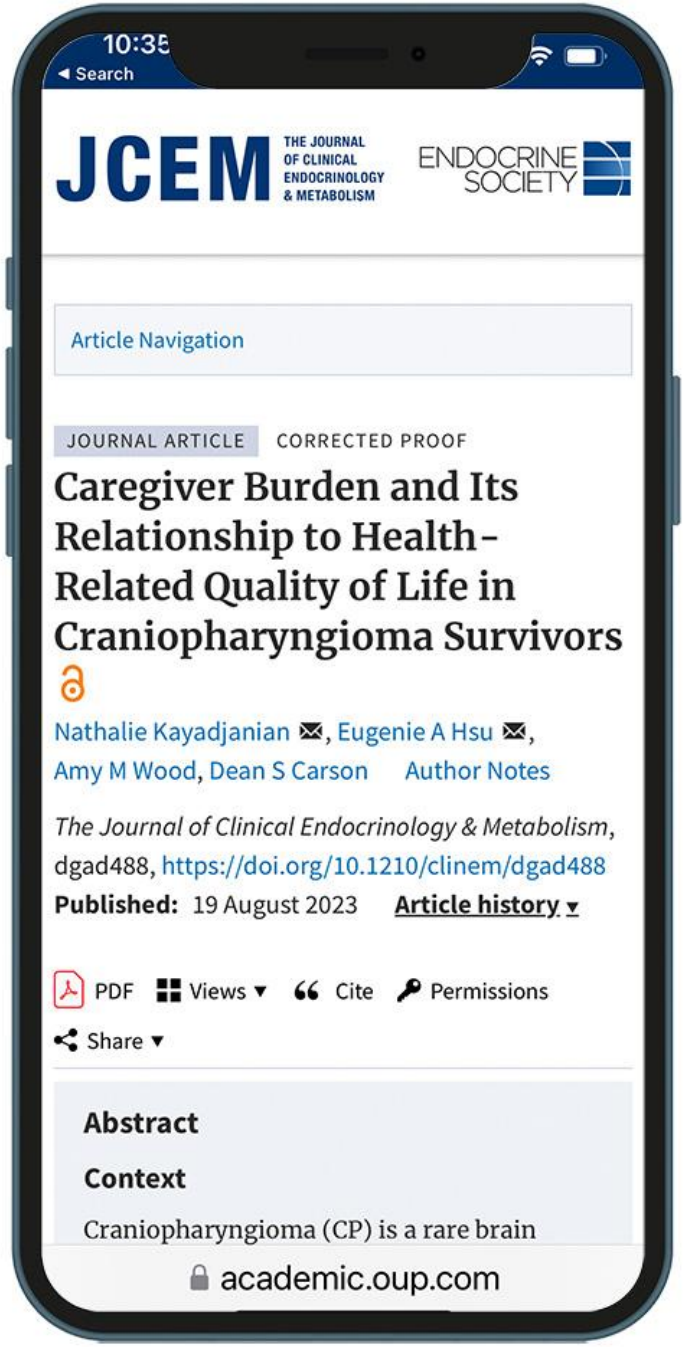
A locked refrigerator and kitchen cabinets are common sightings in households with an HO sufferer.

What if there was a treatment for HO?

Caregiver Burden Study

- The top caregiver-reported problems experienced by survivors were weight problems: 87.8%
- Hyperphagia affected 53.6% of survivors
- 80% of caregivers are at-risk of depression

Raymond A. Wood foundation



What if there was a treatment for HO?

Would Alex be able to **think about other things besides food**?

Would he be able to **make friends now that food is less of an issue**?

Could e**ating meals be an enjoyable family experience**?

Would Alex be able to have some **independence in the future**? Maybe even a job?

HO is Unrelenting

As the days passed, **our once very thin child continued to gain weight extremely quickly,** despite our vigilant attempts at watching his diet.

Hyperphagia is unforgiving and takes Silas over. It is relentless. **He would put himself or others in harm's way in order to get food.**

I wish hypothalamic obesity was only about weight gain. It is not. **HO is about fear, isolation, and hopelessness.** My family has been living in this endless cycle for the past 18 years.

When I developed HO after damage done to my brain due to a brain tumor, **I doubled in size in the span of a few years.** I went from 350 to almost 800 pounds.

Feeling Hopeful for the Future

THANK YOU

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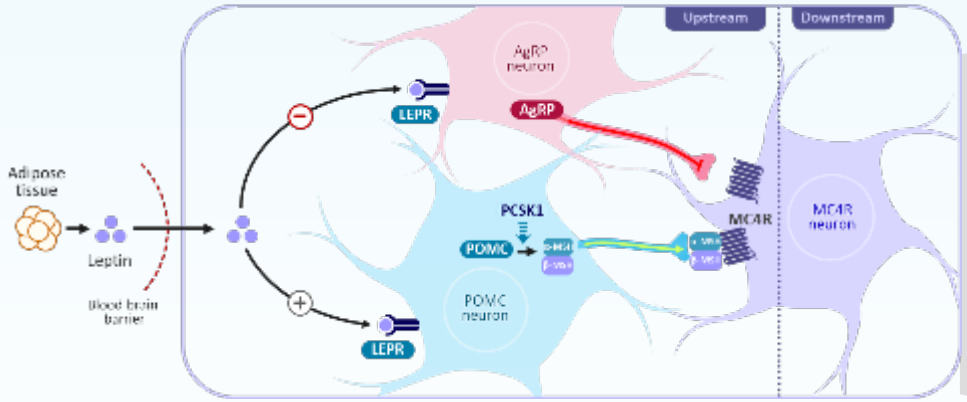
linkedin.com/in/amymwood

Q and A

David Meeker

Overall MC4R Pathway Opportunity



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Heterozygous LEPR insufficiency
SRC1 deficiency
SH2B1 deficiency
53,000 patients in the U.S.*

*Estimated prevalence of U.S. patients based on company estimates; does not include ex-U.S. prevalence estimates.

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Ongoing Phase 3 EMANATE Offers Significant Expansion of Setmelanotide's Potential Addressable Market

Emanate

Obesity and Hunger Clinical Trial

Phase 3 EMANATE Trial€

Four independent sub-studies

6,000†	**Heterozygous POMC/PCSK1 deficiency**
4,000†	**Heterozygous LEPR deficiency**
20,000†	**SRC1 deficiency**
23,000†	**SH2B1 deficiency**

† Estimated U.S. patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results, current estimated responder rates and that 1.7% of the US population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018ł); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017); £ U.S. and EU regulatory submissions for BBS and Alström syndrome filed in September and October 2021, respectively. € Planned EMANATE trial would include patients with variants classified as pathogenic, likely pathogenic or suspected pathogenic;

Phase 2 Daybreak Trial Designed to Evaluate Setmelanotide Across Genes with Strong Relevance to MC4R Pathway

Daybreak

Obesity and Hunger Clinical Trial

Relevance to MC4R Pathway: Rhythm's ClinGen-based framework suggests genes have very strong relevance to MC4R Pathway

Efficient, two-stage trial design

- **16-week, open-label run-in** in allows for fast signal-seeking in individual gene cohorts
- **24-week, double-blind treatment** period enables robust proof of concept

Today: Stage 1 data

2H 2024: Stage 2, PBO-controlled data

Exploratory Phase 2 DAYBREAK Trial

Dorit Koren, MD, MTR

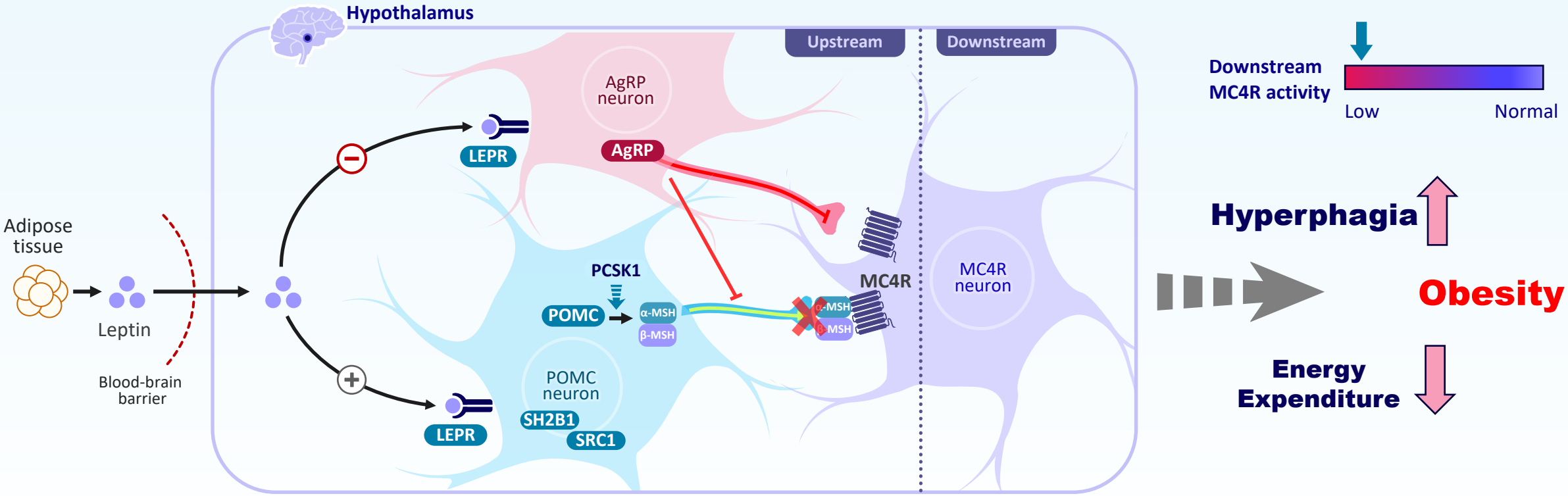
Patrick Sleiman, PhD

Exploratory Phase 2 DAYBREAK Trial

Stage 1 Topline Data

Dorit Koren, MD, MTR

MC4R Pathway Biology is Clear and Strong: Regulates Hunger, Caloric Intake, Energy Expenditure and, Consequently, Body Weight[1-4]



AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

1. Abuzzahab et al. *Horm Res Paediatr.* 2019;91:128-136. **2.** Erfurth. *Neuroendocrinology.* 2020;110:767-779. **3.** Rose et al. *Obesity (Silver Spring).* 2018;26:1727-1732. **4.** Roth. *Front Endocrinol (Lausanne).* 2011;2:49.

Rhythm® PHARMACEUTICALS

First MC4R Pathway Genes Related to Obesity

Approved

POMC

PCSK1

BBS1-21

LEPR

IMCIVREE®
(setmelanotide) injection

Phase 3

SRC1

SH2B1

h-LEPR

h-POMC

h-PCSK1

Emanate
Obesity and Hunger Clinical Trial

Validated Gene Selection Methodology[1,2] Led to Initial Selection of ~30 Genes for Exploratory Phase 2 DAYBREAK Study

Gene expression

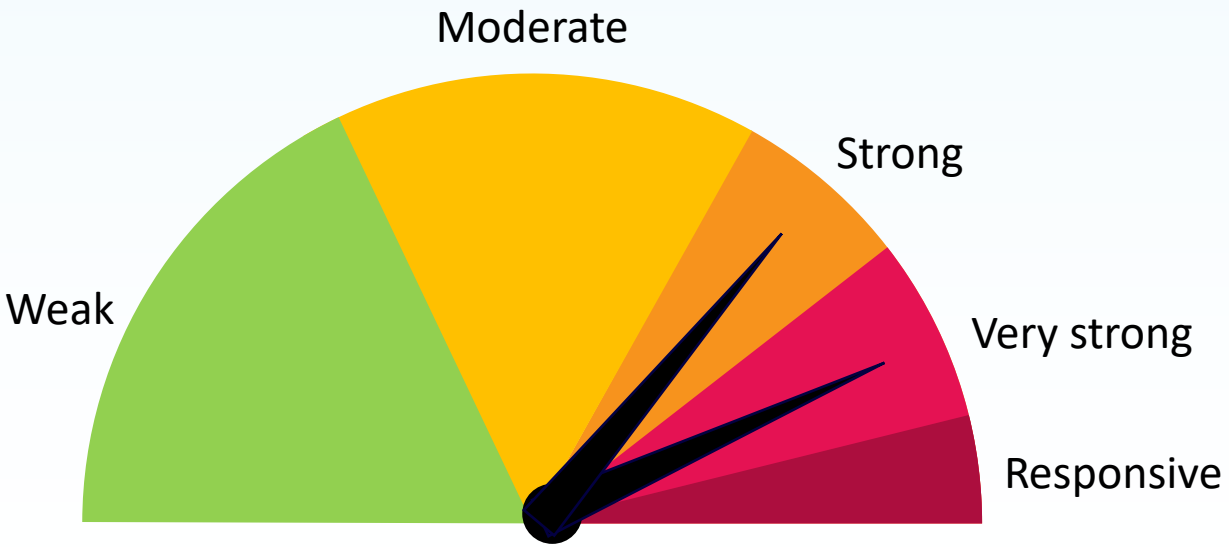
Cellular and molecular function

Physiological function

Functional rescue

Obesity-related epidemiology

Clinical response



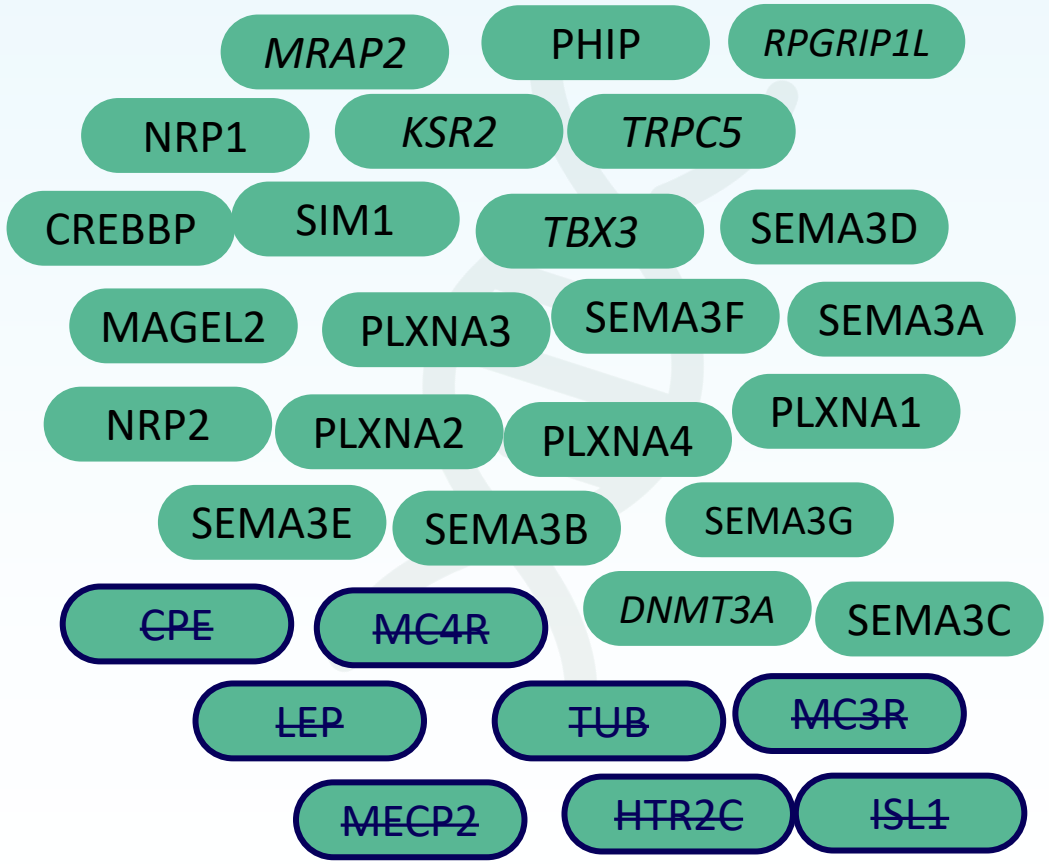
MC4R, melanocortin-4 receptor.

1. Strande et al. *Am J Hum Genet.* 2017;100:895-906. **2.** Vogel et al. Poster presented at: American College of Medical Genetics and Genomics (ACMG)Annual Clinical Genetics Meeting; March 22-26, 2022.

Phase 2 DAYBREAK Trial Designed to Evaluate Setmelanotide Across Genes with Strong Relevance to MC4R Pathway

Daybreak

Obesity and Hunger Clinical Trial



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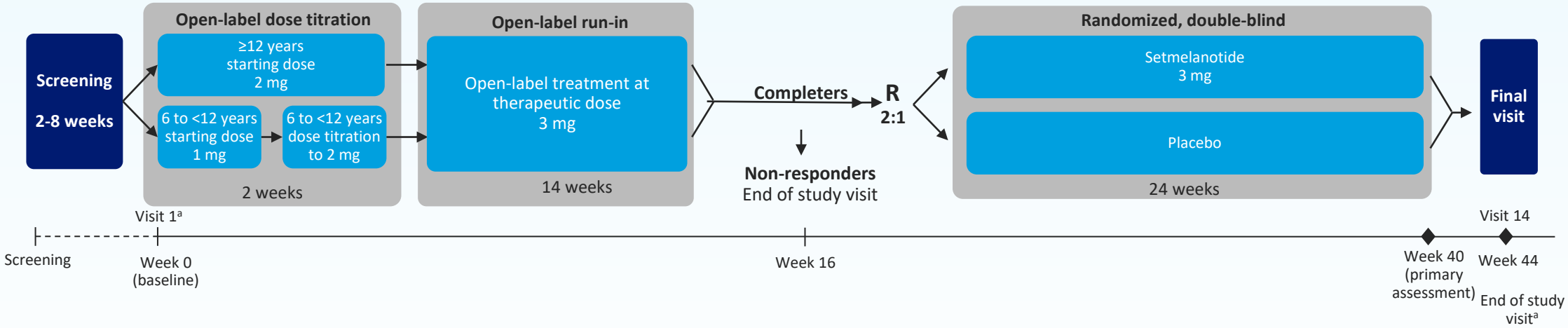
DAYBREAK 2-Stage Design: 16-Week Run-in Followed by 24-week Randomized Withdrawal and Double-blind, Placebo-controlled

Stage 1: Open-label Run-in

Stage 2: Double-blind, Placebo-controlled



Eligibility criteria:

- Genetic confirmation in patients 6-65 years
- Obesity: BMI ≥40 kg/m2 (adults ≥18 years) or BMI ≥97th percentile for age and sex (children <18 years)

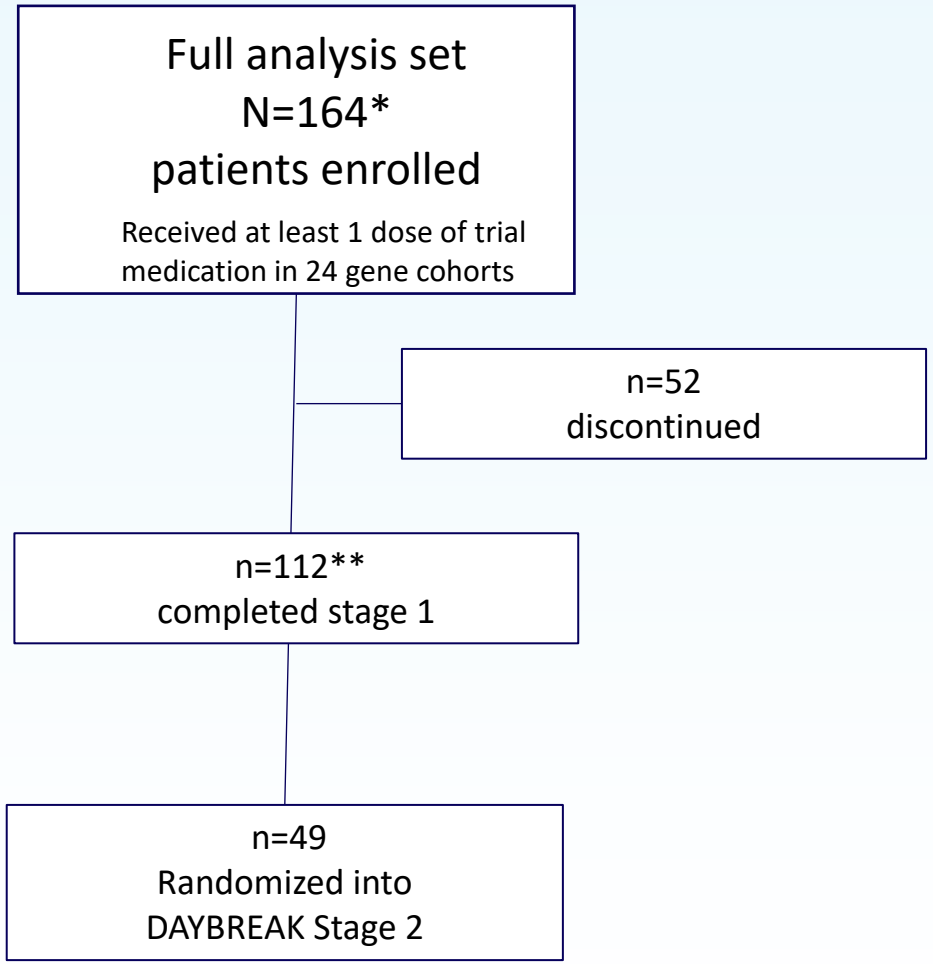
Primary Endpoint: proportion of patients by genotype who achieve a BMI reduction of ≥5% from baseline in response to setmelanotide at the end of Stage 1

[a]Virtual visit. R, randomization.

Baseline Demographics

Parameter	Total N=164
Mean age at baseline (± standard deviation SD)	30.2 (±16.9)
Male n (%)	54 (32.9%)
Female n (%)	110 (67.1%)
Mean BMI at Baseline (kg/m^2) (± SD) (adults age ≥18 years)	48.5 (±8.1) (Range 40-74.4) n=109
Mean BMI-Z score at Baseline (±SD) (age <18 years)	2.6 (±0.4) n=55

DAYBREAK Patient Dispositions



*165 patients consented and enrolled and one discontinued before 1 dose;
** Includes 12 discontinued patients who withdrew prior to week 16 but had their end-of-study visit within 2 weeks of 16; their data is included in completer analyses.

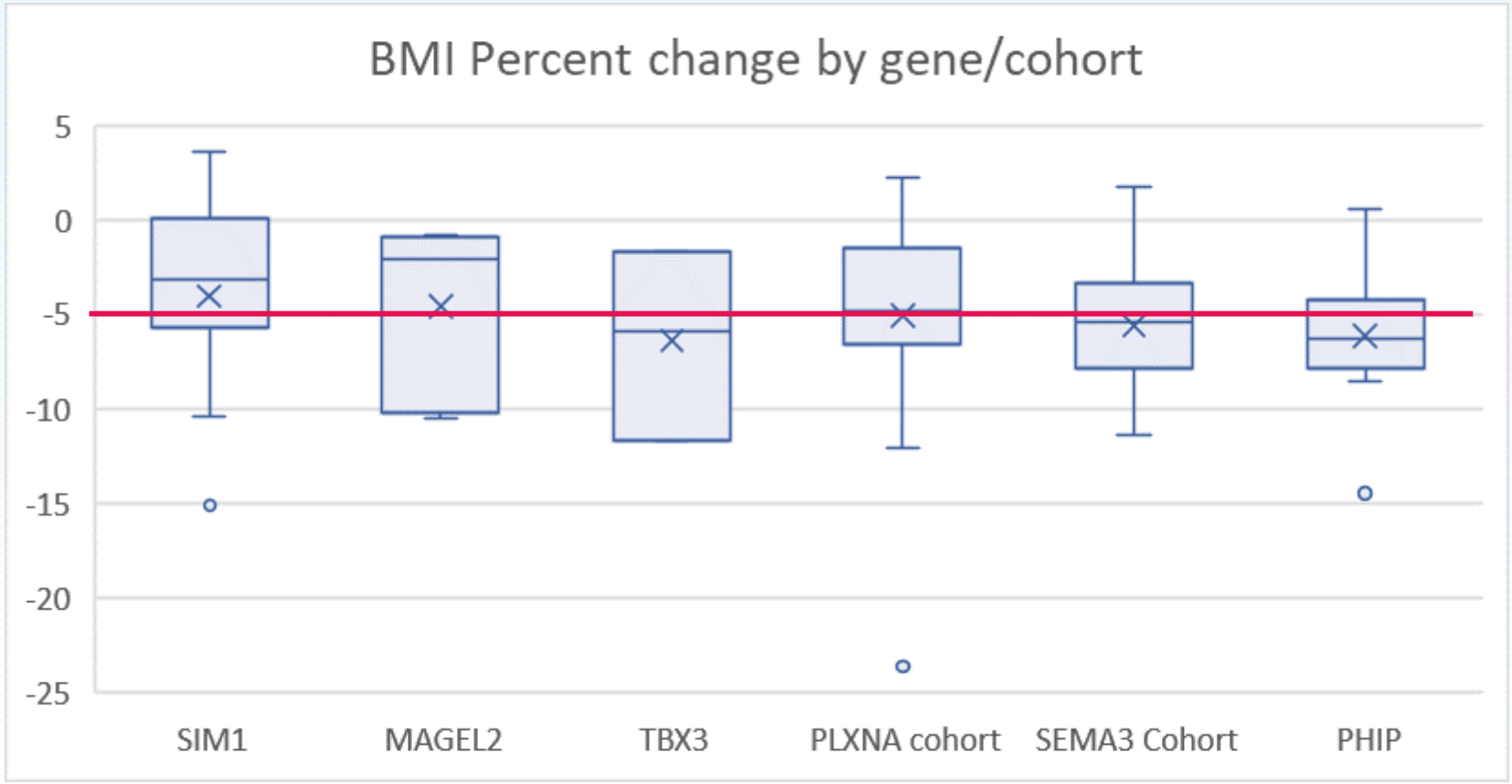
Potential Efficacy Observed Across Multiple Gene or Gene Group Cohorts in Full Analysis Set

Strongest Potential Efficacy in Most Patients Observed in *PHIP* and *SEMA3*

SEMA3	***PLXNA***	***PHIP***	***TBX3***	***MAGEL2***	***SIM1***
30% **(12 of 40)**	**35.6%** **(16 of 45)**	**56.3%** **(9 of 16)**	**40%** **(2 of 5)**	***30%*** ***(3 of 10)***	**25%** **(5 of 20)**

patients responded with ≥ **5% reduction in BMI** at 16 weeks

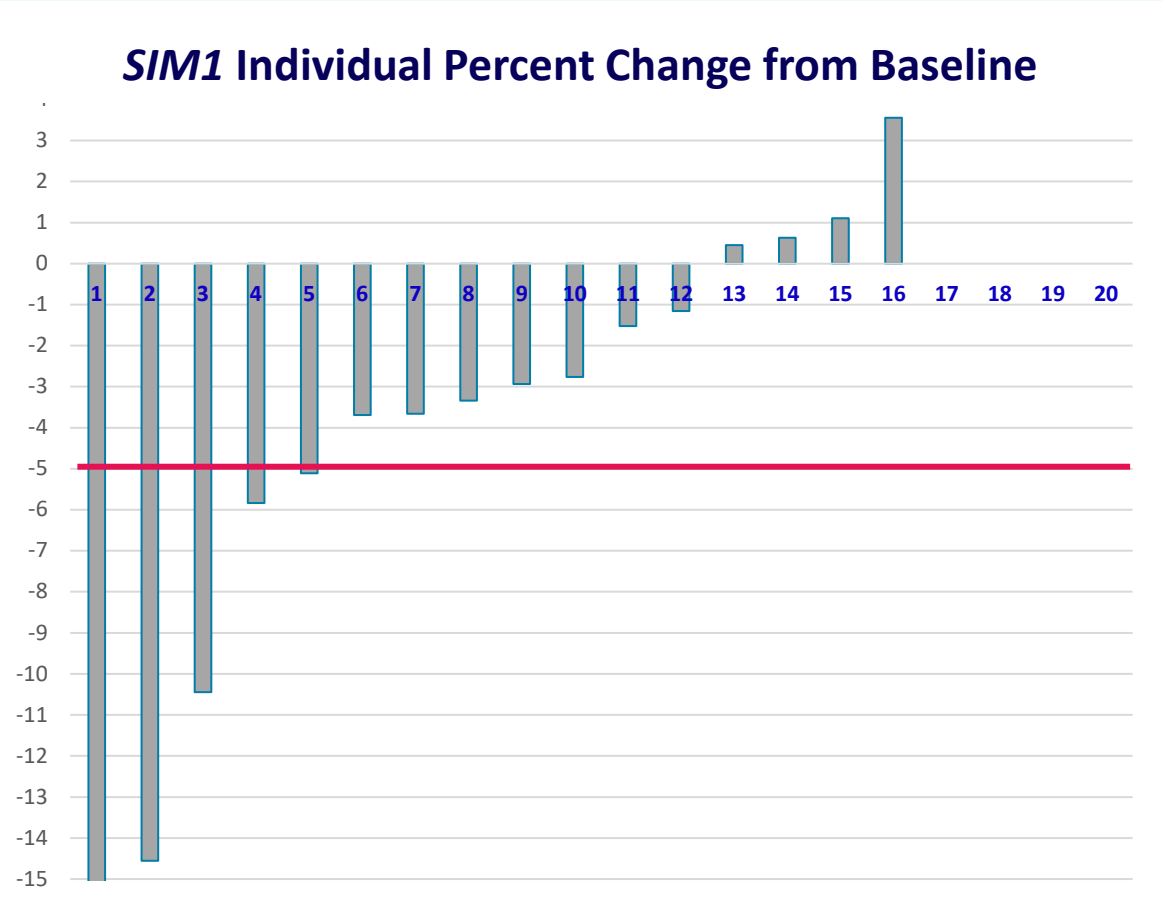
BMI % Change by Gene Cohort (Completers): *PHIP* Strongest, High Variability at 16 Weeks



Number, average and median BMI % change per gene/cohort

SIM1: (n=16)	MAGEL2: (n=7)	TBX3: (n=3)	PLXNA1-4: (n=27)	SEMA3A-G: (n=26)	PHIP: (n=13)
Mean: -4.02	Mean: -4.60	Mean: -6.41	Mean: -5.09	Mean: -5.60	Mean: -6.12
Median: -3.14	Median: -2.06	Median: -5.86	Median: -4.84	Median: -5.40	Median: -6.32

Completers with Variants in *SIM1* Gene Showed Low Responder Rate, Strong Response in a Few Individuals



SIM1

25%

(5 of 20)

patients responded with

≥ 5% reduction in BMI

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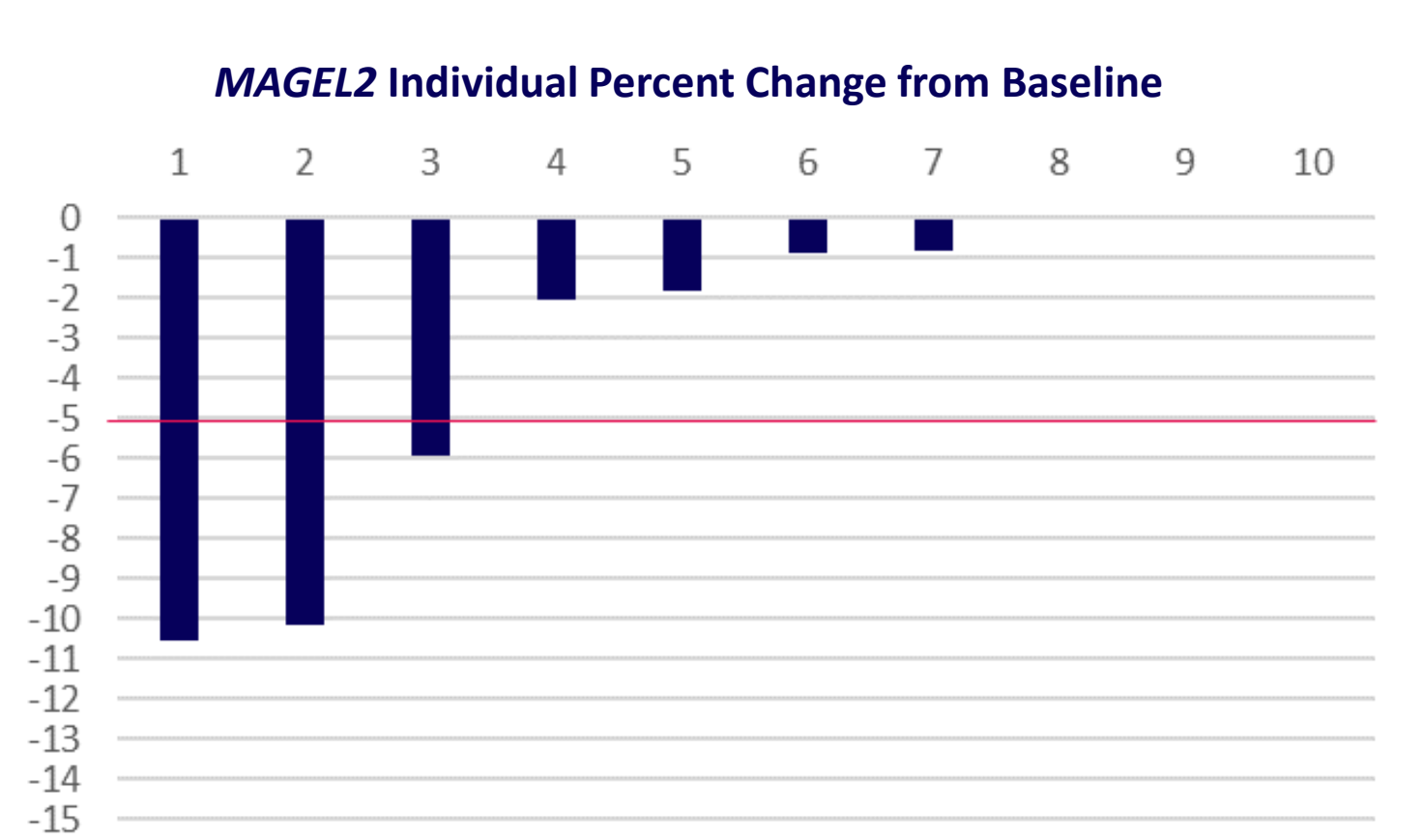
Individual Completers with Variants in *MAGEL2* Gene Showed Strong Response in Few Responders at 16 Weeks



MAGEL2

30%

(3 of 10)

patients responded with

≥ 5% reduction in BMI

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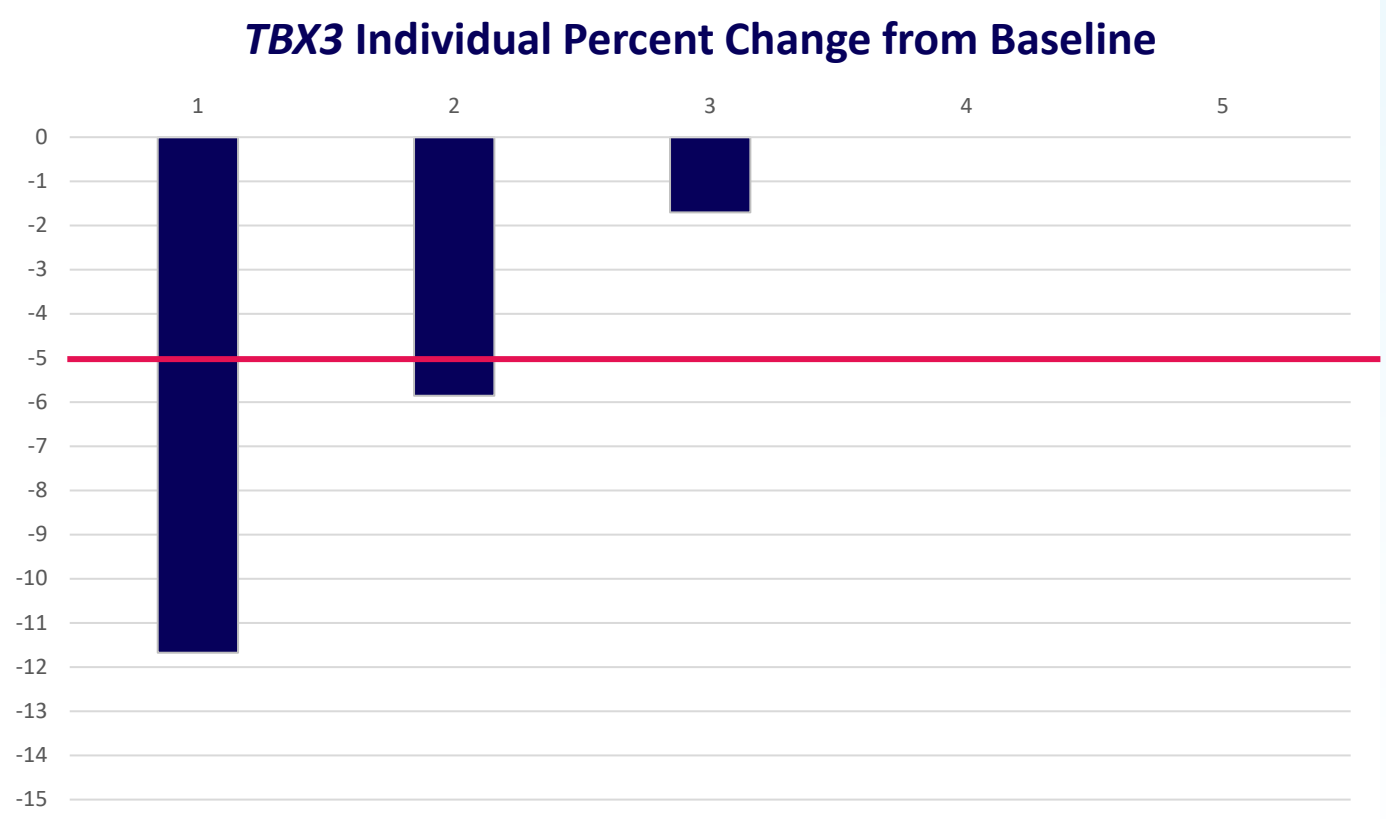
Small Number of Individual Completers with Variants of *TBX3* Gene Show BMI Reduction at 16 Weeks



TBX3

40%

(2 of 5)

patients responded with

≥ 5% reduction in BMI

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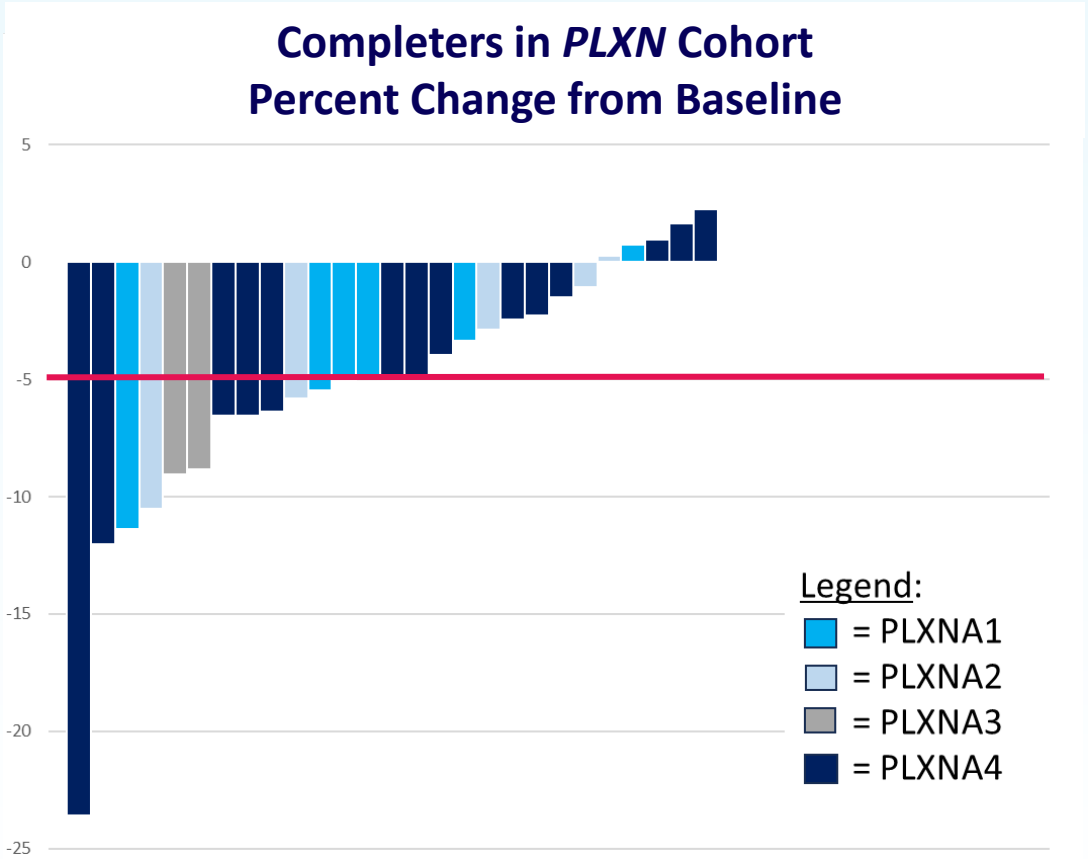
Completers in *PLXN* Genes Cohort Showed Strong Response with Variability



PLXNs

30%

(12 of 40*)

patients responded with

> 5% reduction in BMI

44.4%

(12 of 27)

completers responded with **≥ 5% reduction in BMI**

* Full analysis set.

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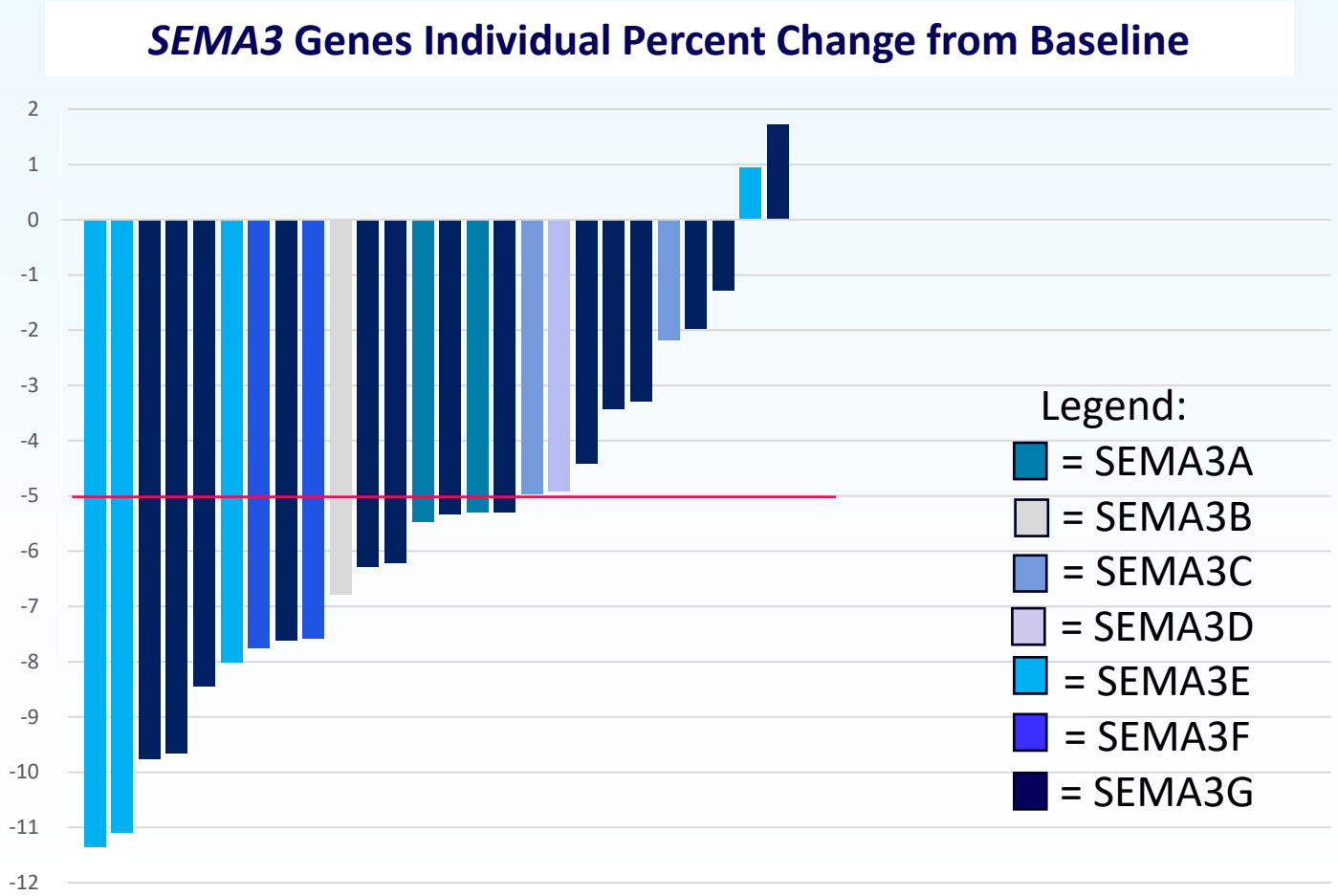
Majority of Completers with Variants in *SEMA3* Genes Showed Strong Response



* Full analysis set.

SEMA3s

35.6%

(16 of 45*)

patients responded with **> 5% reduction in BMI**

61.5%

(16 of 26)

completers responded with **≥ 5% reduction in BMI**

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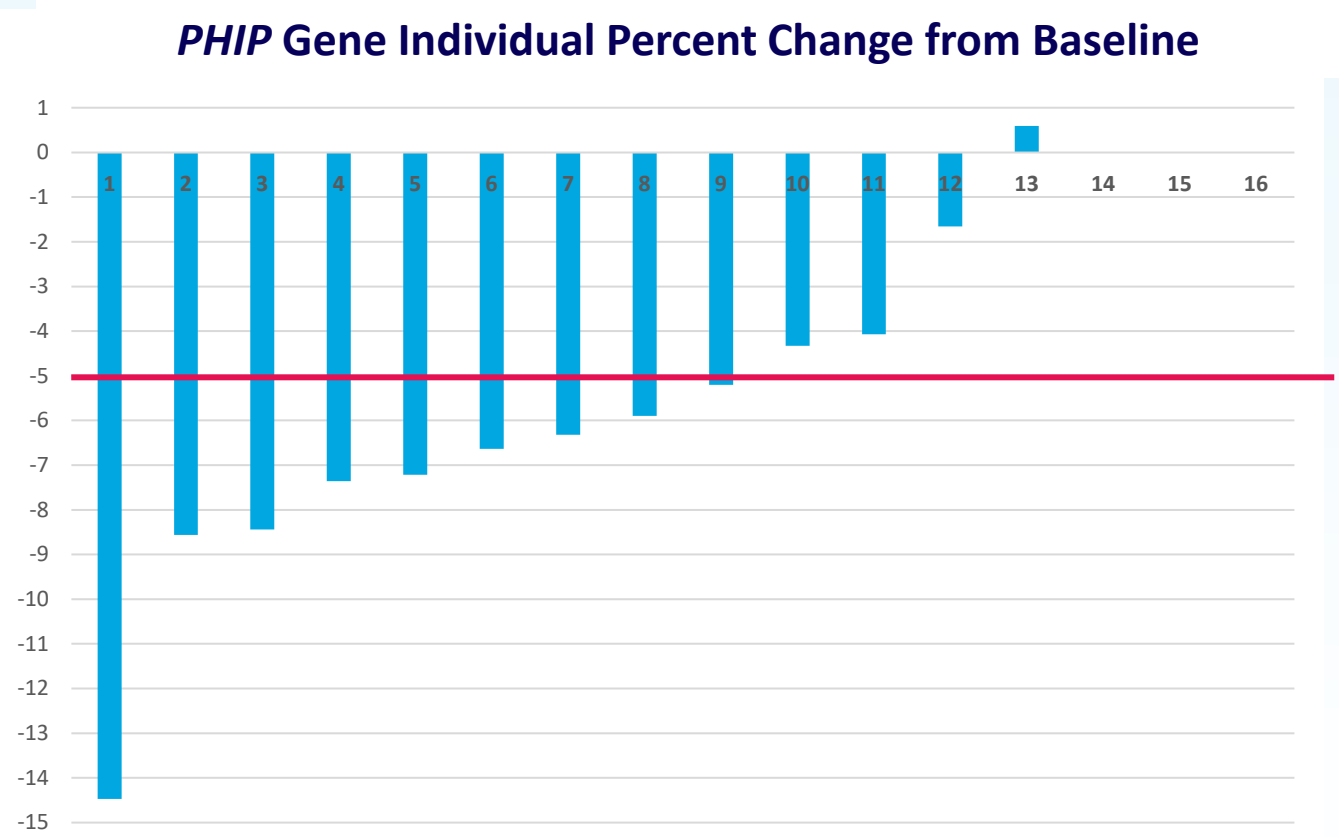
Nearly 70% of Completers with Variants in *PHIP* Gene Respond



PHIP

56.3%

(9 of 16*)

patients responded with

≥ 5% reduction in BMI

69.2%

(9 of 13)

completers responded with **≥ 5% reduction in BMI**

* Full analysis set.

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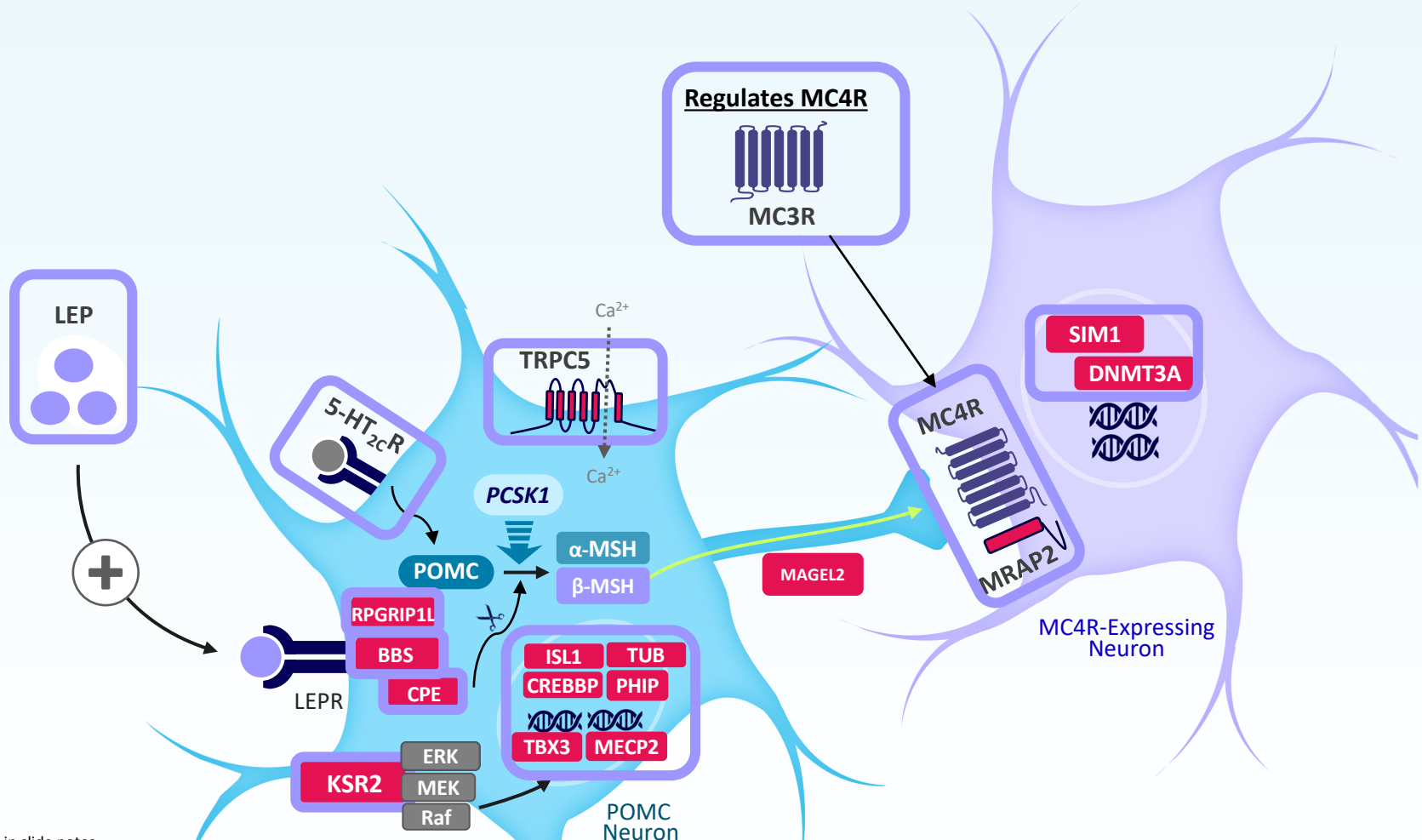
The Genetics behind the Exploratory Phase 2 DAYBREAK Trial

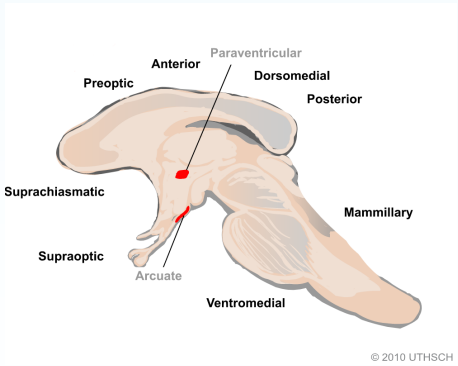
Patrick Sleiman, PhD

Summary of Genes in DAYBREAK Trial[1-28]



Regulates development of hypothalamic neurons and their projections

NRP1	SEMA3A
NRP2	SEMA3B
PLXNA1	SEMA3C
PLXNA2	SEMA3D
PLXNA3	SEMA3E
PLXNA4	SEMA3F
	SEMA3G



Abbreviations are in slide notes.

1. Nyamugenda et al. *iScience.* 2020;23:101114. **2.** Yazdi et al. *PeerJ*. 2015;3:e856. **3.** Srisai et al. *Nat Commun.* 2017;8:713. **4.** Chan et al. *Proc Natl Acad Sci U S A.* 2009;106:6146-6151. **5.** Yazdi et al. *PeerJ*. 2015;3:e856. **6.** Pearce et al. *Cell.* 2013;155:765-777. **7.** Guo et al. *Mol Metab.* 2016;6:194-205. **8.** Revelli et al. *Obesity (Silver Spring).* 2011;19:1010-1018. **9.** Lam et al. *Endocrinology*. 2008;149:1323-1328. **10.** Cawley et al. *Endocr Rev.* 2012;33:216-253. **11.** Moreno et al. *PLoS One.* 2016;11:e0166381. **12.** Harris et al. *J Clin Invest.* 2001;107:111-120. **13.** MacKay et al. *Nat Commun.* 2019;10:5364. **14.** Kohno et al. *J Neurosci.* 2014;34:15288-15296. **15.** Lee et al. *Development.* 2016;143:3763-3773. **16.** Nasif et al. *Proc Natl Acad Sci U S A.* 2015;112:E1861-E1870. **17.** Mercer et al. *PLoS Genet.* 2013;9:e1003207. **18.** Pravdivyi et al. *Hum Mol Genet.* 2015;24:4276-4283. **19.** Ghamari-Langroudi et al. *Sci Adv.* 2018;4:eaat0866. **20.** Calton et al. *Hum Mol Genet*. 2009;18:1140-1147. **21.** Wang et al. *Diabetologia.* 2014;57:236-245. **22.** van der Klaauw et al. *Cell.* 2019;176:729-742.e18. **23.** Marenne et al. *Cell Metab.* 2020;31:1107-1119.e12. **24.** Proenca da Fonseca et al. *J Diabetes Complications*. 2017;31:1549-1561. **25.** Beck et al. *J Biol Chem.* 2013;288:19471-19483. **26.** Gao et al. *Cell Rep.* 2017;18:583-592. **27.** Quarta et al. *Nat Metab.* 2019;1:222-235. **28.** Stratigopoulos et al. *Cell Metab.* 2014;19:767-779.

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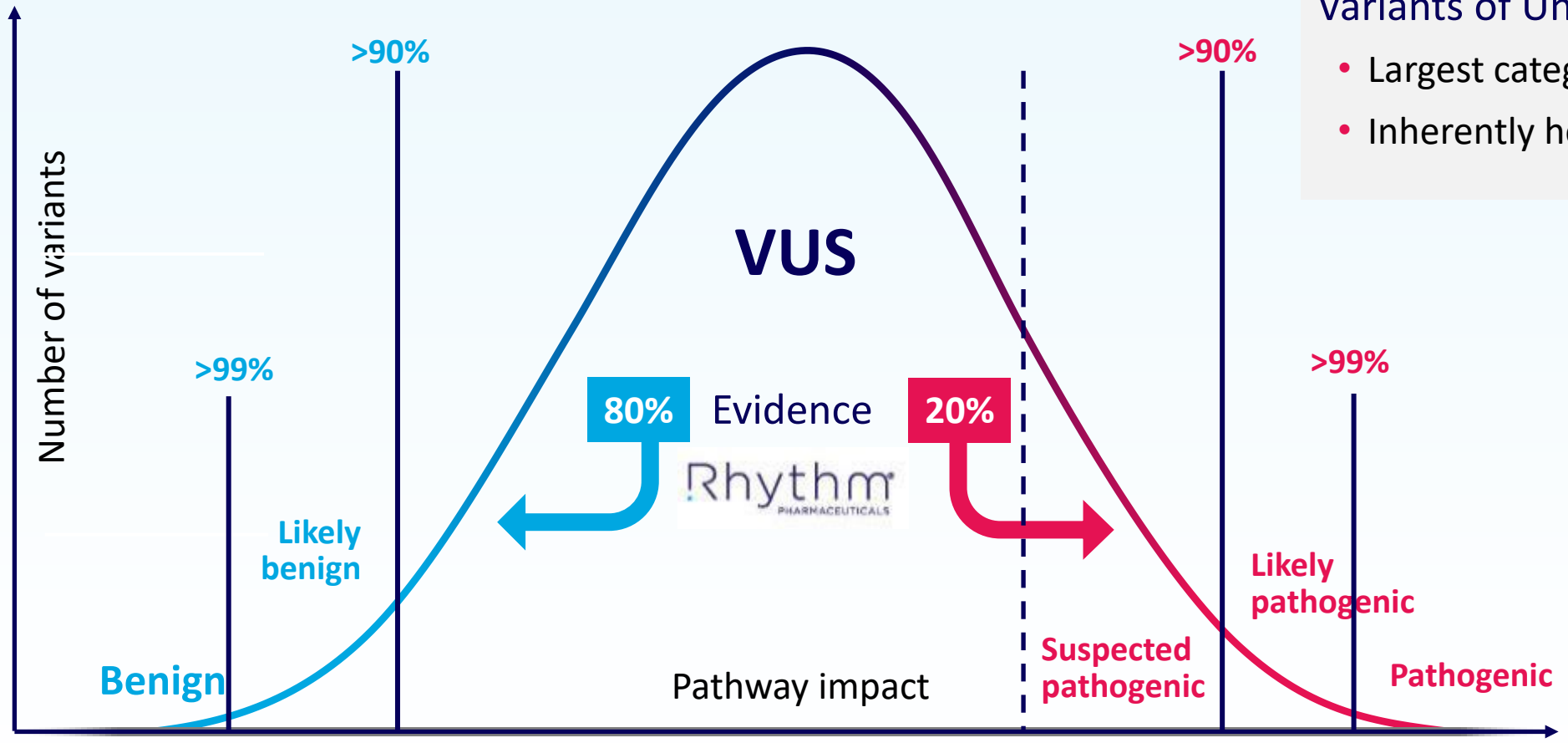
ACMG Variant Classification Can Inform MC4R Pathway Deficit and Potentially Setmelanotide Response

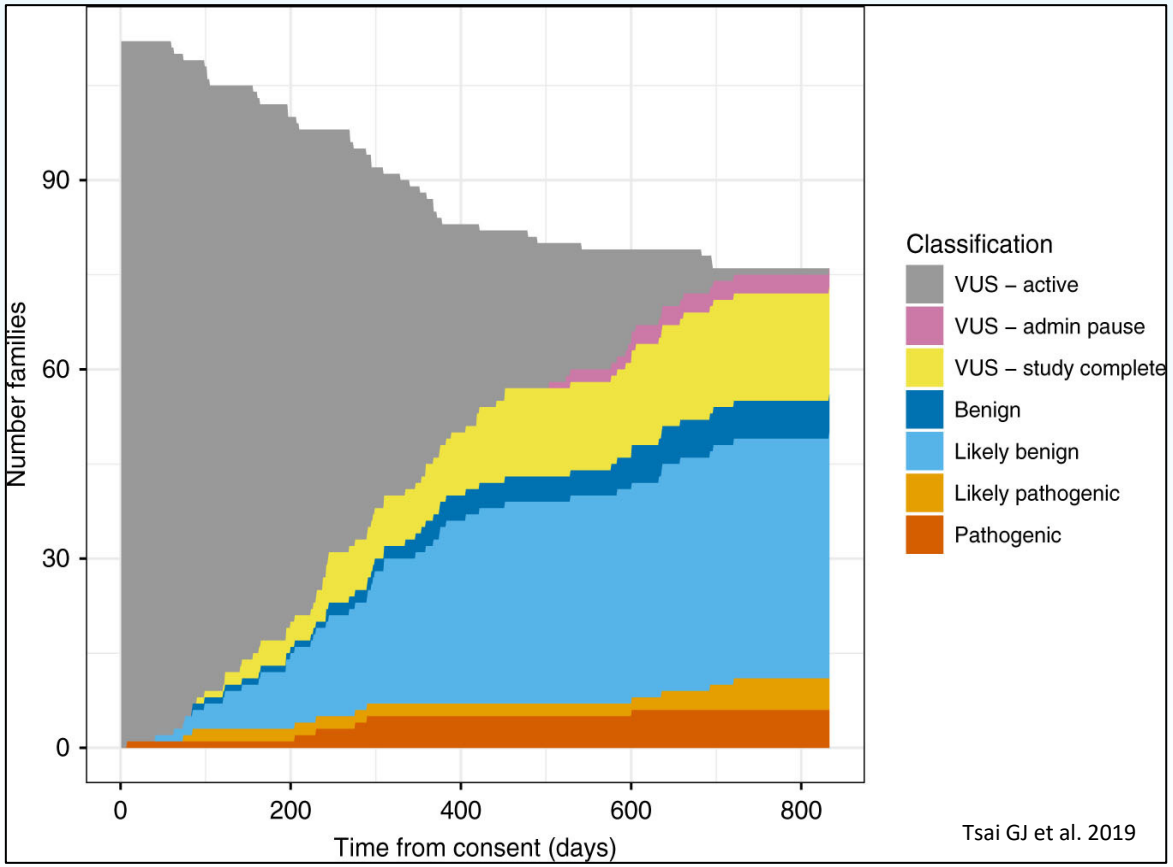


Variants of Uncertain Significance

- Largest category of rare variants
- Inherently heterogeneous

*ACMG Guidelines Richards et al, 2015

~80% of VUS Re-classifications are to Likely Benign or Benign



Sources of evidence that enable VUS resolution include:

- New data resources (e.g. frequency data gnomAD)
- New tools – (prediction algorithms e.g. SpliceAI)
- Testing family members
- Functional data (*in vitro* assays, MAVEs)

Kobayashi et al., ASHG 2023
Tsai et al., Genet Med. 2019 Jun;21(6):1435-1442.
Harrison et al., Genome Medicine **volume 11**, Article number: 72 (2019)

Functional Characterization of Missense Variants in the *POMC, PCSK1, LEPR* Genes has Resulted in the Reclassification of 90 VUS Variants

Original Research

Functional characterization of all missense variants in *LEPR*, *PCSK1*, and *POMC* genes arising from single-nucleotide variants

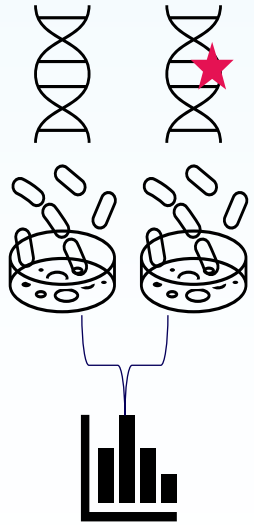
Bhavik P. Shah, Patrick M. Sleiman, Jessica Mc Donald, Ida H. Moeller & **Patrick Kleyn**

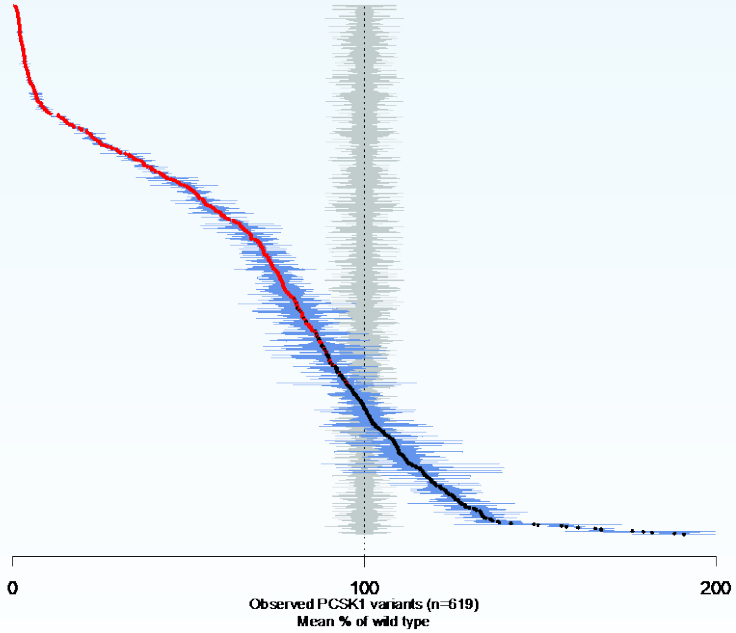
Received 23 Dec 2022, Accepted 09 Feb 2023, Accepted author version posted online: 16 Feb 2023

Download citation https://doi.org/10.1080/17446651.2023.2179985 Check for updates

Functional characterization

- Assess impact of variants directly on protein function
- Evaluate contribution of variant to disease and potentially Setmelanotide response
- High throughput
- Assist clinical genetic laboratories in reclassifying VUS variants





Results of *in vitro* functional assays across all theoretical and observed 619 missenses in *PCSK1*

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SEMA3G: Five *SEMA3G* Variants Reclassified from VUS or LP to B/LB During Trial by Prevention Genetics According to ACMG Criteria

Ad hoc analysis of patients with week 16 data at V7: N=112

Gene	Variant	Responder	Starting ACMG clasification	Recalssification	
SEMA3G	p.Ser25Arg	-9.8	VUS	VUS	
SEMA3G	p.Arg392Trp	-9.6	VUS	VUS	
SEMA3G	p.Asn127Lys	-8.4	VUS	Likely Benign	←
SEMA3G	p.Arg82Trp	-7.6	VUS	VUS	
SEMA3G	p.Ile674Thr	-6.3	VUS	VUS	
SEMA3G	p.Thr782Lys	-6.2	VUS	VUS	
SEMA3G	p.Arg167Trp	-5.3	VUS	VUS	
SEMA3G	p.Thr782Lys	-5.3	VUS	VUS	
SEMA3G	p.Arg91Trp	-4.4	Likely Pathogenic	Likely Benign	←
SEMA3G	p.Arg167Trp	-3.4	VUS	VUS	
SEMA3G	p.Arg169Trp	-3.3	Likely Pathogenic	Likely Benign	←
SEMA3G	p.Asp64Asn	-1.9	VUS	VUS	
SEMA3G	p.Arg91Trp	-1.3	Likely Pathogenic	Likely Benign	←
SEMA3G	p.Leu15Phe	1.7	VUS	Likely Benign	←

8/14 responders (57%)

7/9 responders (77.8%)

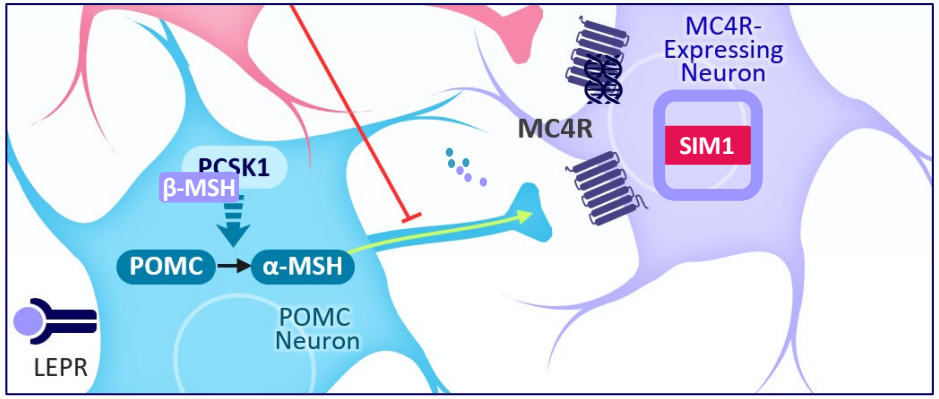
4/6 nonresponders reclassified to Likely Benign

SIM1 Variants Are Associated With Obesity[1-3]

SIM1 encodes a **transcription factor** that regulates **PVN development and function**[4-6]

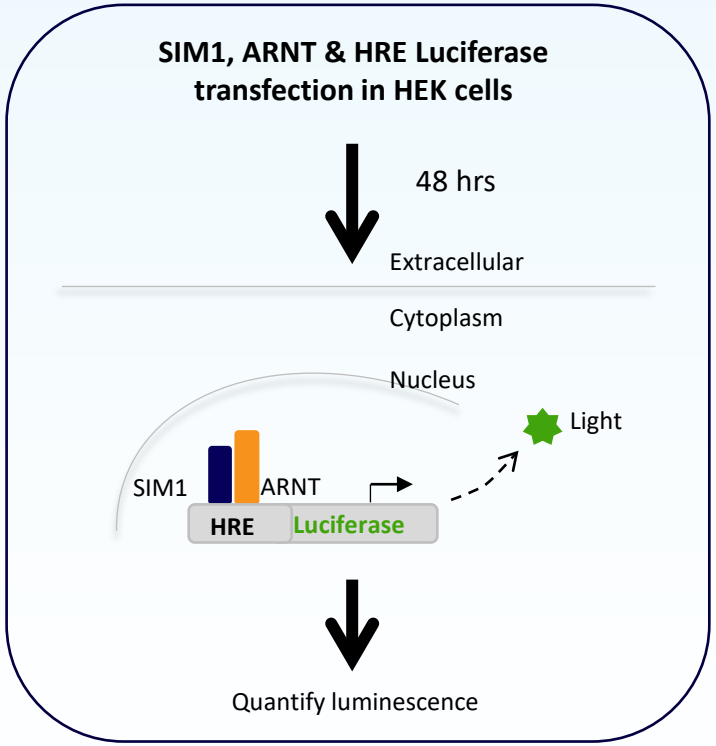
MC4R neurons express SIM1, which is **critical for** their **development**[7]

SIM1 in the MC4R Pathway[8,9]



in vitro biological assay of *SIM1*

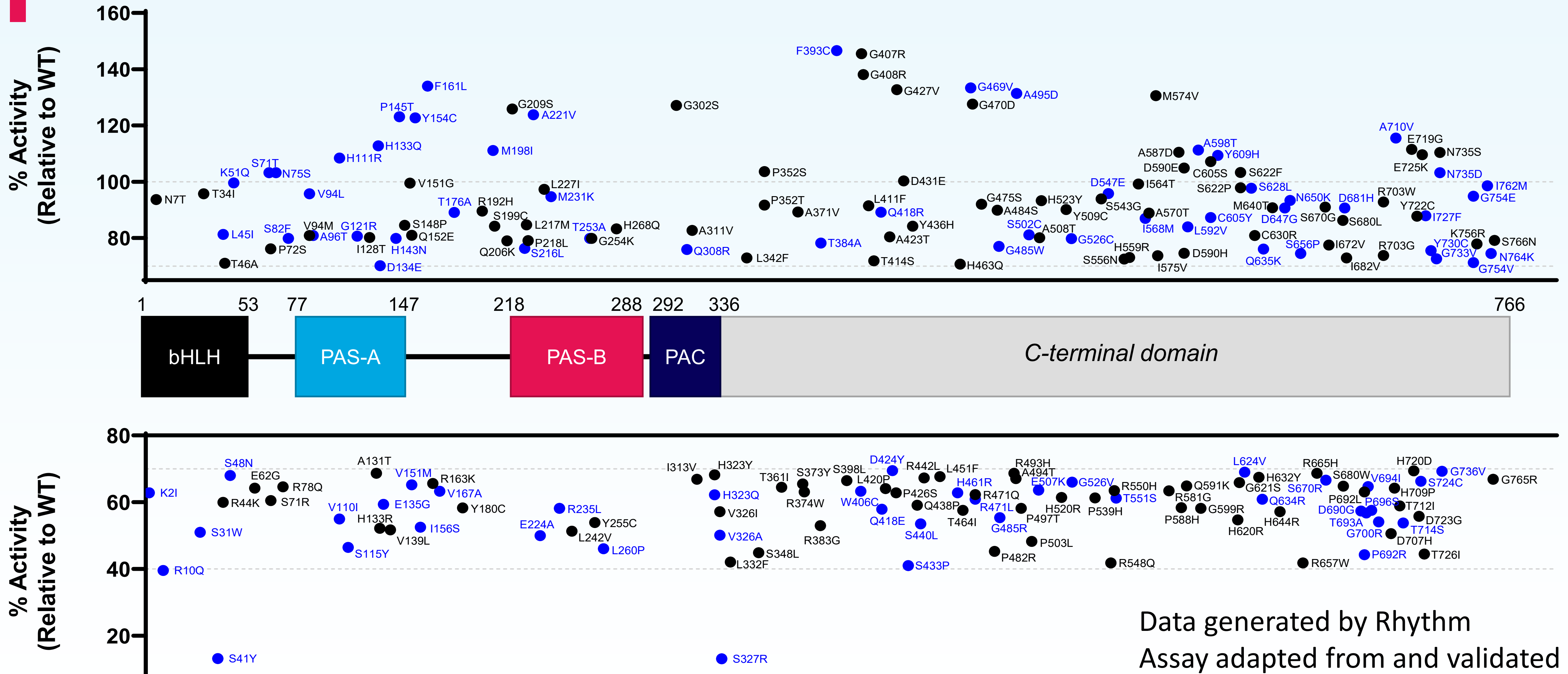
Quantifies effect of mutations on protein function



Adapted and validated against Bonnefond et al.[a] Ramachandrappa et al.[b], Sullivan et al.[c], Zegers et al.[d]

1. Ackinci et al. *J Clin Res Pediatr Endocrinol.* 2019;11:341-349. **2.** Swarbrick et al. *Obesity (Silver Spring).* 2011;19:2394-2403. **3.** Montagne et al. *Obesity.* 2014;22:2621-2624. **4.** Shah et al. *Proc Natl Acad Sci U S A.* 2014;111:13193-13198. **5.** Michaud et al. *Genes Dev.* 1998;12:3264-3275. **6.** Michaud et al. *Hum Mol Genet.* 2001;10:1465-1473. **7.** Li et al. *Neuron.* 2019;102:653-667.e6. **8.** Nyamugenda et al. *iScience.* 2020;23:101114. **9.** Yazdi et al. *PeerJ.* 2015;3:e856.

Functional Characterization of 213 *SIM1* Missense Variants



[1]Bonnefond et al. J Clin Invest. 2013;123:3037-3041. [2]Ramachandrappa et al. J Clin Invest. 2013;123:3042-3050.
[3] Sullivan et al. Biochem J. 2014;461:403-412. [4]Zegers et al. Int J Obes. 2014;38:1000-1004

Data generated by Rhythm
Assay adapted from and validated against published data[1-4]

Loss of Function *SIM1* Variants Enriched in Responder Group

Gene	% BMI Δ BL	Variant	ACMG	Published Functional assays[1,2]	Rhythm Functional assay
SIM1	-15.1	p.Asp707His	VUS	[1]Moderately Damaging	Moderate LOF
SIM1	-14.5	p.Thr712Ile	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-10.4	p.Ser71Arg	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-5.8	p.Glu14Asp	VUS	NA	NA
SIM1	-5.1	p.Leu238Arg	VUS-SP	[1]Severely Damaging	NA
SIM1	-3.7	p.Thr712Ile	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-3.6	GT donor	VUS-SP	NA	NA
SIM1	-3.3	p.Asp707His	VUS	[1]Moderately Damaging	Moderate LOF
SIM1	-2.9	p.Pro352Ser	VUS	NA	WT
SIM1	-2.8	p.Leu479Pro	VUS	NA	NA
SIM1	-1.5	p.Arg550His	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-1.2	p.Gln152Glu	VUS	[2]Mild effect	WT
SIM1	0.4	p.Ser680Leu	VUS	[1]Uncertain	WT
SIM1	0.6	p.Ile564Thr	VUS	NA	WT
SIM1	1.1	p.Asp707His	VUS	[1]Moderately Damaging	Moderate LOF
SIM1	3.6	p.Gly302Ser	VUS	NA	WT

Responders:
4/5 variants assayed
All (100%) display Loss of Function

Non-responders:
9/11 variants assayed
5/9 (56%) show Wild-Type activity

Excluding WT variants SIM1 response rate increases from 31% (5/16) to 45% (5/11)

p.Asp707His: Moderately damaging variant of variable penetrance[1]

1. Ramachandrappa,.. Farooqi Rare variants in single-minded 1 (SIM1) are associated with severe obesity J Clin Invest . 2013 Jul;123(7):3042-50. PMID: 23778139
2. Bonnefond,.. Froguel Loss-of-function mutations in SIM1 contribute to obesity and Prader-Willi–like features J Clin Invest. 2013 Jul 1; 123(7): 3037–3041.

Loss of Function *SIM1* Variants Enriched in Responder Group

Gene	% BMI Δ BL	Variant	ACMG	Published Functional assays[1,2]	Rhythm Functional assay
SIM1	-15.1	p.Asp707His	VUS	[1]Moderately Damaging	Moderate LOF
SIM1	-14.5	p.Thr712Ile	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-10.4	p.Ser71Arg	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-5.8	p.Glu14Asp	VUS	NA	NA
SIM1	-5.1	p.Leu238Arg	VUS-SP	[1]Severely Damaging	NA
SIM1	-3.7	p.Thr712Ile	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-3.6	GT donor	VUS-SP	NA	NA
SIM1	-3.3	p.Asp707His	VUS	[1]Moderately Damaging	Moderate LOF
SIM1	-2.9	p.Pro352Ser	VUS	NA	WT
SIM1	-2.8	p.Leu479Pro	VUS	NA	NA
SIM1	-1.5	p.Arg550His	VUS	[1]Severely Damaging	Moderate LOF
SIM1	-1.2	p.Gln152Glu	VUS	[2]Mild effect	WT
SIM1	0.4	p.Ser680Leu	VUS	[1]Uncertain	WT
SIM1	0.6	p.Ile564Thr	VUS	NA	WT
SIM1	1.1	p.Asp707His	VUS	[1]Moderately Damaging	Moderate LOF
SIM1	3.6	p.Gly302Ser	VUS	NA	WT

Responders:
4/5 variants assayed
All (100%) display Loss of Function

Non-responders:
9/11 variants assayed
5/9 (56%) show Wild-Type activity

Excluding WT variants SIM1 response rate increases from 31% (5/16) to 45% (5/11)

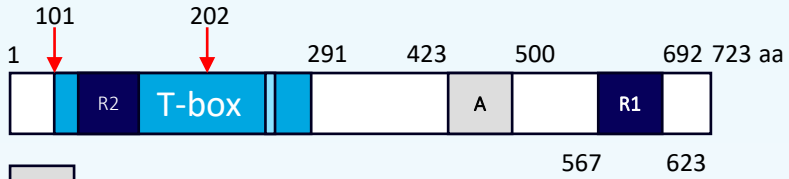
p.Asp707His: Moderately damaging variant of variable penetrance[1]

1. Ramachandrappa,.. Farooqi Rare variants in single-minded 1 (SIM1) are associated with severe obesity J Clin Invest . 2013 Jul;123(7):3042-50. PMID: 23778139
2. Bonnefond,.. Froguel Loss-of-function mutations in SIM1 contribute to obesity and Prader-Willi–like features J Clin Invest. 2013 Jul 1; 123(7): 3037–3041.

Variants in *TBX3* Cause Ulnar-Mammary Syndrome and Obesity[1,4]

TBX3

TBX3 encodes a **transcription factor** that **directs postnatal neuronal fate**[1-4]



A Activation Domain

R Repression Domains

T-box DNA binding domain [6]

Disease associated missense mutations map to highly conserved DNA binding domain (T-box)[7]

TBX3 is critical for **defining peptidergic identity (POMC, AgRP/NPY) of neurons** in the melanocortin pathway; disruptions in *TBX3* may affect energy balance[3,4]

Loss of TBX3 leads to decrease in POMC neurons[3-5]

Responders carry mutations that map to T-box.
Functionally rescuing reduced expression of target

Gene	Variant	ACMG	% BMI Δ BL
TBX3	p.Val202Ile	VUS	-11.6
TBX3	p.Asp101Glu	VUS	-5.8
TBX3	p.Lys91Arg	VUS	-1.7
TBX3	p.Met608Leu	VUS	Discon
TBX3	p.Asn514Ser	VUS	Discon

AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; TBX3, T-Box 3.

1. Galazzi et al. *Endocr Connect.* 2018;7:1432-1441. **2.** Bamshad et al. *Am J Hum Genet.* 1999;64:1550-1562. **3.** Sanz et al. *J Neurosci.* 2015;35:5549-5556. **4.** Quarta et al. *Nat Metab.* 2019;1:222-235. **5.** Yazdi et al. *PeerJ.* 2015;3:e856. **6.** Coll et al., Structure Vol. 10, 343–356, 2002. **7.** Shi et al., Science Advances 16 Nov 2022 Vol 8, Issue 46

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Ad Hoc Analysis of Primary Endpoint, Responder Rate of Participants with Week 16 Data with BMI Reduction ≥5% at Week 16

Gene	Response rate of Completers	PG ACMG reconfirmation	Estimated US prevalence*	Presentation
Overall	43.8% (n=112)	45.6% (48.5%) **(n=101)**	-	---
SEMA3 family	61% (n=26)	72% **(n=21)**	~25,000	Monogenic [1]
PHIP	69.2% (n=13)	69.2% **(n=13)**	~4,000	Chung-Jansen Syndrome [2]
TBX3	66.7% (n=3)	66.7% (100%) **(n=3 or (2))**	~2,300	Ulnar-Mammary Syndrome [3]
PLXN family	44% (n=27)	44% **(n=27)**	~34,000	Monogenic [1]

*U.S. prevalence estimates based on results from Rhythm's Uncovering Rare Obesity genetic program with samples from more than 36,000 participants, classification of variants for pathogenic, likely pathogenic and 20% of VUS and applied to established estimate of approximately 5 million people in the US with early-onset obesity; **1.** van der Klaauw et al. *Cell*. 2019;176:729-742.e18. **2.** Marenne et al. *Cell Metab.* 2020;31:1107-1119.e12. **3.** Bamshad et al. *Am J Hum Genet.* 1999;64:1550-1562 **4.** Patak et al. *Clin Genet.* 2019;96:493-505. **5.** McCarthy et al. *Am J Med Genet A.* 2018;176:2564-2574. **6.** Ackinci et al. *J Clin Res Pediatr Endocrinol.* 2019;11:341-349. **7.** Swarbrick et al. *Obesity.* 2011;19:2394-2403

Introduction to RM-718

Danica Grujic, PhD

RM-718: Next-generation, Potentially More Selective MC4R Agonist

Phase 1 SAD, MAD studies anticipated to begin in 1H 2024

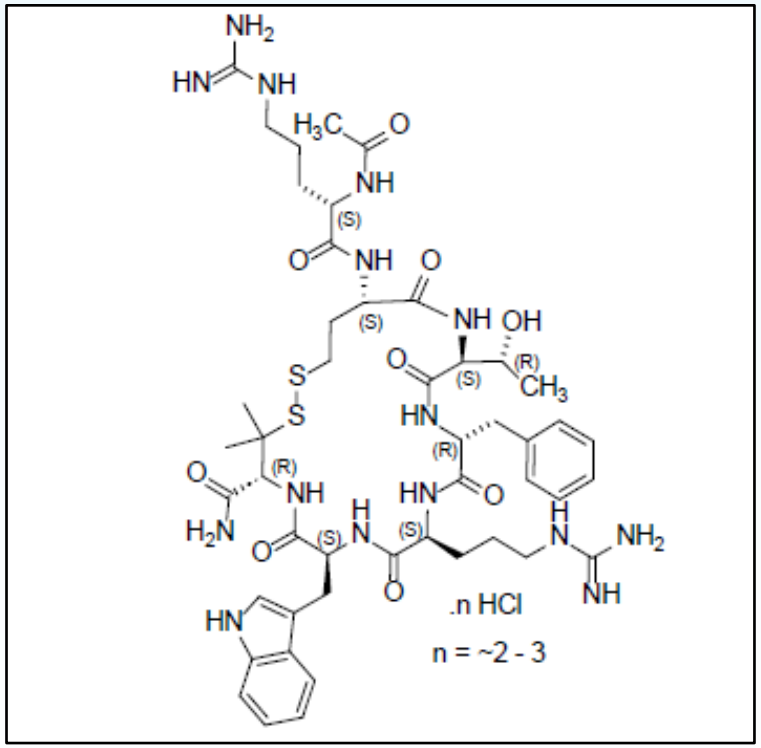
MC4R-specific, designed to be potentially more potent

MC1R-sparing, designed to eliminate hyperpigmentation effect

Weekly formulation with composition of matter **patent protection to 2041***

*Includes patent term adjustment and patent term extension.

Rhythm Set out to Develop Next-Gen Compound with Same or Better Efficacy than Setmelanotide



RM-718: Synthetic, cyclic 7-amino acid peptide (heptamer)

Rhythm library of compounds built closely around setmelanotide template and chemical space

Ten next-gen candidates (all peptides) identified with MC4R potency in vitro, as compared to setmelanotide

RM-718 was chosen due to MCR4 selectivity observed in vitro

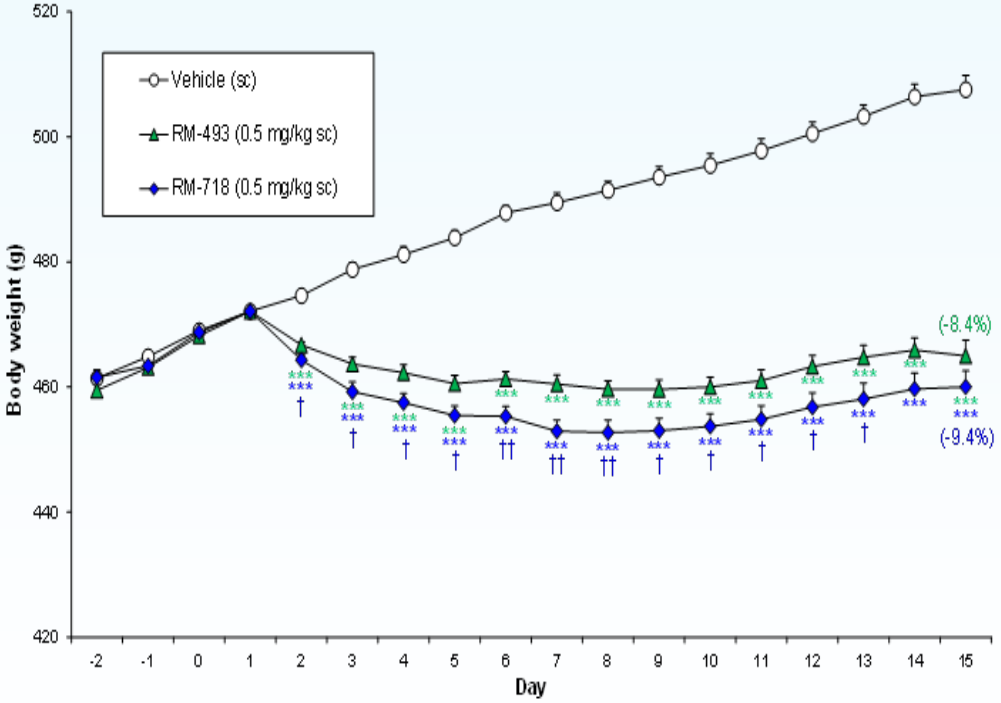
Designed to be MC1R sparing

Designed for sustained release for once-weekly injection

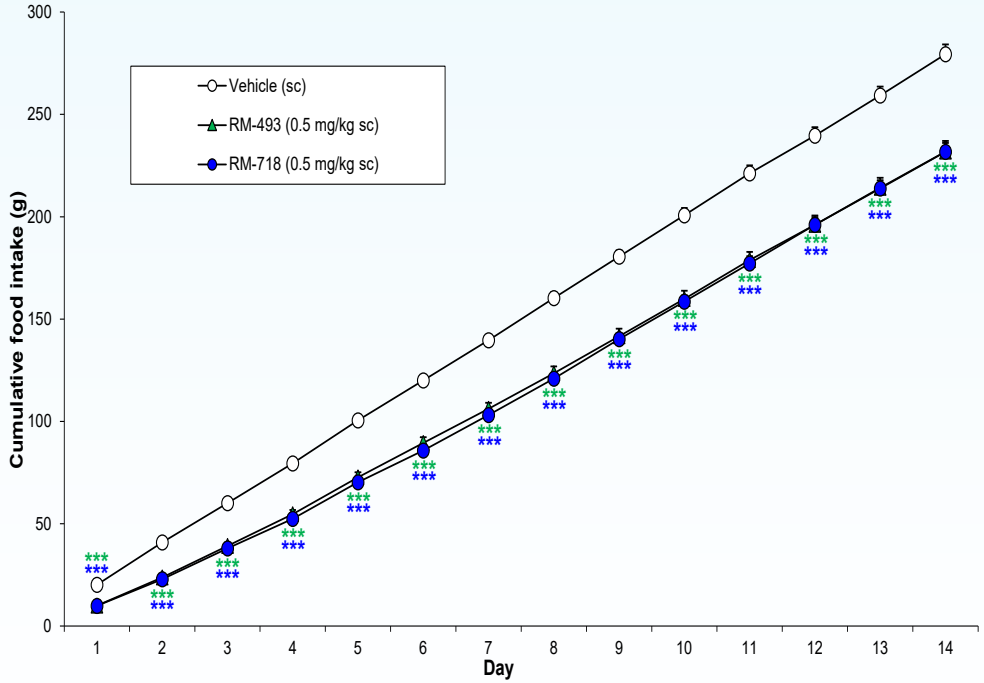
RM-718 Showed Comparable Activity to Setmelanotide on Body Weight and Food Intake Reduction in 14-day Study in DIO Rats

Study design: 3 arms (n=15): Control, Setmelanotide (RM-493) QD and RM-718 QD SC inj. 0.5mg/kg/day

Body Weight



Food Intake

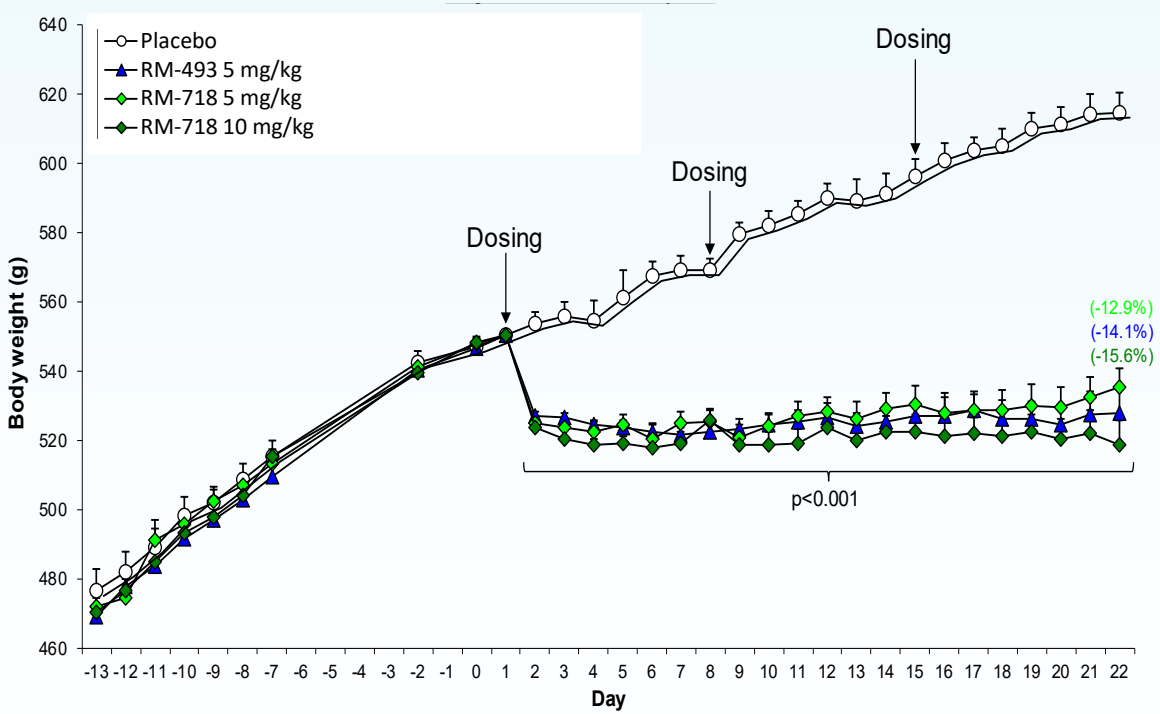


Shown is mean (sem) for n=15/group, ***p<0.001, significant difference vs vehicle, τ<0.05, significant difference RM-718 vs RM-493
Daily formulation of both setmelanotide (RM-493) and RM-718 were used in the study; DIO=diet induced obesity

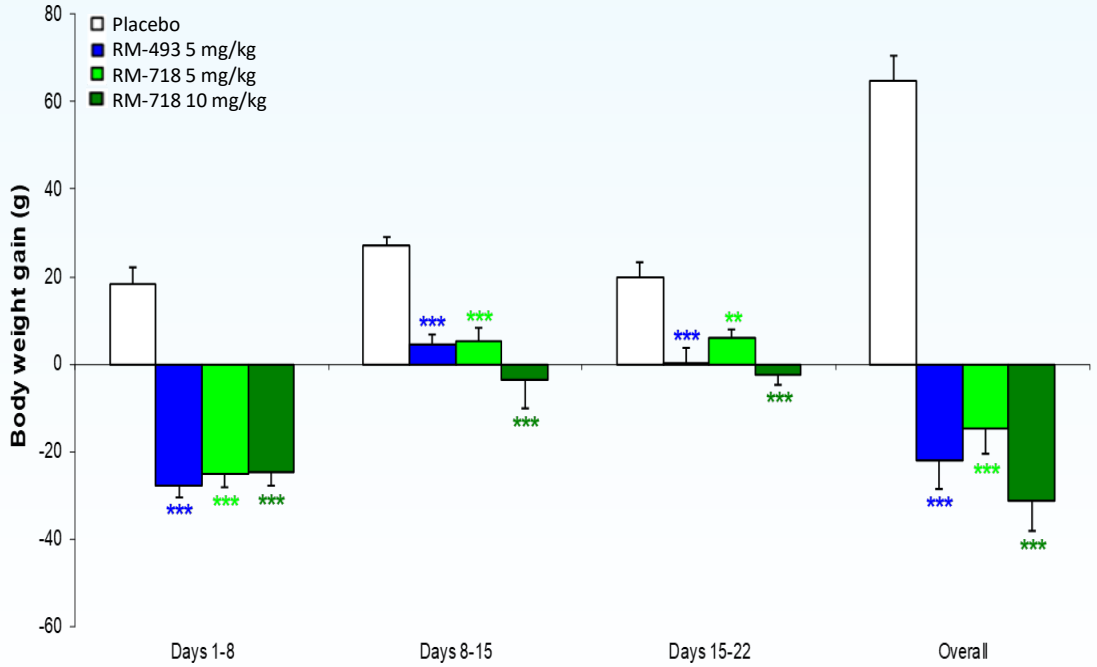
RM-718 Demonstrated Reduction in Body Weight and Body Weight Gain in Obese Zucker Rats (LepR deficient)

21-d parallel study of 4 arms (n=8), Placebo, Setmelanotide (RM-493) QW (5mg/kg) and RM-718 QW (5&10 mg/kg)

Body weight reduction



Body weight gain was significantly reduced



RM-718 QW	Plasma (ng/mL)	CSF (ng/mL)	BW Reduction day 22 vs Placebo
5 mg/kg/week	43.8 (6.9)	0.72 (0.03)	-12.9%
10 mg/kg/week	90.4 (8.8)	1.67 (0.12)	-15.6%

Shown is mean (sem), n=8/arm,
***p<0.001 from Placebo

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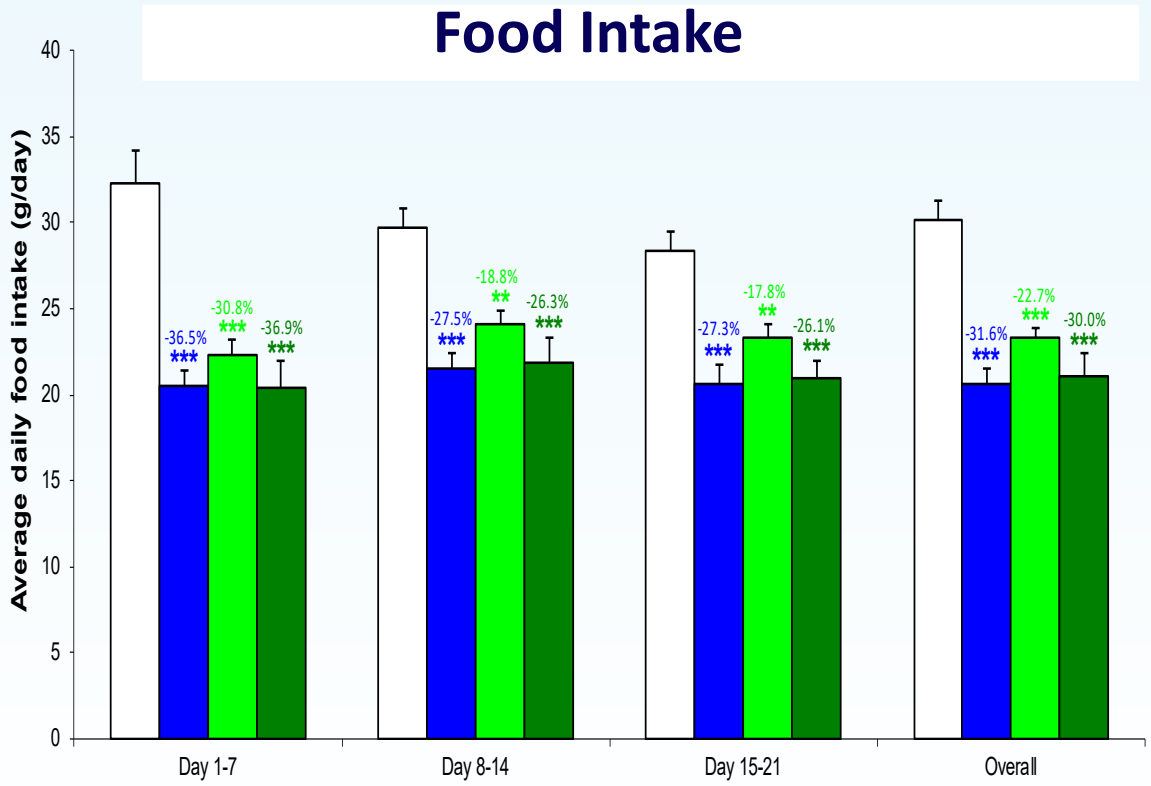
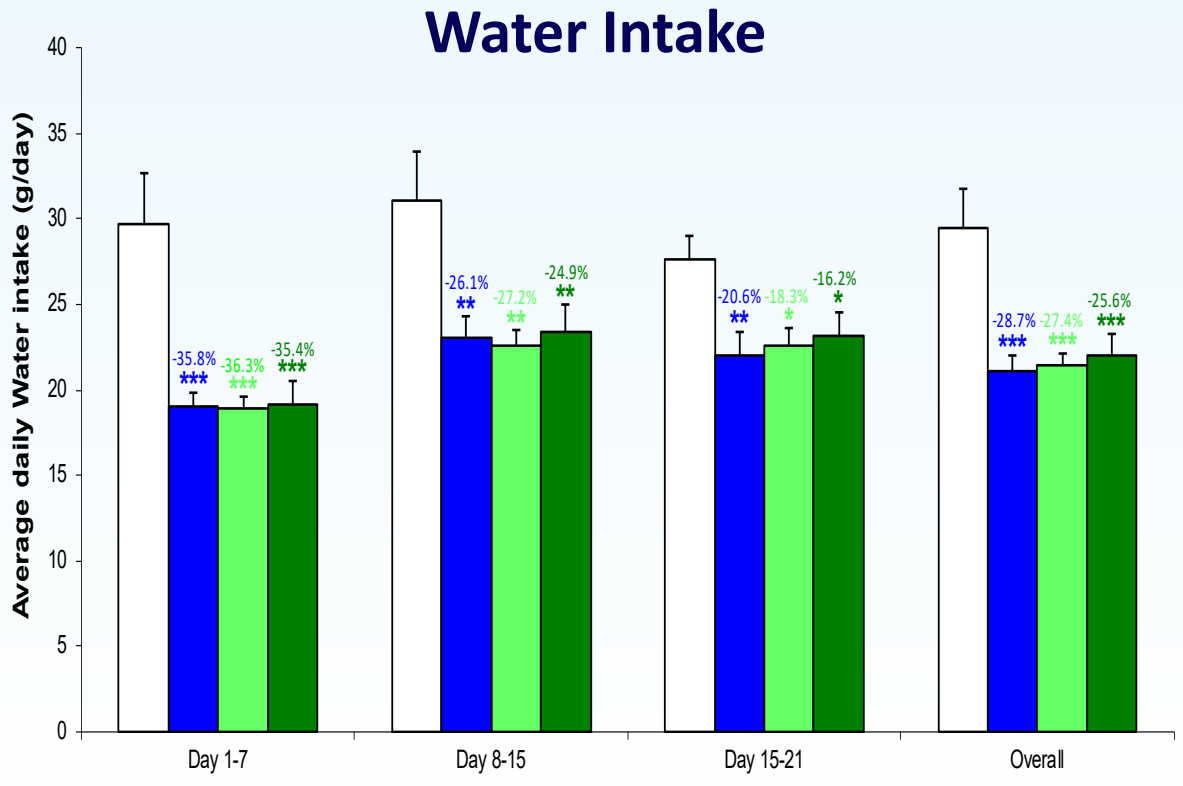
RM-718 QW, Setmelanotide QW Normalized Food and Water Intake





Shown is mean (SE)***p<0.001 for the difference from Placebo, n=8/arm; Normal food & water intake ~20g/day

Placebo
RM-493 5 mg/kg
RM-718 5 mg/kg
RM-718 10 mg/kg

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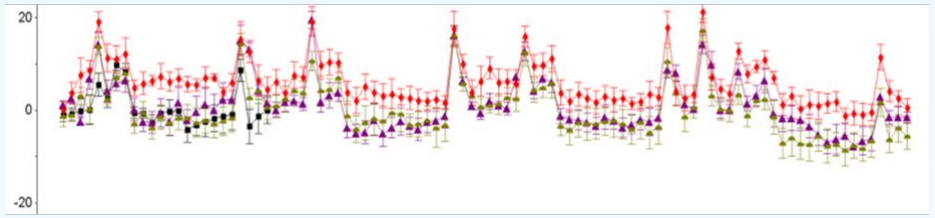
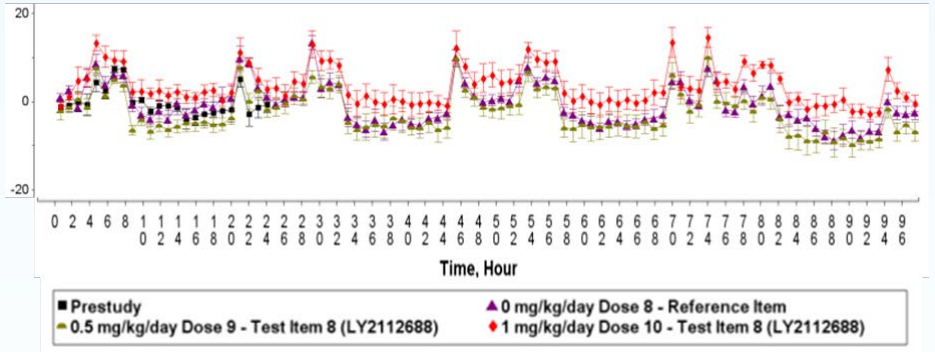
Cardiovascular Safety Observed in Non-Human Primate Studies

3-day sc infusion of RM-718 (1&5 mg/kg) and LY 2112688 (0.5&1 mg/kg) to cynomolgus monkeys

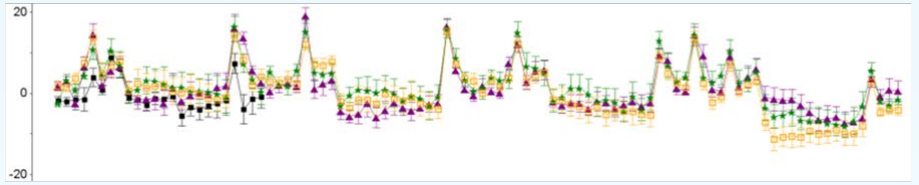
LY2112688 Mean Systolic BP, Change from Predose



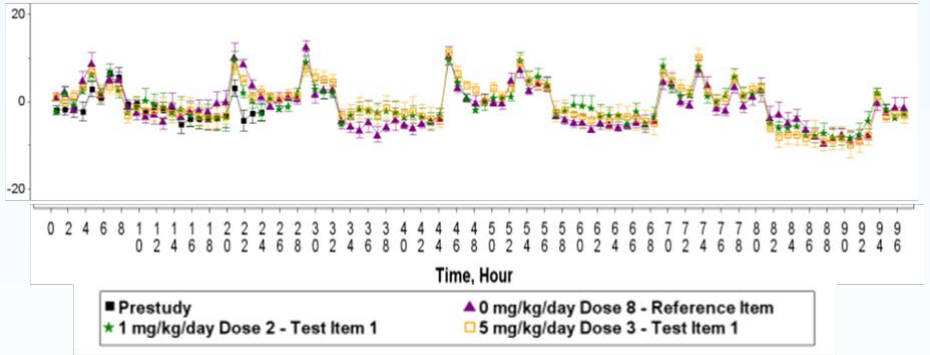
Mean Diastolic BP, Change from Predose



RM-718 Mean Systolic BP, Change from Predose



Mean Diastolic BP, Change from Predose



Shown is a mean (se), Reference item=0.9% sodium chloride, Test Item 1=RM-718, Test Item 9= LY2112688; predose:2d, sc inf:3, follow up:4d

Plasma exposure after 72h infusion

Test Item	0.5 mg/kg/d (ng/mL)	1 mg/kg/d (ng/mL)	5 mg/kg/d (ng/mL)
LY2112688	205	298	-
RM-718	-	321	**1578**

Changes in Blood Pressure and Heart Rate with LY 2112688

Test Item	Dose Level mg/kg	Mean Pressure[a] mmHg (%)		Systolic Pressure[a] mmHg (%)		Diastolic Pressure[a] mmHg (%)		Heart Rate[a] BPM (%)	
		Average[a]	Maximum	Average[a]	Maximum	Average[a]	Maximum	Average[a]	Maximum
LY2112688	0.5	-2.49 (-2.64%)	-5.58 (-5.93%)	-1.58 (-1.40%)	-6.61 (-5.66%)	-3.14 (-4.17%)	-6.83 (-8.51%)	2.32 (1.83%)	23.93 (17.64%)
	1	4.59 (4.95%)	8.85 (9.80%)	5.53 (4.99%)	10.07 (9.37%)	3.06 (4.12%)	6.10 (8.30%)	3.14 (2.65%)	19.06 (14.05%)

[a] Average baseline-adjusted change, relative to control, from 1 to 20 hours post SOI for LY2112688 for blood pressure and heart rate.

Cardiovascular safety confirmed with RM-718QW with the dose up to 30 mg/kg providing >30x safety margin

Rhythm® PHARMACEUTICALS

First in Human, Three-part Phase 1 Study to Evaluate Safety, Tolerability, and PK of RM-718 QW Anticipated to Begin in 1H 2024

Part A: SAD
RM-718 QW

Screening: 28 days
6 cohorts X 6 subjects ≥18y
n=36
Randomized 2:1 (RM-718: Placebo)
Single doses ascending 3mg - 50mg*
Safety follow up 10-14 days

Part B: MAD
RM-718 QW 4 doses

Screening: 28 days
6 cohorts X 6 subjects ≥18y
n=36
Randomized 2:1 (RM-718: Placebo)
Multiple doses ascending
3mg - 40mg*
Safety follow up 28 days

Part C: MAD Hypothalamic Obesity RM-718 QW 4 doses

Screening: 28 days
8 cohorts X 3 patients ≥12y
n=24
Open-label, multiple doses
ascending 10mg - 40mg*
Safety follow up 28 days
Transition to open-label extension

*Doses may be adjusted upward or downward based on emerging data; 2 additional cohorts may be permitted in Parts A and Part B based on emerging data. Part C dosing will be based on safety, tolerability, and available PK data from Parts A and B. Patients ≥18 years of age will complete Part C cohorts prior to initiating dosing in patients ≥12 to <17 years. Planned starting dose in Part C is 10mg. Part C doses will not exceed the highest Part A or Part B dose for which safety and tolerability data are supportive. Patients in Part C may be eligible to participate in an open-label extension study.

RM-718 has Demonstrated Similar or Improved Safety, Tolerability and Potential Efficacy Compared to Setmelanotide Weekly Formulation

- **Designed to be more selective MC4R agonist**
- **In vivo safety results supportive of no off-target cardiovascular effects, like setmelanotide**
- **No hyperpigmentation observed in vivo**
- **In vivo results suggest potential efficacy for body weight reduction, hyperphagia reduction**
- **Potential for efficient development path with hypothalamic obesity**

David Meeker

Positive Data from Phase 3 Pediatrics Trial

Rare Genetic Diseases Often Present Early In Life

Hyperphagia and obesity of rare MC4R diseases present in infancy

>15%

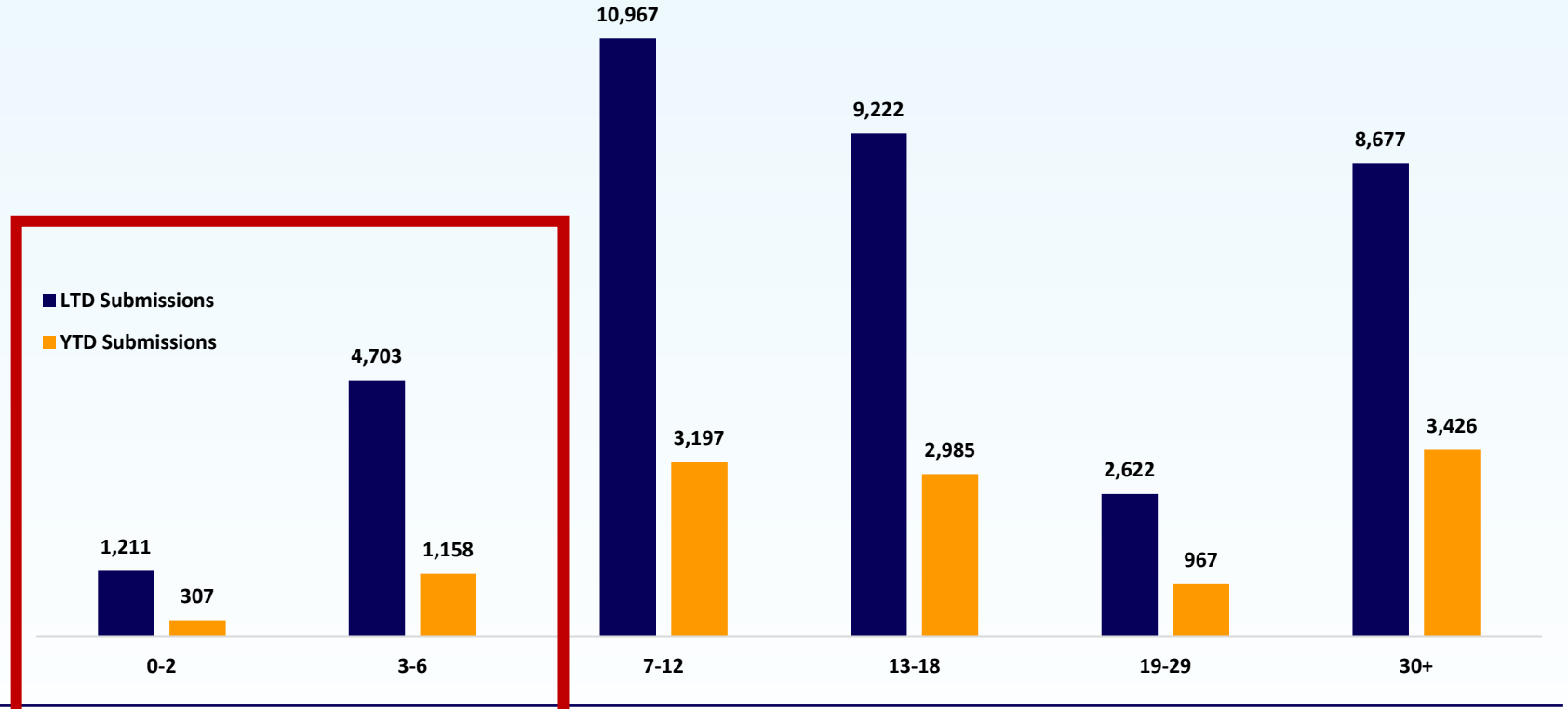
of samples sequenced in URO genetic tests come from children 6yo or younger

Regulatory submissions:

- ✓ Type II variation submitted to seek EMA marketing authorization
  - ○ US FDA in 1H 2024

URO Results Indicative of Unmet Need in Children Younger than 6yo

Tests Submitted by Patient Age @Testing

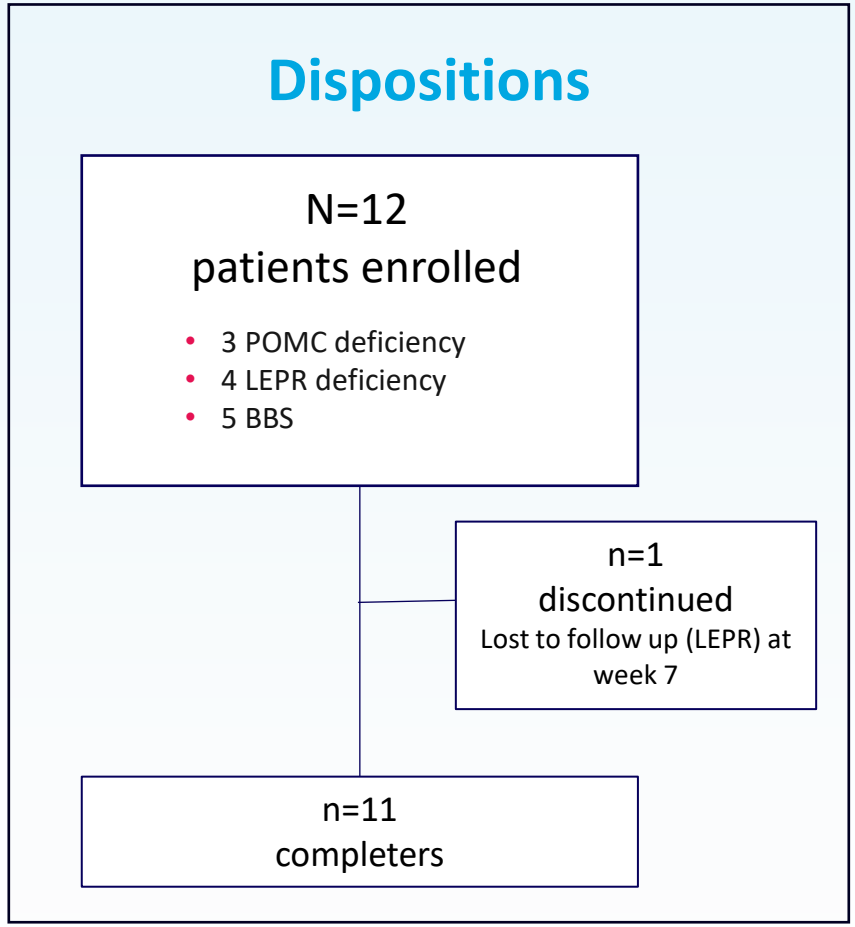


		0-2	3-6	7-12	13-18	19-29	30+
Enrolling Yield	PPL	1.04%	0.11%	0.04%	0.11%	0.12%	0.05%
LTD	BBS	1.65%	0.66%	0.54%	0.63%	0.84%	0.53%

Data as of 10/31/2023; YTD Based on Submission Date

Baseline Demographics and Disposition

Parameter	Statistic	POMC or LEPR Deficiency	BBS	Total
Enrolled patients	n	7	5	**12**
Male	n (%)	5 (71.4%)	2 (40.0%)	**7 (58.3%)**
Female	n (%)	2 (28.6%)	3 (60.0%)	**5 (41.7%)**
BMI at Baseline (kg/m^2)	Mean (SD)	34.347 (7.0673)	23.716 (3.5184)	**29.918 (7.8559)**
BMI-Z score at Baseline	Mean (SD)	10.749 (3.8400)	4.233 (1.0742)	**8.034 (4.4408)**



Setmelanotide Achieved Clinically Meaningful Reductions in BMI and BMI-Z in 2-<6yo Patients with POMC/LEPR Deficiency or BBS

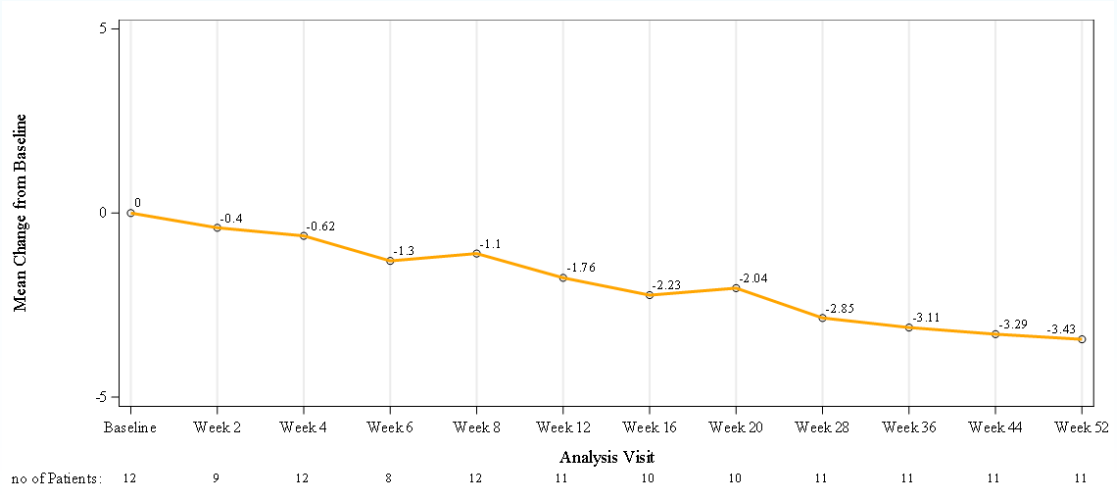
Analysis set population (N=12)

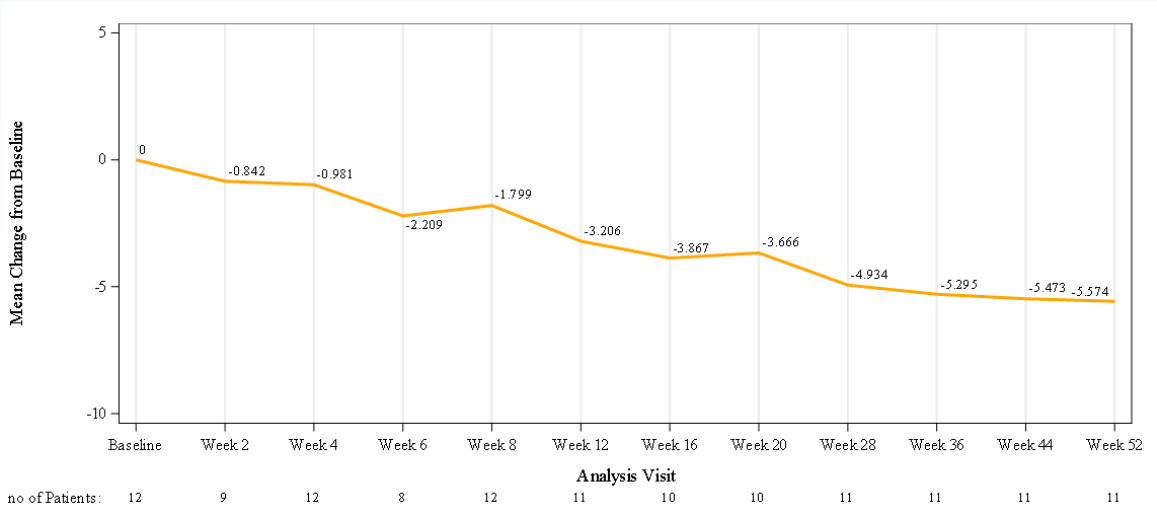
83.3% (10 of 12)

of all patients achieved ≥0.2 reduction in BMI-Z score from baseline to Week 52

-18.380%

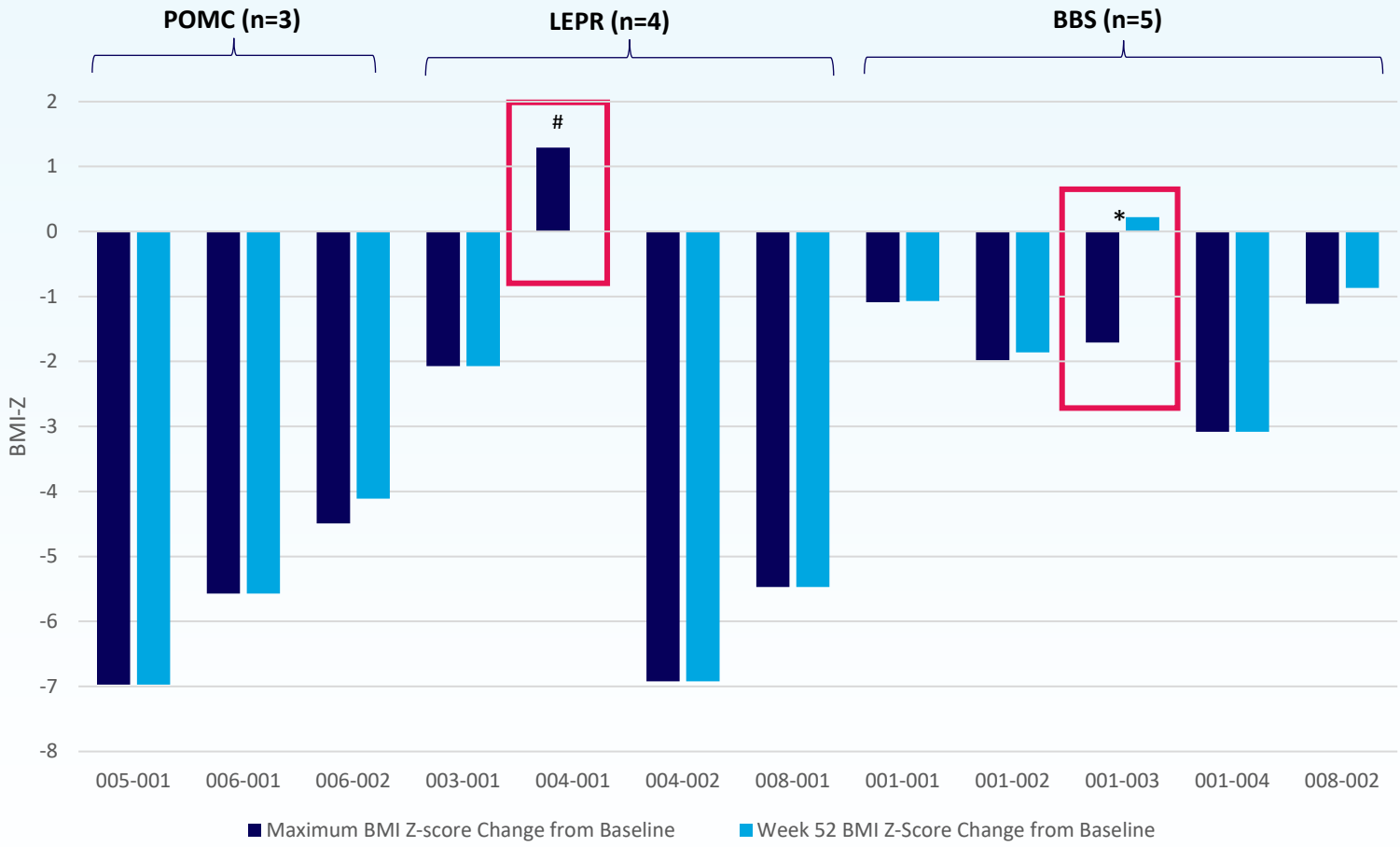
Mean percent change from baseline in BMI at Week 52





Data on file at Rhythm. To be presented at a medical conference.

Setmelanotide Achieved Consistent Reductions in BMI-Z Score



-3.04

Mean change from baseline in BMI-Z at Week 52 (N=12)

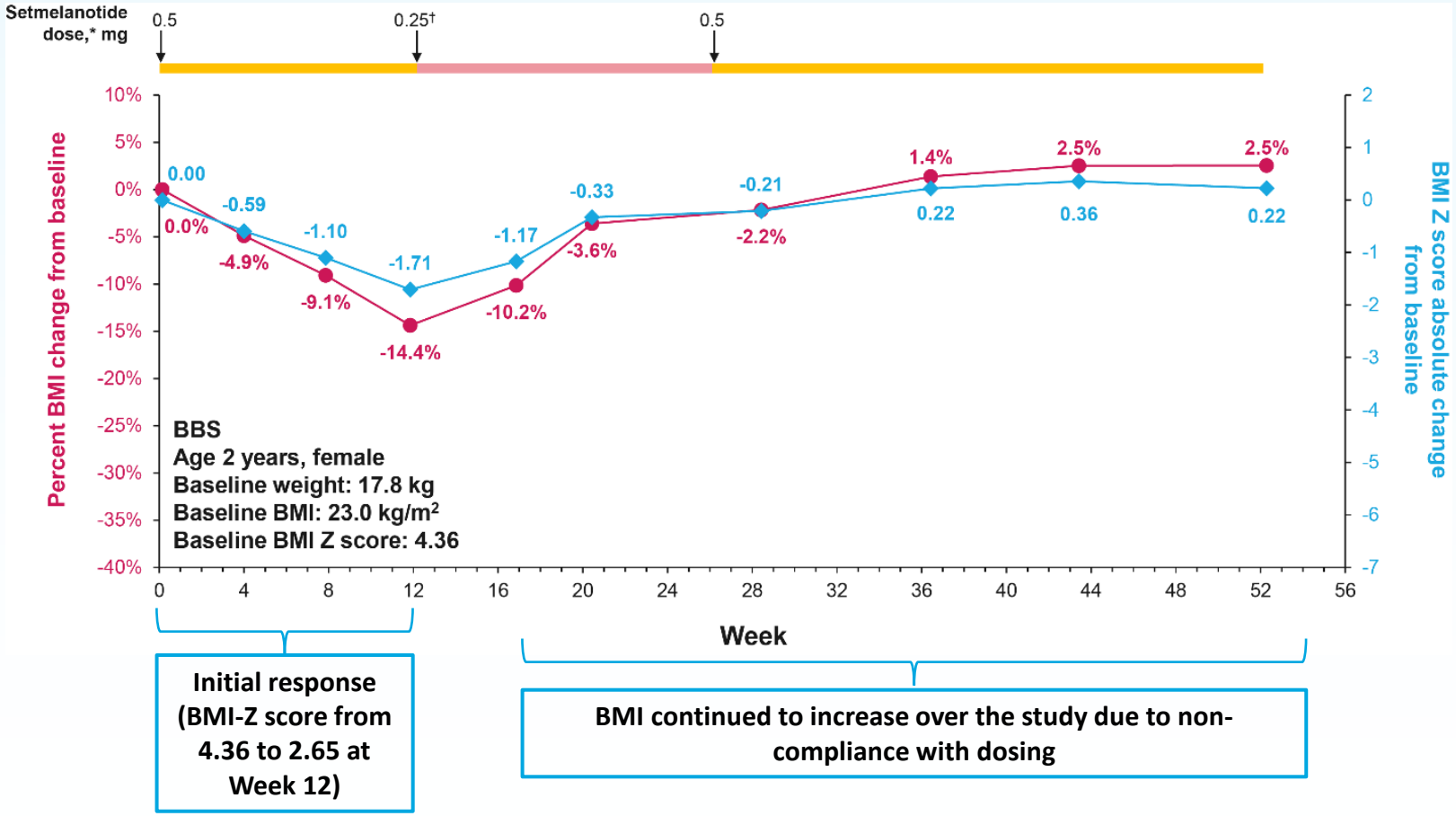
-4.3	**-1.3**
POMC/LEPR (n=7)	BBS (n=5)

**Patient was not compliant with dosing (next slide); #Patient discontinued the study at Week 7 and was subsequently lost to follow-up

For patients who did not achieve their greatest reduction from baseline n BMI-Z score at Week 52 (52-week population), the maximum reduction in Z-score at any time is presented.

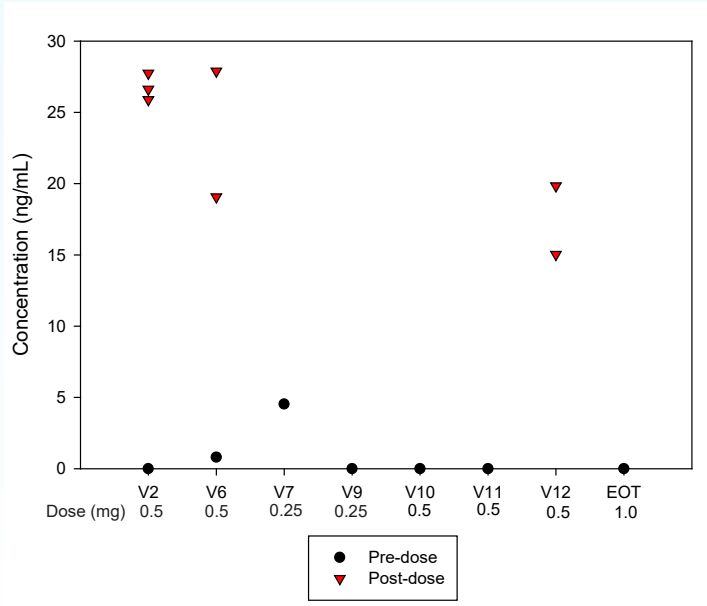
Patient Who Did Not Achieve ≥0.2 BMI-Z Score Reduction at Week 52

Dose reduced due to unrelated AE



Initial response (BMI-Z score from 4.36 to 2.65 at Week 12)

BMI continued to increase over the study due to non-compliance with dosing



Safety Profile in Patients 2-<6yo Consistent with Past Trials Evaluating Setmelanotide in Patients 6 years old and older

AE	POMC or LEPR Deficiency	BBS	Total
Skin hyperpigmentation	5 (71.4%)	4 (80.0%)	9 (75.0%)
Injection site bruising	1 (14.3%)	3 (60.0%)	4 (33.3%)
Injection site pruritus	1 (14.3%)	3 (60.0%)	4 (33.3%)
Vomiting	2 (28.6%)	1 (20.0%)	3 (25.0%)
Abdominal pain	1 (14.3%)	1 (20.0%)	2 (16.7%)

Safety analysis set is defined as all patients who received ≥1 dose of study drug. TEAE, treatment emergent adverse event.

Setmelanotide Demonstrated Safety, Tolerability and Consistent, Clinically Meaningful BMI, BMI-Z Reductions in Patients 2-<6yo

Clinically meaningful reductions in BMI and BMI-Z

Generally well-tolerated and safe, as seen in older patients

Doses of 0.5mg to 2.5mg proposed for patients <6yo

All 11 patients remain on therapy*

8 patients enrolled in bridging program

3 patients who are now 6yo or older are on commercial therapy.

* As of Dec. 5, 2023

Q and A