Rhythm Pharmaceuticals

Interim results from Phase 2 Clinical Trial Evaluating Setmelanotide in Hypothalamic Obesity

July 12, 2022

Agenda

- David Connolly

  Executive Director, Investor Relations and Corporate Communications

- David Meeker, MD

  Chairman, President and CEO

- M. Jennifer Abuzzahab, MD

  Pediatric Endocrinologist at Children's Minnesota

- Hunter Smith

  Chief Financial Officer

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, 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 from the U.S. FDA and EMA, our business strategy and plans, including regarding commercialization of setmelanotide, the application of genetic testing and related growth potential, expectations surrounding the potential market opportunity for our product candidates, the sufficiency of our cash, cash equivalents and short-term investments to fund our operations, and strategy, prospects and plans, including regarding the commercialization of setmelanotide. 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 that interim, “topline” and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data, 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.

David Meeker, MD

Chairman, President and CEO

Rhythm Pharmaceuticals

IMCIVREE®
(setmelanotide) injection

First and only **FDA-approved** and **EC-authorized** therapy that targets a root cause of **hyperphagia** and early-onset, **severe obesity**

Launch for **Bardet-Biedl syndrome (BBS)** in U.S. underway

Achieve **market access** throughout **EU** with EC authorization for **BBS anticipated in 2H2022**

Expand **addressable patient population** with robust clinical development program

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Hypothalamic Obesity: Severe Disease Burden with Significant Unmet Need

Established patient population actively seeking and advocating for an effective therapy

Biology of hypothalamic obesity is tied to melanocortin-4 receptor (MC4R) pathway

No effective treatment for rapid weight gain from injury to hypothalamus

Setmelanotide Achieved Proof of Concept in Interim Analysis of Hypothalamic Obesity Phase 2 Trial

Full analysis set population (n=11)

11 of 11

patients achieved primary endpoint **of ≥5% reduction in BMI** (P<0.0001)

–17.2

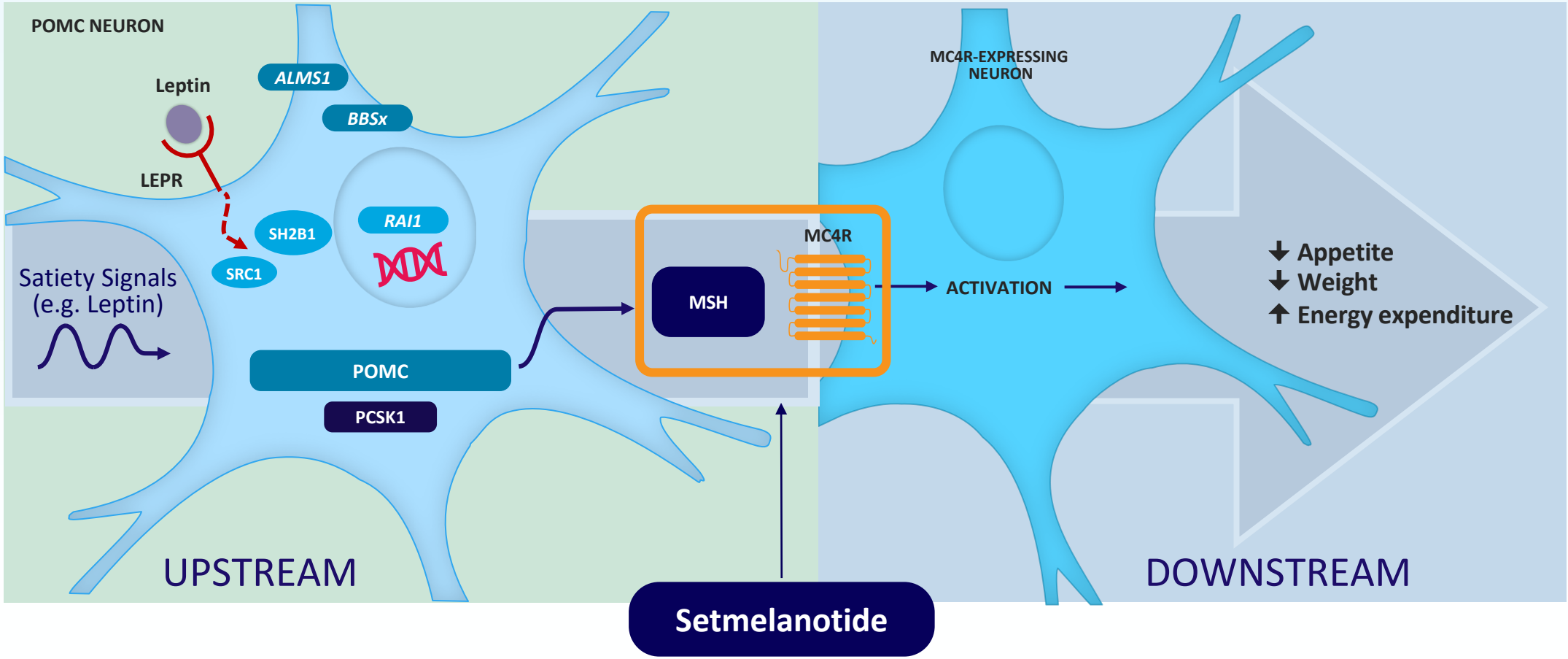
mean % change

in **BMI** over 16 weeks (SD, 9.0%)

Interim analysis as of the data cutoff date of May 6, 2022, of 11 patients evaluable based on being eligible to receive 16 weeks of therapy.

MC4R Pathway Biology is Clear and Strong: Regulates Hunger, Caloric Intake, Energy Expenditure and, Consequently, Body Weight

Setmelanotide can address MC4R pathway impairment contributing to early-onset, severe obesity



Hypothalamic Obesity Represents a Significant U.S. Market Opportunity

5,000 – 10,000*

patients
Estimated U.S. prevalence

~500*

additional cases diagnosed in U.S. each year

2,500 - 7,500	**>1,000**	**>1,500**
HO related to craniopharyngioma	HO related to astrocytoma	HO related to other tumor types

*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.

M. Jennifer Abuzzahab, MD

Pediatric Endocrinologist
at Children's Minnesota

Patient Journey with Hypothalamic Obesity

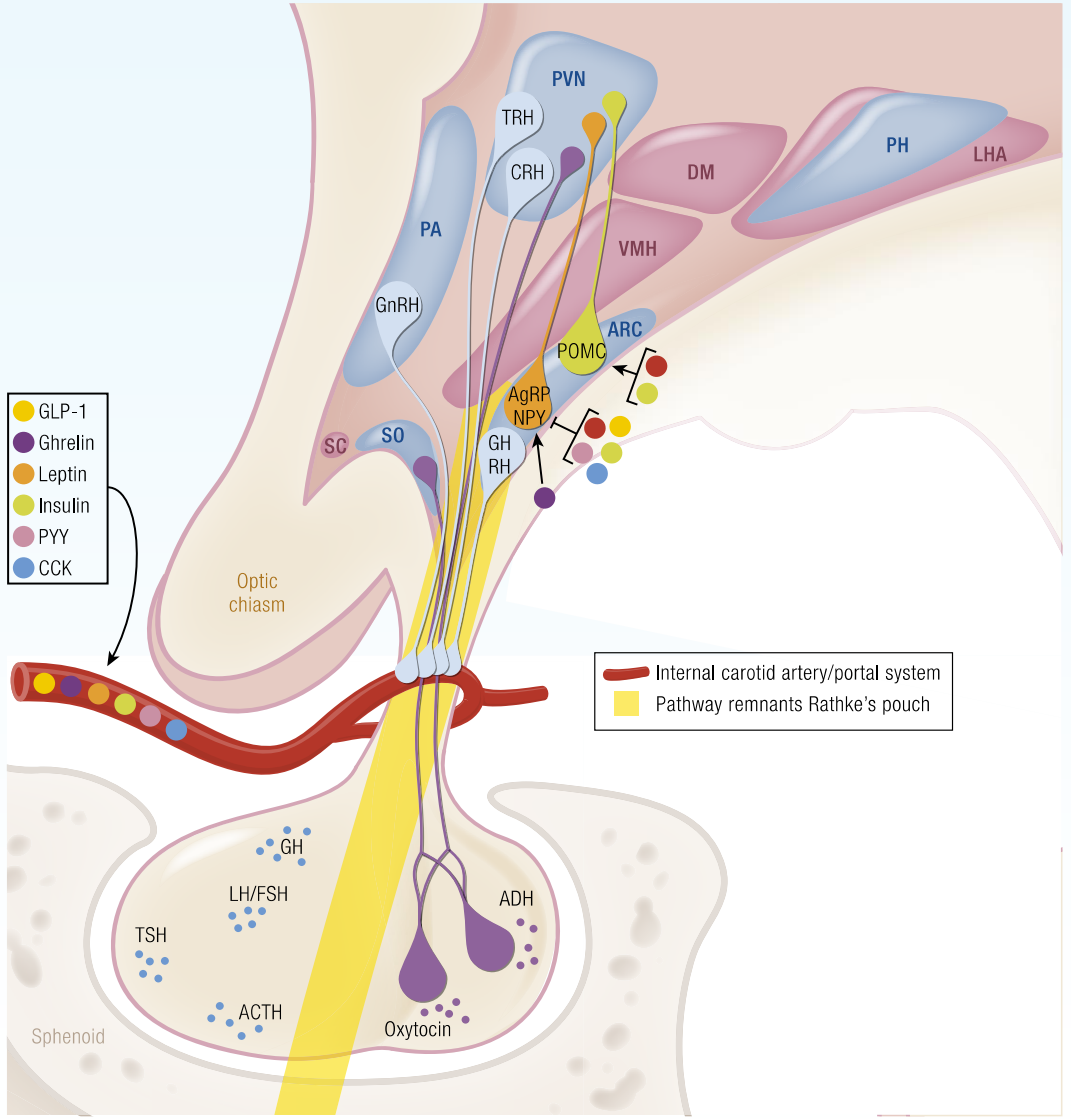
HO-related event	• Damage to the ventromedial hypothalamic nucleus • Most often have craniopharyngioma, other suprasellar tumors, related surgeries, or radiation[1]
Rapid weight gain, hyperphagia	• Strongest increase in weight within the first 6-12 months following HO event[2]
Diagnosis	• Clinical suspicion of HO related event and rapid onset of obesity • Lesions or hypothalamic volume, detected through MRIs[3]
Limited treatment options	• Combination of lifestyle changes, limited pharmacologic treatment or bariatric surgery with variable results[3]

1. Rose SR, et al, doi: 10.1002/oby.22315. Epub 2018 Oct 8. PMID: 30296362; PMCID: PMC6202209; 2. Erfurth EM., doi: 10.1159/000509616. Epub 2020 Jun 24. PMID: 32580186; PMCID: PMC7490511; 3. Müller HL doi: 10.1016/j.ecl.2020.05.009. Epub 2020 Jul 15. PMID: 32741487.

Hypothalamic Obesity: A Rare, Acquired Form of Obesity Following Injury to the Hypothalamic Region

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

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



van Iersel et al. *Endo Rev.* 2020 (PMID: 30247642)

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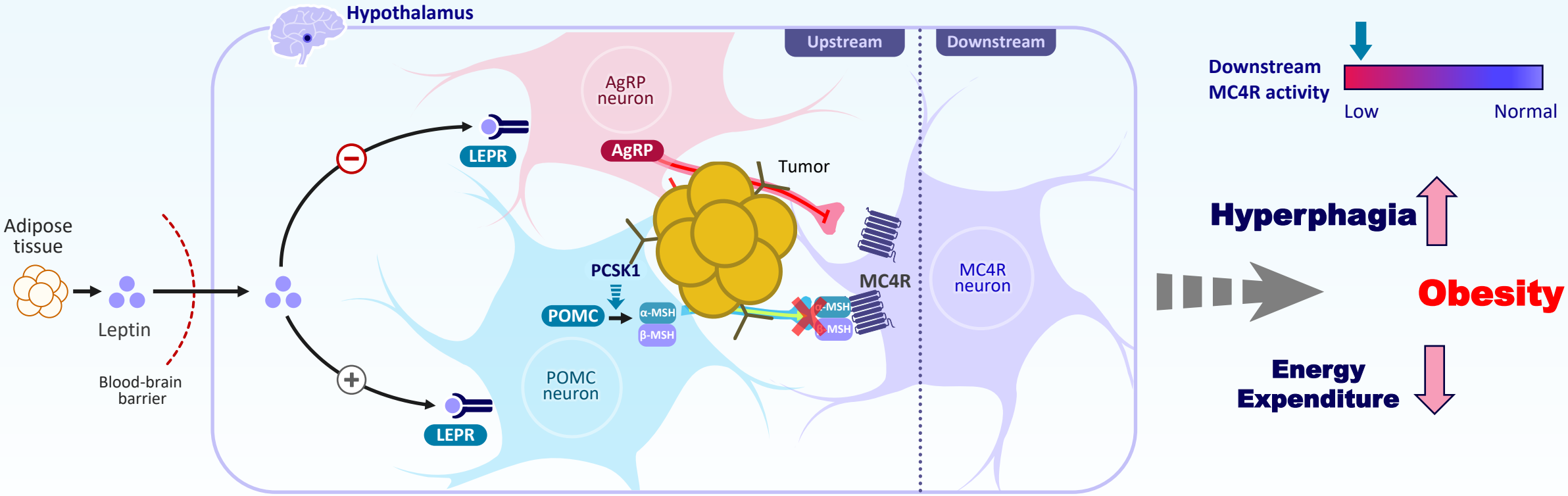
Damage to the Hypothalamus Can Impair MC4R Pathway Signaling Leading to Hyperphagia, Decreased Energy Expenditure and Rapid-onset Obesity[1-4]



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.

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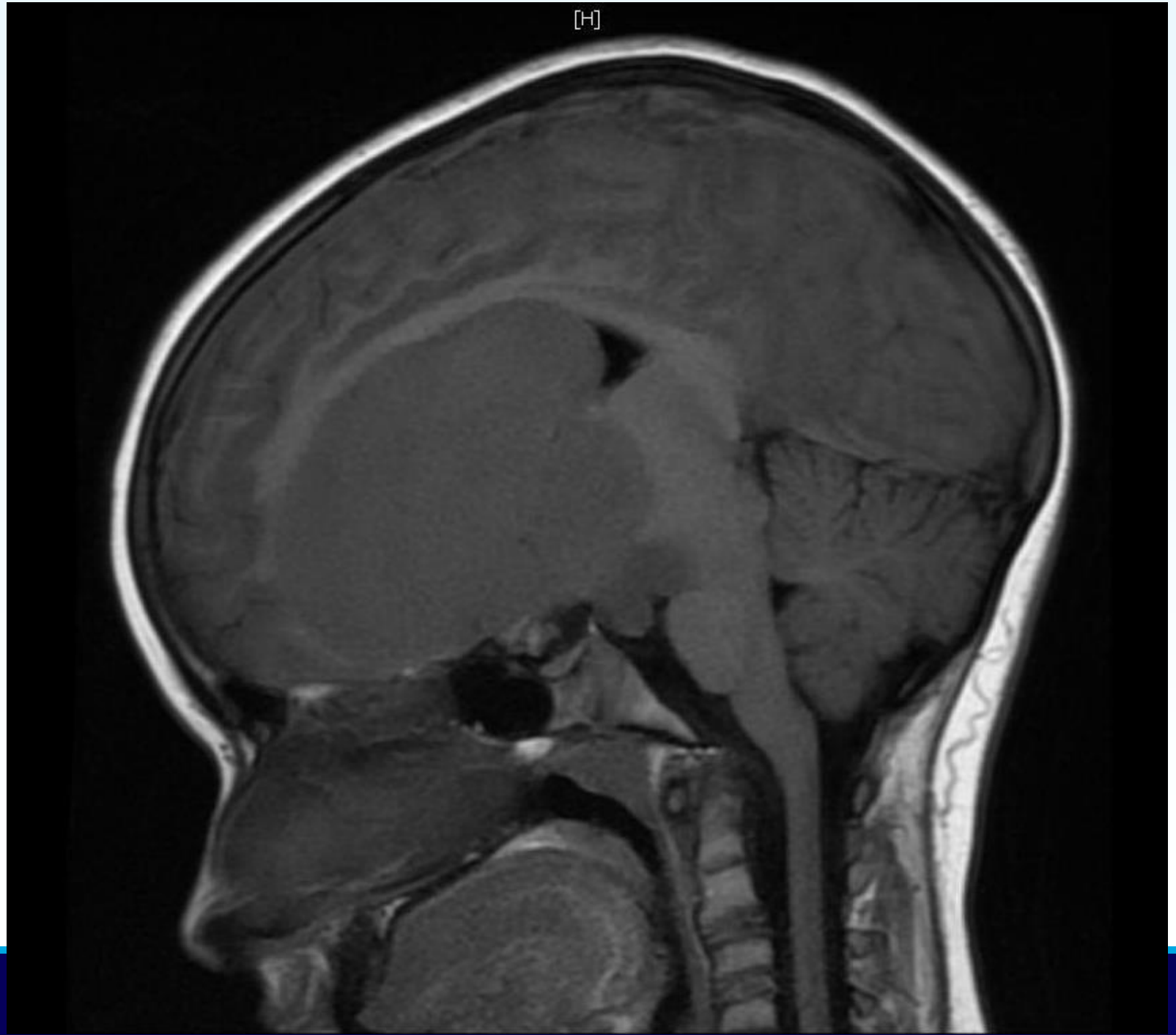

Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota

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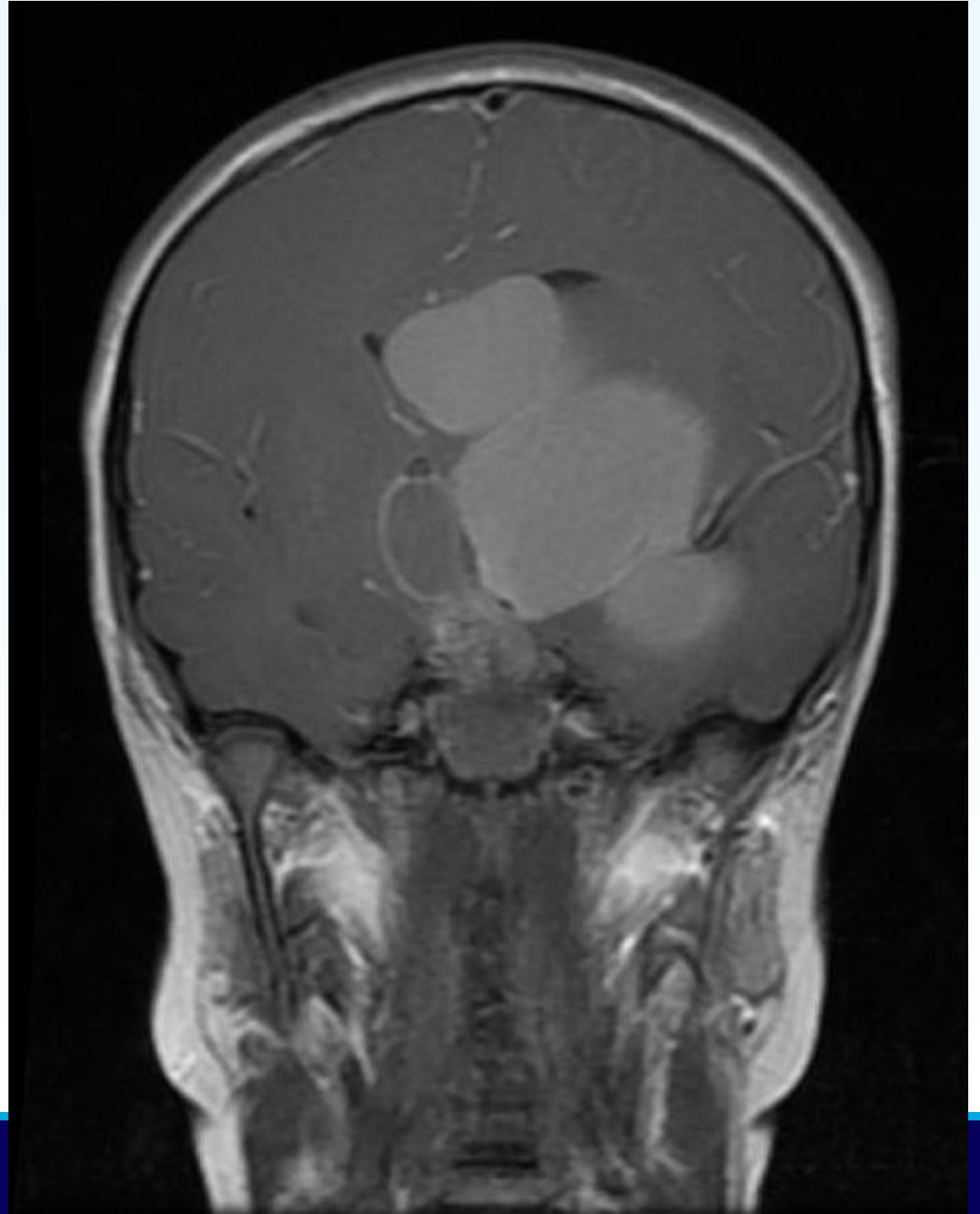
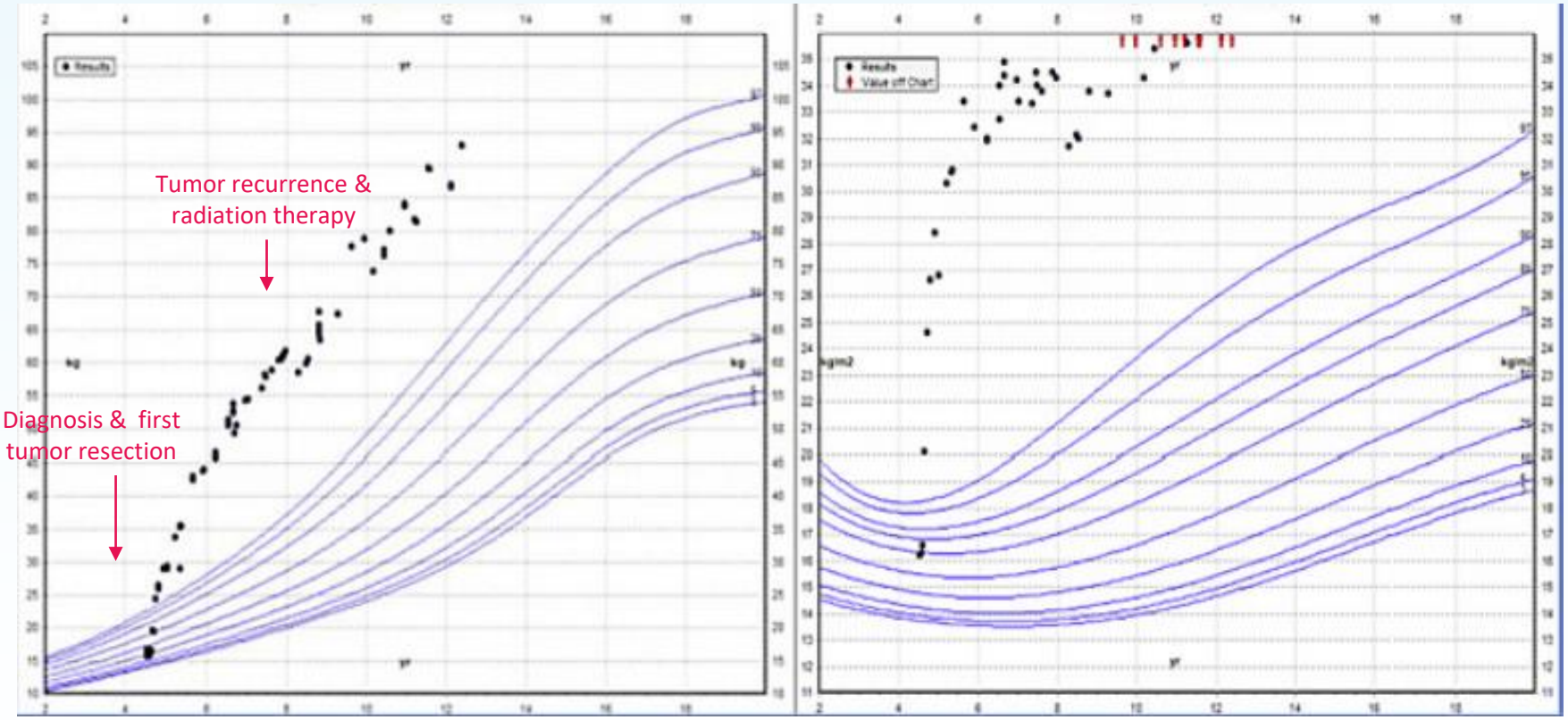


Patient case of M. Jennifer Abuzzahab, MD, Pediatric Endocrinologist, at Children's Minnesota

HO: Aggressive, Rapid Weight Gain follows Therapy for CP

Weight for age 2 - 20 years old Boys

BMI for age 2 - 20 years old Boys



Typical growth pattern of a patient with HO following CP therapy, with persistent weight gain. The first plotted point is diagnosis at 4 years and 8 months. His tumor was treated with surgical excision. He had multiple hormone deficiencies at the time of diagnosis. The tumor recurred at age 6 years and 8 months, and he had proton beam radiation. Growth hormone therapy was initiated at age 11 years and 2 months.

Adapted from Abuzzahab, MJ et. Al., *Horm Res Paediatr* 2019;91:128–136; https://doi.org/10.1159/000496564

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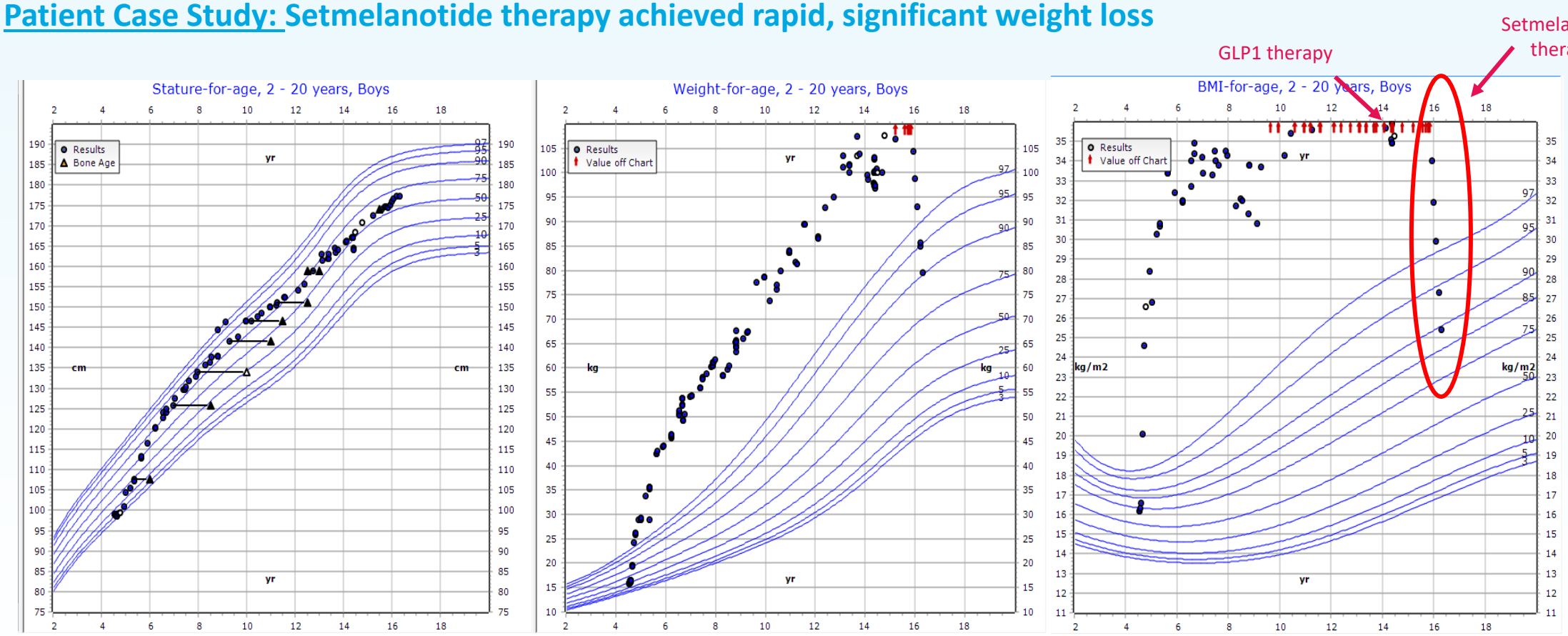
HO: Aggressive, Rapid Weight Gain follows Therapy for CP

Patient Case Study: Setmelanotide therapy achieved rapid, significant weight loss



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

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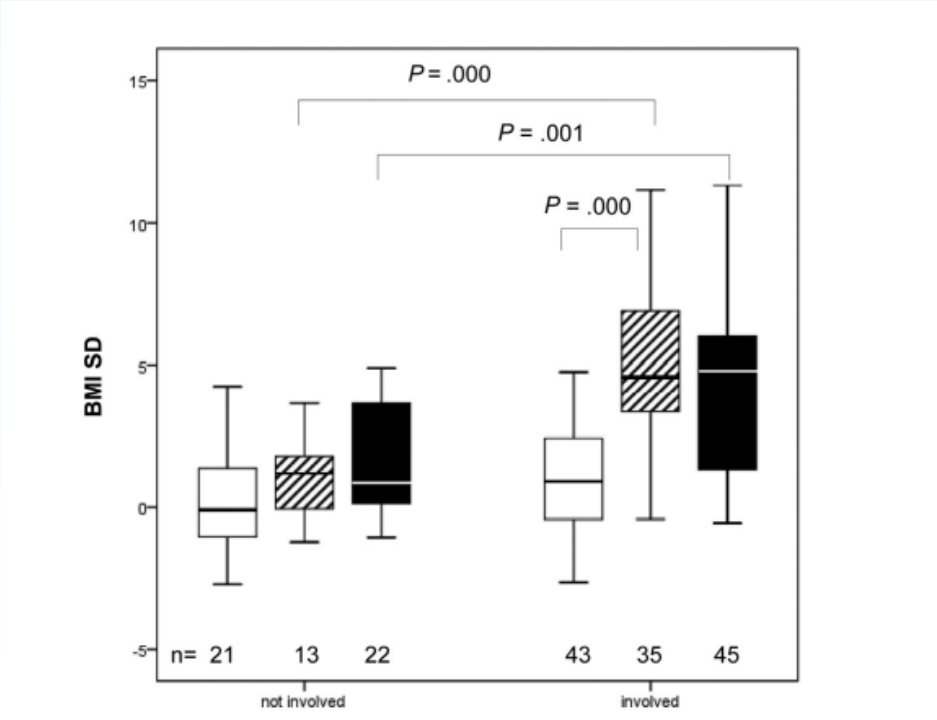
Longitudinal Analysis of Patients with Childhood-onset Craniopharyngioma Illustrates Impact of Hypothalamic Involvement in BMI

Patients with CP with hypothalamic involvement develop significant increase in BMI standard deviation



+0.80

Median change in BMI SD

Patients with CP **without hypothalamic involvement** at diagnosis had a minimal median BMI SD increase during the first 8-12 years after diagnosis.

+4.29

Median change in BMI SD

Patients with CP and **with hypothalamic involvement** at diagnosis developed a significant increase in BMI standard deviation during the first 8–12 years after diagnosis

KEY: Body mass index (BMI) SDs is shown for patients at time of diagnosis of CP (white box), 8-12 years after diagnosis (hatched box) and 12+ years after diagnosis. The horizontal line in the middle of each box depicts the median; top and bottom edges of each box respectively mark the 25th and 75th percentiles.

Adapted from Sterkenburg, et. al., *Neuro Oncol*. 2015; doi: 10.1093/neuonc/nov044

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No Effective Treatment Options for Hypothalamic Obesity

Patients with HO are unresponsive to lifestyle and diet modifications

No pharmaceutical agent for treatment has been approved by the FDA or shown to be effective in late-stage trials

Bariatric treatment with invasive , nonreversible methods in pediatric patients is controversial (ethical, medical and legal concerns)

Current recommendations are limited to hypothalamus-sparing surgical and radio-oncological strategies

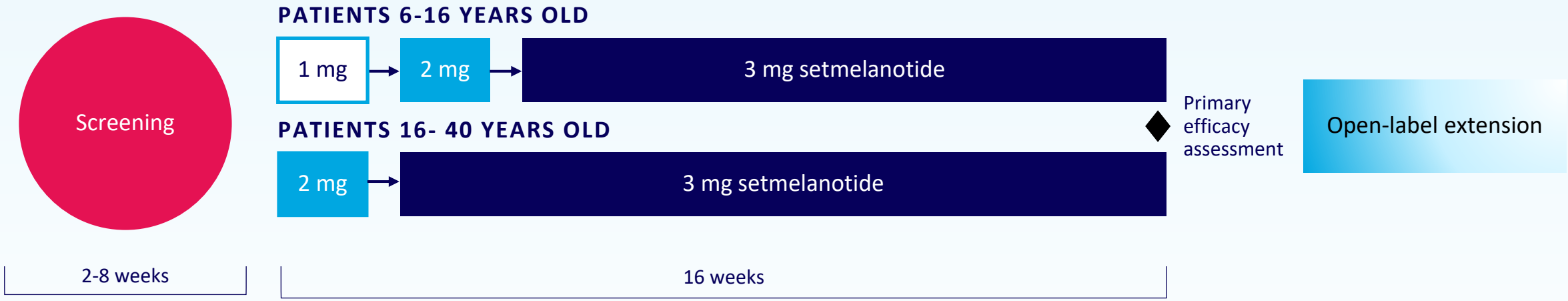
In part because of the unique pathophysiology of HO compared to general obesity, conventional pharmacologic approaches have shown limited to no benefit

David Meeker, MD

Chairman, President and CEO

Rhythm Pharmaceuticals

Phase 2 Open-label Trial Designed to Evaluate Setmelanotide's Therapeutic Effect in Patients with Hypothalamic Obesity



Enrollment criteria: Documented evidence of hypothalamic obesity, treated at least 6 months previously; Obesity, with documented change post HO treatment of BMI increase >5% and ≥35 kg/m2 in adults, or BMI Z score increase ≥0.2 and BMI ≥95th percentile for age and gender in patients <18 years old.

Primary Endpoint: Proportion of patients who achieve at least 5% reduction from baseline in BMI

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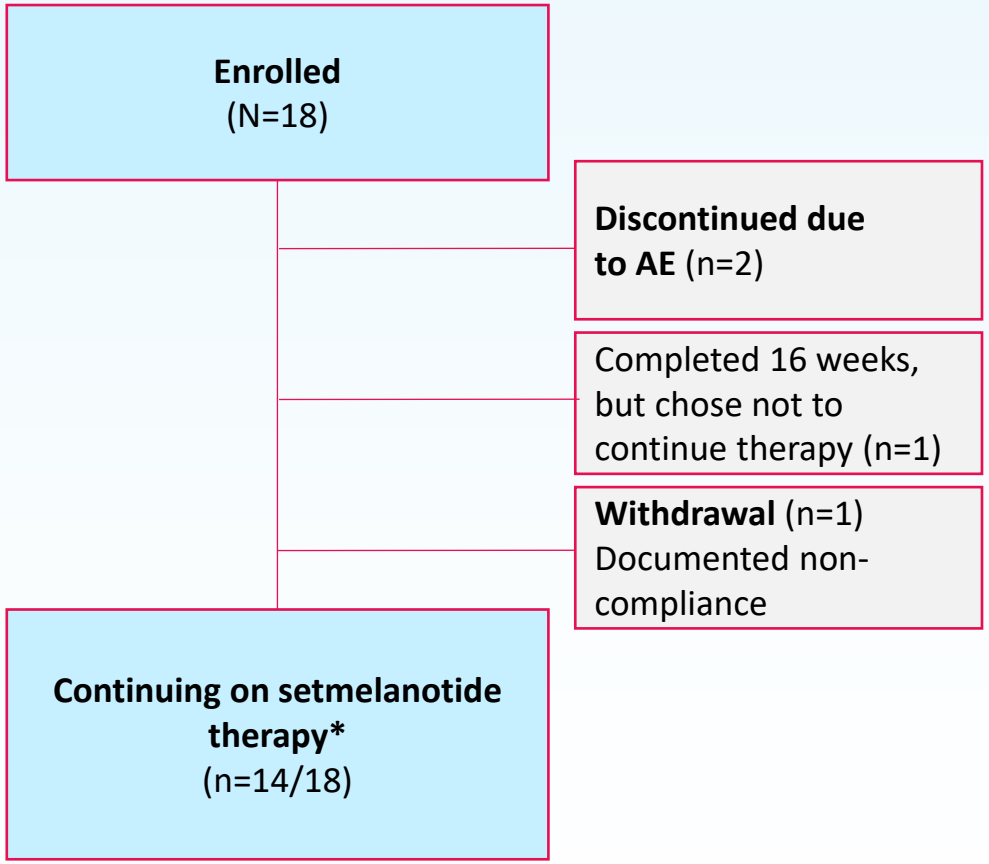
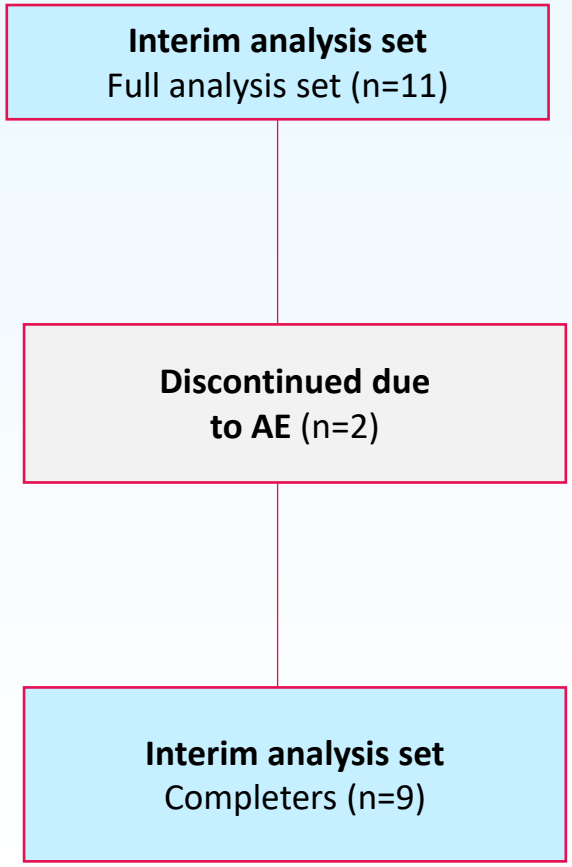
Disposition of Patients Enrolled in Phase 2 Study

All patients enrolled in Ph 2 study



Today's interim analysis



*As of July 11, 2022; AE, adverse event.

Interim Data Analysis is Based on Enrollment of 11 Patients

Baseline characteristic		Total (n=11)
Age, years	Mean (SD)	**14.6 (4.8)**
	Range	**6-23**
	<18 years old, n	**9**
	≥18 years old, n	**2**
Sex, n (%)	Female / Male	**5 (45.5) / 6 (54.5)**
Race, n (%)	White	**11 (100)**
Ethnicity, n (%)	Hispanic or Latino	**2 (18.2)**
	Not Hispanic or Latino	**9 (81.8)**
Weight, kg	Mean (SD)	**107.1 (26.8)**
	Range	**39.0-141.4**
BMI, kg/m^2	Mean (SD)	**38.7 (5.7)**
	Range	**22.9-44.4**

As of the data cutoff date of May 6, 2022; BMI, body mass index; FAS, full analysis set; HO, hypothalamic obesity; SD, standard deviation.

Setmelanotide Resulted in Mean BMI Reduction of -19.5% in 9 Completers at 16 Weeks

FAS population (n=11)

–17.2

mean % change

in **BMI** over 16 weeks
(SD, 9.0%)

–15.8 mean % change

in **body weight** after 16 weeks of setmelanotide (SD, 8.4%)

Completers (n=9)

–19.5

mean % change

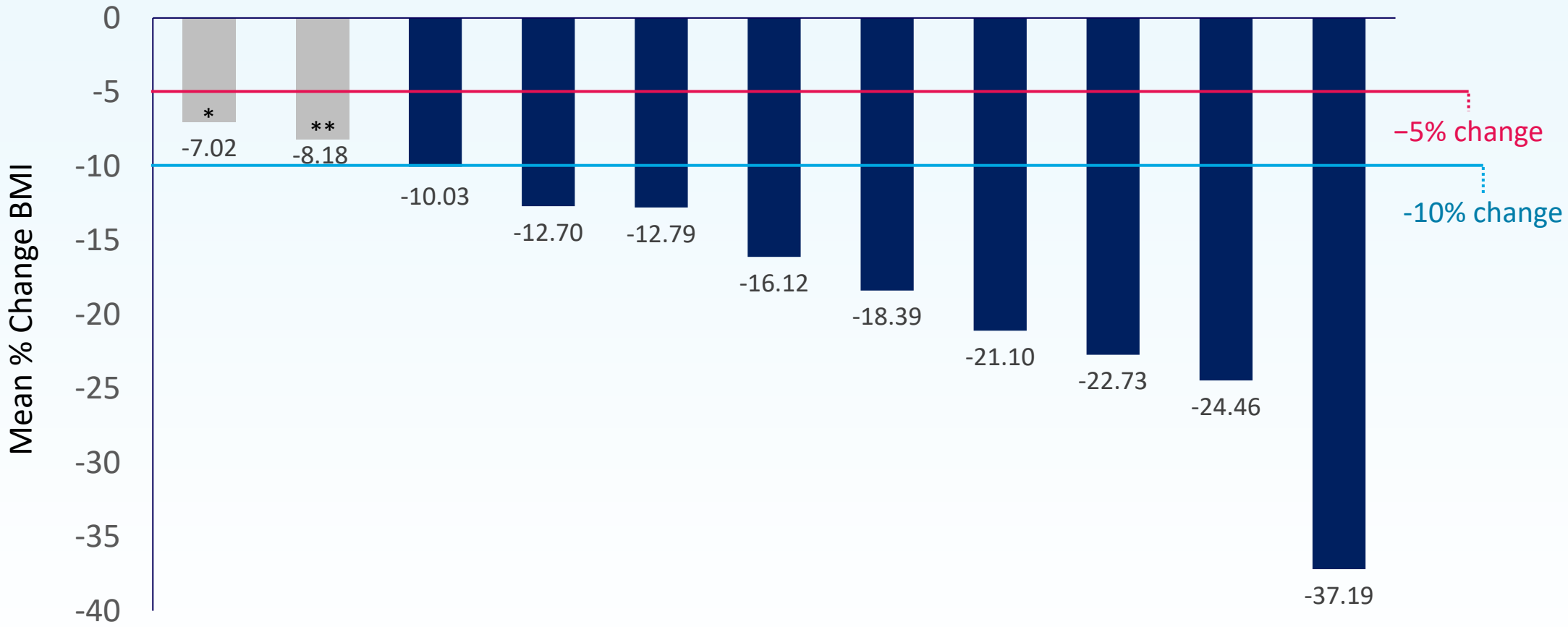
in **BMI** over 16 weeks
(SD, 8.2%)

–17.8 mean % change

in **body weight** after 16 weeks of setmelanotide (SD, 7.9%)

Interim analysis as of the data cutoff date of May 6, 2022; BMI, body mass index; FAS, full analysis set; SD, standard deviation.

Clinically Meaningful Reductions Observed in All Patients by 16 Weeks



Interim analysis as of the data cutoff date of May 6, 2022; BMI, body mass index. Two patients discontinued drug early (grey bars): * last on-treatment visit at Week 4 (-7.02%) and last visit (off-treatment) at Week 8 (-6.85%); ** last on-treatment visit at Week 13 (-8.18%) and last visit (off-treatment) at Week 16 (-6.67%). Grey bars show the BMI % reduction at last on-treatment visit.

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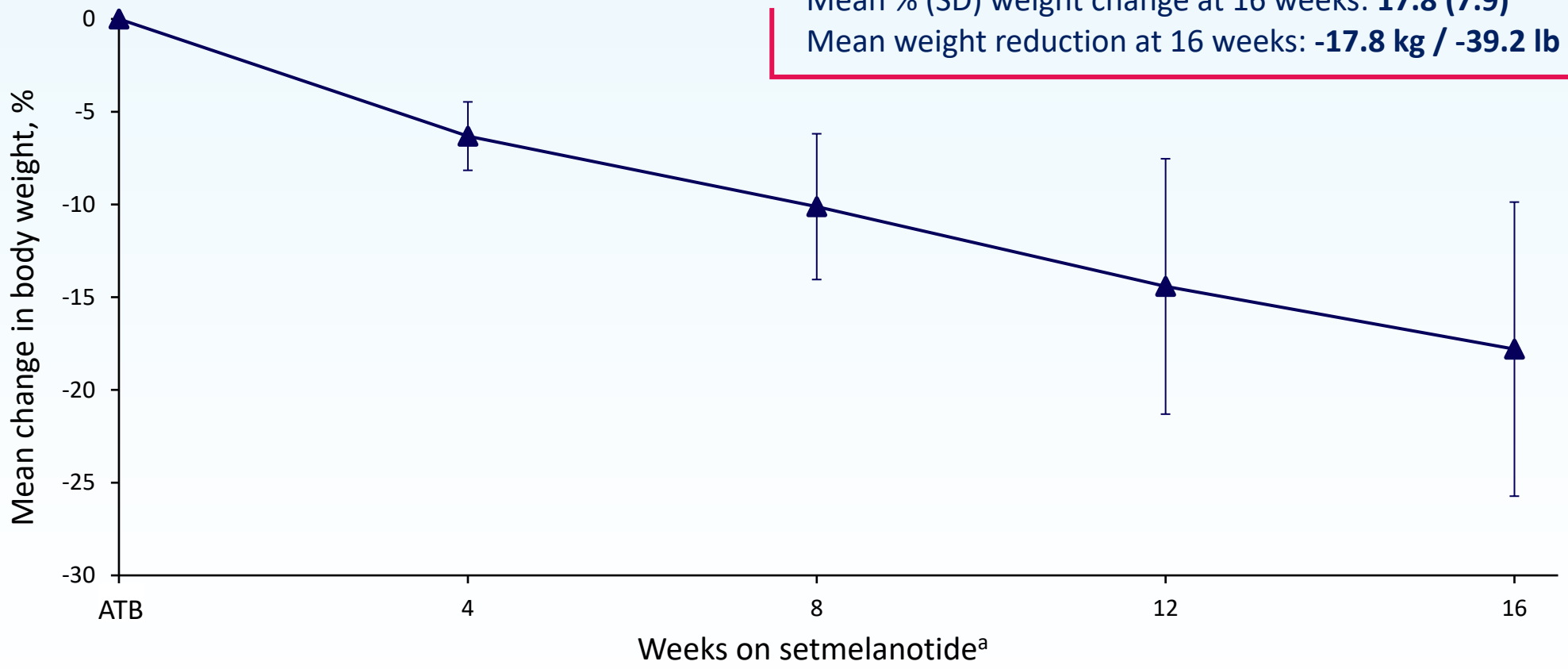
Setmelanotide Resulted in 17.8% Reduction in Body Weight at 16 Weeks

Completers (n=9)

Baseline mean (SD) weight: **107.8 kg (29.9)/ 237.7 lb (65.9)**
16-week mean (SD) weight: **90.0 kg (27.7)/ 198.4 lb (61.1)**
Mean % (SD) weight change at 16 weeks: **17.8 (7.9)**
Mean weight reduction at 16 weeks: **-17.8 kg / -39.2 lb**



Interim analysis as of the data cutoff date of May 6, 2022; [a]Error bars are the standard deviation (SD). ATB, active treatment baseline (defined as last measurement before the first dose of setmelanotide).

Setmelanotide Treatment Resulted in Statistically Significant Reduction in BMI Z Score in All Patients <18 Years Old

–1.1 point

mean change in **BMI Z score** after 16 weeks of setmelanotide (n=9; SD, 1.24 points)

3.56

Mean BMI Z at baseline

2.48

Mean BMI Z at 16 weeks

-30.2%

Mean % change in BMI Z at 16 weeks

Interim analysis as of the data cutoff date of May 6, 2022; BMI, body mass index; FAS, full analysis set; SD, standard deviation. BMI-Z represents the number of standard deviations from median BMI by child age and sex.

Setmelanotide Achieved Meaningful Reduction in "Most" Hunger Score at 16 Weeks in Patients with HO ≥12 years old

	Baseline (n=8)	16 weeks on therapy (n=7)	Change from baseline
Mean "Most" hunger (0-10) (Min, Max)	**7.18** (5.4, 8.7)	**4.55** (1.0, 7.6)	**-2.66** (-7.0, 0.4)

Interim analysis as of the data cutoff date of May 6, 2022; [b]Weekly average of scores reported for participants ≥12 years of age assessed daily using a numeric rating score from 0-10, with 0 = not hungry at all and 10 = hungriest possible.

Safety and Tolerability Was Consistent With Setmelanotide Data

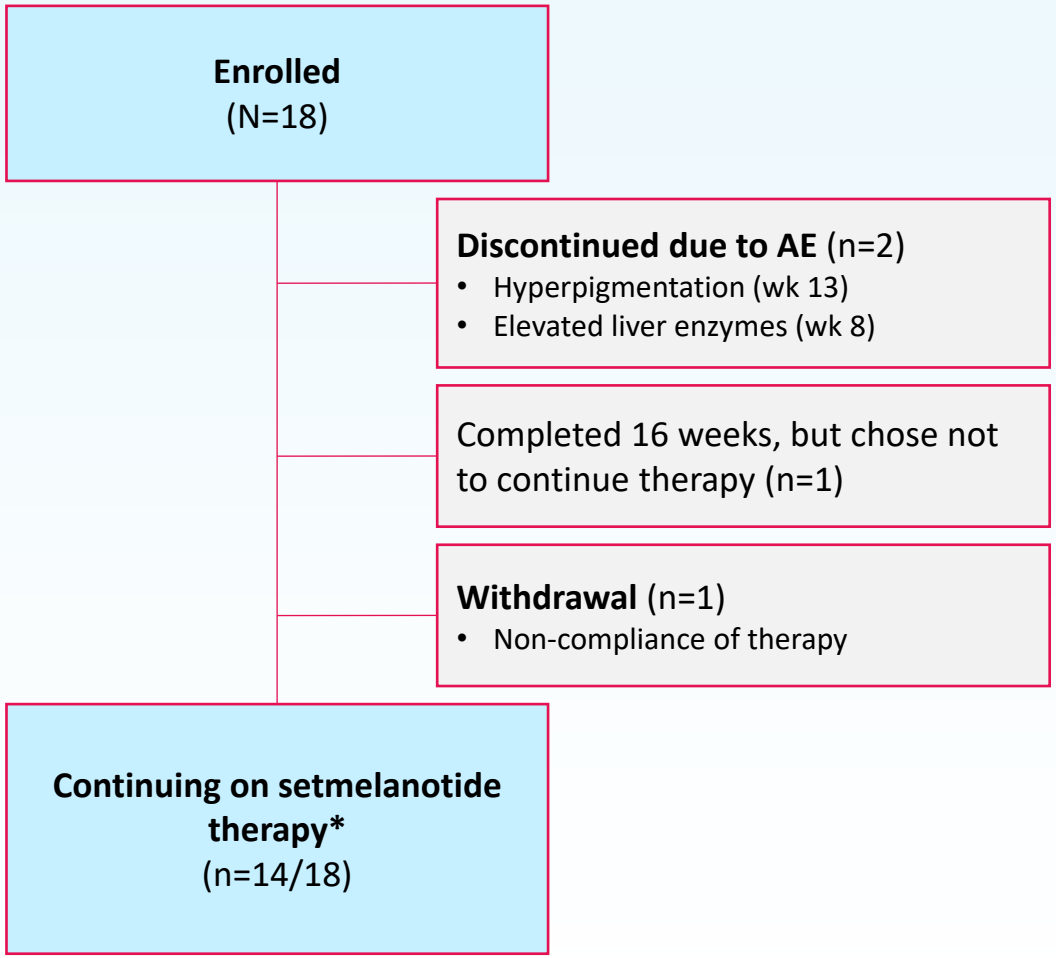
	N=11 n (%)
Treatment-related AEs	11 (100.0)
Serious AEs	2 (18.2)
Serious treatment-related AEs	1 (9.1)
Treatment-related AEs leading to drug discontinuation[a]	2 (18.2)
AEs leading to death	0

- The majority of AEs were mild, transient
- The tolerability profile in patients with hypothalamic obesity was consistent with that seen in rare genetic diseases of obesity[1-3]

	N=11 n (%)
Treatment-emergent AEs occurring in ≥20% of patients	
Nausea	7 (63.6)
Vomiting	5 (45.5)
COVID-19	5 (45.5)
Diarrhea	4 (36.4)
Injection site reaction	4 (36.4)
Abdominal pain	3 (27.3)

As of the data cutoff date of May 6, 2022; Safety analysis set is defined as all patients who received ≥1 dose of study drug; [a]Hepatic enzyme increased (n=1); skin hyperpigmentation (n=1).
AE, adverse event; 1. Clément et al. *Lancet Diabetes Endocrinol*. 2020;8:960-970. 2. Kühnen et al. *N Engl J Med*. 2016;375:240-246. 3. Haws et al. *Diabetes Obes Metab*. 2020;22:2133-2140.

Disposition of 18 Patients Enrolled in Phase 2 Study



*As of the July 11, 2022; AE, adverse event.

Rhythm Advancing Setmelanotide towards Potential Registration for Hypothalamic Obesity

Planning to present full data from 18 patients in Phase 2 trial in Fall of 2022

End of Phase 2 meeting with FDA anticipated in 2H2022

Initiate Phase 3 trial in 1H2023 to support potential registration

Appendix

An Estimated 2,500 – 7,500 Patients Live with HO Related to Craniopharyngioma in the United States

325,719,178[1]

U.S. population, all ages, in 2020

5,000 – 15,000 [2]

Estimate of craniopharyngioma prevalence based on incidence and literature-based prevalence.

2,500 – 7,500 [2, 4]

Estimated U.S. prevalence of hypothalamic obesity due to craniopharyngioma.

~600 [3]

Estimated U.S. incidence based on patients newly diagnosed with craniopharyngioma in 2020.

~250 [4]

Estimated U.S. incidence of craniopharyngioma with hypothalamic obesity per year.

1. US census. American Community Survey – DP05 ACS demographic estimates 2020;
2. 10-year CP prevalence was estimated by applying overall survival rates reported in Teng 2021 [Int J of Gen Med 14/2021: 3517-27] to the expected number of new CP cases/year as reported in the CBRTUS 2021 report Central Brain Tumor Registry of the United States (CBTRUS) 2021 Report https://cbtrus.org/reports/
3. The number of patients with HO was estimated based on targeted literature reviews of obesity development rates after CP diagnosis (short and long-term).
4. Long-term obesity post-diagnosis ranged from 6 to 91%, with a cluster around 50%. Roth CL, et. al (2015). *Obesity (Silver Spring)*; 23(6):1226-33.

An Estimated ~1,000 Patients Live with HO Related to Astrocytoma[1] in the United States

82,519,040[2]
U.S. population, children

~14,300[3]
Estimated U.S. prevalence based on patients diagnosed with astrocytoma in 2005-2019 and alive in 2020

~1,100[4]
Estimated U.S. incidence of based on patients newly diagnosed with astrocytoma in 2020

~2,500 [5]
Astrocytoma in hypothalamic region

~200 [5]
Astrocytoma in hypothalamic region

~1,000[6]
Estimated U.S. prevalence of hypothalamic obesity diagnosed up to 15 years of Astrocytoma diagnosis

~100[6]
Estimated U.S. incidence of astrocytoma with hypothalamic obesity per year

1. Includes pilocytic astrocytoma [incl. optic nerve glioma], diffuse astrocytoma, anaplastic astrocytoma, oligoastrocytic tumors, unique astrocytoma variants; excludes glioblastoma;
2. US census. American Community Survey – DP05 ACS demographic estimates 2020;
3. The 15-year AC prevalence was estimated by applying overall AC survival rates reported in Fisher 2008 [Ped blood and cancer. 51[2]:245-50] to the expected number of new AC cases per year as reported in the CBRTUS 2021 Report
4. Central Brain Tumor Registry of the United States (CBTRUS) 2021 Report https://cbtrus.org/reports/
5. Assumed 18.3% of ACs located in the hypothalamic region based on results from Fisher 2008 (Ped blood and cancer. 51[2]:245-50);
6. The number of patients with HO was estimated based on targeted literature reviews of overweight/obesity development rates after AC overall (yearly, up to 15 yrs; 53% at 15 yrs) from Armstrong et al (Neuro-oncology. 2011 Feb 1;13(2):223-34)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