Rhythm Pharmaceuticals

Phase 2 and Long-term Extension Data from Trials Evaluating Setmelanotide for the Treatment of Hypothalamic Obesity at ObesityWeek® and Plans to Initiate Phase 3 Trial in Early 2023

November 2, 2022

Forward Looking Statements

This presentation contains certain statements that are forward-looking within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and that involve risks and uncertainties, including without limitations statements regarding the potential, safety, efficacy, and regulatory and clinical progress of setmelanotide, including the anticipated timing for initiation of a Phase 3 clinical trial in hypothalamic obesity, our expectations surrounding potential regulatory submissions, approvals and the timing thereof, our business strategy, prospects and plans, including regarding commercialization of setmelanotide, and the expectations surrounding the potential market opportunity for our product candidates. Statements using words such as "expect", "anticipate", "believe", "may", "will" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including but not limited to, our ability to enroll patients in clinical trials, the outcome of clinical trials, the impact of competition, the impact of management departures and transitions, the ability to achieve or obtain necessary regulatory approvals, risks associated with data analysis and reporting, our expenses, the impact of the COVID-19 pandemic on our business operations, including our preclinical studies, clinical trials and commercialization prospects, and general economic conditions, and other risks as may be detailed from time to time in our Annual Reports on Form 10-K and Quarterly Reports on Form 10-Q and other reports we file with the Securities and Exchange Commission. Except as required by law, we undertake no obligations to make any revisions to the forward-looking statements contained in this presentation or to update them to reflect events or circumstances occurring after the date of this presentation, whether as a result of new information, future developments or otherwise.

Agenda

- David Connolly
  Executive Director, Investor Relations and Corporate Communications
- David Meeker, MD
  Chairman, President and CEO
- Christian Roth, MD
  Seattle Children's Research Institute and Division of Endocrinology, Department of Pediatrics, University of Washington
- Hunter Smith
  Chief Financial Officer

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 for **BBS** and **POMC** and **LEPR deficiency obesities**

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

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
- ✓ Patients are identified; no genetic testing required
- ✓ Patients are engaged with the system receiving specialist care for pituitary complications

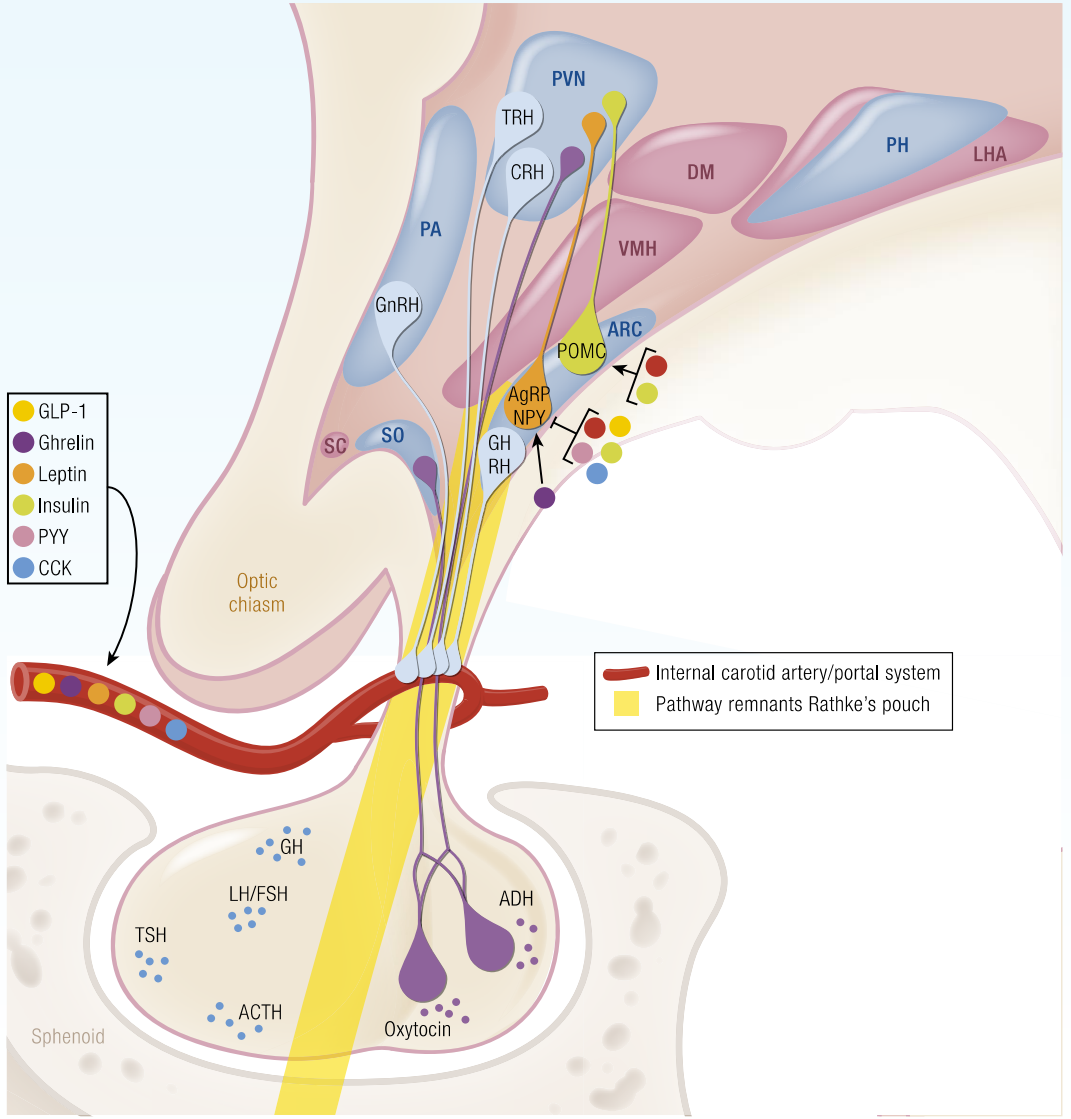
*To estimate the number of patients with incident and prevalent craniopharyngioma and astrocytoma with obesity, Rhythm analyzed the literature and used the number of new cases of each per year in the United States, overall survival rates after a diagnosis of each brain tumor type and obesity rates among those patients at diagnosis or post-diagnosis. See appendix for details.

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 most common cause

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

No approved treatments available



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

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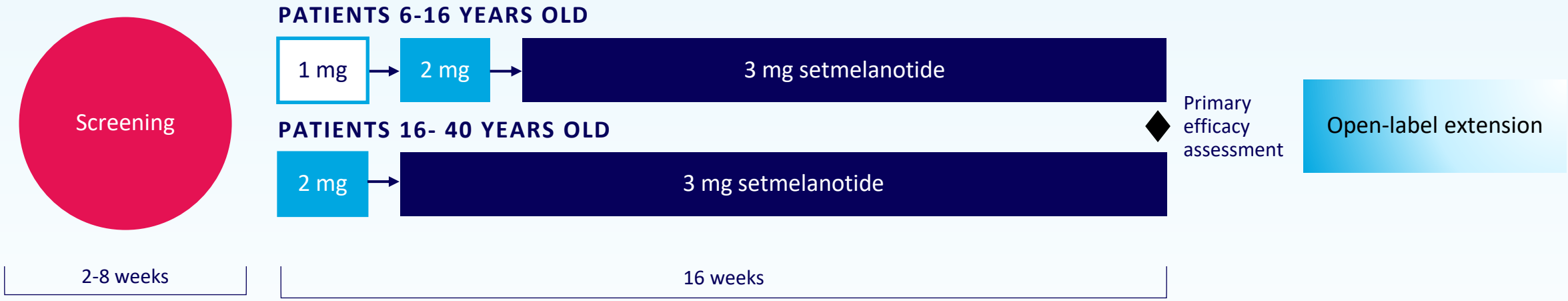
Phase 2 Trial Enrolled Heterogeneous Patient Population with Hypothalamic Obesity with Varied Tumor Presentation and Age

Baseline characteristic		Total (n=18)
Age, years	Mean (SD)	**14.6 (4.8)**
Sex, n (%)	Female / Male	**7 (38.9) /11 (61.1)**
Weight, kg	Mean (SD)	**102.8 (30.1)**
BMI, kg/m^2	Mean (SD)	**38.0 (6.5)**
Baseline BMI Z Score	Mean (SD)[b]	**3.9 (0.9)**

Tumor Type	N
Craniopharyngioma	**13**
Hamartoma	**3**
Pilocytic Astrocytoma	**1**
Adamantinomatous Craniopharyngioma	**1**

[a]Baseline weight reported for patients ≥18 years of age (n=2). [b]Baseline BMI Z score reported for patients ≥6 to <18 years of age (n=9). BMI, body mass index; SD, standard deviation.

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

Setmelanotide Achieved Significant BMI Reduction at 16 Weeks in Patients with Hypothalamic Obesity in Phase 2 Trial

Full analysis set population (N=18)

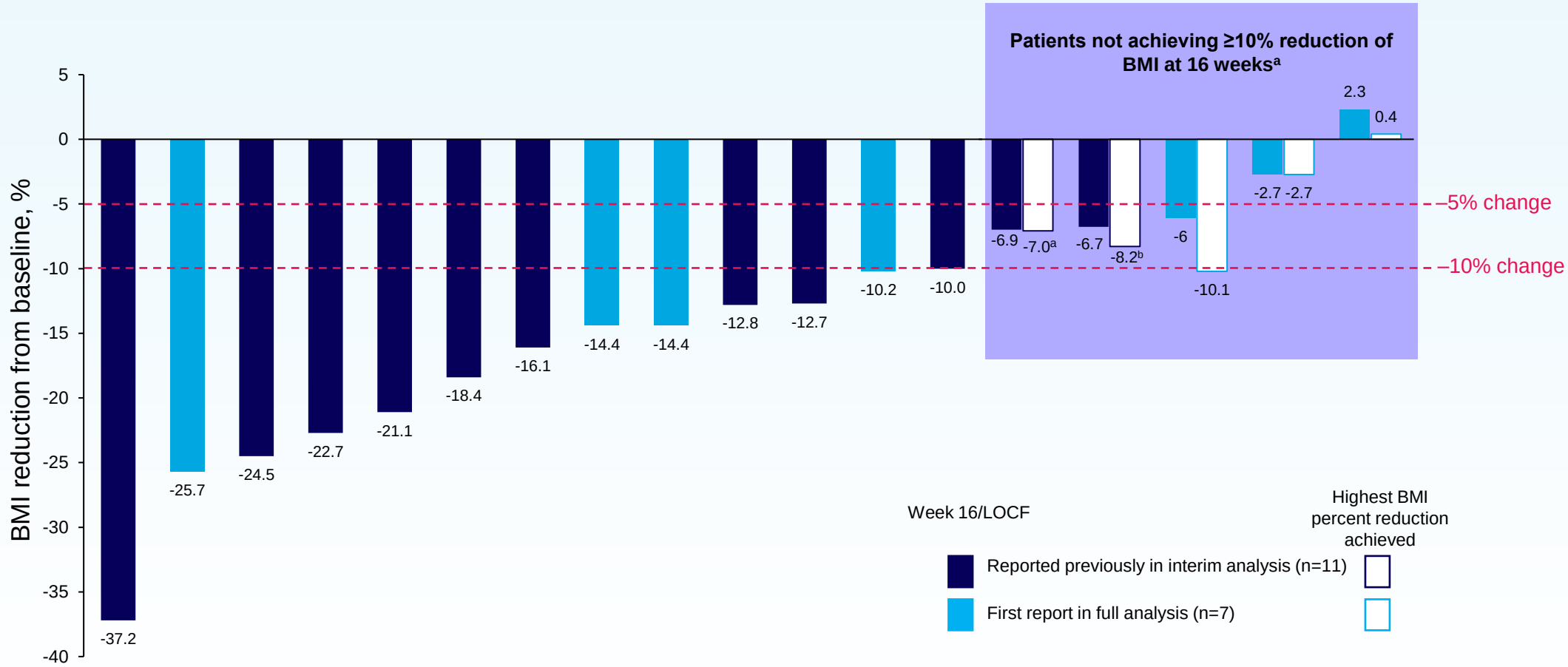
16 of 18
patients achieved
primary endpoint
of ≥5% reduction in BMI
(P<0.0001)

14 of 18
patients achieved
≥10% reduction
in BMI

–14.5%
mean change
in **BMI** at 16 weeks

As presented during The Obesity Society's ObesityWeek® 2022, November 1-4, 2022 in San Diego, CA

Setmelanotide Achieved Consistent BMI Reduction at 16 Weeks



[a]–7.0% last on treatment Week 4. [b]–8.2% last on treatment Week 12. BMI, body mass index; LOCF, last observation carried forward. As presented during The Obesity Society's ObesityWeek® 2022.

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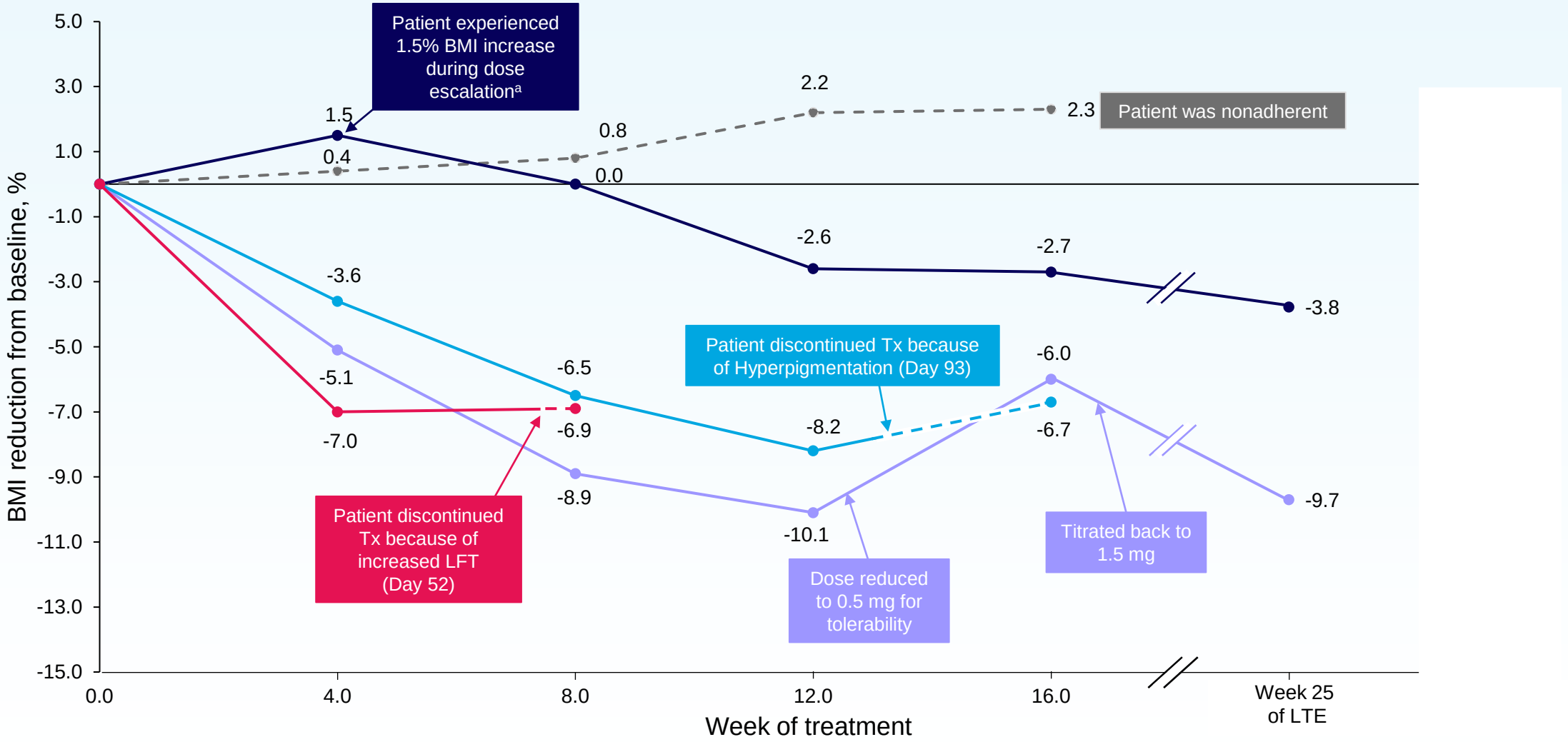
Details of Patients Not Achieving 10% Reduction in BMI



[a]Patient at therapeutic dose of 3 mg setmelanotide. BMI, body mass index; LFT, liver function test; LTE, long-term extension; Tx, treatment.

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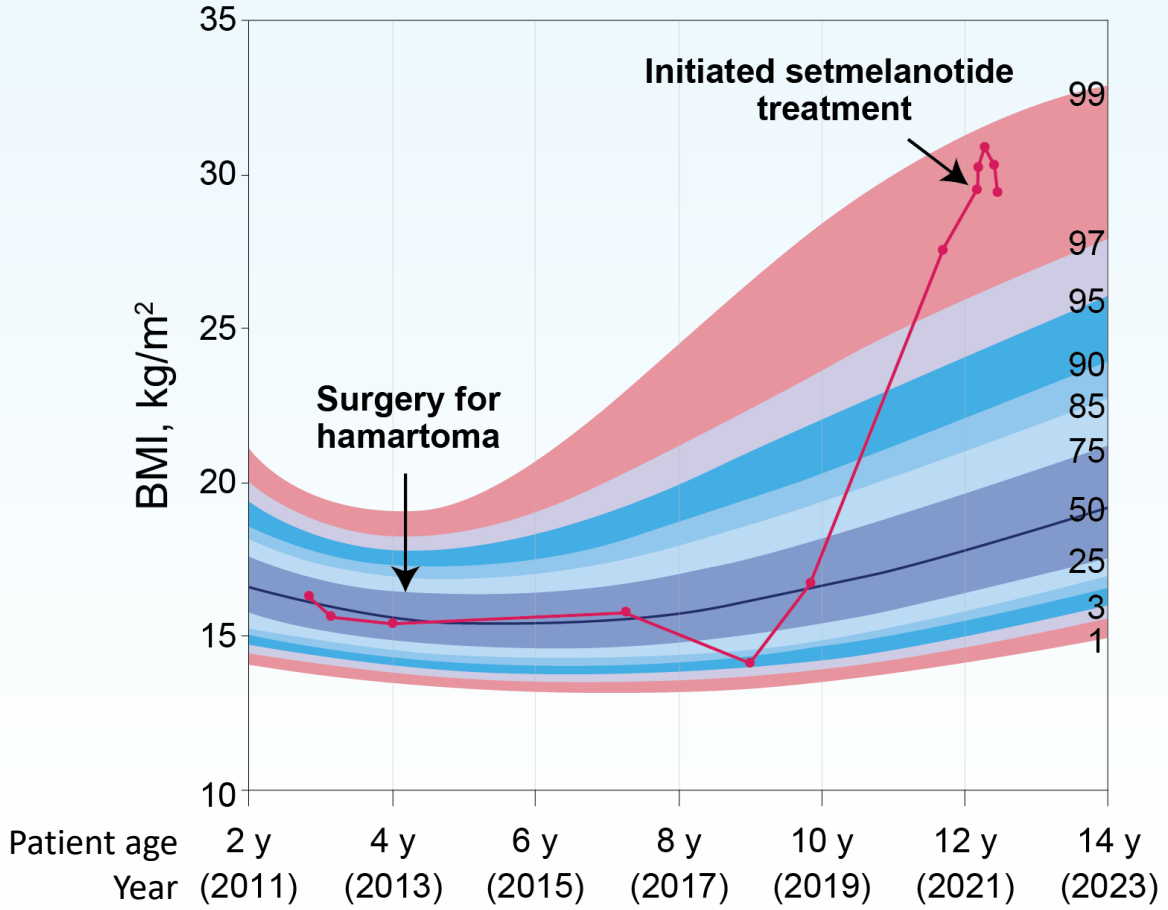
BMI Growth Chart of Patient Who Did Not Achieve ≥0.5% BMI Reduction



Patient was diagnosed with bilateral hypothalamic hamartoma that was surgically removed in 2013. Patient was 11 years of age at the time trial participation. Patient initially gained 1.5% BMI during dose escalation but once receiving therapeutic dose of 3 mg, patient experienced 2.7% BMI reduction (4.2% BMI reduction from peak weight), which continued to decline. Shaded bands represent typical trajectory of BMI percentiles over development for children aged 2-20 years (as outlined by the Centers for Disease Control and Prevention). BMI, body mass index. As presented during The Obesity Society's ObesityWeek® 2022

Patients >12 years Reported Significant Decrease in Maximal Daily Hunger at 16 Weeks

-2.9

change in mean
maximal hunger score
from baseline (n=11)

-45%*

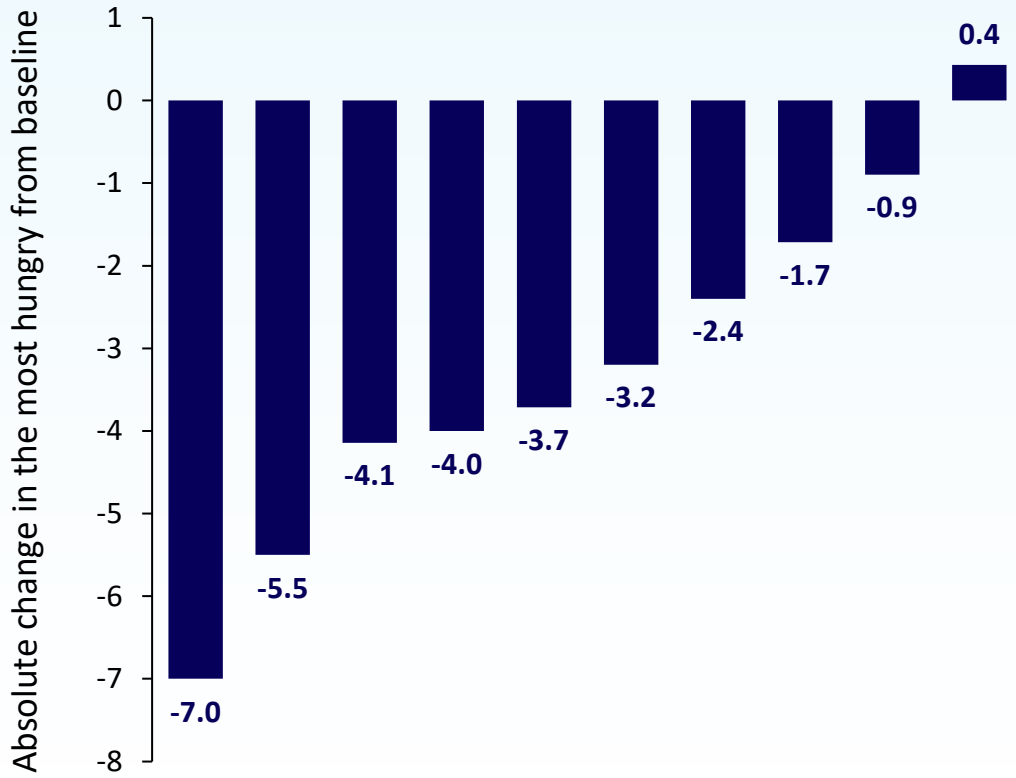
change in
maximal hunger score
(n=11)

Mean (SD) baseline hunger score was 6.6 (1.6), compared with 3.7 (2.5) at Week 16

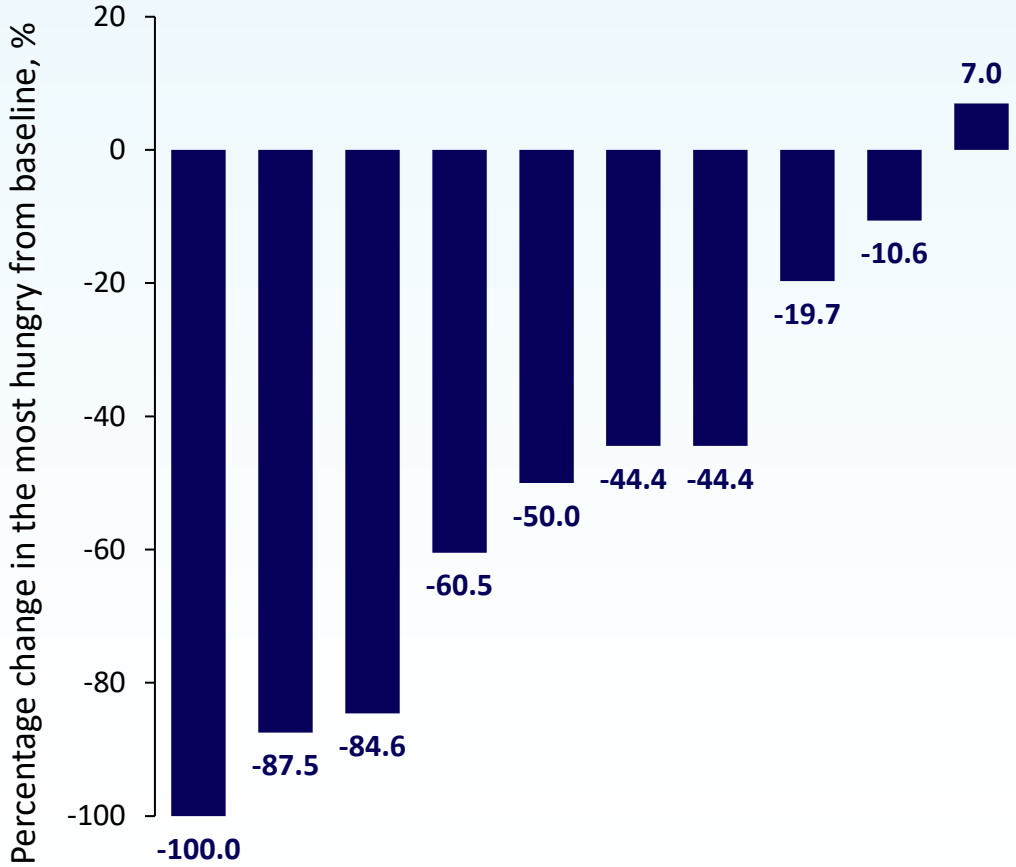
*90% confidence interval; Range (-64.8, -25.1); As presented during The Obesity Society's ObesityWeek® 2022

Setmelanotide Achieved Meaningful Reduction in Hunger Consistently across Patients >12yo at 16 Weeks on Setmelanotide

Absolute change in Mean daily most hungry scores.



Percent change in Mean daily most hungry scores



Data on file.

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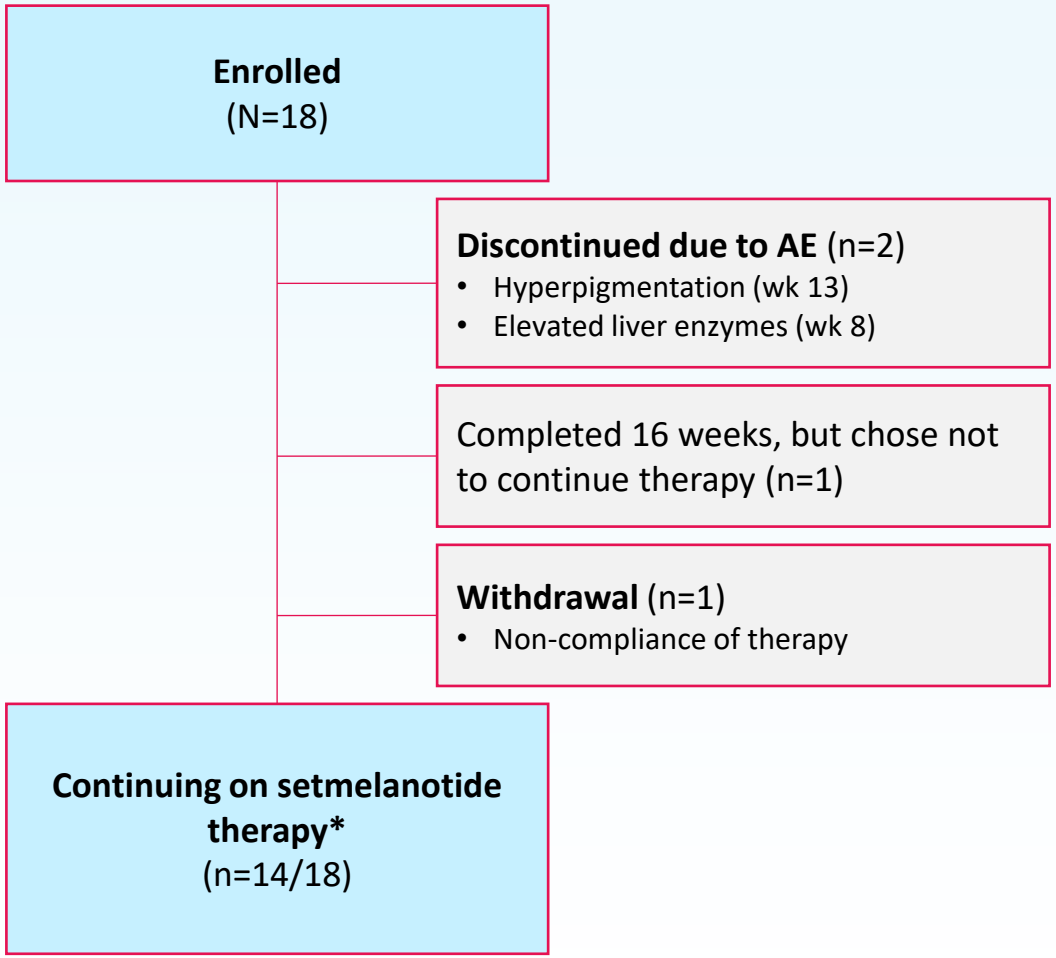
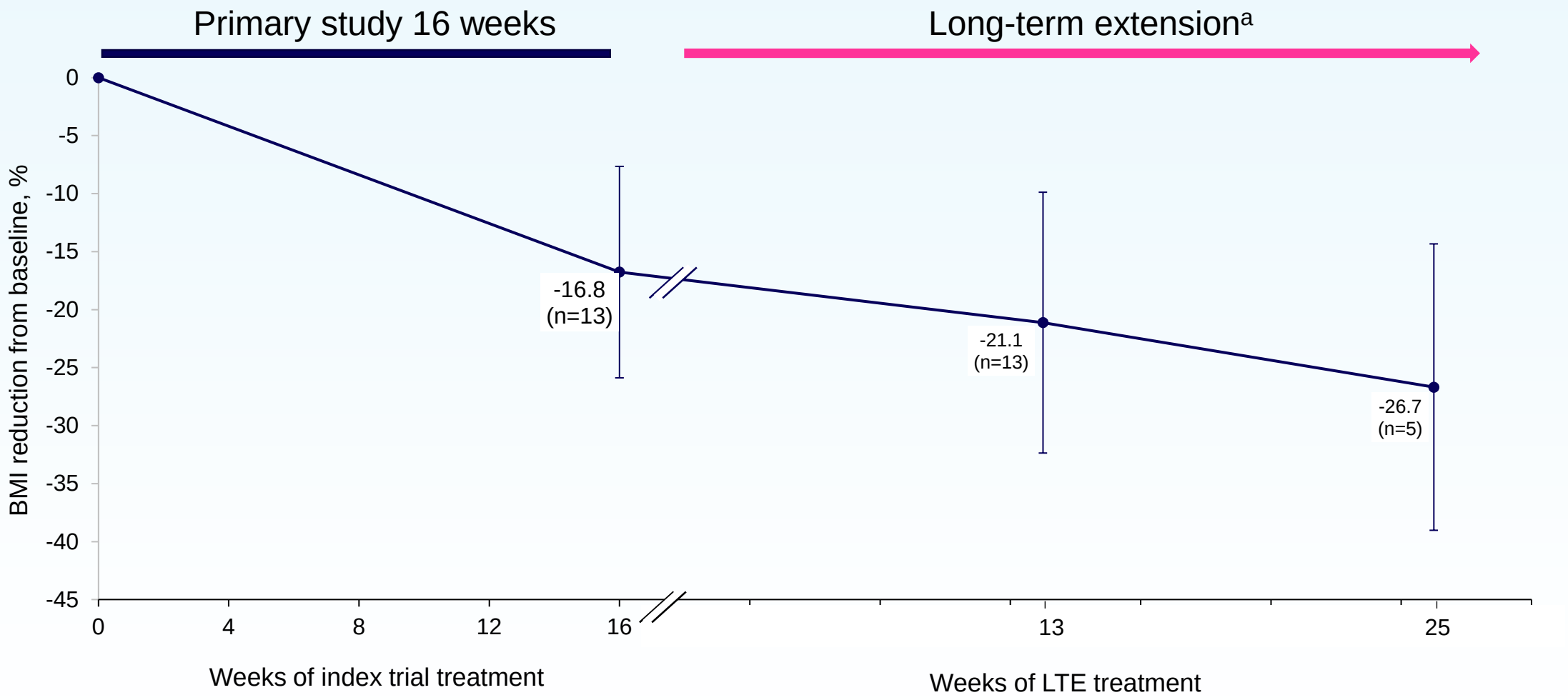
Disposition of 18 Patients Enrolled in Phase 2 Study



*As of a cut-off date of September 23, 2022; AE, adverse event.

Mean Percent Change in BMI in Patients With ≥3 Months of Follow-up in the Long-term Extension Trial



Errors bars are the standard deviation. [a]Fourteen patients have entered the long-term extension trial; one patient had not reached 3 months as of a cut-off date of September 23, 2022. BMI, body mass index. As presented during The Obesity Society's ObesityWeek® 2022.

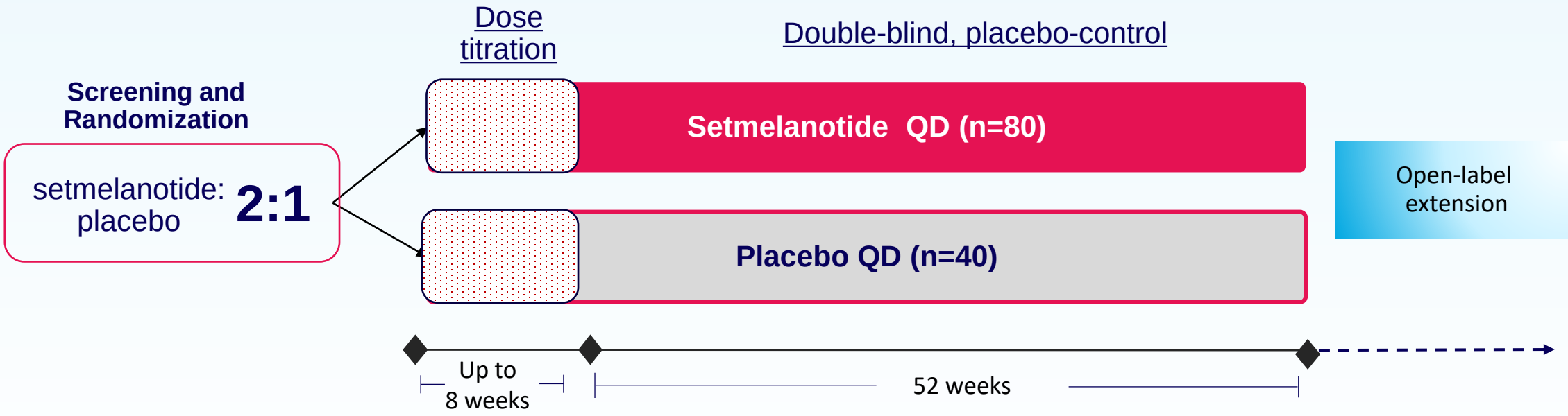
Successful Interactions with FDA

Completed Type C meeting

Achieved alignment with on trial design achieved

Received Break Through Designation for hypothalamic obesity

Phase 3 Double-blind, Randomized Controlled Trial with 120 Patients Expected to Begin in Early 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.

Primary Endpoint and Key Secondary Endpoints

Primary

- Mean % change in BMI from baseline to after approximately 52 weeks on a therapeutic regimen of setmelanotide compared with placebo
  - *With the planned sample size of N=120 patients and 2:1 randomization ratio, the trial provides ~99.5% power to detect a treatment difference of -10% in percent change of BMI from baseline at 2-sided alpha of 0.05, assuming a common standard deviation of 10% (estimate based on phase 2 data)*

Key Secondary Endpoints

- The proportion of patients with ≥5% reduction from Baseline in BMI in adult patients (≥18 years of age), and BMI Z-score reduction of ≥0.2 in pediatric patients from Baseline to after approximately 52 weeks on a therapeutic regimen of setmelanotide compared with placebo
- Mean change in the weekly average of the daily most hunger score in patients ≥12 years from Baseline to after approximately 52 weeks on a therapeutic regimen of setmelanotide compared with placebo

Questions