

# Rhythm Pharmaceuticals

Positive Topline Results from Phase 2 Trial Evaluating Oral MC4R Agonist  
Bivamelagon in Patients with Acquired Hypothalamic Obesity

July 9, 2025

Rhythm<sup>®</sup>  
PHARMACEUTICALS

# Forward-looking Statements

This presentation and the accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding our Phase 2 study to assess the efficacy and safety of bivamelagon in patients with acquired hypothalamic obesity and the potential for bivamelagon to treat hypothalamic obesity; the safety, efficacy, potential benefits of, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of bivamelagon, setmelanotide and other product candidates; the clinical design or progress of any of our products or product candidates at any dosage or in any indication; the potential benefits of any of the Company's products or product candidates for any specific disease indication or at any dosage, including the potential benefits of bivamelagon and setmelanotide for patients with acquired hypothalamic obesity or congenital hypothalamic obesity; our participation in upcoming events and presentations, and the date, time and content thereof; the sufficiency of our cash, cash equivalents and short-term investments to fund our planned operations; and the timing of any of the foregoing. 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, uncertainties, including, but not limited to, our ability to enroll patients in clinical trials, the design and 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 ability to successfully commercialize setmelanotide, our liquidity and expenses, our ability to retain our key employees and consultants, and to attract, retain and motivate qualified personnel, and general economic conditions, and the other important factors, including those discussed under the caption "Risk Factors" in Rhythm's Quarterly Report on Form 10-Q for the three months ended March 31, 2025 and our other filings 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 release or to update them to reflect events or circumstances occurring after the date of this release, whether as a result of new information, future developments or otherwise.

## Industry and Other Data

Unless otherwise indicated, information contained in this presentation concerning our industry and the markets in which Rhythm operates, including its general expectations, market position and market opportunity, is based on its management's estimates and research, as well as industry and general publications and research, surveys and studies conducted by third parties. While we believe the information from these third-party publications, research, surveys and studies is reliable, it does not guarantee the accuracy or completeness of such information, and Rhythm has not independently verified this information. Management's estimates are derived from publicly available information, their knowledge of the company's industry and their assumptions based on such information and knowledge, which they believe to be reasonable. This data involves a number of assumptions and limitations which are necessarily subject to a high degree of uncertainty and risk due to a variety of factors, including those described in our periodic reports filed with the Securities and Exchange Commission under the captions "Cautionary Note Regarding Forward Looking Statements," "Summary Risk Factors" and "Risk Factors." These and other factors could cause Rhythm's future performance and market expectations to differ materially from its assumptions and estimates.

# Bivamelagon Achieved Statistically Significant, Clinically Meaningful BMI Reductions in Patients with Acquired Hypothalamic Obesity at 14 Weeks

Bivamelagon achieved BMI reductions comparable to 12- and 16-week reductions seen in similar patient populations in setmelanotide trials

Safety and tolerability results generally consistent with a MC4R MOA and setmelanotide trials in acquired hypothalamic obesity, with limited instances of localized hyperpigmentation

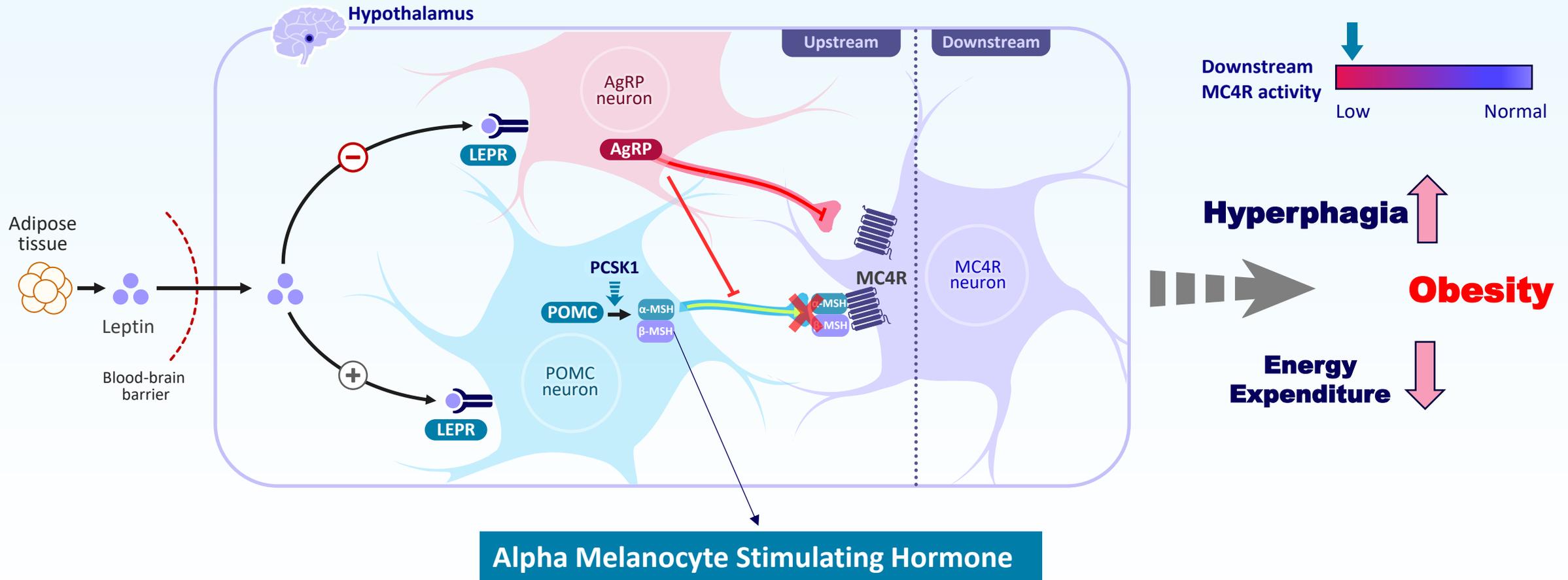
26 of 28 patients continued on to receive bivamelagon treatment in the open label extension; 26 remained in open-label extension\*

RYTM to request End-of-Phase 2 meeting with FDA with intentions to move forward to Phase 3

\*As of July 7, 2025.

Note: the comparison to setmelanotide's results are not based on a head-to-head analysis and that differences exist between study designs and patient characteristics.

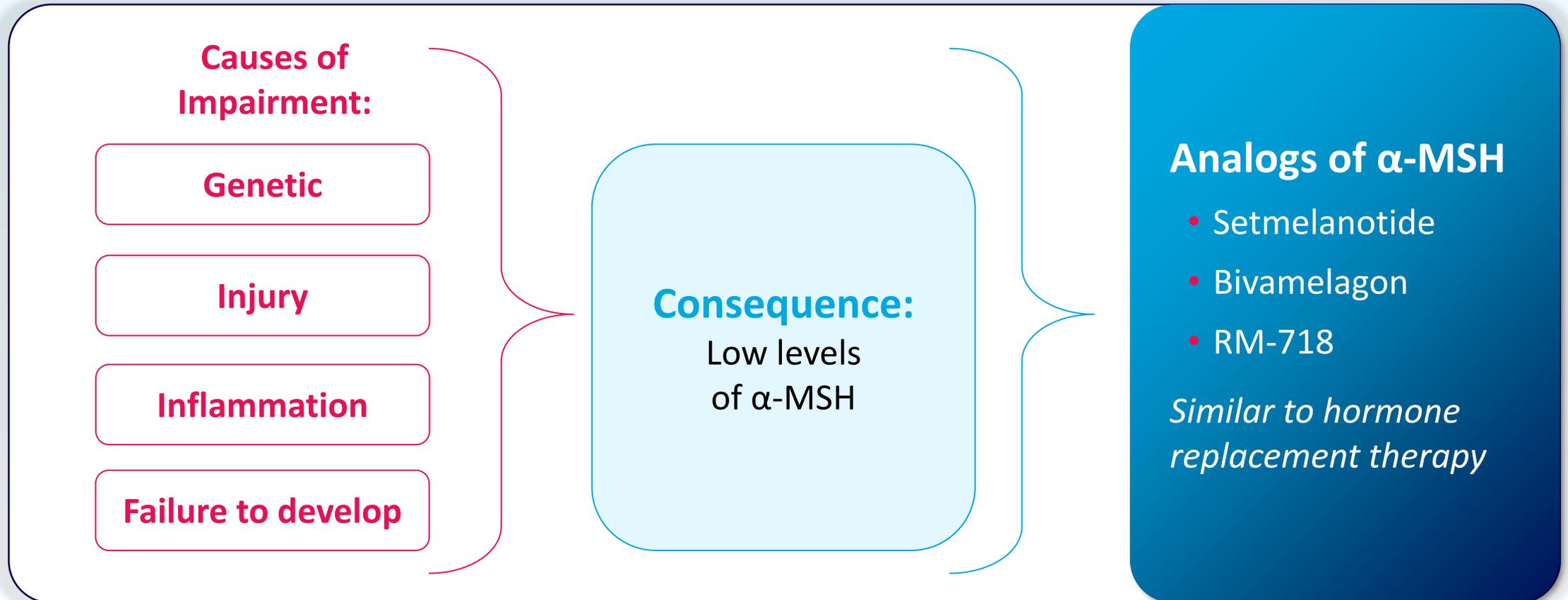
# Genetic, Traumatic and Inflammatory Impairments of MC4R Pathway Signaling Leads to Hyperphagia, Reduced Energy and Severe Obesity



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.

# MC4R Agonism Shown to Address Impaired Pathway Function



# Significant Market Opportunity for MC4R Agonists

U.S. patent protection for bivamelagon and RM-718 extends into 2040s

**Approved for IMCIVREE  
(setmelanotide) in U.S., EU,+**

**4,000 – 5,000\***

Bardet-Biedl syndrome

**600 – 2,500\***

POMC, PCSK1 and LEPR deficiencies

**Acquired hypothalamic obesity**

**5,000 – 10,000**

estimated U.S. prevalence<sup>1</sup>

**3,500 – 10,000**

estimated European prevalence<sup>2</sup>

**5,000 – 8,000**

estimated Japanese prevalence<sup>3</sup>

**Additional potential**

**~29,000\*\***

EMANATE

Lead indications

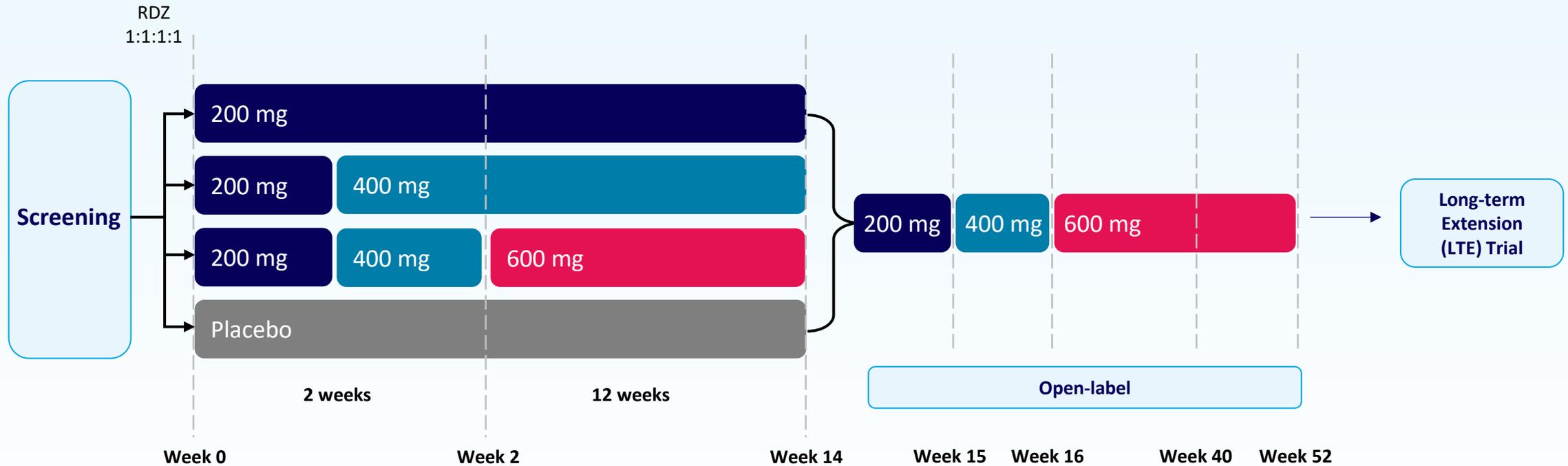
**+DAYBREAK Ph2:**

Positive signals observed  
in **six new genes and  
gene families**

\*Estimated prevalence of U.S. patients based on company estimates; does not include ex-U.S. prevalence estimates. Estimated U.S. patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results that factor in variant classifications, as applicable, current estimated responder rates and that 1.7% of the U.S. population (328M; 2019 US census) presents with severe early onset obesity (Hales et al 2018†); ~95% of individuals with severe early onset obesity remain obese into adulthood (Ward et al 2017). \*\*Estimated prevalence in United States of SH2B1 and POMC and/or PCSK1 cohorts.

1. U.S. estimates based on reported incidence of hypothalamic obesity following craniopharyngioma and long-term survival rates, (Zacharia, et al., *Neuro-Oncology* 14(8):1070–1078, 2012. doi:10.1093/neuonc/nos142; and Muller, et al., *Neuro-Oncology* 17(7), 1029–1038, 2015 doi:10.1093/neuonc/nov044.); 2. European estimates limited to the EU4 (Germany, France, Spain, Italy), UK and the Netherlands and prevalence of 0.1-0.3 in 10,000 patients; 3. Rhythm estimates the prevalence of acquired hypothalamic obesity in Japan to be approximately 5,000 to 8,000 based on our review of tumor registries and claims data; Prevalence is 2-3 times higher than in the USA & Europe due to a higher reported frequency of craniopharyngioma.

# SIGNAL Trial: 14-week, Phase 2 Open-label Trial Evaluating Bivamelagon in Patients with Hypothalamic Obesity



## Inclusion criteria

≥18yo BMI ≥30 kg/m<sup>2</sup>

12-<18 yo ≥95th percentile

Setmelanotide-naive

# Overall Baseline Demographics

Overall  
bivamelagon  
population

**N=28**

**38.7 kg/m<sup>2</sup>**

Mean BMI

**46.4%**

Female

**82.1%**

Patients with  
craniopharyngioma

**25.4yo**

Mean Age  
(13 of 28 <18yo)

**7 years**

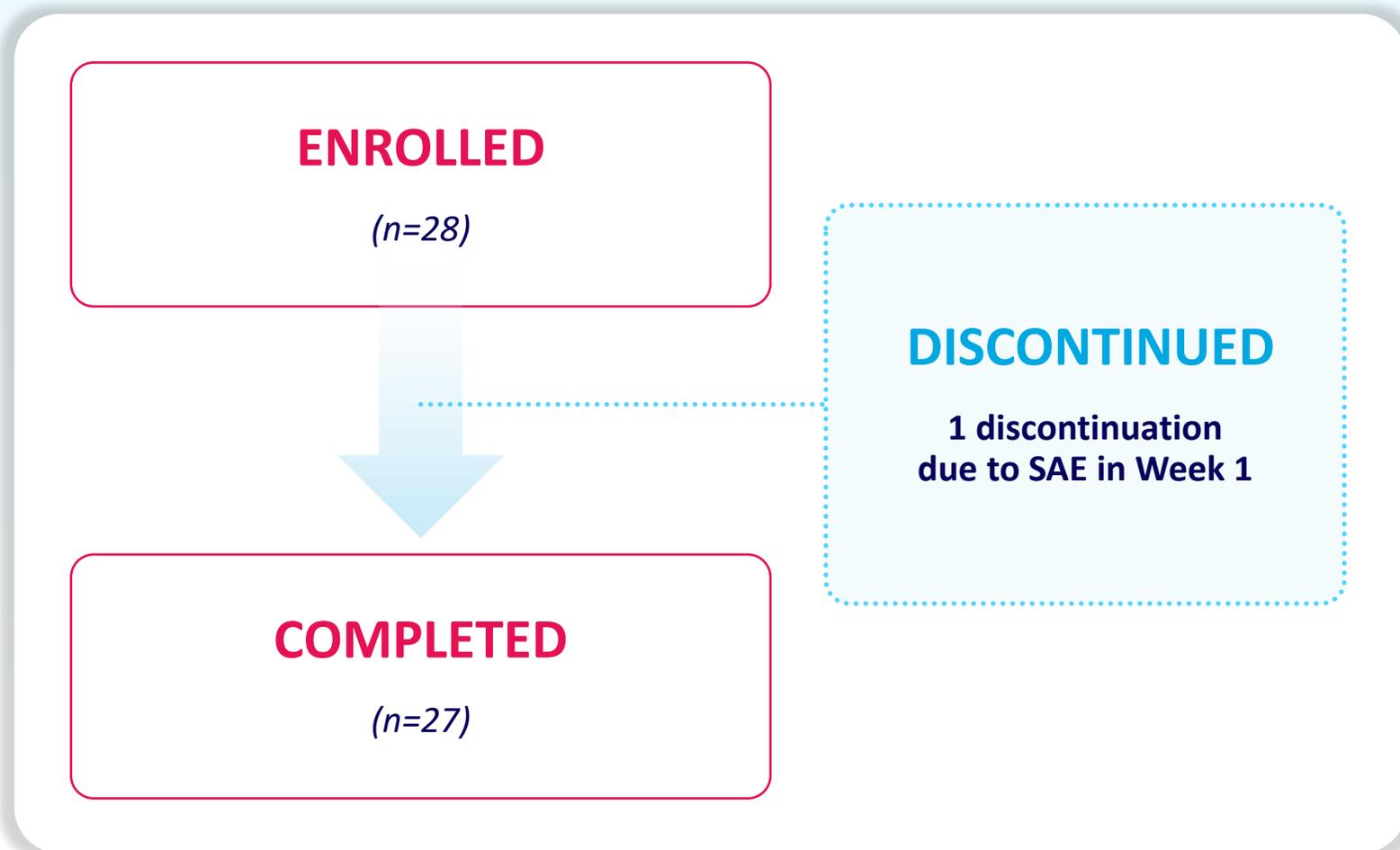
Mean time from hypothalamic  
injury to trial enrollment

# Baseline Demographics

BASELINE CHARACTERISTICS		Biva 200 mg (N=6)	Biva 400 mg (N=7)	Biva 600 mg (N=8)	Placebo (N=7)
Age, years	Mean (SD)	20.2 (9.2)	21.0 (7.9)	31.9 (23.0)	27.0 (20.2)
Sex, n (%)					
	Female	3 (50.0)	4 (57.1)	3 (37.5)	3 (42.9)
	Male	3 (50.0)	3 (42.9)	5 (62.5)	4 (57.1)
Race, n (%)					
	White	6 (100.0)	5 (71.4)	5 (62.5)	6 (85.7)
	Black or African American	1 (16.7)*	0	1 (12.5)	1 (14.3)
	Asian	0	2 (28.6)	1 (12.5)	0
	Not reported	0	0	1 (12.5)	0
Ethnicity, n (%)					
	Hispanic or Latino	0	0	2 (25.0)	2 (28.6)
	Not Hispanic or Latino	6 (100.0)	7 (100.0)	6 (75.0)	5 (71.4)
Hypothalamic involvement, n (%)					
	Bilateral	3 (50.0)	1 (14.3)	4 (50.0)	5 (71.4)
	Unilateral	1 (16.7)	2 (28.6)	2 (25.0)	0
	Unknown	2 (33.3)	4 (57.1)	2 (25.0)	2 (28.6)
Weight, kg	Mean (SD)	118.0 (35.6)	103.0 (29.3)	106.2 (22.4)	108.0 (42.3)
BMI, kg/m <sup>2</sup>	Mean (SD)	38.0 (6.2)	37.7 (9.0)	41.4 (10.7)	37.0 (7.7)
BMI Z-score (<18 years)	Mean (SD [n])	3.0 (0.5 [3])	2.4 (0.6 [3])	3.7 (1.8 [4])	3.2 (1.4 [3])
Waist circumference, cm	Mean (SD)	120.0 (14.4)	112.8 (22.7)	119.4 (21.0)	113.4 (20.3)

BMI, body mass index. \*More than one response can be provided for Race and, as such, the percentage may total more than 100%.

# Vast Majority of Patients Transitioned to Open-label Extension and Have Remained on Bivamelagon Therapy



**26 of 27** eligible participants transitioned to open-label extension (OLE) phase for up to 38 weeks

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OLE participants retitrated from 200mg to maximum 600mg dose, as tolerated, to preserve blind

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**26** patients remained in OLE as of July 7, 2025

# Bivamelagon Achieved Statistically Significant BMI Reductions at All Doses

**Placebo**

**+2.18%**

Mean BMI increase  
from baseline  
(n=7)

**200 mg**

**-2.68%**

Mean BMI reduction  
from baseline  
(n=6)  
**p-value = 0.0180**

**400 mg**

**-7.69%**

Mean BMI reduction  
from baseline  
(n=7)  
**p-value = 0.0002**

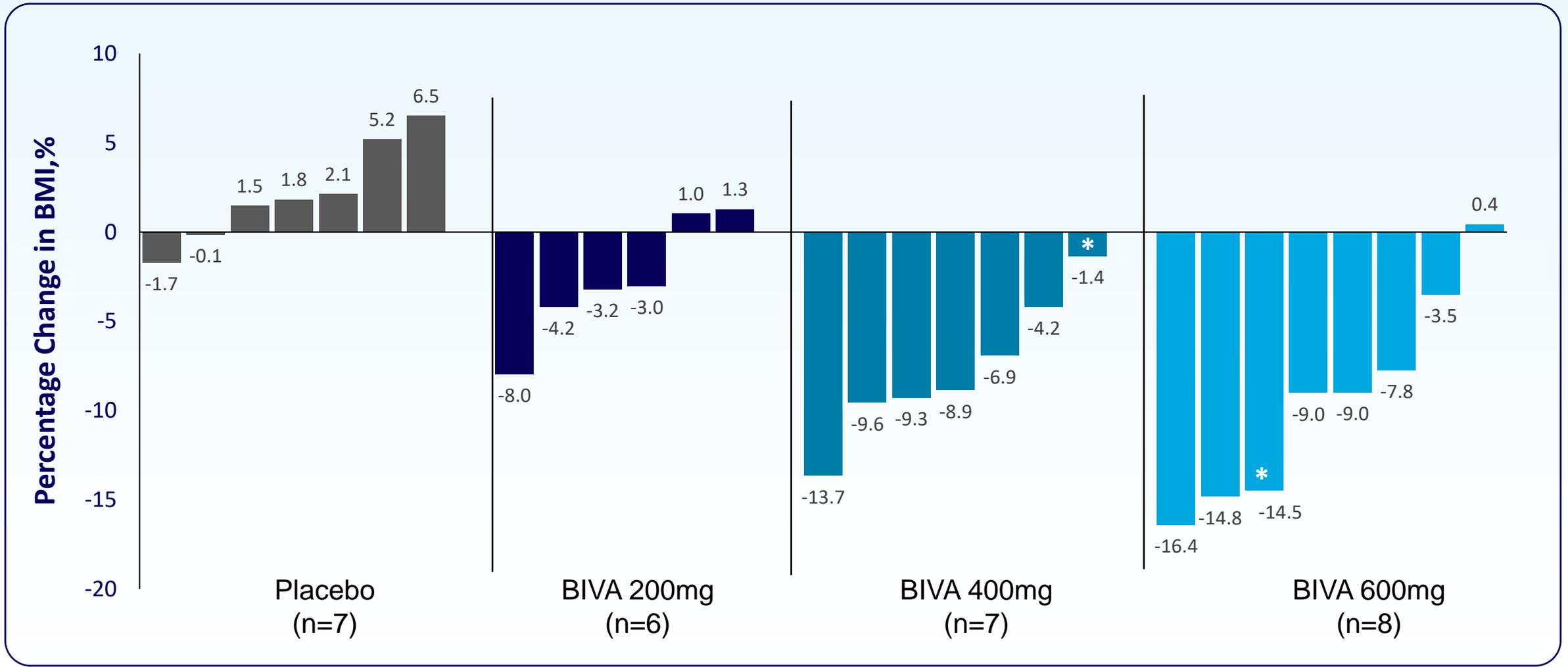
**600 mg**

**-9.31%**

Mean BMI reduction  
from baseline  
(n=8)  
**p-value = 0.0004**

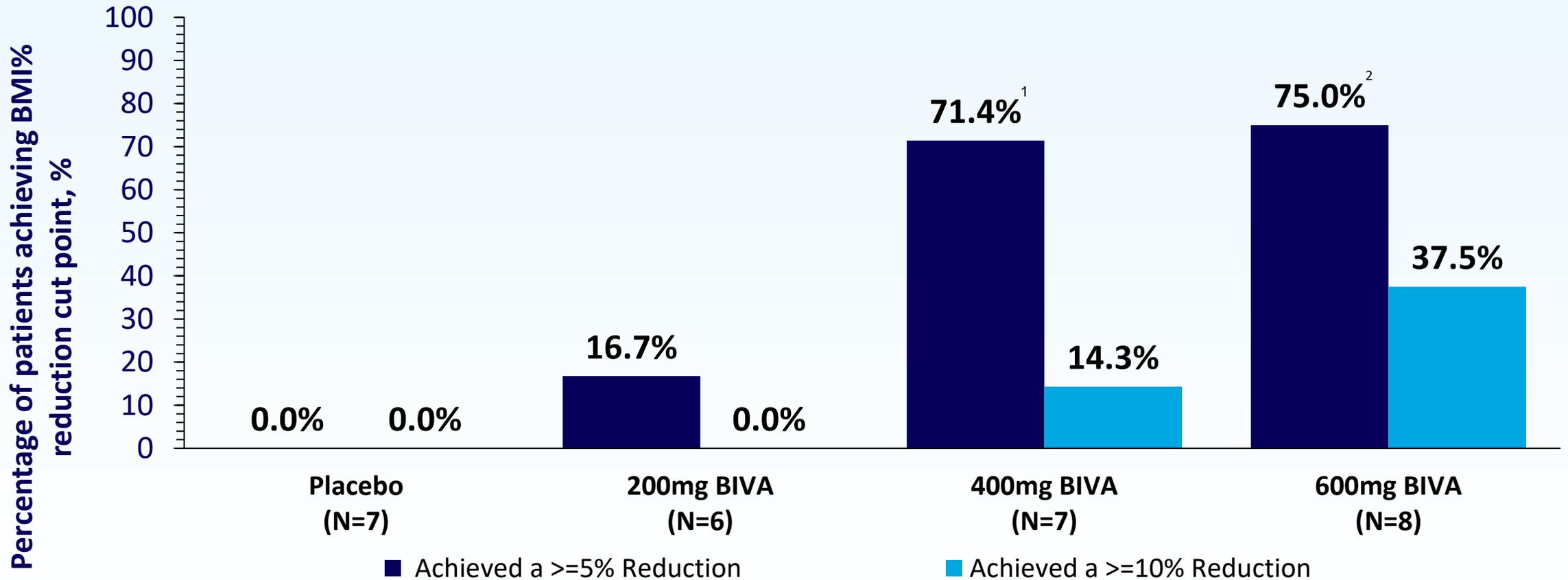
Note: Arithmetic means and p-values from 2-sided t-test shown above.

# Individual Percentage Change in BMI from Baseline to Week 14



\* Last observation carried forward (LOCF): One patient in 400mg cohort discontinued therapy at week one.

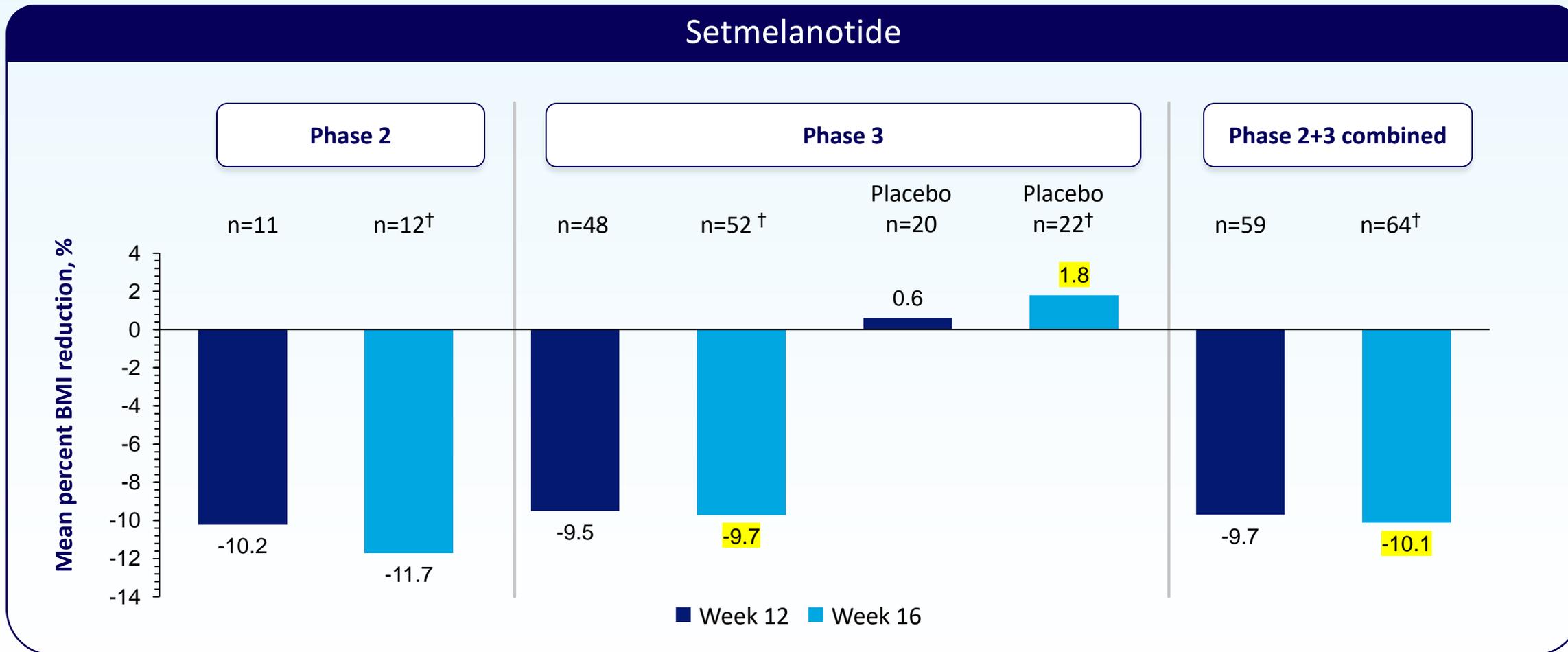
# Patients Achieved BMI Reductions of at least 5%, 10% at Week 14



1. P=0.0105

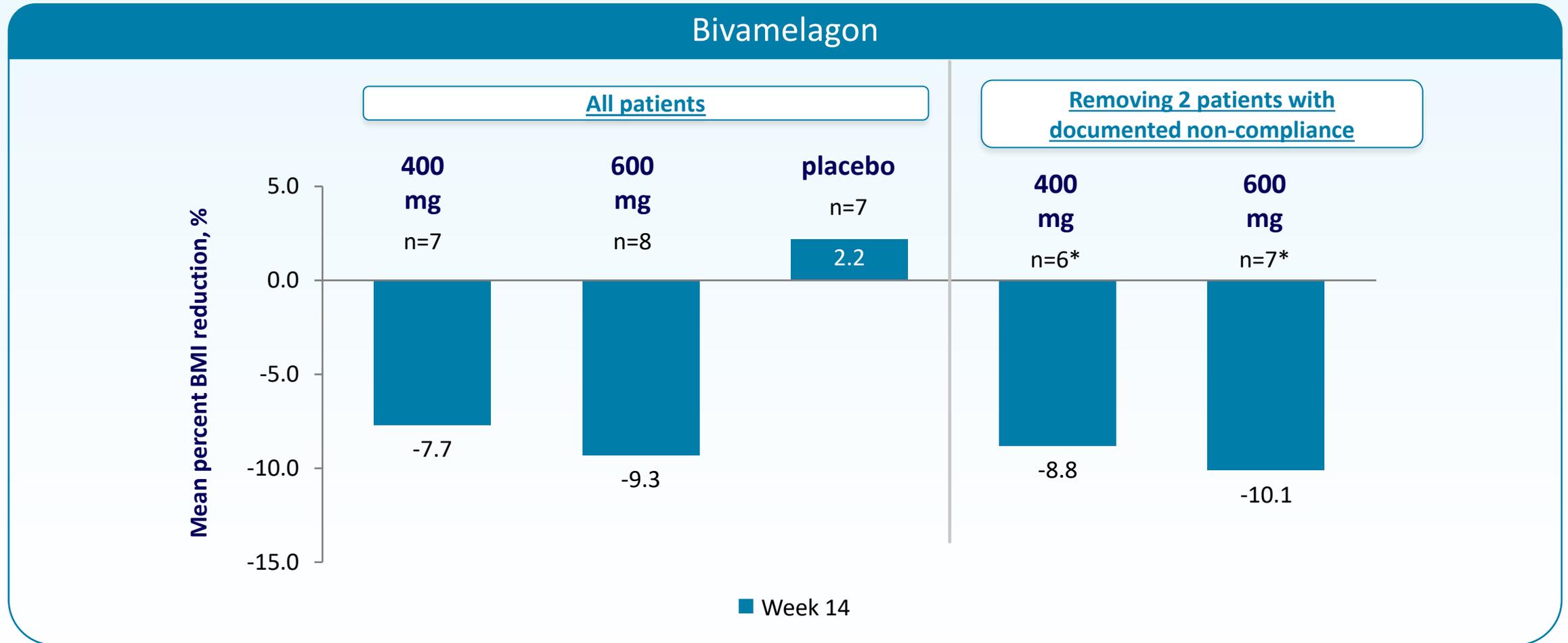
2. P= 0.0056 vs placebo

# Setmelanotide Results in Ph2, Ph3 Trials at 12 and 16 Weeks in Patients >12 Years Old



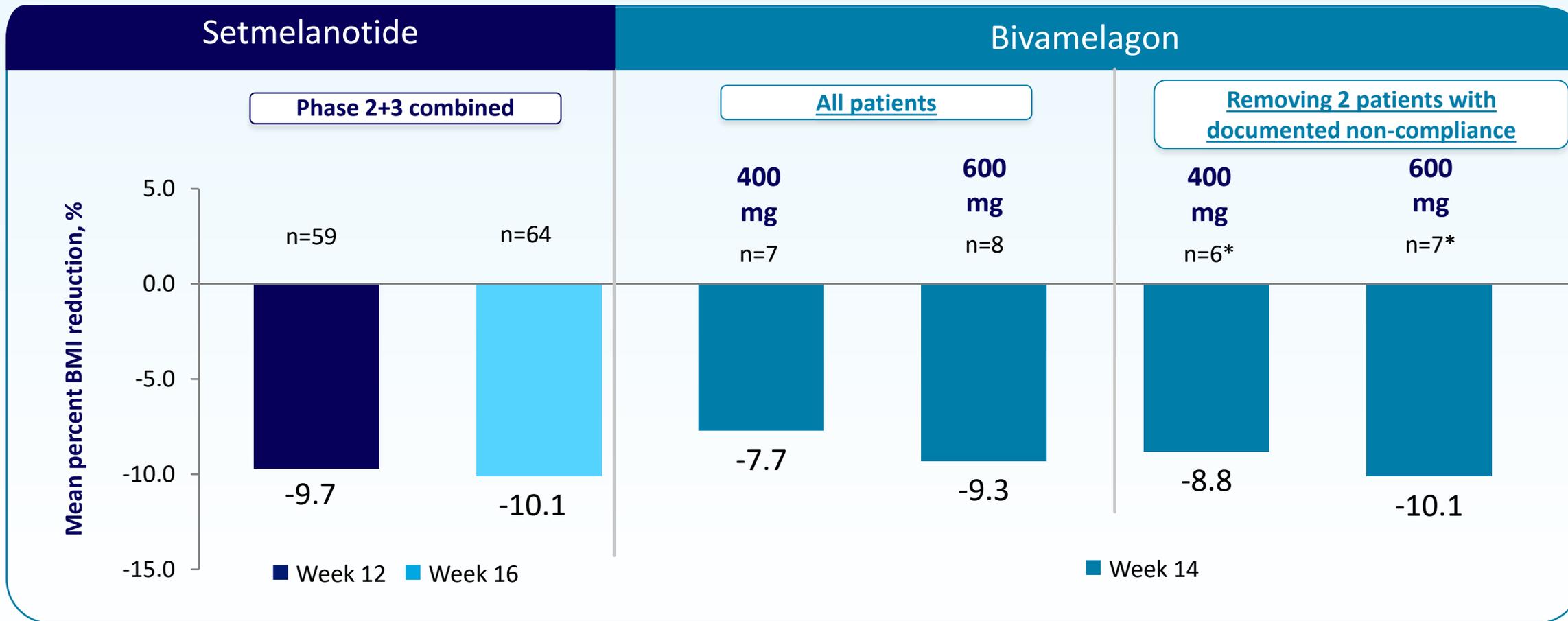
These values represent patients who demonstrated compliance and no concomitant GLP1 therapy (no patients who enrolled in the Phase 2 bivalmelagon were on concomitant GLP1 therapy). Patients deemed non-compliant were excluded. <sup>†</sup>LOCF performed for week 16 only.

# Bivamelagon BMI Reductions at Week 14



\*1 patient in 400 mg arm and 1 patient in 600 mg arm removed due to Week 1 discontinuation and documented partial compliance respectively.

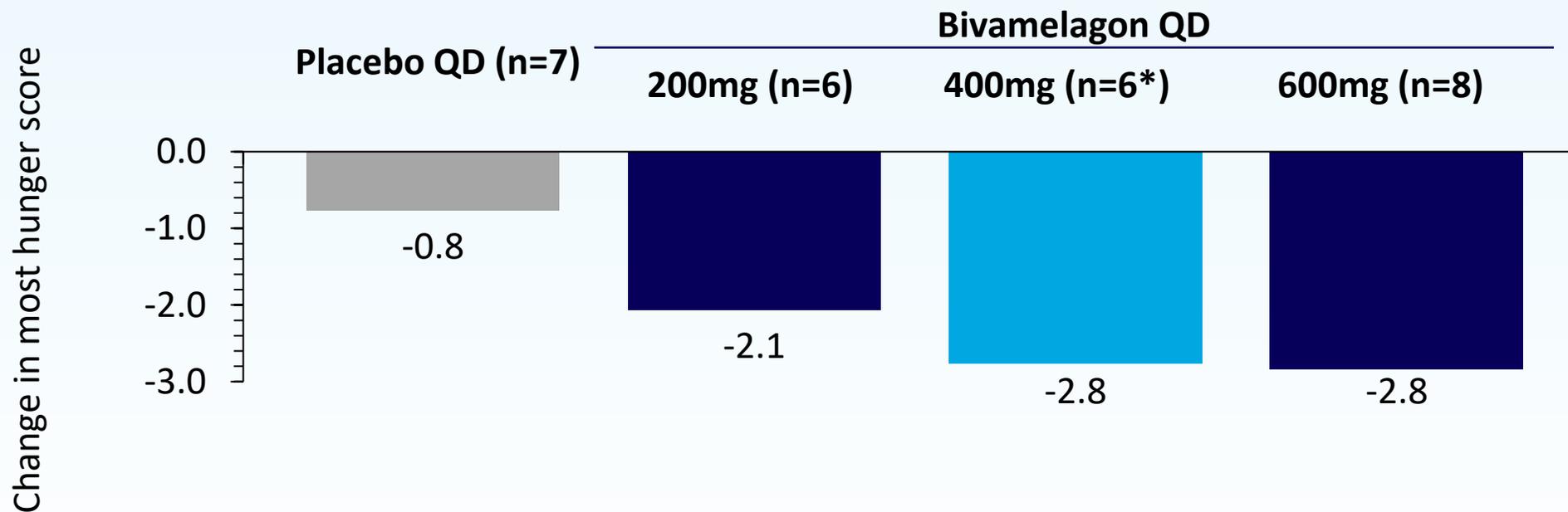
# Bivamelagon Achieved BMI Reductions Consistent with Setmelanotide



\*1 patient in 400 mg arm and 1 patient in 600 mg arm removed due to Week 1 discontinuation and documented partial compliance respectively.

\* LOCF (LOCF not performed for Wk12, patients not included in those means)

# Bivamelagon Achieved Meaningful Reductions in 'Most' Hunger Scores at Week 14



Weekly average of daily scores on a 10-point scale with 10 being 'most' hungry.

\*One patient 400mg bivamelagon who did not complete trial did not have Week 14 score and is not included

# AEs consistent with MC4R Mechanism, Setmelanotide Trials in Acquired Hypothalamic Obesity

n (%)	BIVA 200mg (N=6)	BIVA 400mg (N=7)	BIVA 600mg (N=8)	Placebo (N=7)
Any AEs	6 (100)	7 (100)	8 (100)	6 (86)
Serious AEs	0 (0)	1 (14)	0	1 (14)
Treatment-Related AEs	6 (100)	7 (100)	8 (100)	3 (43)
Treatment-Related SAEs	0	1 (14)	0	0
Grade ≥3 AE	0	2 (29)	0	1 (14)
AEs Leading to Study Intervention Discontinuation	0	1(14)*	0	0
<b>AEs with ≥10% in all BIVA dosing (N=21)</b>				
Nausea	6 (100)	5 (71)	4 (50)	2 (29)
Diarrhea	2 (33)	5 (71)	3 (37)	1 (14)
Vomiting	2 (33)	4 (57)	4 (50)	2 (29)
Headache	1 (17)	5 (71)	0 (0)	2 (29)
<b>AEs of Special Interest</b>	2 (33)	3 (43)	0	0
Skin Pigmentation**	2 (33)	2 (29)	0	0
Adrenal Adverse Events	0	1 (14)	0	0

\*Rectal bleeding; \*\* In addition to the four patients on study drug, one placebo-treated participant had skin hyperpigmentation that was not treatment related and therefore not included as an AE of special interest.

# Developing New, Smaller Bivamelagon Tablet Potentially to Improve Tolerability

## Current Phase 2 tablet

- 200 mg tablet (26% drug load)
- Total weight 823 mg
- 18 mm x 8.6 mm



## New Formulation Tablet

- 600 mg Tablet (90% drug load)
- Total weight 760 mg
- 18 mm x 8.33 mm



*Size 1 Capsule 19.4 mm x 6.91 mm and  
Size 0 Capsule 21.6 mm x 7.64 mm*



# Next Anticipated Steps for Development of Bivamelagon

## Data presentations

- ENDO 2025
- Update on open-label extension study

## Regulatory feedback

- Request End-of-Phase 2 meeting with U.S. FDA
- Seek scientific advice from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA)

**Initiate Phase 3 trial to evaluate bivamelagon in hypothalamic obesity in 2026**

# Questions?