UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d)
of **the Securities Exchange Act of 1934**

Date of Report (Date of earliest event reported): January 9, 2026

RHYTHM PHARMACEUTICALS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**001-38223**	**46-2159271**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification Number)

222 Berkeley Street
12th Floor
Boston, MA 02116
(Address of principal executive offices) (Zip Code)

Registrant's telephone number, including area code: **(857) 264-4280**

N/A
(Former name or former address, if changed since last report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)
☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)
☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))
☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.001 par value per share	RYTM	The Nasdaq Stock Market LLC (Nasdaq Global Market)

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 2.02. Results of Operations and Financial Condition.

On January 9, 2026, Rhythm Pharmaceuticals, Inc. (the "Company") issued a press release announcing, among other things, the Company's preliminary unaudited net product revenues for the fourth quarter of 2025 and the fiscal year ended December 31, 2025. The full text of the press release issued by the Company is furnished as Exhibit 99.1 to this Current Report on Form 8-K.

The information contained in Item 2.02 of this Current Report on Form 8-K (including Exhibit 99.1) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended (the "Securities Act"), or the Exchange Act, except as expressly provided by specific reference in such a filing.

Item 7.01. Regulation FD Disclosure.

On January 9, 2026, in connection with its participation in the J.P. Morgan Healthcare Conference, the Company posted a corporate slide presentation in the "Investors" portion of its website at www.rhythmtx.com. A copy of the presentation is furnished as Exhibit 99.2 to this Current Report on Form 8-K. The Company undertakes no obligation to update, supplement or amend the materials attached hereto as Exhibit 99.2.

The information contained in Item 7.01 of this Current Report on Form 8-K (including Exhibit 99.2) shall not be deemed "filed" for purposes of Section 18 of the Exchange Act, or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act, or the Exchange Act, except as expressly provided by specific reference in such a filing.

Item 8.01. Other Events

On January 9, 2026, the Company announced preliminary unaudited net revenues from global sales of IMCIVREE® (setmelanotide) of approximately $57 million for the fourth quarter of 2025, an increase of 11% percent on a sequential basis from the third quarter of 2025. Net product revenues for the full year of 2025 are expected to be approximately $194 million, compared to $130 million for the full year of 2024, an increase of approximately 50% year over year. U.S. sales of IMCIVREE contributed approximately 68% of fourth quarter preliminary unaudited net product revenues and approximately 69% of full-year 2025 preliminary unaudited net product revenues.

The Company also provided an update on anticipated upcoming milestones:

Setmelanotide

Acquired Hypothalamic Obesity (HO)
- Launch IMCIVREE in the United States for the treatment of acquired hypothalamic obesity pending FDA approval; the FDA's assigned PDUFA goal date is March 20, 2026;
- Announce topline data in the 12-patient Japanese cohort of the setmelanotide Phase 3 trial in acquired HO in the first quarter of 2026.

Congenital HO
- Complete enrollment in the setmelanotide Phase 3 trial substudy in congenital HO in the first half of 2026.

Genetically Caused MC4R Pathway Diseases

- Announce topline data in the Phase 3 EMANATE trial evaluating setmelanotide in genetically caused MC4R pathway diseases in the first quarter of 2026.

Prader-Willi Syndrome (PWS)

- In December 2025, Rhythm announced positive preliminary data for the exploratory phase 2 trial of setmelanotide in patients with PWS that showed BMI and hyperphagia reductions at month 3 and month 6, as well as safety and tolerability consistent with setmelanotide's well-established clinical profile. Rhythm anticipates announcing six-month results from 18 patients from the ongoing Phase 2 trial in the first half of 2026.

Bivamelagon

- Pending further feedback from U.S. and European regulatory agencies, initiate a pivotal Phase 3 trial evaluating bivamelagon in acquired HO in 2026.

RM-718

- Complete enrollment in the Phase 1, Part C trial evaluating the weekly, MC4R agonist RM-718 in patients with acquired HO in the first quarter of 2026.

Financial Disclosure Advisory

This Current Report on Form 8-K contains certain estimated preliminary financial results for the fourth quarter and fiscal year ended December 31, 2025. These estimates are based on the information available to the Company at this time. The Company's financial closing procedures for the fourth quarter and full year 2025 are not yet complete and, as a result, actual results may vary from the estimated preliminary results presented here due to the completion of the Company's financial closing and audit procedures. The estimated preliminary financial results have not been audited or reviewed by the Company's independent registered public accounting firm. These estimates should not be viewed as a substitute for the Company's full interim or annual financial statements. Accordingly, you should not place undue reliance on this preliminary data.

Forward-Looking Statements

This Current Report on Form 8-K contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this Current Report that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding the Company's anticipated financial performance for any period of time, including preliminary unaudited revenues, for the fourth quarter and full year ending December 31, 2025; the potential, safety, efficacy, and regulatory and clinical progress, potential regulatory submissions, approvals and timing thereof of setmelanotide and other product candidates, including bivamelagon (LB54640) and RM-718; the announcement of data from our clinical trials, including our global Phase 3 trial evaluating setmelanotide in patients with acquired hypothalamic obesity; the ongoing enrollment of patients in our clinical trials; our participation in upcoming events and presentations; and the timing of any of the foregoing. Statements using words such as "expect", "anticipate", "believe", "may", "will", "aim" and similar terms are also forward-looking statements. Such statements are subject to numerous risks and uncertainties, including, but not limited to, our actual financial results for the fourth quarter and full year 2025 may differ from our preliminary estimates; our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, failure to identify and develop additional product candidates, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, the impact of competition, risks relating to product liability lawsuits, inability to maintain collaborations, or the failure of these collaborations, our reliance on third parties, risks relating to intellectual property, our ability to hire and retain necessary personnel, general economic conditions, risks related to internal control over financial reporting, and the other important factors discussed under the caption "Risk Factors" in our Quarterly Report on Form 10-Q for the quarter ended September 30, 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 Current Report release or to update them to reflect events or circumstances occurring after the date of this Current Report, whether as a result of new information, future developments or otherwise.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

The following Exhibits 99.1 and 99.2 relate to Items 2.02 and 7.01, respectively and shall be deemed to be furnished, and not filed:

Exhibit No.	Description
99.1	Press release dated January 9, 2026
99.2	Corporate Presentation dated January 2026
104	Cover Page Interactive Data File (embedded within the inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

RHYTHM PHARMACEUTICALS, INC.

Date: January 9, 2026

By: /s/ Hunter C. Smith
Hunter C. Smith
Chief Financial Officer

EXHIBIT 99.1

Rhythm Pharmaceuticals Announces Preliminary, Unaudited Fourth Quarter and Full Year 2025 Net Product Revenues and Upcoming Milestones

-- Q4 2025 preliminary net product revenues from global sales of IMCIVREE® (setmelanotide) of approximately $57 million for the fourth quarter of 2025, an 11% increase over Q3 2025 --

-- FY 2025 preliminary net product revenue of approximately $194 million, approximately 50% increase from FY2024 --

-- March 20, 2026 PDUFA goal date for sNDA for setmelanotide in acquired hypothalamic obesity --

-- On track to report topline data from 12-patient Japanese cohort of setmelanotide Phase 3 trial in acquired hypothalamic obesity in first quarter of 2026 --

-- On track to report topline data from Phase 3 EMANATE trial evaluating setmelanotide in genetically caused MC4R pathway diseases in first quarter of 2026 --

BOSTON, January 9, 2026 – Rhythm Pharmaceuticals, Inc. (Nasdaq: RYTM), a global commercial-stage biopharmaceutical company focused on transforming the lives of patients living with rare neuroendocrine diseases, today announced preliminary unaudited net product revenues from global sales of IMCIVREE® (setmelanotide) for the fourth quarter and full year of 2025 and upcoming milestones.

“2025 was a year of strong execution and reflects significant progress toward our mission of transforming the lives of patients with rare neuroendocrine diseases,” said David Meeker, M.D., Chairman, Chief Executive Officer and President of Rhythm. “Our preliminary fourth quarter and full-year 2025 net product revenues reflect consistent growth in both the United States and international markets, driven by a steady increase in patients on reimbursed therapy and continued progress in securing access to IMCIVREE.”

Dr. Meeker continued, “Looking ahead, we are focused on delivering sustainable, long-term growth as we prepare to launch IMCIVREE for patients with acquired hypothalamic obesity (HO) in the United States, pending FDA approval. Additionally in 2026, we are excited about top-line data readouts from the Japanese cohort of our Phase 3 trial in acquired HO and the Phase 3 EMANATE trial, initiating a Phase 3 trial to evaluate our oral MC4R agonist, bivamelagon, in acquired HO and advancing setmelanotide and RM-718 for patients with Prader-Willi syndrome.”

Preliminary Unaudited Fourth Quarter and Full Year 2025 Net Product Revenues

Based on preliminary unaudited financial information, Rhythm expects net product revenues from global sales of IMCIVREE to be approximately $57 million for the fourth quarter of 2025, an increase of 11% percent on a sequential basis from the third quarter of 2025. Net product revenues for the full year of 2025 are expected to be approximately $194 million, compared to $130 million for the full year of 2024, an increase of approximately 50% year over year. U.S.

sales of IMCIVREE contributed approximately 68% of fourth quarter preliminary unaudited net product revenues and approximately 69% of full-year 2025 preliminary unaudited net product revenues. The Company plans to report its fourth quarter and full year 2025 financial results in late February 2026.

Anticipated Upcoming Milestones

Setmelanotide

Acquired Hypothalamic Obesity (HO)

- Launch IMCIVREE in the United States for the treatment of acquired hypothalamic obesity pending FDA approval; the FDA's assigned PDUFA goal date is March 20, 2026;
- Announce topline data in the 12-patient Japanese cohort of the setmelanotide Phase 3 trial in acquired HO in the first quarter of 2026.

Congenital HO

- Complete enrollment in the setmelanotide Phase 3 trial substudy in congenital HO in the first half of 2026.

Genetically Caused MC4R Pathway Diseases

- Announce topline data in the Phase 3 EMANATE trial evaluating setmelanotide in genetically caused MC4R pathway diseases in the first quarter of 2026.

Prader-Willi Syndrome (PWS)

- In December 2025, Rhythm announced positive preliminary data for the exploratory phase 2 trial of setmelanotide in patients with PWS that showed BMI and hyperphagia reductions at month 3 and month 6, as well as safety and tolerability consistent with setmelanotide's well-established clinical profile. Rhythm anticipates announcing six-month results from 18 patients from the ongoing Phase 2 trial in the first half of 2026.

Bivamelagon

- Pending further feedback from U.S. and European regulatory agencies, initiate a pivotal Phase 3 trial evaluating bivamelagon in acquired HO in 2026.

RM-718

- Complete enrollment in the Phase 1, Part C trial evaluating the weekly, MC4R agonist RM-718 in patients with acquired HO in the first quarter of 2026.

Financial Disclosure Advisory

This release contains certain estimated preliminary financial results for the fourth quarter and fiscal year ended December 31, 2025. These estimates are based on the information available to the Company at this time. The Company's financial close process for the fourth quarter and full year 2025 is not yet complete and, as a result, actual results may vary from the estimated preliminary results presented here. The estimated preliminary financial results have not been audited or reviewed by the Company's independent registered public accounting firm. These

estimates should not be viewed as a substitute for the Company's full interim or annual financial statements. Accordingly, you should not place undue reliance on this preliminary data.

About Rhythm Pharmaceuticals
Rhythm is a commercial-stage biopharmaceutical company committed to transforming the lives of patients and their families living with rare neuroendocrine diseases. Rhythm's lead asset, IMCIVREE® (setmelanotide), an MC4R agonist designed to treat hyperphagia and severe obesity, is approved by the U.S. Food and Drug Administration (FDA) to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients 2 years of age and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or genetically confirmed pro-opiomelanocortin (POMC), including proprotein convertase subtilisin/kexin type 1 (PCSK1), deficiency or leptin receptor (LEPR) deficiency. Both the European Commission (EC) and the UK's Medicines & Healthcare Products Regulatory Agency (MHRA) have authorized setmelanotide for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or genetically confirmed loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 2 years of age and above. Additionally, Rhythm is advancing a broad clinical development program for setmelanotide in other rare diseases, as well as investigational MC4R agonists bivamelagon and RM-718, and a preclinical suite of small molecules for the treatment of congenital hyperinsulinism. Rhythm's headquarters is in Boston, MA.

Setmelanotide Indication
In the United States, setmelanotide is indicated to reduce excess body weight and maintain weight reduction long term in adult and pediatric patients aged 2 years and older with syndromic or monogenic obesity due to Bardet-Biedl syndrome (BBS) or Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS).

In the European Union and the United Kingdom, setmelanotide is indicated for the treatment of obesity and the control of hunger associated with genetically confirmed BBS or loss-of-function biallelic POMC, including PCSK1, deficiency or biallelic LEPR deficiency in adults and children 2 years of age and above. In the European Union and the United Kingdom, setmelanotide should be prescribed and supervised by a physician with expertise in obesity with underlying genetic etiology.

Limitations of Use

Setmelanotide is not indicated for the treatment of patients with the following conditions as setmelanotide would not be expected to be effective:

- Obesity due to suspected POMC, PCSK1, or LEPR deficiency with POMC, PCSK1, or LEPR variants classified as benign or likely benign
- Other types of obesity not related to BBS or POMC, PCSK1, or LEPR deficiency, including obesity associated with other genetic syndromes and general (polygenic) obesity

Contraindication

Prior serious hypersensitivity to setmelanotide or any of the excipients in IMCIVREE. Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported.

WARNINGS AND PRECAUTIONS

Disturbance in Sexual Arousal: Spontaneous penile erections in males and sexual adverse reactions in females have occurred. Inform patients that these events may occur and instruct patients who have an erection lasting longer than 4 hours to seek emergency medical attention.

Depression and Suicidal Ideation: Depression, suicidal ideation and depressed mood have occurred. Monitor patients for new onset or worsening depression or suicidal thoughts or behaviors. Consider discontinuing IMCIVREE if patients experience suicidal thoughts or behaviors, or clinically significant or persistent depression symptoms occur.

Hypersensitivity Reactions: Serious hypersensitivity reactions (e.g., anaphylaxis) have been reported. If suspected, advise patients to promptly seek medical attention and discontinue IMCIVREE.

Skin Hyperpigmentation, Darkening of Pre-existing Nevi, and Development of New Melanocytic Nevi: Generalized or focal increases in skin pigmentation, darkening of pre-existing nevi, development of new melanocytic nevi and increase in size of existing melanocytic nevi have occurred. Perform a full body skin examination prior to initiation and periodically during treatment to monitor pre-existing and new pigmented lesions.

Risk of Serious Adverse Reactions Due to Benzyl Alcohol Preservative in Neonates and Low Birth Weight Infants: IMCIVREE is not approved for use in neonates or infants. Serious and fatal adverse reactions including “gasping syndrome” can occur in neonates and low birth weight infants treated with benzyl alcohol preserved drugs.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥20%) included skin hyperpigmentation, injection site reactions, nausea, headache, diarrhea, abdominal pain, vomiting, depression, and spontaneous penile erection.

USE IN SPECIFIC POPULATIONS

Treatment with IMCIVREE is not recommended when breastfeeding. Discontinue IMCIVREE when pregnancy is recognized unless the benefits of therapy outweigh the potential risks to the fetus.

To report SUSPECTED ADVERSE REACTIONS, contact Rhythm Pharmaceuticals at +1 (833) 789-6337 or FDA at 1-800-FDA-1088 or http://www.fda.gov/medwatch. See section 4.8 of the Summary of Product Characteristics for information on reporting suspected adverse reactions in Europe.

Please see the full Prescribing Information for additional Important Safety Information.

Forward-Looking Statements
This press release contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. All statements contained in this press release that do not relate to matters of historical fact should be considered forward-looking statements, including without limitation statements regarding our preliminary, unaudited revenues for the fourth quarter and full year 2025; the safety, efficacy, potential benefits of, and clinical design or progress of any of our products or product candidates at any dosage or in any indication, including, setmelanotide, bivamelagon, and RM-718; the potential use of setmelanotide in patients with acquired hypothalamic obesity; the commercial growth of IMCIVREE; our expectations surrounding potential regulatory submissions, progress, or approvals and timing thereof for any of our product candidates; the estimated market size and addressable population for our drug products, including setmelanotide for the treatment of hypothalamic obesity; the future announcement of data from our ongoing clinical trials, including the Japanese cohort of our Phase 3 trial evaluating setmelanotide for patients with acquired hypothalamic obesity, the substudy evaluating setmelanotide for patients with congenital hypothalamic obesity, the Phase 3 EMANATE trial evaluating setmelanotide in genetically caused MC4R pathway diseases; Part C of the Phase 1 trial evaluating RM-718, and the open-label Phase 2 trial evaluating setmelanotide in patients with Prader-Willi syndrome; the ongoing enrollment in our clinical trials; 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 and 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, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, 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 September 30, 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 press release or to update them to reflect events or circumstances occurring after the date of this press release, whether as a result of new information, future developments or otherwise.

Corporate Contact:
David Connolly
Head of Investor Relations and Corporate Communications
Rhythm Pharmaceuticals, Inc.
dconnolly@rhythmtx.com

Media Contact:
Layne Litsinger
Real Chemistry
llitsinger@realchemistry.com

EXHIBIT 99.2

Rhythm Pharmaceuticals

Corporate Presentation

January 2026

Forward Looking Statements

This presentation and the accompanying oral presentation contain forward-looking statements within the meaning of the Private Securities Litigation Reform Act 1995. All statements contained in this presentation that do not relate to matters of historical fact should be considered forward-looking statements, including wit limitation statements regarding our preliminary, unaudited revenues for the fourth quarter and full year 2025; sufficiency of our cash and cash equivalents; the sa efficacy, potential benefits of, and clinical design or progress of any of our products or product candidates at any dosage or in any indication, including, setmelanc bivamelagon, and RM-718; the potential use of setmelanotide in patients with acquired hypothalamic obesity; our expectations surrounding potential regulatory submissions, progress, or approvals and timing thereof for any of our product candidates; the estimated market size and addressable population for our drug pro including setmelanotide for the treatment of hypothalamic obesity; the future announcement of data from our ongoing clinical trials, including the Japanese coh our Phase 3 trial evaluating setmelanotide for patients with acquired hypothalamic obesity, the substudy evaluating setmelanotide for patients with congenital hypothalamic obesity, the Phase 3 EMANATE trial evaluating setmelanotide in genetically caused MC4R pathway diseases; Part C of the Phase 1 trial evaluating RM 718, and the open-label Phase 2 trial evaluating setmelanotide in patients with Prader-Willi syndrome; the ongoing enrollment in our clinical trials; and the timing any of the foregoing. Statements using words such as “expect”, “anticipate”, “believe”, “may”, “will”, “aim” and similar terms are also forward-looking statements. statements are subject to numerous risks and uncertainties, including, but not limited to, our ability to enroll patients in clinical trials, the design and outcome of clinical trials, the ability to achieve necessary regulatory approvals, risks associated with data analysis and reporting, failure to identify and develop additional pro candidates, unfavorable pricing regulations, third-party reimbursement practices or healthcare reform initiatives, risks associated with the laws and regulations governing our international operations and the costs of any related compliance programs, the impact of competition, risks relating to product liability lawsuits, in to maintain collaborations, or the failure of these collaborations, our reliance on third parties, risks relating to intellectual property, our ability to hire and retain necessary personnel, general economic conditions, risks related to internal control over financial reporting, and the other important factors discussed under the caption “Risk Factors” in our Form 10-Q for the quarter ended September 30, 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 press release or to update them to reflect events or circumstances occurring after the date of this press release, whether as a result of new information, future developments or otherwise.

Financial Disclosure Advisory

This release contains certain estimated preliminary financial results for the fourth quarter and fiscal year ended December 31, 2025. These estimates are based o the information available to the Company at this time. The Company’s financial closing and audit procedures for the fourth quarter and full year 2025 are not yet complete and, as a result, actual results may vary from the estimated preliminary results presented here. The estimated preliminary financial results have not bee audited or reviewed by the Company’s independent registered public accounting firm. These estimates should not be viewed as a substitute for the Company’s fu interim or annual financial statements. Accordingly, you should not place undue reliance on this preliminary data.

Well Positioned to Deliver Long-term, Sustained Growth

Established **global commercial infrastructure** with IMCIVREE® (setmelanotide) available **>25 countries** for BBS, POMC, LEPR deficiencies

Acquired hypothalamic obesity represents significant, near-term growth opportunity in United States, Europe and Japan (PDUFA goal date of March 20, 2026)

Setmelanotide, MC4R agonism advancing to address significant unmet need in **Prader-Willi syndrome** and additional genetic causes of rare MC4R pathways diseases

Next-generation MC4R-specific agonists, weekly RM-718 and oral bivamelagon, with global patent protection extending into 2040s

As of September 30, 2025, cash, cash equivalents and short-term investments were $416.1 million; sufficient to fund planned operations for at least 24 months

Continued Growth in IMCIVREE Global Sales

Q4 2025 preliminary unaudited net revenues from global sales of **IMCIVREE®** (setmelanotide)

~$57M* Q4 2025

~$194M FY 2025

11% **QoQ** increase from Q3 2025**

68% of **Q4 2025** revenue **from U.S.**

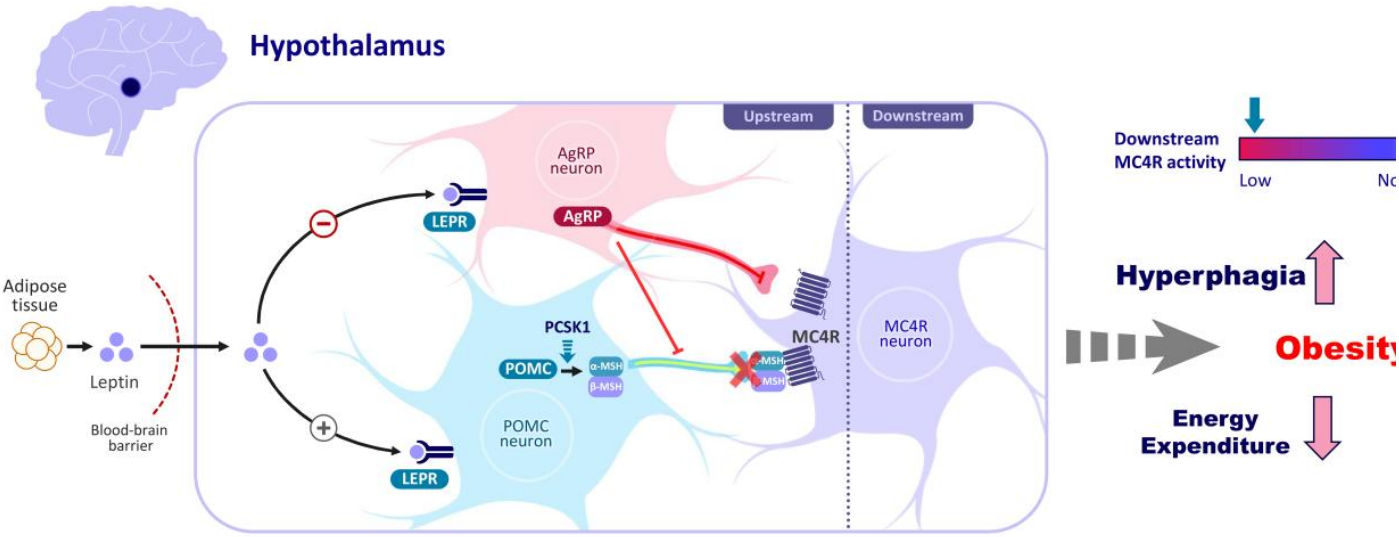
69% of **FY 2025** revenue **from U.S.**

~10% **increase** in number of patients globally on **reimbursed therapy**

The Company plans to report fourth quarter and full year 2025 financial results in February

* Preliminary, unaudited Q4 2025 revenue from vials shipped to U.S. specialty pharma in excess of vials dispensed to patients is approximately $1.7M; **Reminder: During Q3 2025, Rhythm recorded a one-time $3.2 million charge following a final agreement with French authorities for reimbursement for IMCIVREE for POMC/LEPR and BBS.

MC4R Pathway Biology is Clear



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.

Hyperphagia and Early-onset Obesity Have a Significant Impact on Patients and their Families

IMCIVREE Patient Ambassador program launched with 8 patient/caregiver speakers

"I was hungry all day long. I even started sneaking food in the middle of the night because my mind was constantly on my hunger."

"Prior to IMCIVREE, I didn't realize how much of my mental energy was consumed by my hunger. I'm able to free up my mind and do more enjoyable things with my life."

Kathryn, Diagnosed with BBS at 6 years old

BORN WITH:
Autosomal recessive polycystic kidney disease (diagnosed in utero), polydactyly

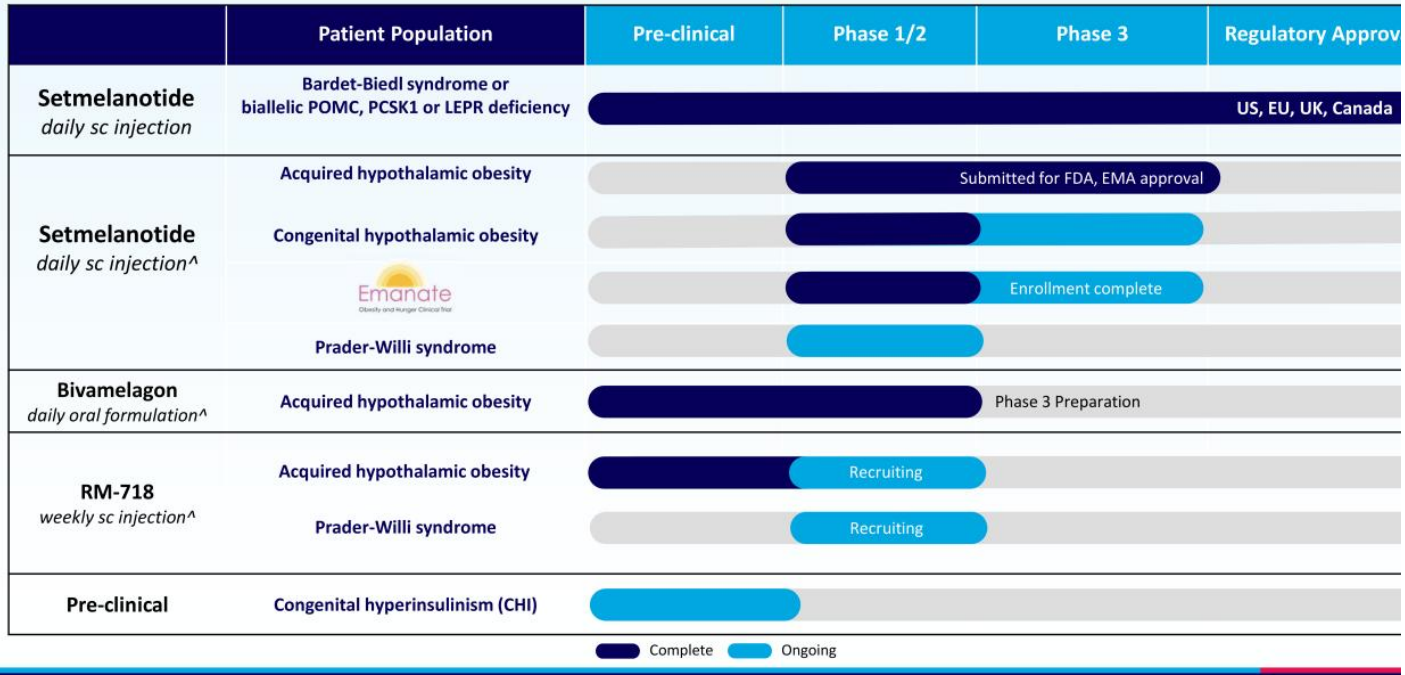
2 YEARS OLD:
Visual impairment and developmental delays emerge

6 YEARS OLD:
Pronounced hyperphagia; clinical presentation prompted BBS diagnosis via genetic testing

TEEN YEARS:
Hyperphagia, obesity, and visual deficits worsen

28 YEARS OLD:
IMCIVREE prescribed by PCP

Expanding Pipeline in Rare Neuroendocrine Diseases



*Approved in Israel & Canada LEPR, leptin receptor; MC4R, melanocortin-4 receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.
^Currently being studied as

Significant Market Opportunity for MC4R Agonists

U.S. patent protection for next-generation assets 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

~10,000
estimated U.S. prevalence[1]

~10,000
estimated European prevalence[2]

5,000 – 8,000
estimated Japanese prevalence[3]

Prader-Willi syndrome

~20,000
estimated U.S. prevalence[4]

~400,000
estimated worldwide prevalence[4]

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 classifcations, 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. 4. Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. In: Adam MP, Bick S, Mirzaa GM, et al, eds. GeneReviews®. 1998:1-41. Updated December 5, 2024. Accessed December 10, 2025. https://www.ncbi.nlm.nih.gov/books/NBK1330/

Multiple Anticipated Milestones

Mar. 20, 2026	**PDUFA goal date** for setmelanotide **in conditions associated with acquired hypothalamic obesity**
Q1 2026	Complete enrollment in **Part C** of **Ph1/2 trial evaluating RM-718** in acquired hypothalamic obesity
Q1 2026	Topline data from **12-patient Japanese cohort** of **Ph3 acquired hypothalamic obesity trial** evaluating setmelanotide
Q1 2026	Topline data from **Ph3 EMANATE trial** evaluating setmelanotide in four genetically-defined, rare MC4R pathway diseases
H1 2026	Complete enrollment in **Ph3 congenital hypothalamic obesity substudy** evaluating setmelanotide
H1 2026	Disclose six-month results from exploratory **Ph2 Prader-Willi trial** evaluating setmelanotide
2026	Initiate **pivotal Ph3 trial** evaluating **oral bivamelagon** in **acquired hypothalamic obesity; complete** enrollment in **Part D** of **Ph1/2 trial evaluating RM-718** in **PWS**

IMCIVREE Global Commercial Execution

First and Only FDA- and EMA-approved Therapy that Targets Early-onset, Severe Obesity and Hyperphagia Associated with BBS

IMCIVREE™
(setmelanotide) injection

IMCIVREE is a melanocortin 4 (MC4) receptor agonist indicated for chronic weight management in patients with **monogenic or syndromic obesity** due to:

- **Bardet-Biedl syndrome** (BBS)
- Pro-opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), or leptin receptor (LEPR) deficiency as determined by an FDA-approved test demonstrating variants in POMC, PCSK1, or LEPR genes that are interpreted as pathogenic, likely pathogenic, or of uncertain significance (VUS)

IMCIVREE available in >25 countries outside the United States

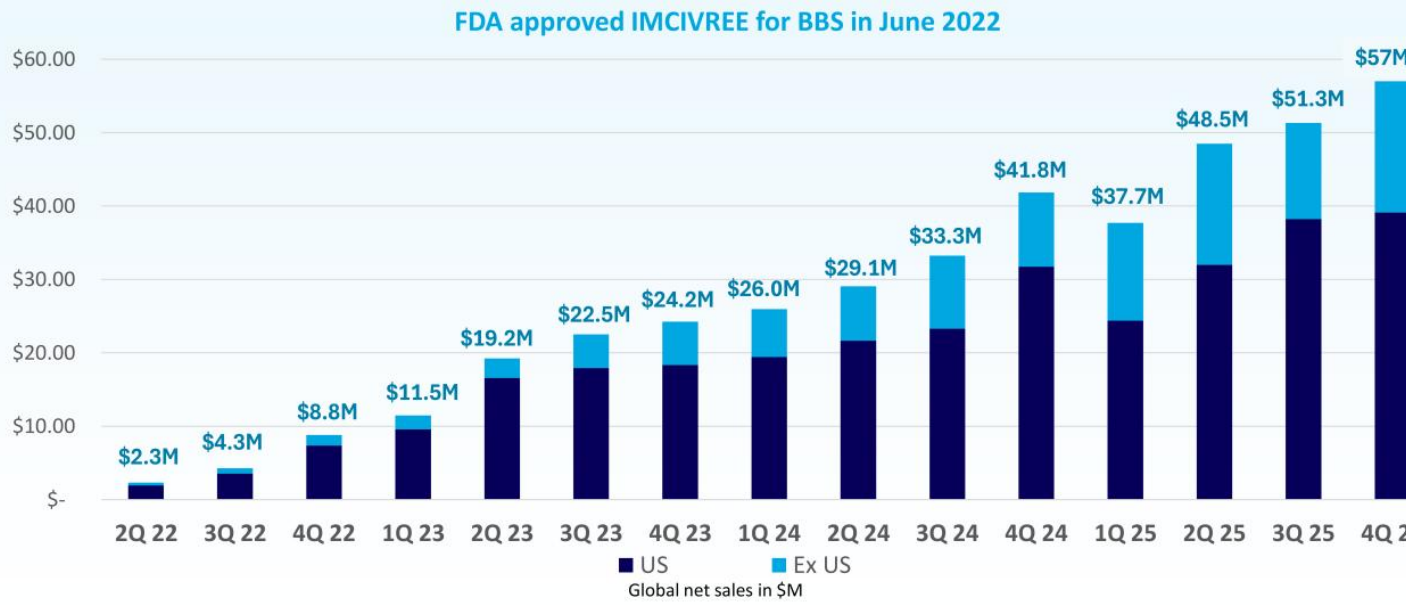
Continued execution

Ongoing BBS, POMC/LEPR sales

Early-access acquired HO programs in France and Italy

Named patient sales

Steady Growth in Net Product Revenues since BBS Launch



*Preliminary, unaudited net product revenues as reported on January 9th, 2026

Rhythm is Ready for a Successful U.S. Launch in Hypothalamic Obesity

PDUFA goal date of March 20, 2026

Significant unmet need

Setmelanotide's demonstrated efficacy

Transformative opportunity

~10,000

estimated U.S. prevalence[1]

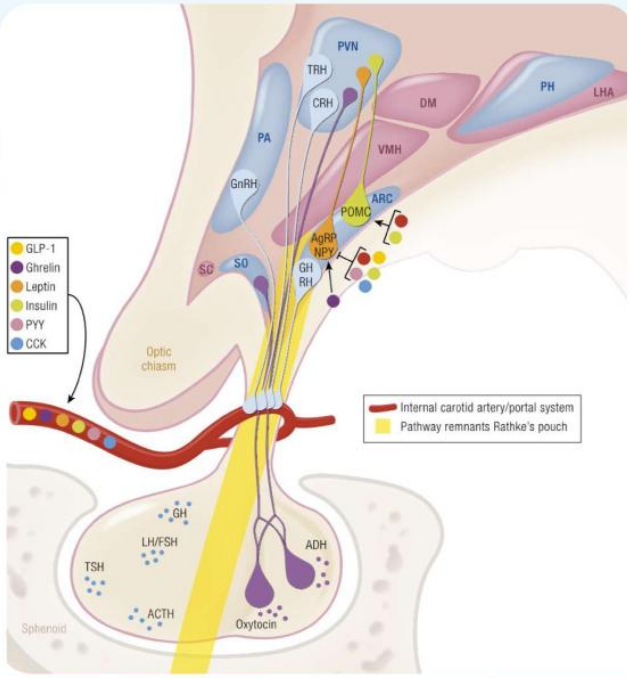
1. U.S. estimates based on reported incidence of hypothalamic obesity following craniopharyngioma and long-term survival rates, (Zacharia, et al., *Neuro-Oncology* 14(8):1070–1078, 2012. doi:10.1093/neuonc/nos142; and Muller, et al., *Neuro-Oncology* 17(7), 1029–1038, 2015 doi:10.1093/neuonc/nov044.);

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

Craniopharyngioma (CP) 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)

Claims Analysis to Inform Physician Targeting

Patients with….

~2,400

Top target physicians

Field Teams Profiling Physicians and Patients Under Their Care in Advance of Launch

Field teams prioritize top tier physicians IDed through claims analysis

Ongoing efforts profiling physicians

>2,000 potential patients*

Suspected to have….
or… diagnosed with
acquired hypothalamic obesity

*Patient identification through physician profiling initially was detailed during Rhythm's Commercial Readiness for Acquired Hypothalamic Obesity event on Sept. 24, 2025, and updated on Rhythm's Q3 2025 earnings conference call on Nov. 4, 2025; In the U.S., there are >75 trial patients enrolled in RYTM's extension trial who potentially would be converted to commercial patients over time, pending FDA approval.

Hypothalamic Obesity
Acquired and Congenital

Severe, Life-long Burden for Patients with Acquired HO

Frequent visits with multiple specialists, a complex regimen of medications, and hospitalization

> **"Treatment of patients with tumor/treatment-related hypothalamic obesity in the first two years following surgical treatment or radiotherapy"**
>
> **Müller et al., 2025**
>
> **scientific** reports

3.7 average hospitalizations during the two years following index;

23% included ICU admission in the first year

12 average number of gene practitioner visits and

20 specialist visits, during t two years following ind

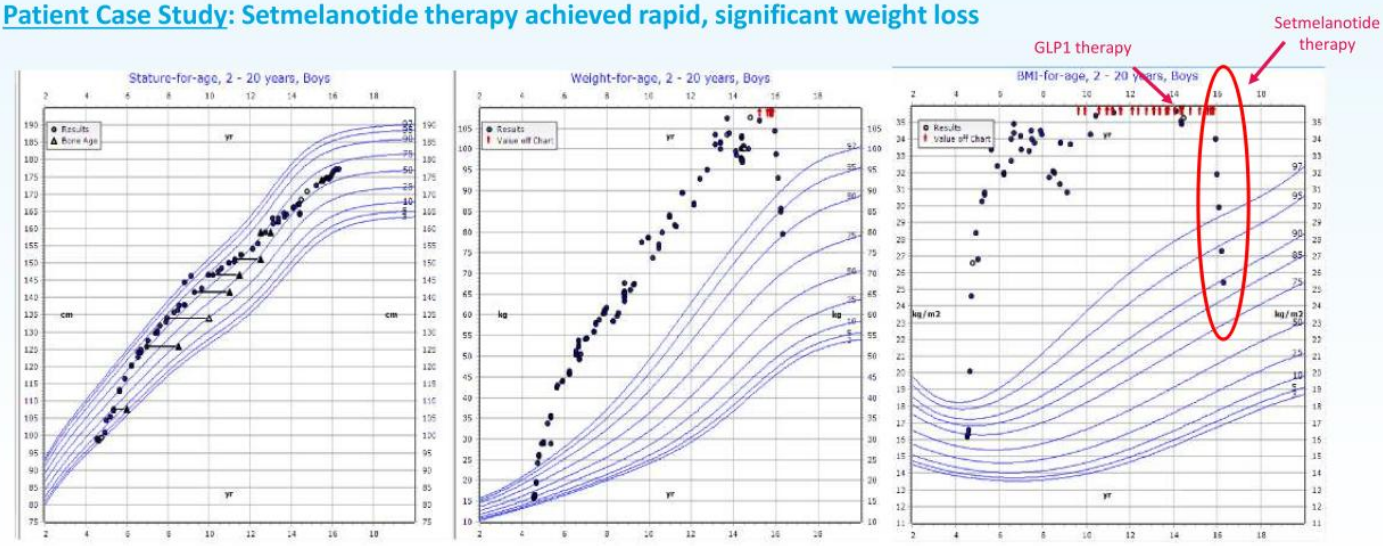
5.5 average active prescriptions per quarter

22.1 average number of unique medications over 2 years

89% were receiving ≥3 therapies for neuroendocrine dysfunction

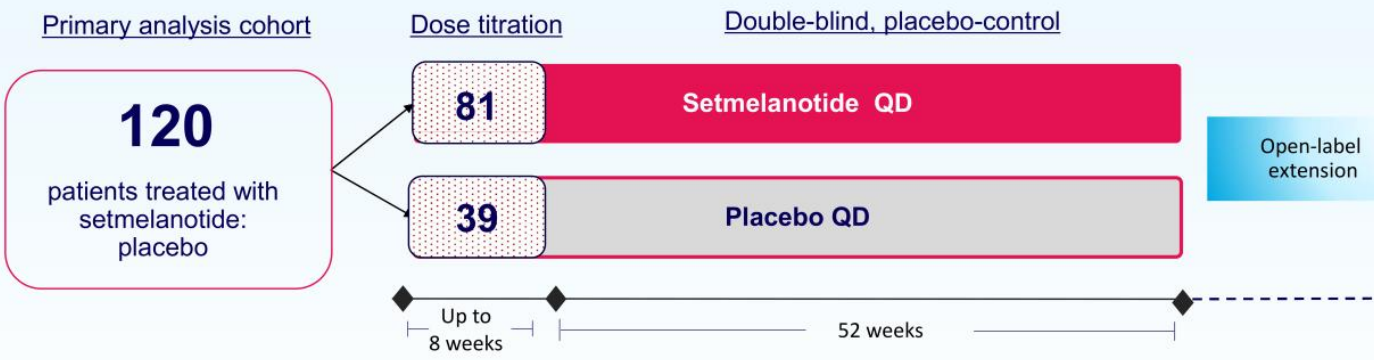
HO: Aggressive, Rapid Weight Gain follows Therapy for CP

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



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

Phase 3 TRANSCEND Trial: Largest and Longest Placebo-controlled Tria in Acquired Hypothalamic Obesity



+12 Japanese patients remain blinded in ongoing supplemental cohort; Data from this supplemental cohort will serve as the basis for a regulatory submission in Japan.

Setmelanotide Achieved Statistically Significant and Highly Clinically Meaningful Reduction in BMI in Phase 3 Acquired HO Trial

Primary analysis cohort (N=120)

-16.5%

BMI change from baseline in

Setmelanotide arm

(n=81)

-19.8%

Placebo-adjusted difference in BMI reduction from baseline

(P<0.0001)

+3.3%

BMI change from baseli

Placebo arm

(n=39)

NOTE: Shown are the least square (LS) means for setmelanotide and placebo groups and the LS mean difference in mean percentage change from baseline in BMI at Week 52, obtained from an analysis of covariance (ANCOVA) model. Rubin's Rule was used to provide the overall estimates of differences in LS means and p-value.

Mean BMI Reduction Consistent Across Stratified Age Groups in Phase 3 Trial Evaluating Setmelanotide in Acquired HO

Significant BMI Reductions Observed in Patients with Prior Use or Concomitant Use of GLP-1s

Prior use of GLP-1 *(n=16)*

-24.7%

Placebo-adjusted difference in BMI reduction from baseline

Concomitant GLP-1 *(n=15)*

-27.1%

Placebo-adjusted difference in BMI reduction from baseline

Congenital HO Represents Additional Opportunity with Significant Unmet Need

Congenital HO occurs due to **dysfunction or damage to the hypothalamus from birth**, with patients often experiencing **hyperphagia** and difficulty managing their weight

The weight gain and appetite changes accompanying HO are often **unresponsive to existing therapies** for obesity

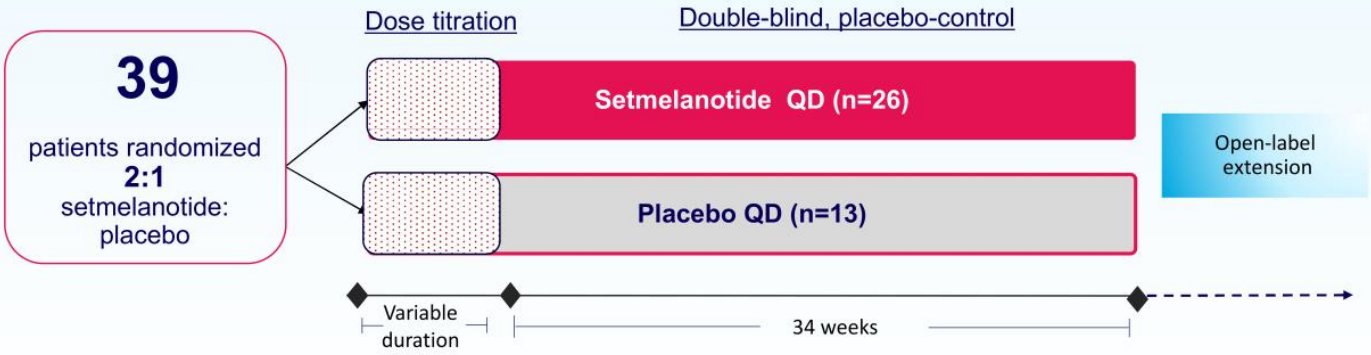
No approved therapies for congenital HO

>1,000 Patients

Estimated prevalence in each the United States and Europe

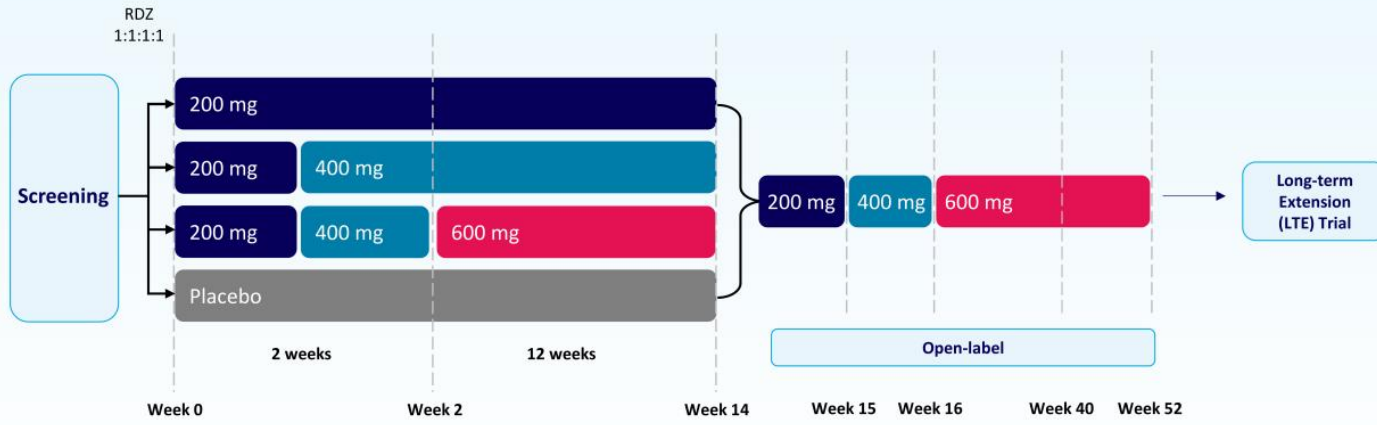
34-week Substudy in Congenital Hypothalamic Obesity Added to Pivotal, Ph3 HO Study

Independent substudy leverages existing Ph3 trial infrastructure; Enrollment completion expected in H2 2025



~90% power to detect a treatment difference (treatment - placebo) of -12% in percent change of BMI from baseline after 26 weeks on a therapeutic regimen (up to 34 weeks) at 2-sided alpha of 0.05

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



Inclusion criteria

≥18yo BMI ≥30 kg/m²	**12-<18 yo ≥95th percentile**	**Setmelanotide-naive**

Overall Baseline Demographics

Overall bivamelagon population

N=28

46.4%
Female

25.4yo
Mean Age
(13 of 28 <18yo)

38.7 kg/m²
Mean BMI

82.1%
Patients with craniopharyngioma

7 years
Mean time from hypothalamic injury to trial enrollment

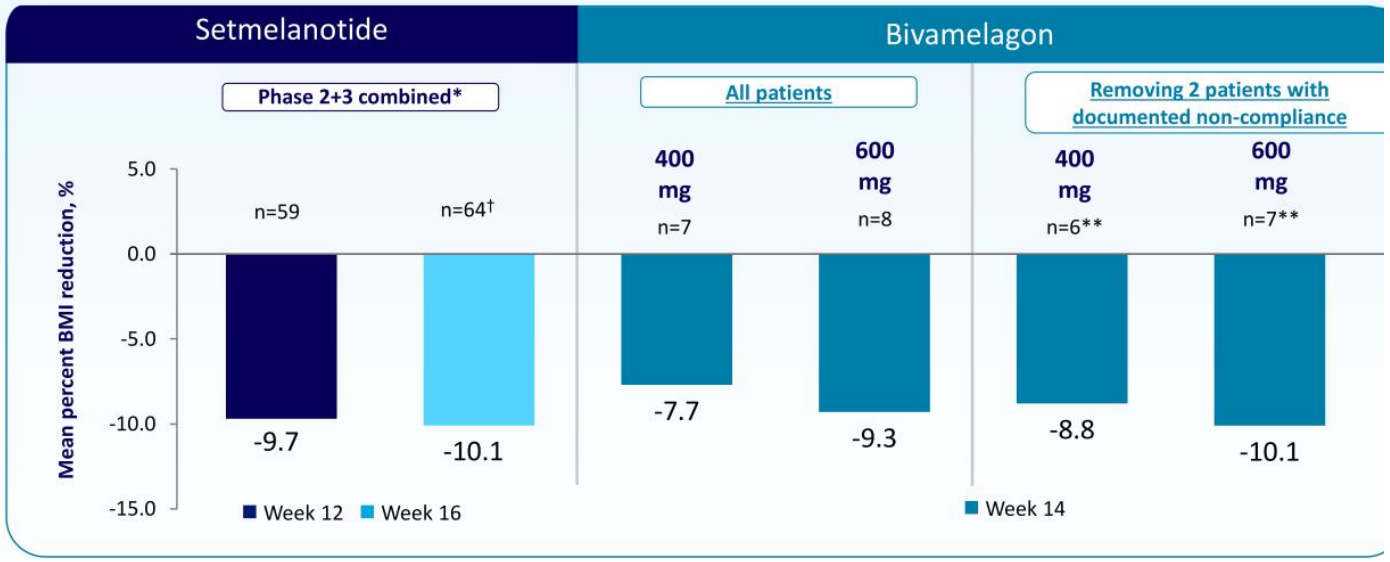
Bivamelagon Achieved Statistically Significant BMI Reductions at All Doses

Placebo	200 mg	400 mg	600 mg
+2.18%	**-2.68%**	**-7.69%**	**-9.31%**
Mean BMI increase from baseline (n=7)	Mean BMI reduction from baseline (n=6) **p-value = 0.0180**	Mean BMI reduction from baseline (n=7) **p-value = 0.0002**	Mean BMI reducti from baseline (n=8) **p-value = 0.0004**

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

Post-hoc analysis:

Bivamelagon Achieved BMI Reductions Consistent with Setmelanotide



These values represent patients who demonstrated compliance and no concomitant GLP1 therapy (no patients who enrolled in the Phase 2 bivamelagon were on concomitan GLP1 therapy). Patients deemed non-compliant were excluded. †LOCF performed for week 16 only; **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 W12, patients not included in those means]

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
AEs with >=10% in all BIVA dosing (N=21)				
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)
AEs of Special Interest	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 a AE of special interest.

Prader-Willi Syndrome

Revisiting Prader-Willi Syndrome

PWS is a **complex, multi-system** disorder

Constant sense of hunger usually begins at 2yo; if not managed by stringent food restrictions and environmental controls, often **results in life-threatening obesity**

Currently **limited therapeutic options** that effectively reduce the **extreme hyperphagia** and address **low resting energy expenditure**

Prior setmelanotide study evaluated **low doses** (up to 2.5mg daily) for **only 4 weeks**; results were not statistically significant

~20,000 Patients

Estimated U.S. prevalence*

~400,000 Patients

Estimated worldwide prevalence*

* Driscoll DJ, Miller JL, Cassidy SB. Prader-Willi Syndrome. In: Adam MP, Bick S, Mirzaa GM, et al, eds. GeneReviews®. 1998:1-41. Updated December 5, 2024. Accessed December 10, 2025. https://www.ncbi.nlm.nih.gov/books/NBK133

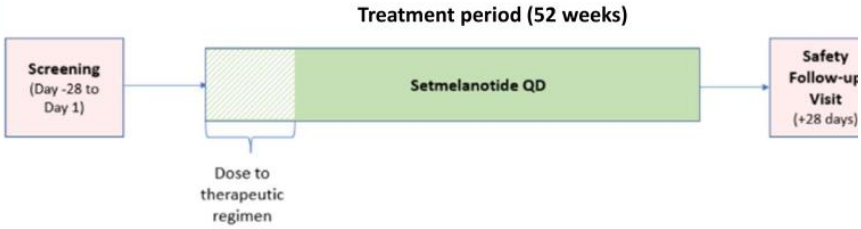
Exploratory Phase 2, Open-label Trial of Setmelanotide in PWS

18 patients with PWS and obesity aged 6 to 65 years old enrolled

Daily dose of setmelanotide escalated up to **5 mg/day** as tolerated for **52 weeks**

Primary endpoints: safety and tolerability

Key secondaries: assessments on **BMI, hyperphagia, body composition** and pharmacokinetics



Baseline Demographics

Parameter	Statistic	Overall (N=18)
Age, years	Mean (SD) (range) <12 years old, n (%) ≥12 years and <18, n (%) ≥18 years old, n (%)	17.1 (5.6) (6 – 23) 3 (16.7) 4 (22.2) 11 (61.1)
Sex, n (%)	Female / Male	8/10 (44.4/55.6)
Race, n (%)	White Multiple Asian	15 (83.3) 2 (11.1) 1 (5.6)
BMI, kg/m²	Mean (SD) Range	39.1 (9.5) 24.2 – 67.0
BMI, kg/m² (n=8*)	Mean (SD) Range	43.7 (10.3) 32.6 – 67.0

*BMI for the 8 patients with ≥3 months' treatment

N=18
Patients enrolled

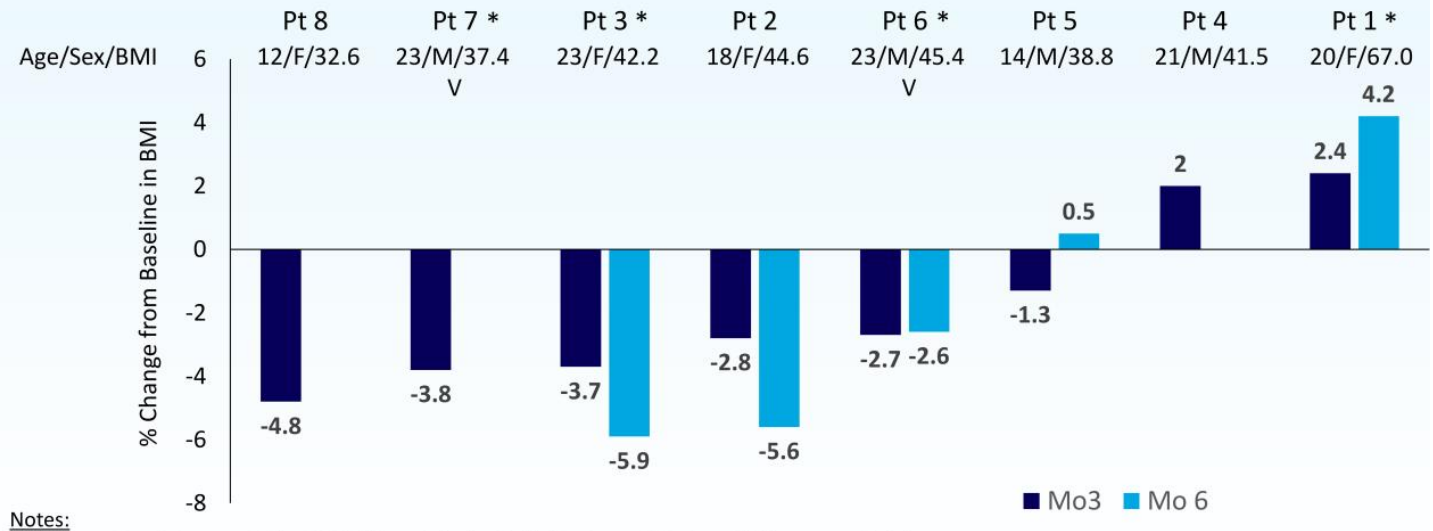
n=8
patients reached Month 3[1]

n=5
patients reached Month 6[1]

17
patients remain on active therapy

1. Data cut-off date is Nov. 14, 2025

Setmelanotide Achieved BMI Reductions from Baseline in Patients with PWS After 3 and 6 Months of Treatment

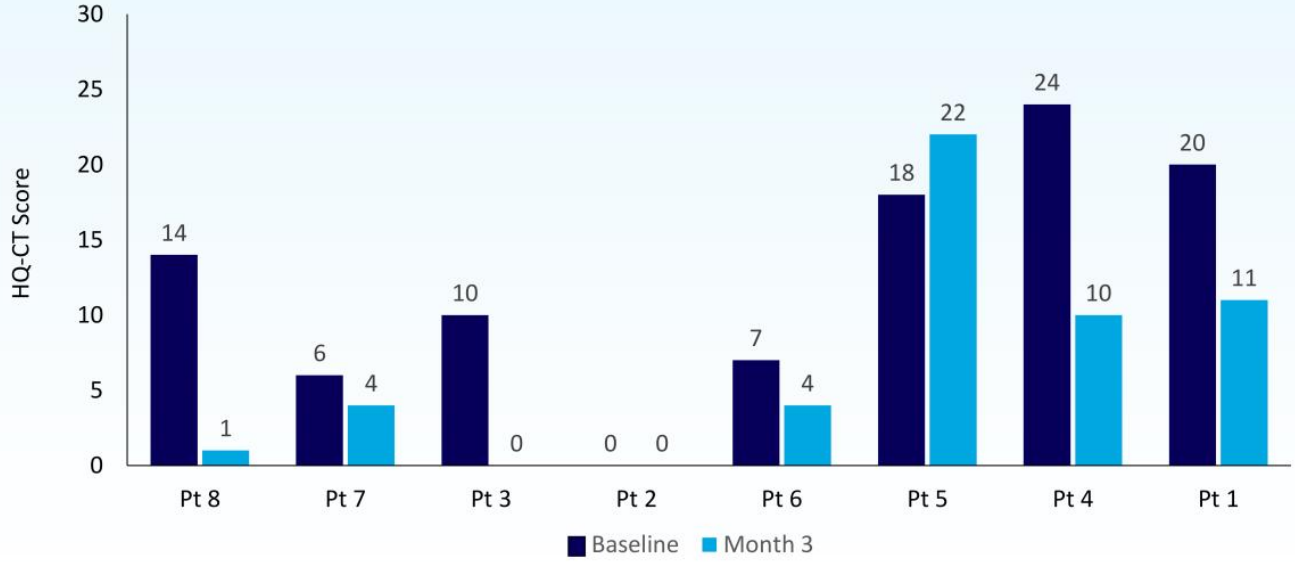


Notes:

V=Patients 7 and 6 are on Vykat™ XR (diazoxide choline); *Patients 7, 3, 6, and 1 have type 2 diabetes.

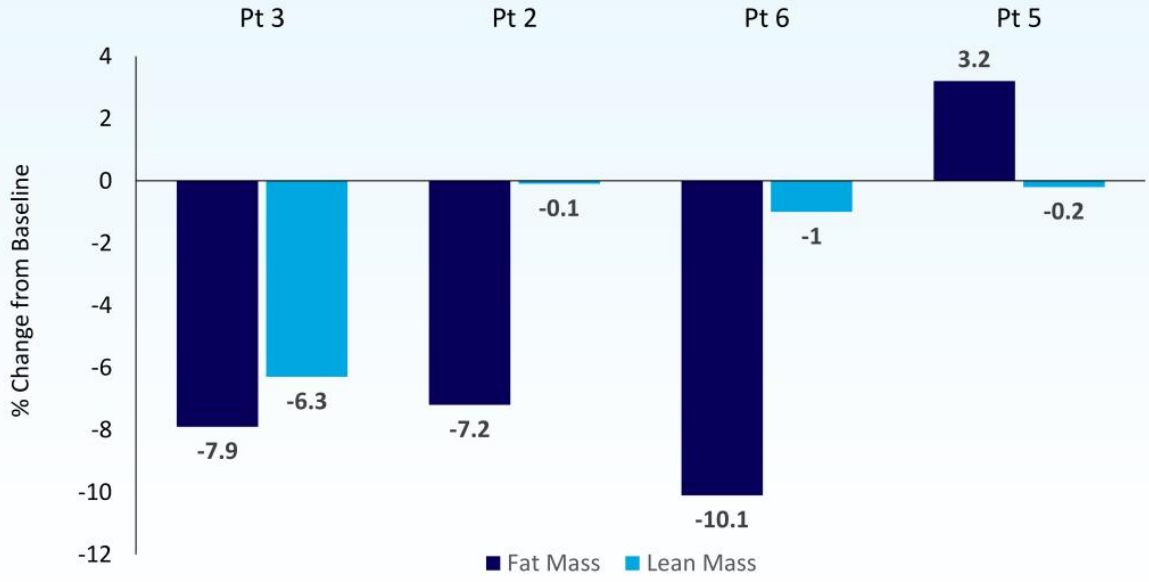
Patient 3: Worsened diabetes control after 13 weeks, started on insulin. **Patient 5:** non compliant after initial response; **Patient 4:** discontinued prior to visit 6. **Patient 1:** poorly controlled diabetes, lipohypertrophy, severe lower extremity lymph edema

HQ-CT[1] Scores Showed Meaningful Hyperphagia Reductions from Baseline Observed in 6 of 7 Evaluable Patients at Month 3



1. The Hyperphagia Questionnaire for Clinical Trials (HQ-CT) is a 9-item, observer-reported outcome measure that assesses changes in hyperphagic behaviors in individuals with PWS. Each item is scored from 0 to 4, for a total possible score of 36.

Positive Body Composition Changes from Baseline to Month 6



Note: There are no DEXA data for Patient 1 (exceeded table's weight limits)

EMANATE and DAYBREAK

Genetically-defined
MC4R Pathway Diseases

EMANATE and DAYBREAK Studies to Drive Significant Expansion of Setmelanotide's Potential Addressable Market

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

Phase 2 DAYBREAK Trial — **Study completed in 2024**

Emanate
Obesity and Hunger Clinical Trial

Daybreak
Obesity and Hunger Clinical Trial

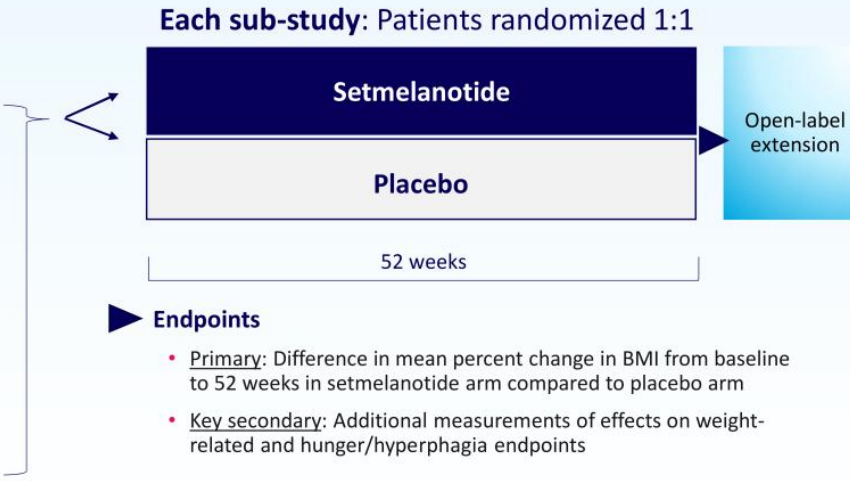
† Estimated U.S. patients based on population with early-onset, severe obesity who may benefit from setmelanotide based on sequencing results, current estimated responder rates and that 1.7% of the US population (328M; 2019 US census) presents with severe earl onset obesity (Hales et al 2018‡); ~95% 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 EMANA trial would include patients with variants classified as pathogenic, likely pathogenic or suspected pathogenic;

Phase 3 EMANATE Trial Comprised of Four Independent Sub-studies

Enrollment completed in 4Q 2024; Topline data anticipated in 1Q 2026

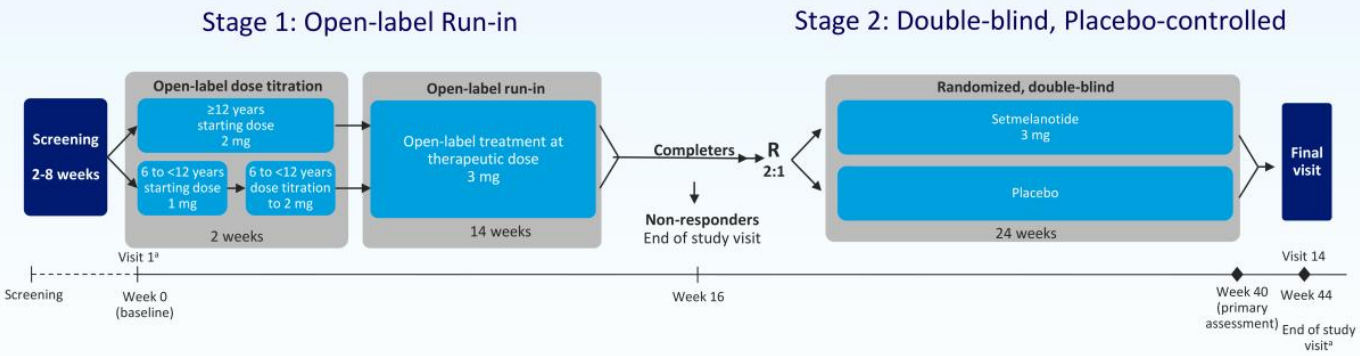
Genetic substudy	Enrolled patients	ACMG Classification
POMC/ PCSK1*	n=79	• Pathogenic • Likely pathogenic • VUS*-Suspected pathogenic
LEPR*	n=23	• Pathogenic • Likely pathogenic • VUS-Suspected pathogenic
SRC1	n=73	• All VUS
SH2B1	n=121	• Pathogenic • Likely pathogenic • VUS

* VUS = Variant of uncertain significance;



NOTE: The SRC1 and LEPR substudies are currently under-enrolled, so additional studies may be necessary in order to seek regulatory approval. We believe the SH2B1 and POMC/PCSK1 substudies are fully enrolled and powered and could enable Rhythm to seek registration, pending success.

DAYBREAK 2-Stage Design: 16-Week Run-in Followed by 24-week Randomized Withdrawal and 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)

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

S2 Eligibility Criteria Reduction at end of S1, from baseline: Adult: Reduction of ≥3% BMI; Pediatric: reduction of ≥3% BMI OR of ≥0.05 BMI Z-score

ªVirtual visit. R, randomization.

Data Highlights from Stage 2 of DAYBREAK Phase 2 Trial

-12.4%

Mean BMI change from baseline
(SD: 8.0%; range 1.2%-35.0%)

n=32

patients on continuous
setmelanotide therapy*

84%

or **27 of 32**
patients on
setmelanotide

VS.

29%

or **5 of 17**
patients on
placebo

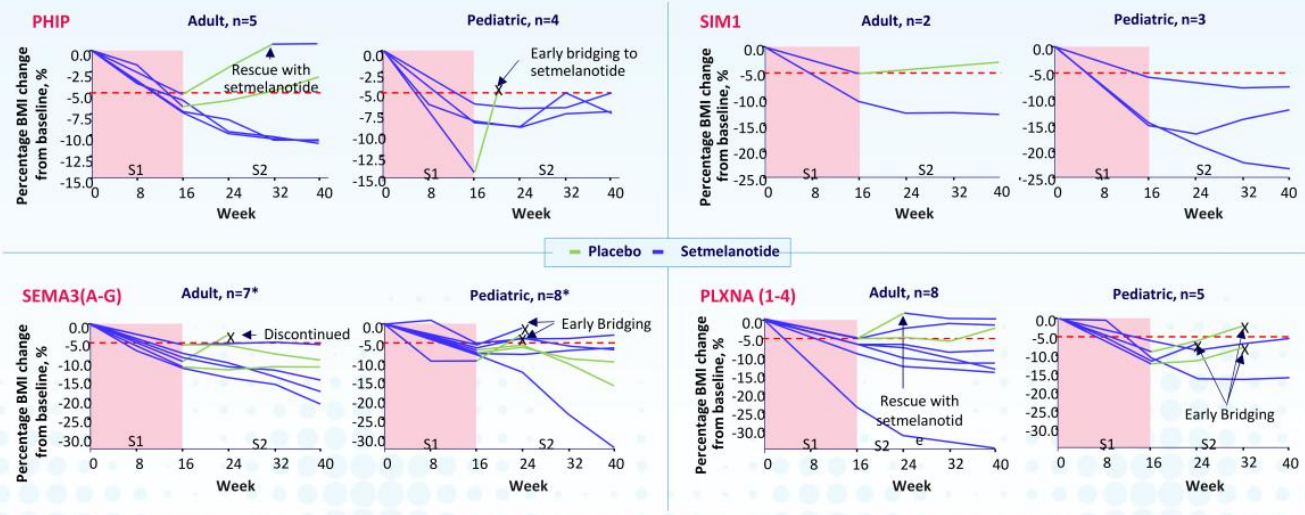
achieved or maintained
>5% BMI reduction from baseline

P=0.001

* Analyses were limited by the small number of PBO-treated pts

Variable Responses Observed in DAYBREAK Stage 2 in Different Genetic Cohorts

Several genetically defined subgroups may merit further study with next-generation MC4R agonists



*One adult and one pediatric SEMA3G patient dropped out of S2 prior to having any data and are not shown

Well Capitalized: Cash Sufficient to Fund Planned Operations for at least 24 Months

$416.1M

Cash, cash equivalents and short-term investments as of September 30, 2025

Guidance

RYTM expects cash to be sufficient to fund planned operations for **at least 24 months**

66.3 Million

Weighted average common shares outstanding as of September 30, 2025

Rhythm Leadership – Strong Team with Broad Biopharma Experience

					
David Meeker, MD *Chair, President and Chief Executive Officer*	**Hunter Smith** *Chief Financial Officer*	**Jennifer Lee** *Executive Vice President, Head of North America*	**Yann Mazabraud** *Executive Vice President, Head of International*	**Joe Shulman** *Chief Technology Officer*	**Alastair Garfield, P** *Chief Scientific Offi*
SANOFI GENZYME	Celgene	SANOFI GENZYME Krystal	SANOFI GENZYME trevi THERAPEUTICS	Ra Pharma novelion THERAPEUTICS	RECTIFY PHARMA Pfi
25-plus years; focus on rare genetic disease treatments, including Aldurazyme®, Fabrazyme® and Myozyme®	*20-plus years in finance, M&A, capital markets; financial leadership for Otezla®*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years leading global commercial strategy in rare diseases*	*20-plus years experience leading CMC, supply chain planning and quality assurance and control*	*20 years experience neurobiology of appe /body weight regulat rare disease drug discovery*

Appendix

German Investigator-led Observational Study Showed Setmelanotide associ with Improvement in Measures of MASLD, Kidney Function in Patients with

26 patients with BBS completed six months on setmelanotide therapy.

100%

of patients (N=26) with both BBS and metabolic dysfunction-associated steatotic liver disease (MASLD)

>80%

of patients exhibited either resolution of MASLD or stabilization at grade S1*

Adapted from Hühne, T., *et al.* (2025). *Impact of the melanocortin-4 receptor agonist setmelanotide on MASLD and kidney function in Bardet-Biedl syndrome*. The Journal of Clinical Endocrinology & Metabolism. https://doi.org/10.1210/clinem/dgaf483; * MASLD improvement was correlated with only liver size, not BMI reduction; This study was funded by the German Federal Ministry of Research and Education and by Rhythm Pharmaceuticals.

Positive Real-world Setmelanotide Data Reported from French Early-access Program in Adult Patients with Acquired Hypothalamic Obesity

N=8*
patients

19.3 years
Mean age at resection

31.4 years
Mean age at initiation of setmelanotide therapy

44.1 kg/m²
Mean BMI at baseline

-5.6%
Mean BMI reduction
■ Month 1

-12.8%
Mean BMI reduction
■ Month 3

-21.3%
Mean BMI reduction
■ Month 6

*50% male; all aged ≥18 years, with a previous resection of craniopharyngioma (n=7) or of Rathke cleft cyst (n=1); Adapted from "3-Month Real-World Setmelanotide Hunger and Weight Outcomes in Patients with Hypothalamic Obesi poster presented ObesityWeek®; November 3-6, 2024, in San Antonio, TX, USA.

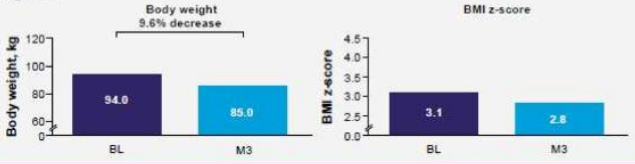
Real-world Case Reports from French Early-access Program Suggest Setmelanotide may be Effective Treatment for Congenital HO

Case reports presented at 62nd annual meeting of the European Society for Paediatric Endocrinology (EPSE)

Case Report 3 (Congenital HO)

- Patient 3, female, had septo-optic dysplasia (SOD), combined pituitary hormone deficiency and valgus foot as co-morbidity. Age of onset of obesity was not reported
- Setmelanotide treatment was started at 15 years of age, with dose escalation from 0.5 mg at BL to 1 mg at M3
  - As ongoing treatment, patient was on hormonal replacement therapy
- Patient had a 9.6% decrease in body weight and -0.3 BMI z-score change at M3 of treatment (**Figure 3**)

Figure 3:

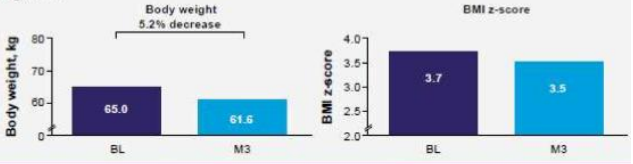


- For the 4 questions included in the scoring of hunger scores, the reported change was 5-5-0-6 (BL) to 5-5-0-5 (M3). Physician noted difficulty in interpretation and scoring with the questionnaire
- During treatment, patient reported injection site reaction and intermittent diarrhoea at 2 weeks of treatment which was resolved. Angina, sore throat and hyperpigmentation was reported at M3

Case Report 4 (Congenital HO)

- Patient 4, male, 2.5 years at onset of obesity, had pituitary stalk interruption syndrome (PSIS), corticotr thyrotropic and growth hormone (GH) deficiency as co-morbidity
- Setmelanotide treatment was started at 9 years of age, with dose escalation from 0.5 mg at BL to 2 mg at M3
  - As ongoing treatment, patient was on hormonal replacement therapy
- Patient had a 5.2% decrease in body weight and -0.2 BMI z-score change at M3 of treatment (**Figure**

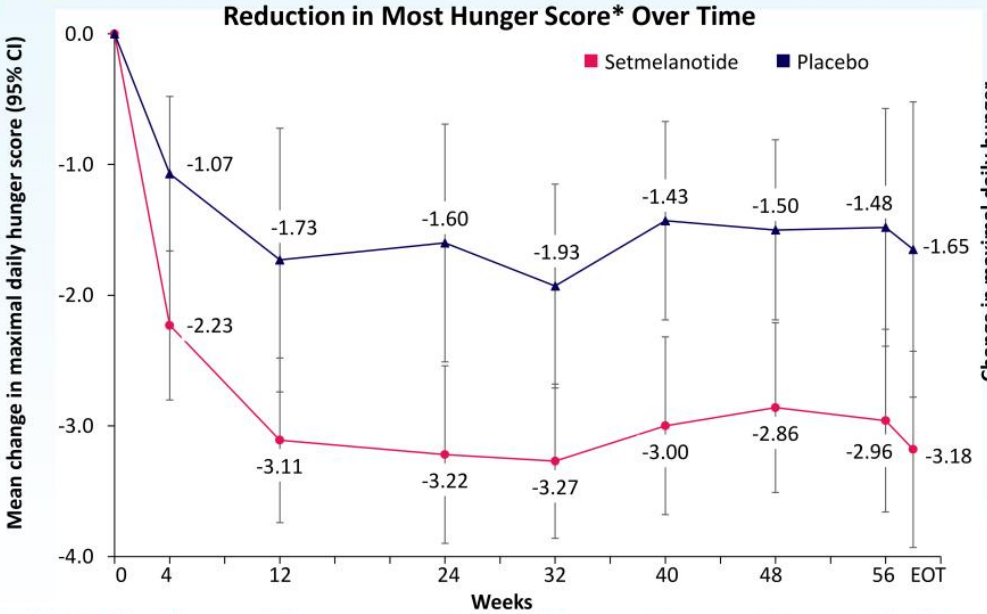
Figure 4:



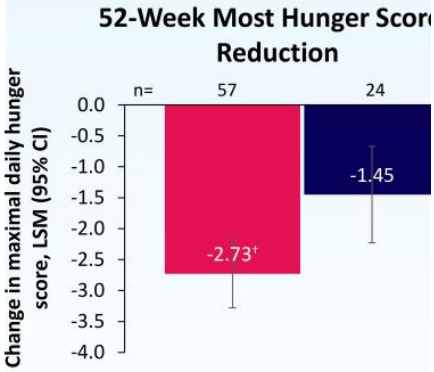
- For the hunger outcomes, patient reported a qualitative improvement rather than quantitative, as norm reflected by hunger scores. Initially, the patient described feeling moderately hungry at BL, slightly hun at M1, and not hungry at all by M3 of treatment
- During treatment, no adverse events were reported for the patient

Adapted from '3-Month real-world setmelanotide hunger and weight outcomes in four French paediatric patients with acquired or congenital hypothalamic obesity,' presented at ESPE on November 18, 2024, by Dr. Ahlam Azar-Kolake et al.

Rapid and Statistically Significant Hunger Reduction in Patients with HO Aged ≥12 Years



Setmelanotide, n 57	52	53	44	50	46	44	44	39
Placebo, n 24	18	19	23	22	19	18	17	15



PBO-adjusted difference **-1.28**

†*P*=0.0086 vs placebo.

As presented at END

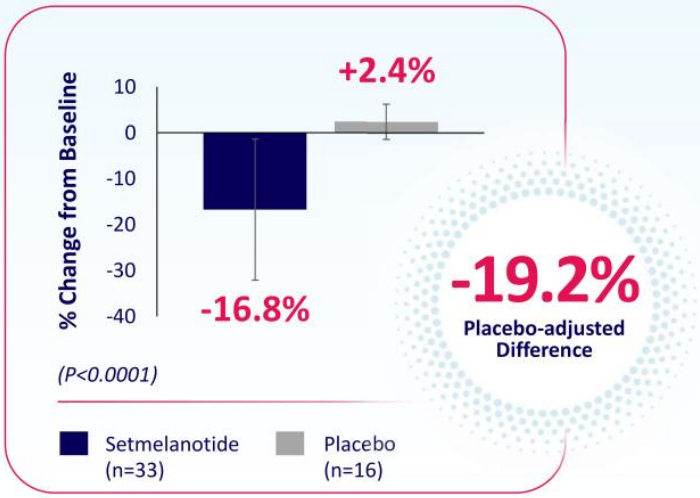
51

*Weekly average of daily scores. participants ≥12 years of age who were able to self-report were administered the questionnaire. Participants were asked to rate their most hunger on an 11-point numerical rating scale from 0 to 10, where 0 = not hungry at all and 10 = hungriest possible via the question, "In the last 24 hours, how hungry did you feel when you were the most hungry?" CI, confidence interval; LSM, least squares mean.

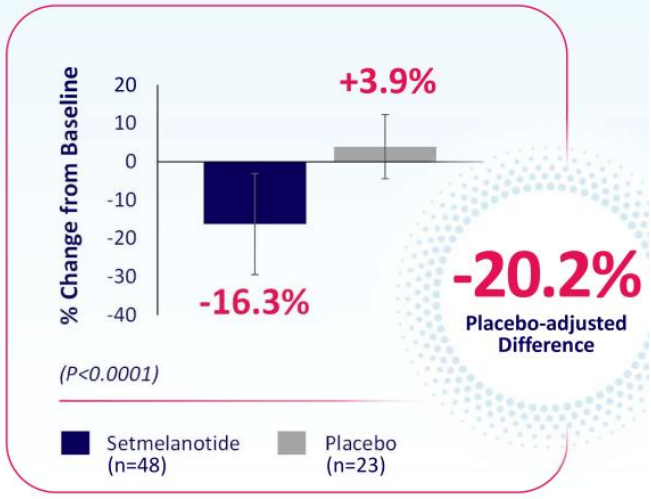
Rhyt

Significant Reductions in BMI Observed in both Adults and Children in Phase 3 Trial Evaluating Setmelanotide in Acquired HO

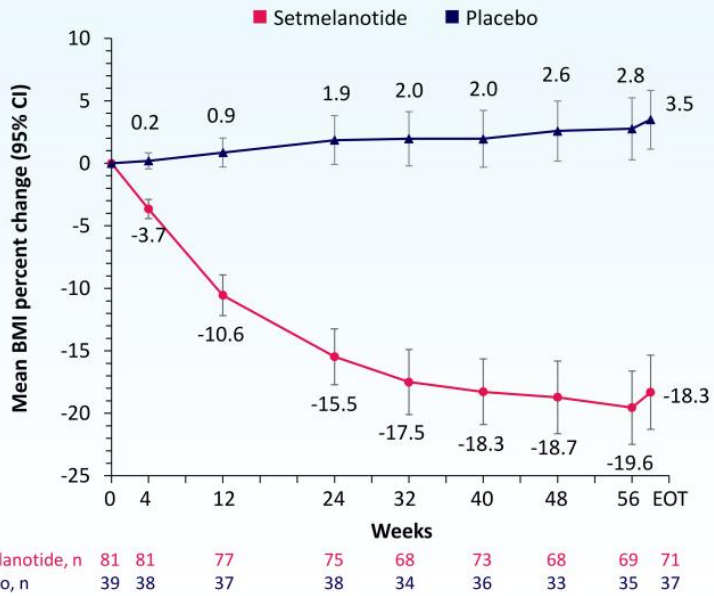
≥18 Years Old *(n=49)*



<18 Years Old *(n=71)*

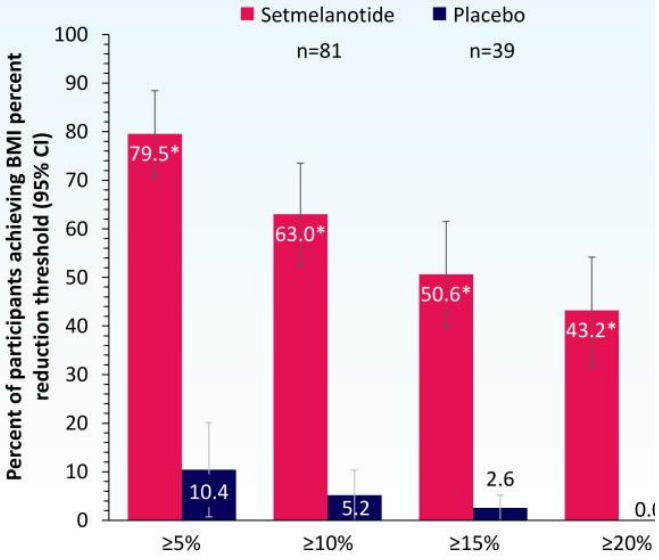


Rapid and Significant BMI Percent Reduction Starting at Week 4



Setmelanotide, n	81	81	77	75	68	73	68	69	71
Placebo, n	39	38	37	38	34	36	33	35	37

A Higher Proportion Achieved Perc BMI Reductions for All BMI Thresh



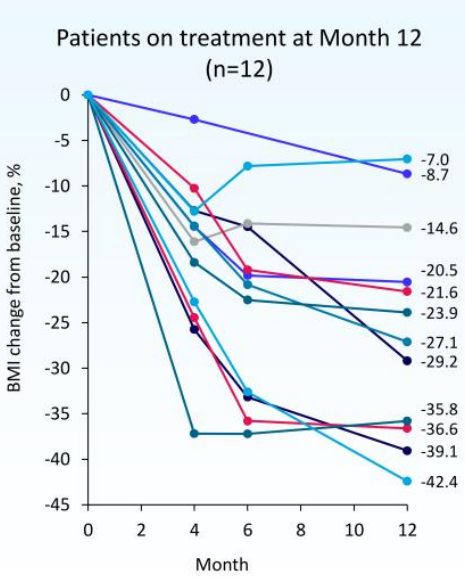
*P<0.0001 vs placebo.

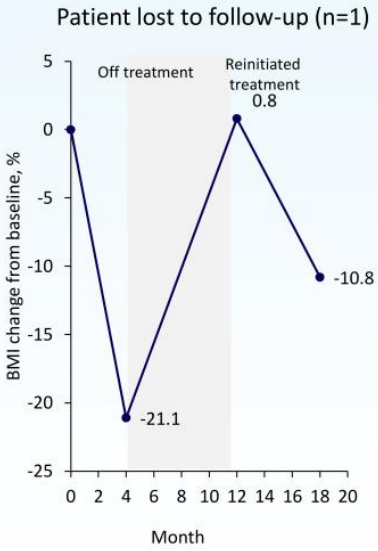
As presented at END

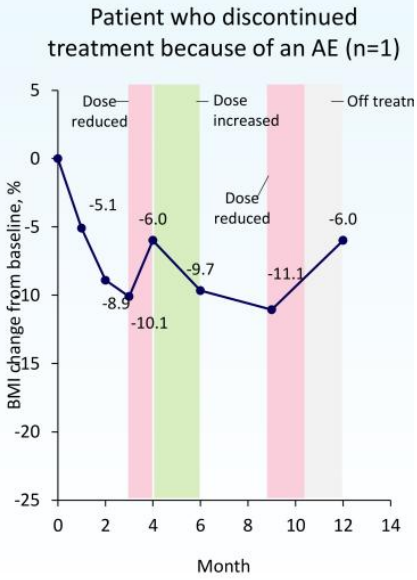
BMI, body mass index; CI, confidence interval.

Rhyt

Hypothalamic Obesity: Patients Achieved 25.5% Mean BMI Reduction at One Year of Setmelanotide Therapy in Long-term Ext. Trial



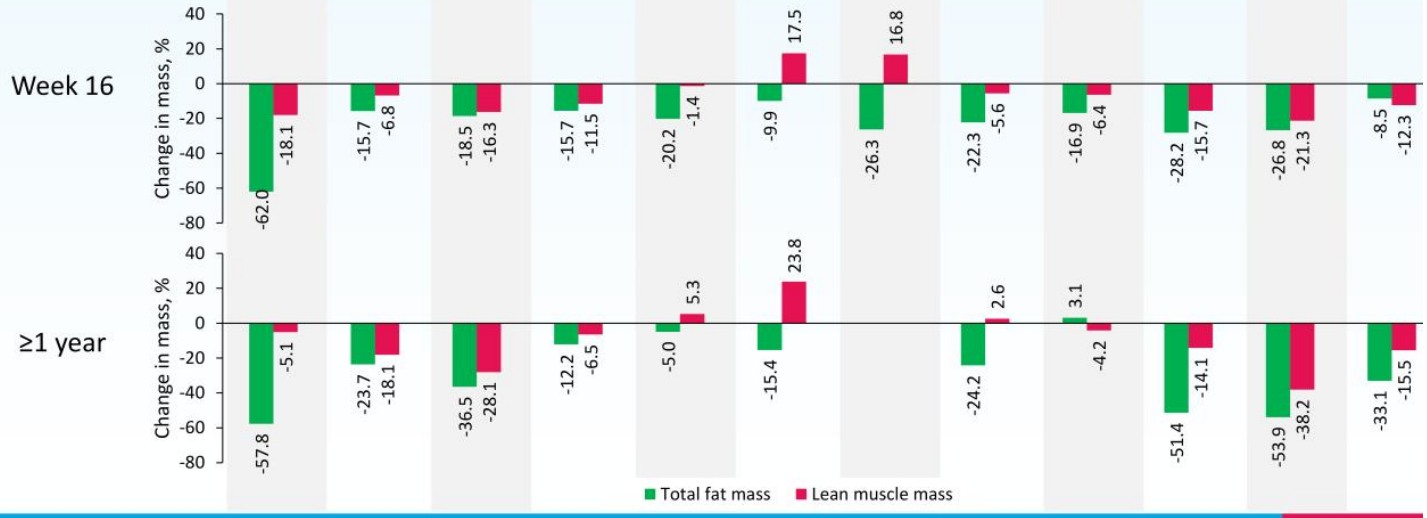




As presented during The Obesity Society Annual Meeting (TOS 2023) on October 17, 2023, in Dallas.

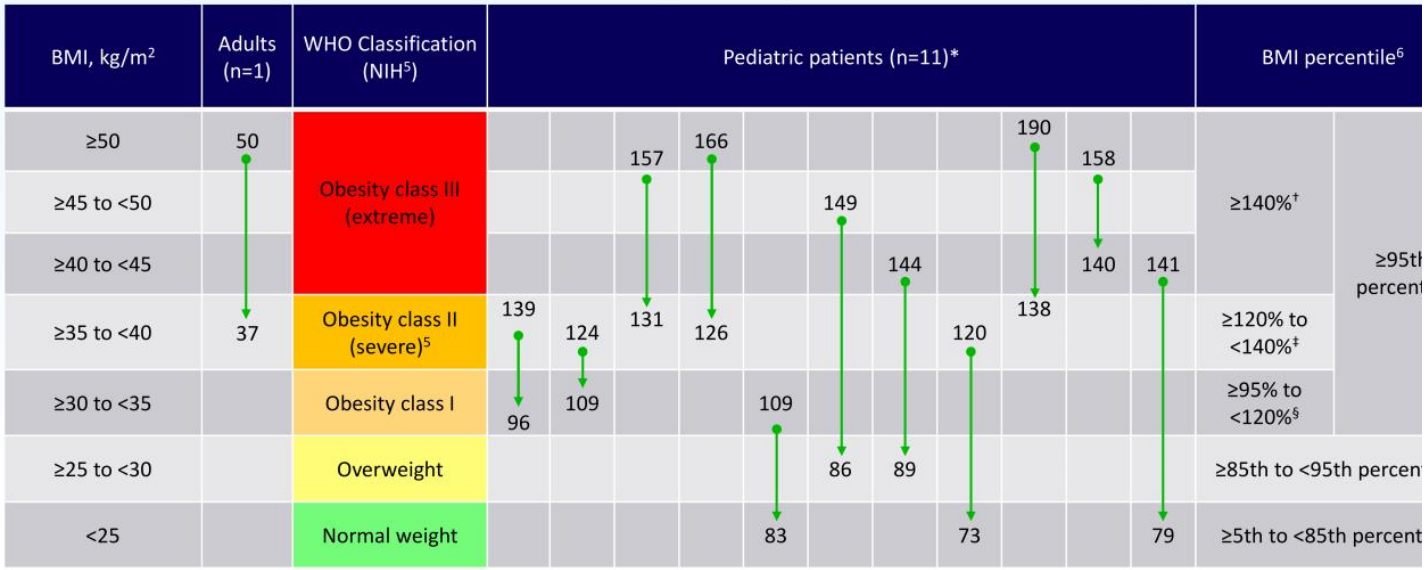
Body Composition Data Show Greater Decreases in Total Fat Mass vs. Lean Muscle Mass

Patient number	1	2	3	4	5	6	7	8	9	10	11	12
Age at baseline	6	9	9	10	11	12	13	14	15	15	16	24
Percent change in BMI from baseline to Month 12	-35.8	-20.5	-39.1	-23.9	-7	-8.7	-21.6	-29.2	-14.6	-36.6	-42.4	-27.1



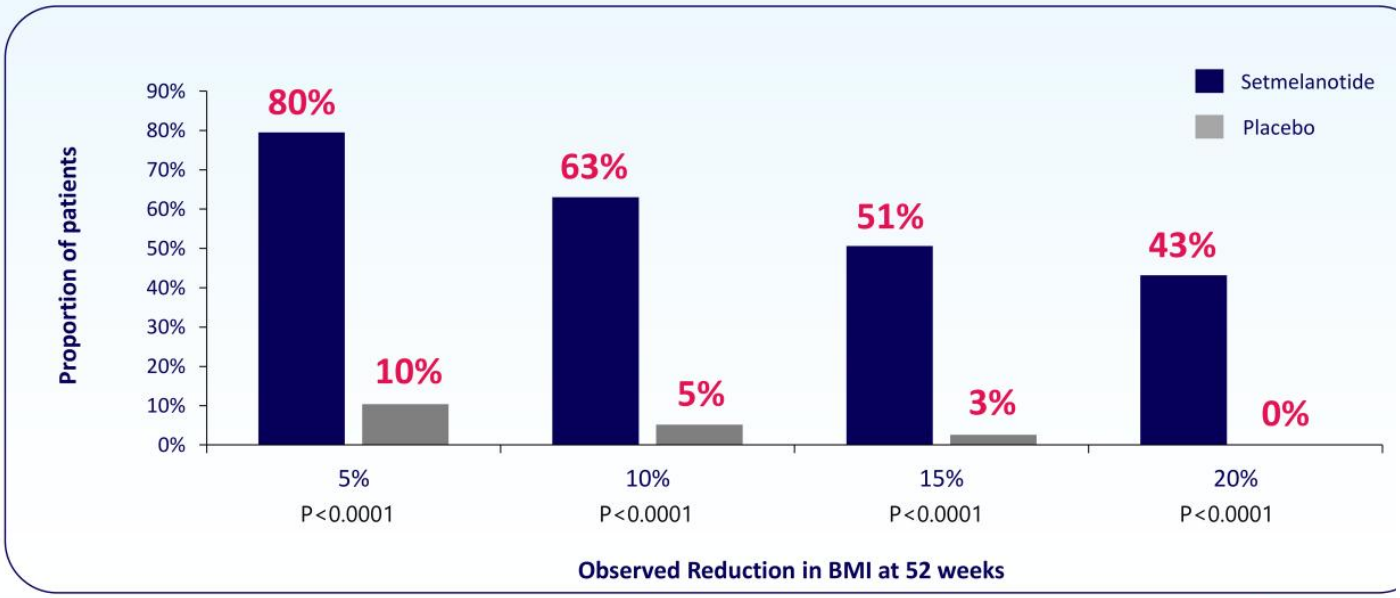
All Patients Achieved a Decrease in Obesity Severity at One Year

Three of 11 pediatric patients achieved normal weight at one year based on NIH, WHO weight classifications

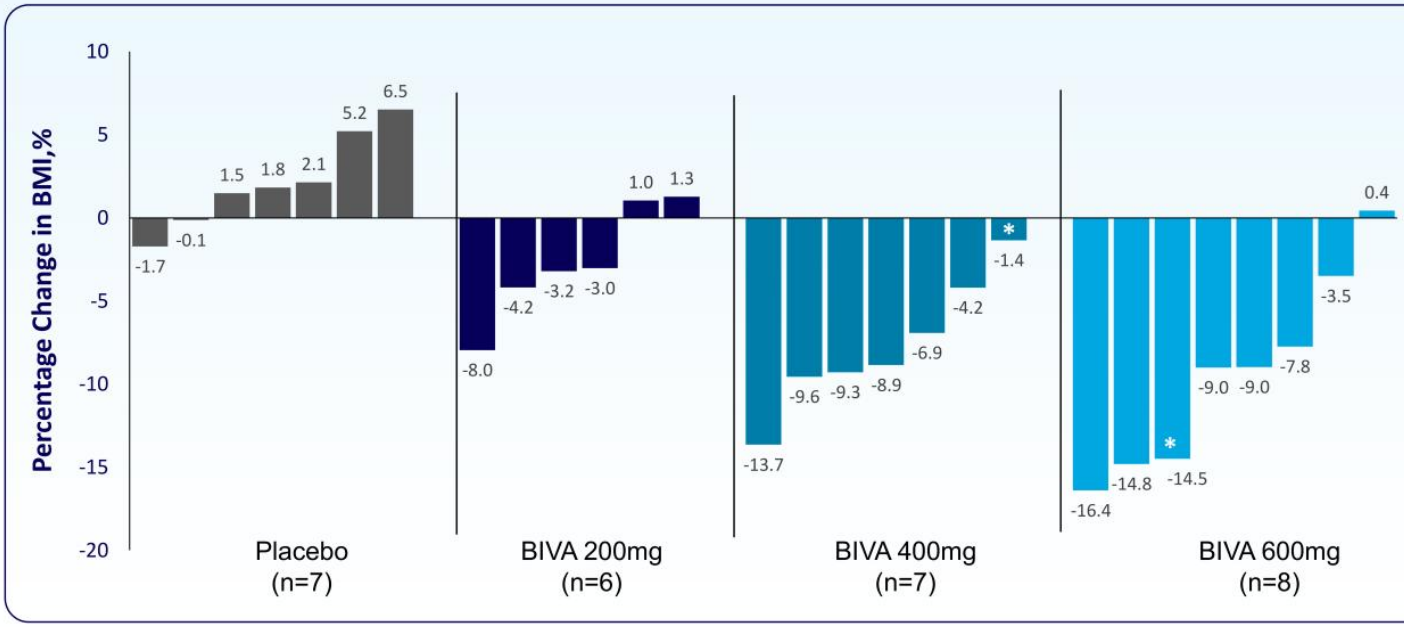


*Pediatric patients reported as %BMI95. †Or BMI ≥40 kg/m2 (whichever is lower). ‡Or BMI ≥35 to <40 kg/m2 (whichever is lower). §Or BMI ≥30 to <35 kg/m2 (whichever is lower). %BMI95, percent of the 95th percentile for BMI; BMI, body mass index; NIH, National Institutes of Health; WHO, World Health Organization.

Consistent Response to Setmelanotide Therapy Observed across Majority of Patients in Phase 3 Trial in Acquired HO



Individual Percentage Change in BMI from Baseline to Week 14

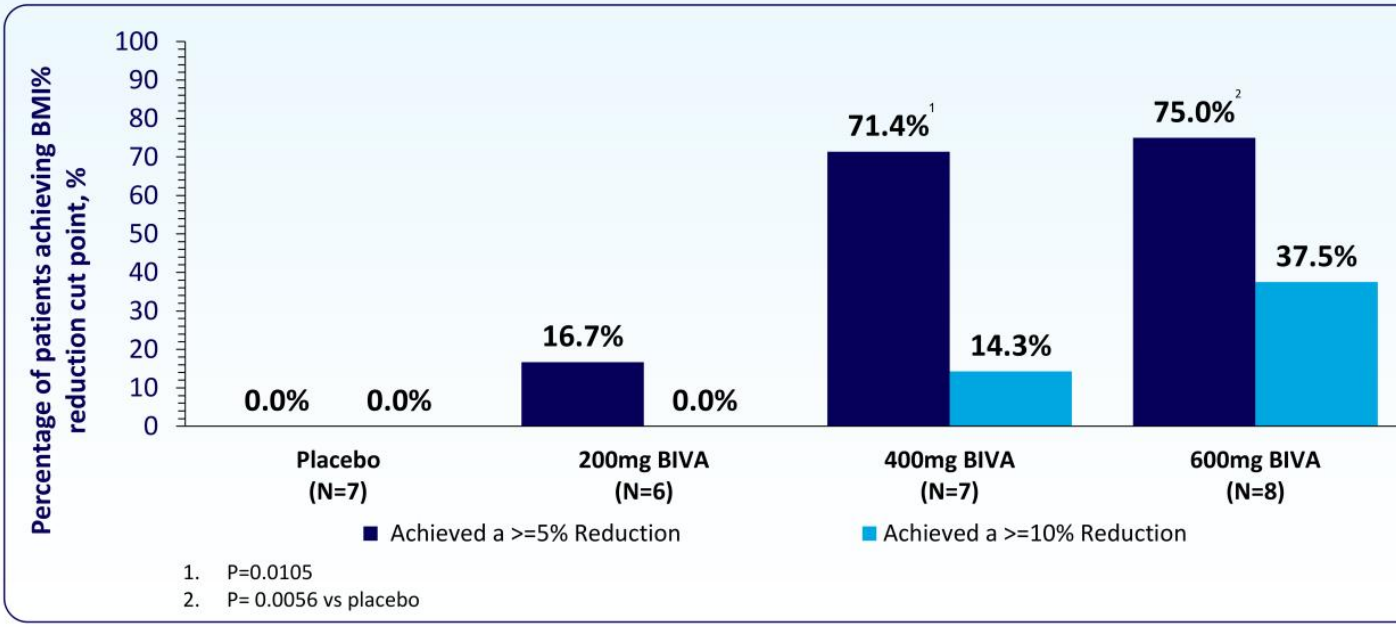


* Last observation carried forward (LOCF): One patient in 400mg cohort discontinued therapy at week one.

*LOCF (BIVA 400mg participant discontinued Tx Week 1; BIVA 600mg participant Week 101; BIVA, Bicomelagon

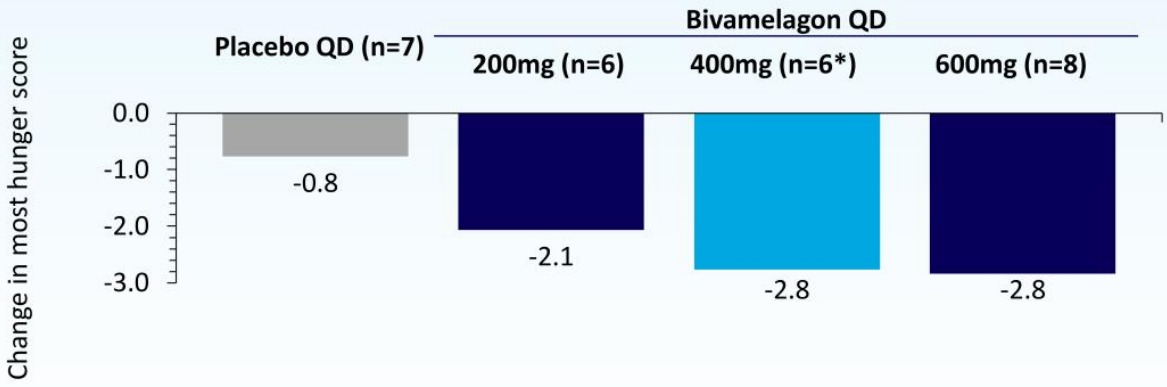
Rhyt

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



1. P=0.0105
2. P= 0.0056 vs placebo

Bivamelagon Achieved Meaningful Reductions in 'Most' Hunger Score 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

Thank you