Rhythm Pharmaceuticals

Phase 3 EMANATE Trial Topline Results

March 16, 2026

On Today's Call

- David Connolly, Executive Director of Investor Relations and Corporate Communications
- David Meeker, MD, Chair, President and Chief Executive Officer
- Alastair Garfield, Chief Scientific Officer
- Hunter Smith, Chief Financial Officer

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 the potential 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; clinical design, enrollment, or progress, and preliminary, interim and final data readouts; potential benefits from our EMANATE topline results, including our ability to identify true loss-of-function variants and develop our next-generation MC4R agonists; potential regulatory submissions, approvals and timing thereof of setmelanotide, bivamelagon, or RM-718; 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 setmelanotide, bivamelagon or RM-718 for patients with MC4R pathway diseases; expectations surrounding pending and potential regulatory submissions and approvals, including within the United States, the EU and other regions; business strategy and plans, including regarding commercialization of setmelanotide in the United States, the EU and other regions; 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" 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, 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 discussed under the caption "Risk Factors" in Rhythm's Annual Report on Form 10-K for the year ended December 31, 2025 and 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.

David Meeker, MD

Chair, President and CEO

Phase 3 EMANATE Topline Results

- Encouraging signals seen in POMC Hets and SRC1 substudies to inform development of next-generation MC4R agonists
  - Post hoc LOCF analyses demonstrated setmelanotide achieved statistically significant BMI reduction in POMC Hets and SRC1 substudies
- Deepened understanding across MC4R pathway genetics and variant classification
- Placebo effect potentially confounded analysis of intent-to-treat (ITT) population
- High discontinuation rate across all four substudies negatively affected topline results
  - Multiple imputation statistical analysis for calculating missing values and discontinued patients confounded primary endpoint analysis

Topline Results from Phase 3 EMANATE Trial of Setmelanotide

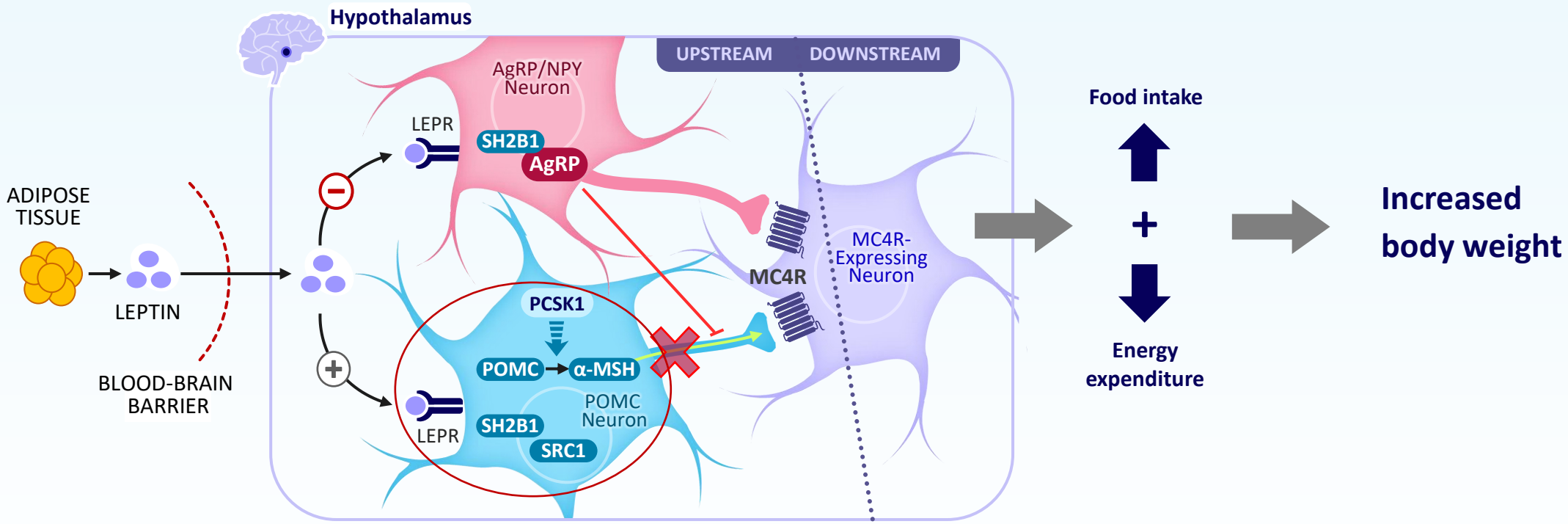
PRIMARY ENDPOINT: Difference in mean percent change in BMI from baseline to 52 weeks vs. placebo analyzed with pre-specified multiple imputation analysis of mITT population[1]

POMC/PCSK1 Hets	LEPR Hets	SRC1 (NCOA1)	SH2B1
-4.3%	**-3.6%**	**-4.0%**	**-1.7%**
(N=78*)	(N=23)	(N=73)	(N=121)
p-value = 0.15	**p-value = 0.94**	**p-value = 0.12**	**p-value = 0.43**

MITT, modified intent-to-treat

1. ANCOVA least-squares mean (LSM) difference in mean percent change in BMI from baseline to 52 weeks in setmelanotide arm compared to placebo arm using multiple imputation to replace missing values using placebo data for modified intent-to-treat analysis set; *One randomized patient discontinued before initial dose.

MC4R Pathway Impairment May Lead to Increased Hunger, Decreased Energy Expenditure and Early-onset Obesity



AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin; SH2B1, SH2B adaptor protein 1; SRC1, steroid receptor coactivator 1.

1. Farooqi et al. Nat Clin Pract Endocrinol Metab. 2008;4:569-577. 2. Yazdi et al. PeerJ. 2015;3:e856. 3. Yang et al. Nat Commun. 2019;10:1718.
2. Jiang L, Su H, Wu X, Shen H, Kim MH, Li Y, Myers MG Jr, Owyang C, Rui L. Leptin receptor-expressing neuron Sh2b1 supports sympathetic nervous system and protects against obesity and metabolic disease. Nat Commun. 2020 Mar 23;11(1):1517. doi: 10.1038/s41467-020-15328-3. Erratum in: Nat Commun. 2020 Oct 15;11(1):5310. PMID: 32251290; PMCID: PMC7089966.

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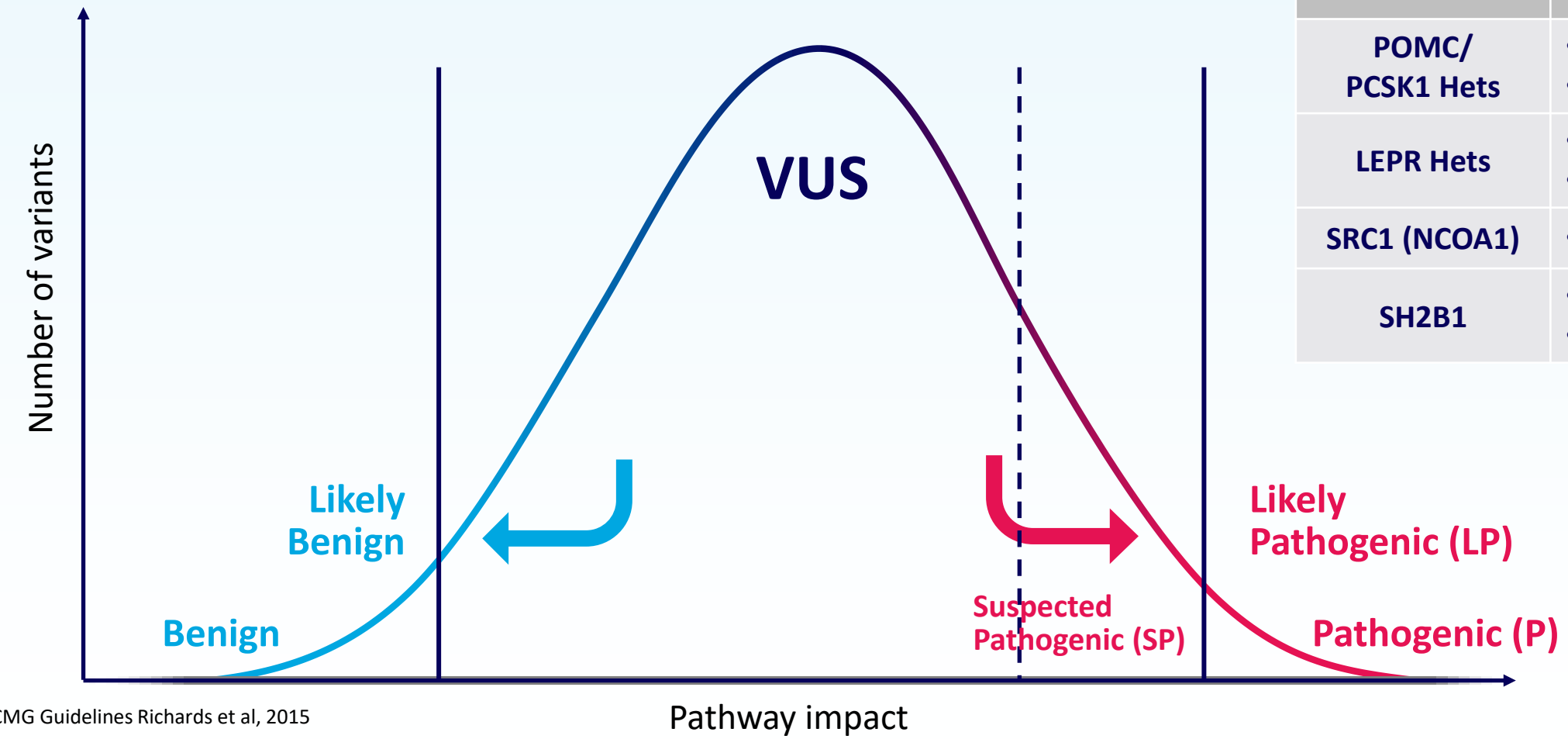
Variant Pathogenicity Defines MC4R Pathway Dysfunction and Is Subject to Reclassification



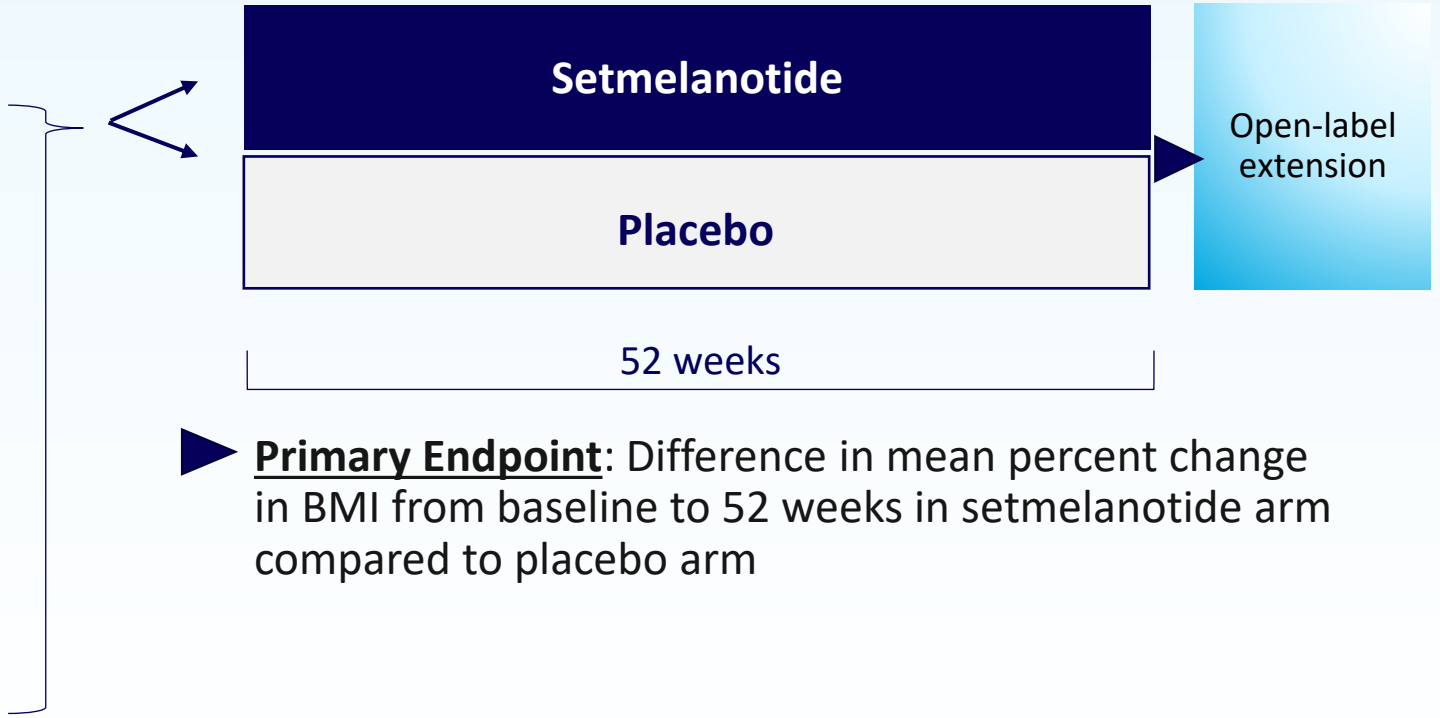
EMANATE Sub-study	ACMG Classification entry criteria
POMC/ PCSK1 Hets	• P/LP • VUS-SP
LEPR Hets	• P/LP • VUS-SP
SRC1 (NCOA1)	• All VUS
SH2B1	• P/LP • VUS

*ACMG Guidelines Richards et al, 2015

Phase 3 EMANATE Trial Comprised of Four Independent Sub-studies

Genetic sub-study	Enrolled patients
POMC/ PCSK1 Hets	**N=79***
LEPR Hets	**N=23**
SRC1 (NCOA1)	**N=73**
SH2B1	**N=121**

Each sub-study: Patients randomized 1:1



Primary Endpoint: Difference in mean percent change in BMI from baseline to 52 weeks in setmelanotide arm compared to placebo arm

VUS, Variant of uncertain significance
*One randomized patient discontinued before initial dose.

Baseline Demographics

		POMC / PCSK1 hets (N=79)	LEPR hets (N=23)	SRC1 (NCOA1) (N=73)	SH2B1 (N=121)
Age, years	Mean (SD) (Range)	25.3 (17.09)	23.0 (13.94)	29.0 (18.16)	27.2 (17.98)
	<12 years old, n	20 (25.3)	7 (30.4)	11 (15.1)	29 (24.0)
	≥12 years and <18, n	22 (27.8)	5 (21.7)	23 (31.5)	28 (23.1)
	≥18 years old, n	37 (46.8)	11 (47.8)	39 (53.4)	64 (52.9)
Sex, n (%)	Female / Male	44 (55.7) / 35 (44.3)	13 (56.5) / 10 (43.5)	49 (67.1) / 24 (32.9)	70 (57.9) / 51 (42.1)
Race, n (%)	White	71 (89.9)	18 (78.3)	56 (76.7)	92 (76.0)
	Black or African American	3 (3.8)	2 (8.7)	7 (9.6)	15 (12.4)
	Other	3 (3.8)	0	6 (8.2)	5 (4.1)
	Not Reported	2 (2.5)	2 (8.7)	0	6 (5.0)
Ethnicity, n (%)*	Hispanic or Latino	8 (10.1)	3 (13.0)	22 (30.1)	28 (23.1)
	Not Hispanic or Latino	69 (87.3)	17 (73.9)	51 (69.9)	87 (71.9)
Weight, kg	Mean (SD)	110.88 (35.330)	127.64 (46.200)	119.93 (40.909)	119.94 (40.478)
	Range	40.4, 193.6	35.1, 224.3	38.3, 284.7	35.8, 236.0
BMI, kg/m^2	**Mean (SD)**	**41.03 (9.104)**	**45.40 (13.120)**	**44.12 (11.461)**	**43.51 (11.118)**
	Range	**22.8, 76.2**	**20.1, 69.2**	**24.5, 85.9**	**21.5, 75.3**
BMI z-score	Mean (SD)	3.41 (1.384) (n=42)	3.78 (1.491) (n=12)	3.28 (1.214) (n= 34)	3.41 (1.309) (n= 57)
	Range	1.85, 8.01	1.66, 6.10	1.66, 6.20	1.80, 7.70

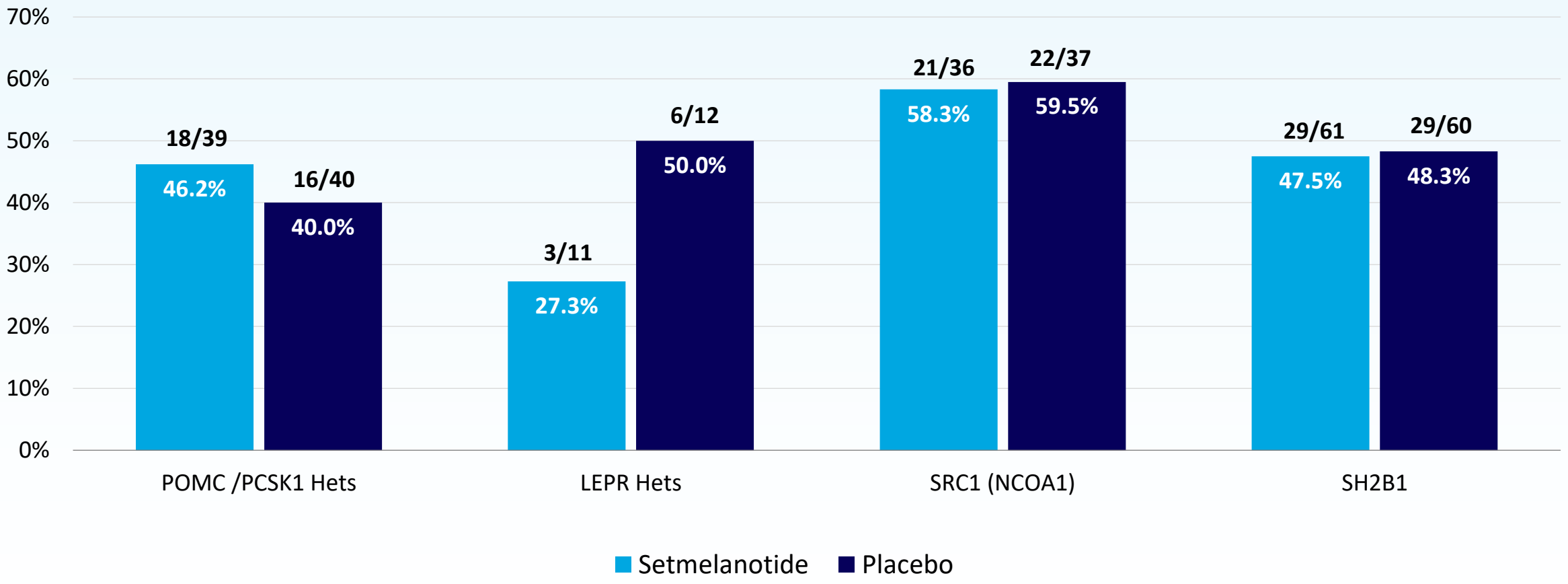
*Not reported: POMC/PCSK1 hets, n=2; LEPR hets, n=3; SH2B1, n=28.

Common Adverse Events with Setmelanotide

Adverse Event Events with ≥30% incidence in a setmelanotide (Set) arm in any substudy are shown	**POMC/PCSK1 Hets**		**LEPR Hets**		**SRC1 (NCOA1)**		**SH2B1**	
	PBO N=39 n (%)	SET N=39* n (%)	PBO N=12 n (%)	SET N=11 n (%)	PBO N=37 n (%)	SET N=36 n (%)	PBO N=60 n (%)	SET N=61 n (%)
Injection site erythema	17 (43.6)	14 (35.9)	4 (33.3)	6 (54.5)	20 (54.1)	14 (38.9)	30 (50.0)	25 (41.0)
Injection site induration	12 (30.8)	13 (33.3)	2 (16.7)	3 (27.3)	13 (35.1)	9 (25.0)	12 (20.0)	20 (32.8)
Injection site pain	14 (35.9)	13 (33.3)	3 (25.0)	4 (36.4)	14 (37.8)	14 (38.9)	19 (31.7)	17 (27.9)
Injection site pruritus	8 (20.5)	9 (23.1)	1 (8.3)	3 (27.3)	16 (43.2)	16 (44.4)	13 (21.7)	21 (34.4)
Skin hyperpigmentation	7 (17.9)	32 (82.1)	3 (25.0)	10 (90.9)	10 (27.0)	30 (83.3)	23 (38.3)	52 (85.2)
Nausea	11 (28.2)	17 (43.6)	2 (16.7)	1 (9.1)	6 (16.2)	17 (47.2)	15 (25.0)	26 (42.6)
Vomiting	7 (17.9)	12 (30.8)	1 (8.3)	1 (9.1)	3 (8.1)	11 (30.6)	7 (11.7)	13 (21.3)
Headache	8 (20.5)	9 (23.1)	3 (25.0)	3 (27.3)	7 (18.9)	6 (16.7)	6 (10.0)	20 (32.8)
Melanocytic nevus	5 (12.8)	20 (51.3)	1 (8.3)	6 (54.5)	2 (5.4)	15 (41.7)	6 (10.0)	25 (41.0)

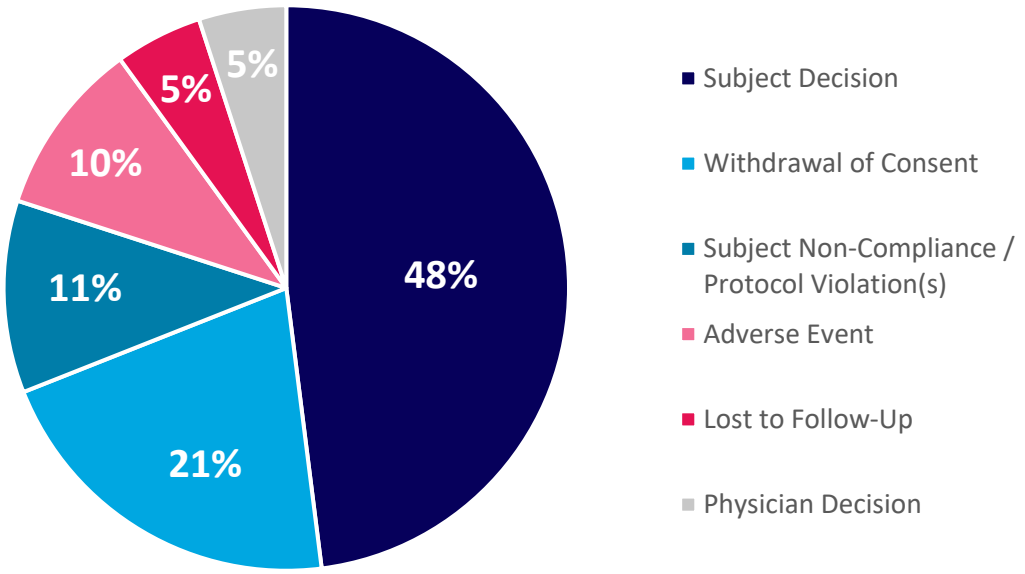
*One patient transitioned from placebo to setmelanotide/rescue therapy during the study due to weight gain. This patient was included in the placebo arm for efficacy analysis due to their initial randomization, but have been included in the active arm for safety analysis due to setmelanotide exposure.

High Discontinuation Rate across All Cohorts

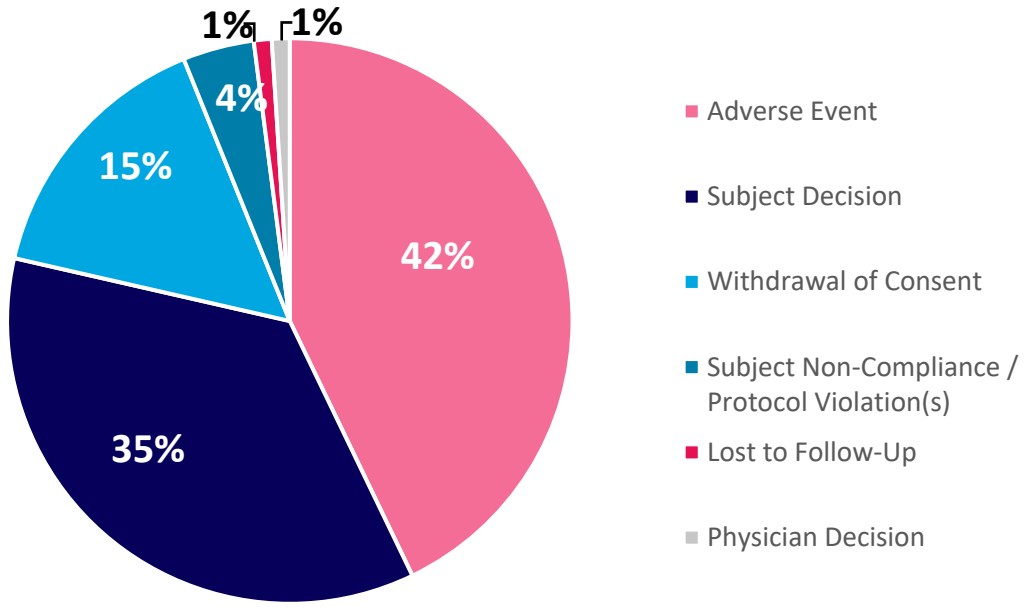


Discontinuation Rates Driven by Multiple Factors in Placebo and Active Arms

Discontinuations – Placebo (All Substudies)



Discontinuations – Setmelanotide (All Substudies)*



*Across the four substudies, 29 patients in the active (setmelanotide arm) discontinued treatment before week 52. The most common AEs leading to discontinuation included hyperpigmentation, nausea and vomiting.

POMC / PCSK1 Hets

POMC/PCSK1 Hets: Setmelanotide Achieved Statistically Significant BMI Reduction in mITT Patients Based on LOCF Analysis

	Placebo (N=40)	Setmelanotide (N=38)
% change BMI baseline to week 52: Mean (SE)	0.98 (1.151)	-4.65 (1.106)
ANCOVA LSM (SE) [95% CI]	0.75 (1.329) [-1.90, +3.39]	-4.79 (1.367) [-7.51, -2.06]
LSM difference (SE) [95% CI], setmelanotide-placebo		**-5.53** (1.612) [-8.75, -2.32]
P-Value for LSM difference		0.0010

Post hoc analysis of mITT cohort based on last observation carried forward (LOCF)

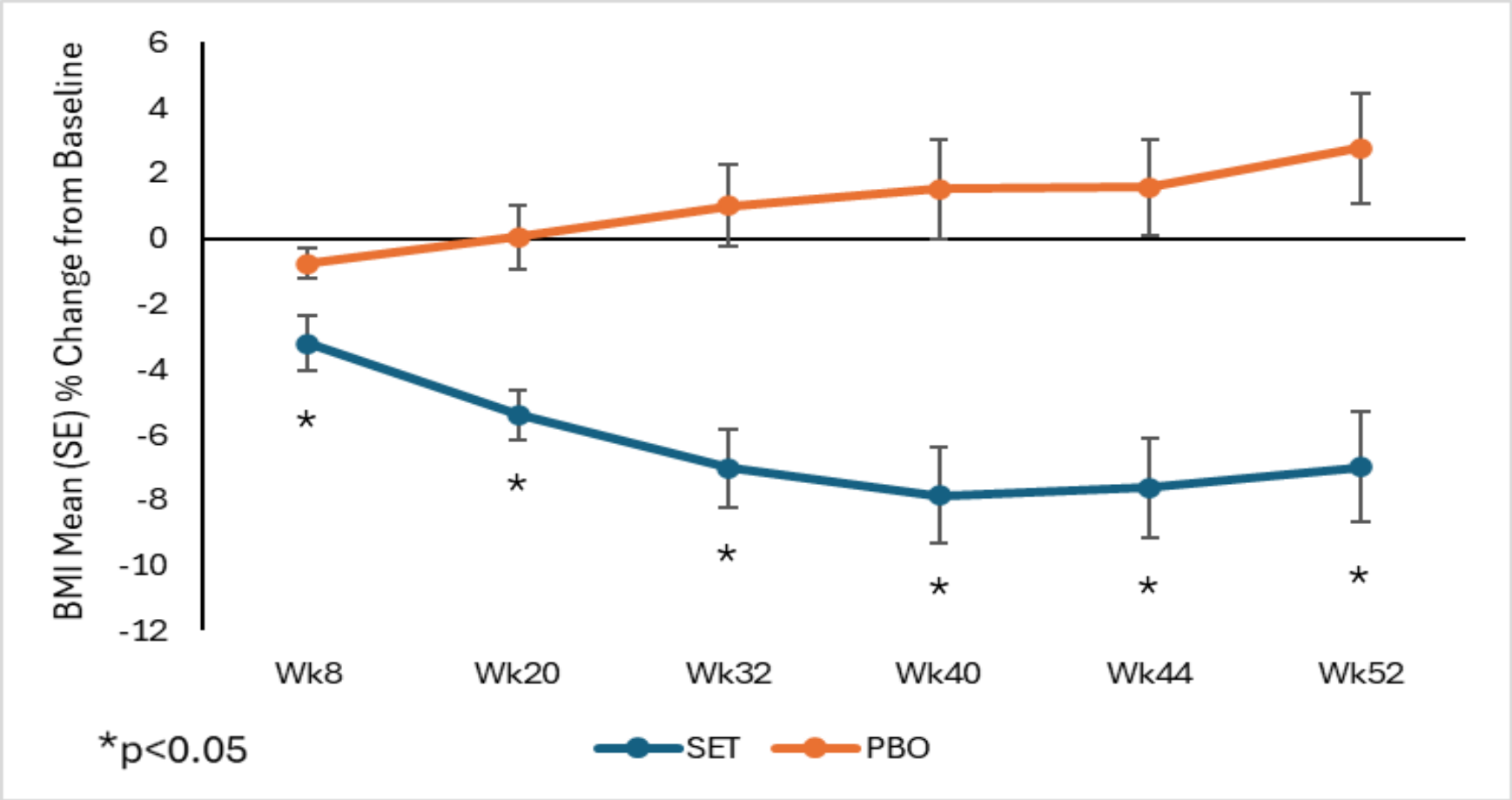
mITT, modified intent-to-treat

POMC/PCSK1 Hets: Setmelanotide Achieved Statistically Significant BMI Reduction in Genetically Confirmed Patients Based on LOCF Analysis

	Placebo (N=35)	Setmelanotide (N=32)
% change BMI baseline to week 52: Mean (SE)	2.20 (1.290)	-5.04 (1.171)
ANCOVA LSM (SE) [95% CI]	2.61 (1.628) [-0.64, 5.87]	-4.17 (1.511) [-7.19, -1.15]
LSM difference (SE) [95% CI], setmelanotide-placebo		**-6.78** (1.775) [-10.33, -3.23]
P-Value for LSM difference		0.0003

Post hoc analysis of genetically confirmed patients based on last observation carried forward (LOCF)

POMC/PCSK1 Hets: Setmelanotide Achieved Statistically Significant BMI Reduction in Genetically Confirmed Patients who Reached Week 52



Placebo, N	21	21	21	20	20	21
Setmelanotide, N	20	20	20	19	20	20

-9.7%

Week 52 placebo-adjusted difference

(PBO n=21; SET n=20)

p=0.0002

NOTE: Post hoc analysis of genetically confirmed completers using a student's T-test.

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LEPR Hets

Highlights from the LEPR Hets Substudy

Eligible LEPR Hets patients were rare and hard to recruit

Eight (8) of 11 setmelanotide-assigned patients were down classified (predominantly one variant)

Positive response in 3 setmelanotide-assigned patients who had a pathogenic variant achieved BMI reductions of: -4.3%, -7.2%*, -13.3%

*Patient with -7.2% BMI reduction at Week 28 subsequently discontinued treatment.

SRC1 (NCOA1)

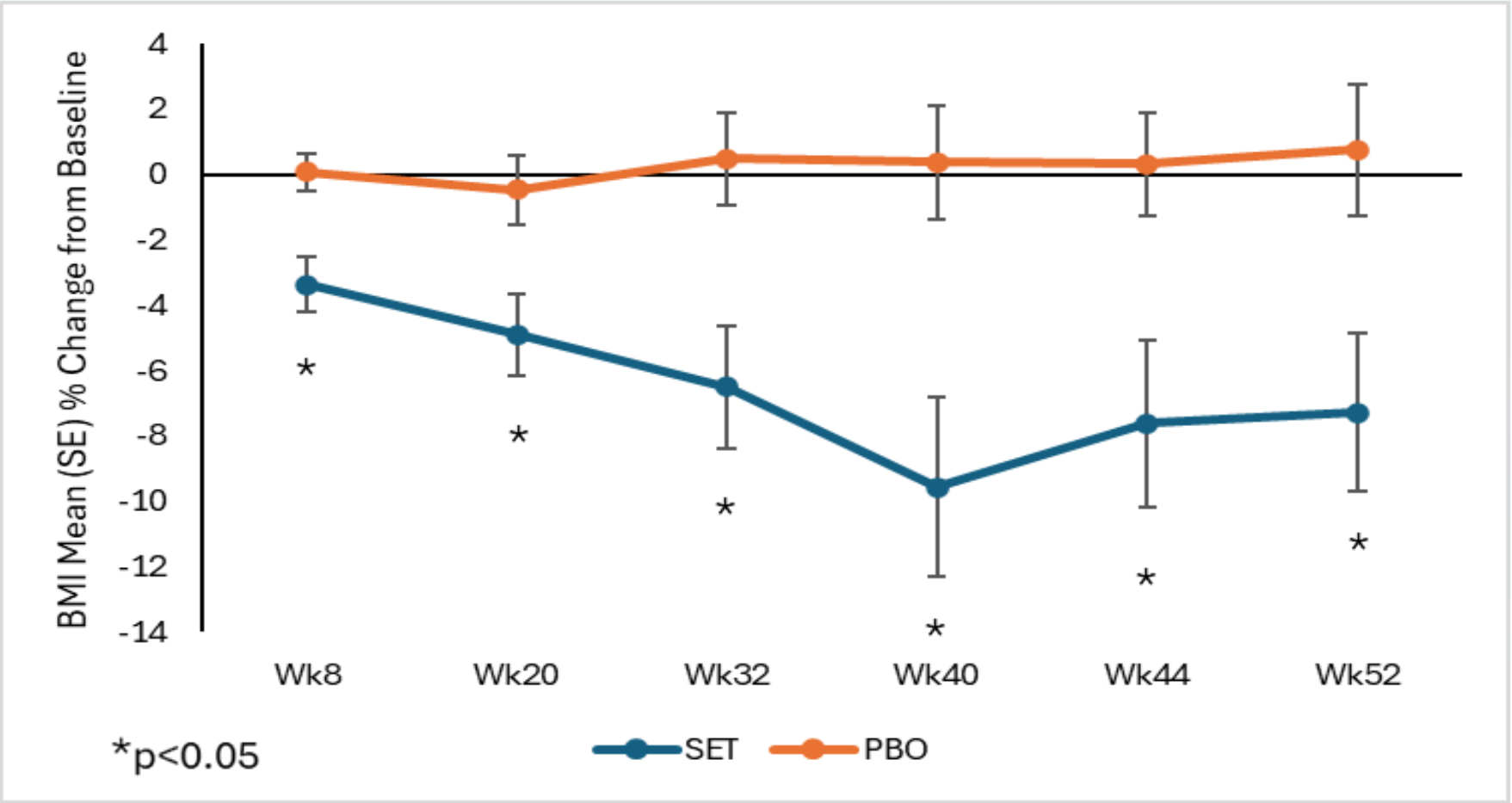
SRC1 (NCOA1): Setmelanotide Achieved Statistically Significant BMI Reduction in mITT Patients Based on LOCF Analysis

	Placebo (N=37)	Setmelanotide (N=36)
% change BMI baseline to week 52: Mean (SE)	1.44 (0.837)	-4.87 (1.192)
ANCOVA LSM (SE) [95% CI]	1.73 (1.115) [-0.50, +3.95]	-4.51 (1.68) [-6.84, -2.18]
LSM difference (SE) [95% CI], setmelanotide-placebo		**-6.24** (1.499) [-9.33, -3.25]
P-Value for LSM difference		<0.0001

Post hoc analysis of mITT cohort based on last observation carried forward (LOCF)

mITT, modified intent-to-treat

SRC1 (NCOA1): Setmelanotide Achieved Statistically Significant BMI Reduction in Genetically Confirmed Patients who Reached Week 52



Placebo, N	15	15	15	13	15	15
Setmelanotide, N	14	14	14	12	14	14

-8.0%

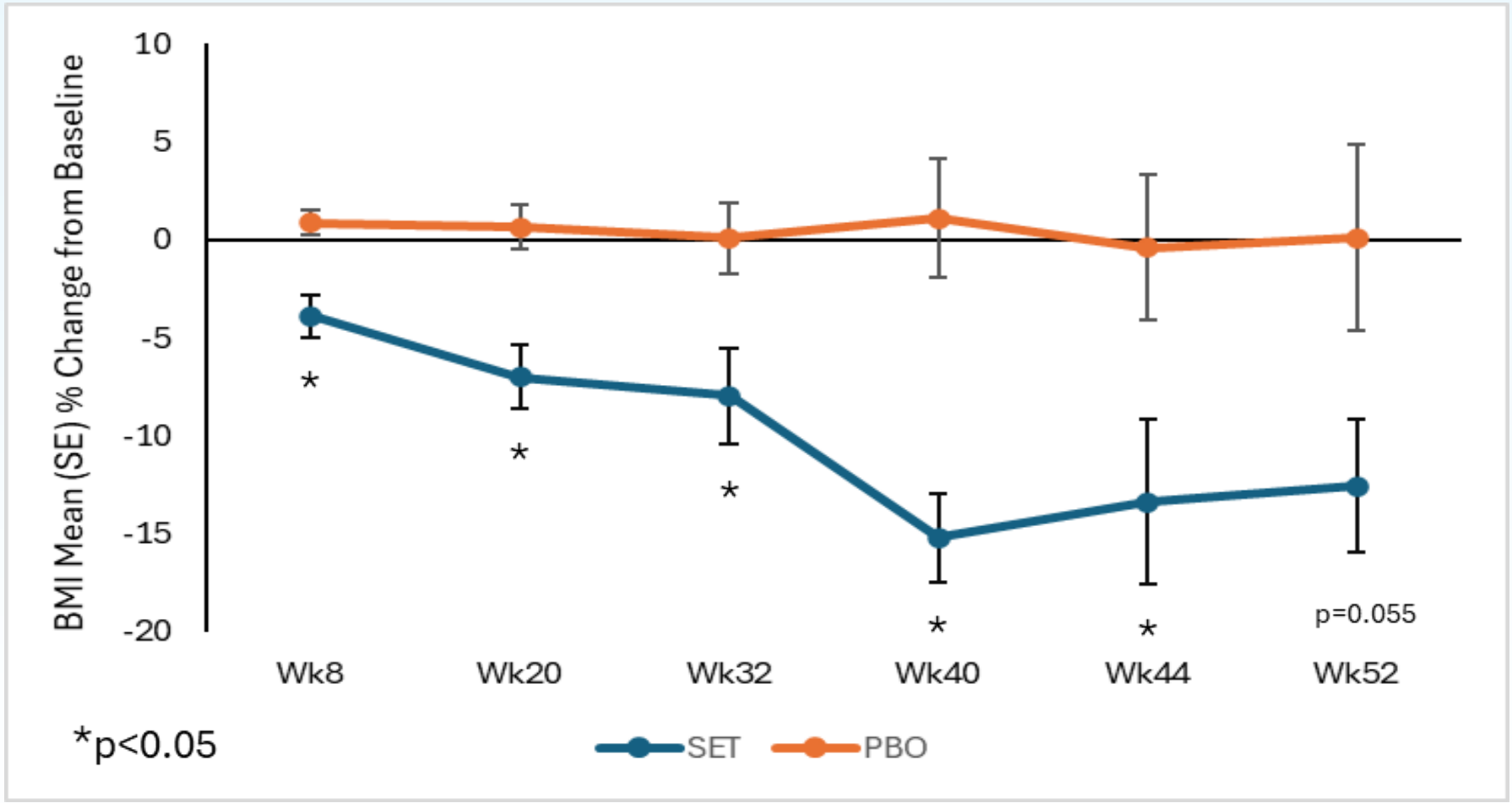
Week 52 placebo-adjusted difference

(PBO N=15; SET N=14)

p=0.0158

NOTE: Post hoc analysis of genetically confirmed completers using a student's T-test.

SRC1 (NCOA1): Analysis of Genetically Confirmed Patients with Variants in Critical Protein Binding Domain Demonstrate Compelling Response



Placebo, N	9	9	8	7	6	6
Setmelanotide, N	10	9	8	5	6	6

-12.7%

Week 52 placebo-adjusted difference

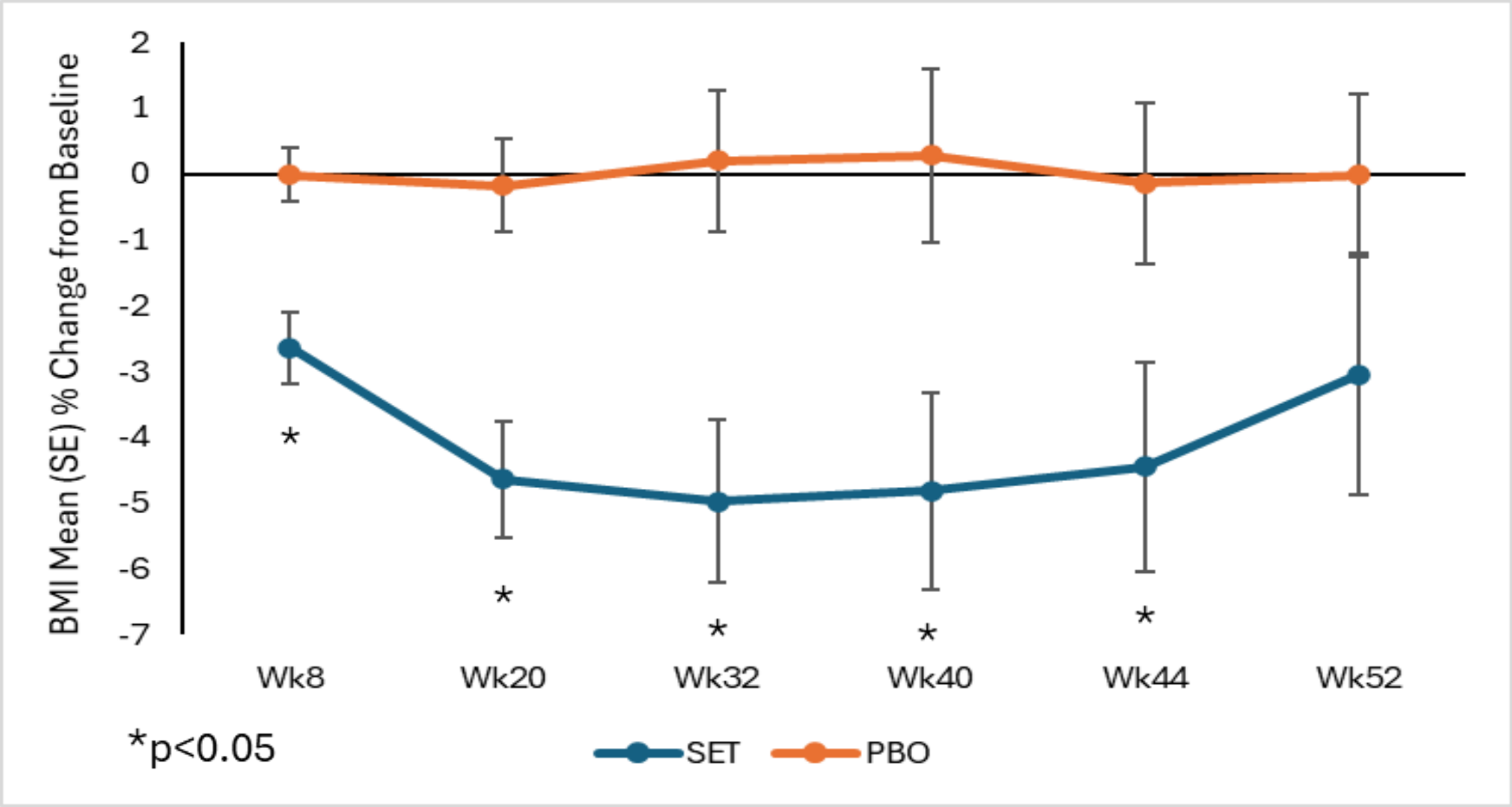
(PBO N=6; SET N=6)

p=0.055

NOTE: Post hoc analysis of genetically confirmed completers using a student's T-test.

SH2B1

SH2B1/16p11.2: Analysis of Genetically Confirmed Completers Shows No Significant Difference in BMI Reduction at Week 52



Placebo, N	30	30	29	25	29	30
Setmelanotide, N	32	32	32	30	32	32

-3.0%

Week 52 Placebo-adjusted difference

(PBO N=30; SET N=32)

p=0.1772

NOTE: Post hoc analysis of genetically confirmed completers using a student's T-test.

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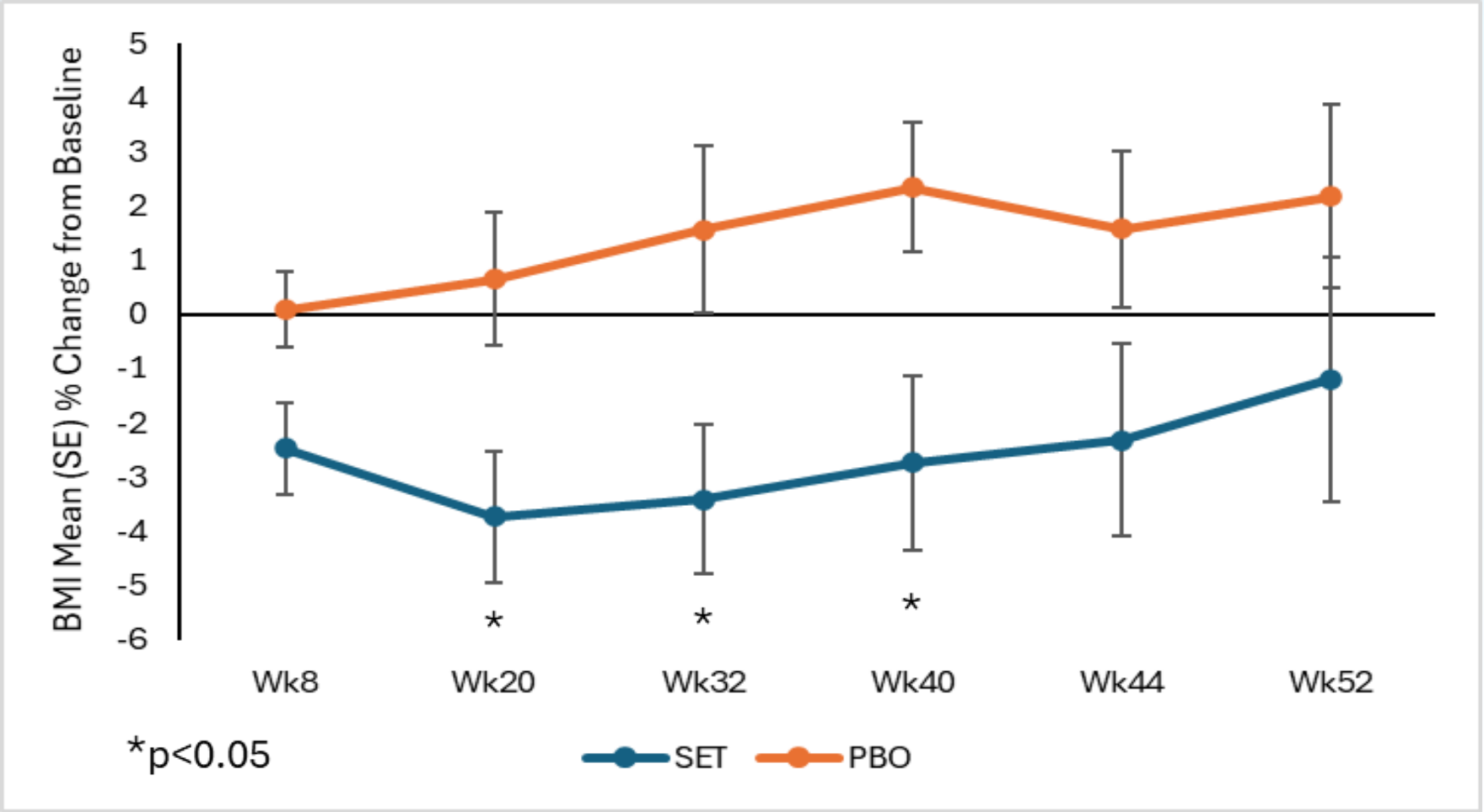
16p11.2 Subgroup Analysis Shows No Significant Difference in BMI Reduction at Week 52



Placebo, N	8	8	8	7	8	8
Setmelanotide, N	13	13	13	12	13	13

-3.4%

Week 52 Placebo-adjusted difference

(PBO n=8; SET n=13)

p=0.3006

NOTE: Post hoc analysis of genetically confirmed completers using a student's T-test.

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Encouraging Results Leading to Next Steps

Encouraged by positive analyses of POMC/PCSK1 and SRC1 substudies

Continue to interrogate POMC/PCSKI, SRC1 plus DAYBREAK genes to improve LOF determination

Advance next-generation MC4R agonists in genetic indications

LOF, loss of function

MC4R Agonism Development Across Three Pillars

Genetic MC4R Pathway Diseases

- Promising signals in POMC Hets and SRC1
- Additional DAYBREAK genes
- Next-generation assets

Hypothalamic Obesity

- U.S. launch*
- EMA authorization**
- Ongoing Ph2 trial with RM-718
- Ph3 trial with bivamelagon by YE 2026

Prader-Willi Syndrome

- Ongoing Ph2 trial with setmelanotide
- Ph1/2 trial with RM-718 initiated

*Pending FDA approval; the FDA's assigned PDUFA goal date is March 20, 2026; **pending regulatory feedback

Questions