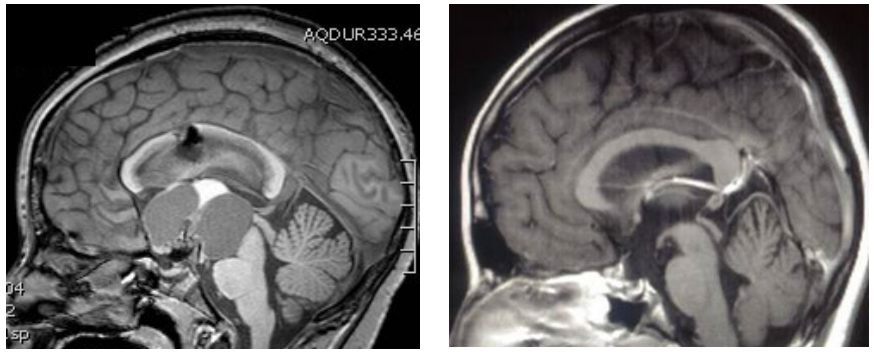
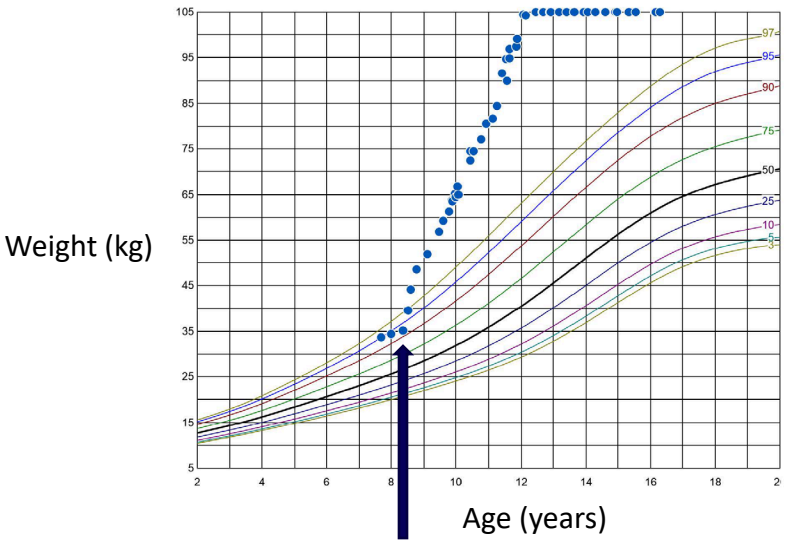
Efficacy of Setmelanotide in Patients with Acquired HO Previously or Concurrently on GLP 1 Therapy

Scan here for a copy of this presentation:

Christian L. Roth, MD, Ashley Shoemaker, MD, Susan A. Phillips, MD, Jill Hamilton, MD, Shana E. McCormack, MD, M. Jennifer Abuzzahab, MD, Martin Wabitsch, Prof Dr med, Mehul T. Dattani, MD, Tomohiro Tanaka, MD, Cecilia Scimia, MD, PhD, Guojun Yuan, MD, PhD, Hanneke M. van Santen, MD, PhD, Hermann L. Müller, MD, and Jennifer L. Miller, MD
on behalf of the TRANSCEND Trial Group

Acquired Hypothalamic Obesity





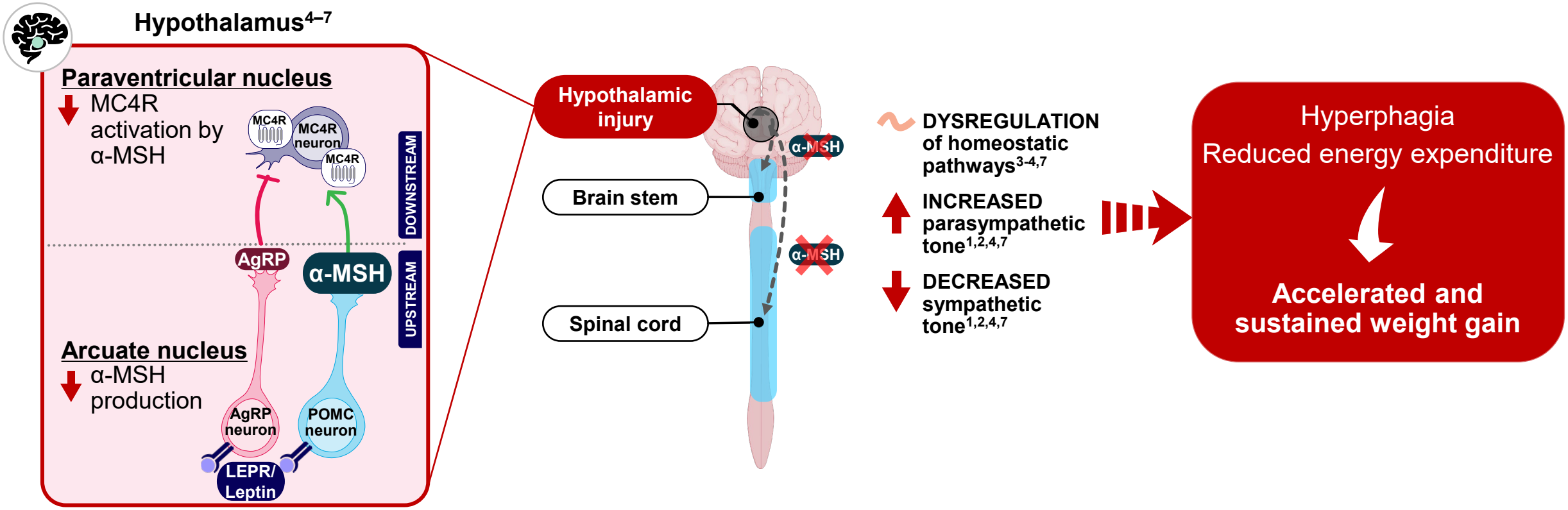
- Acquired hypothalamic obesity (HO) is often caused by craniopharyngiomas and other suprasellar tumors[1,2]
- Up to 4% of pediatric brain tumors are craniopharyngiomas[3]
- ~50% of patients with craniopharyngioma develop acquired HO[4,5]
- Hyperphagia is present in up to 72% of patients with acquired HO[6]
- Acquired HO is associated with an increased risk of cardiovascular disease[7,8]
- Other hypothalamic tumors can cause acquired HO as well (such as astrocytomas, hamartomas, germinomas)[1,2]

HO, hypothalamic obesity.

1. Roth, et al. *Diabetes Obes Metab*. 2024. 2. Rose, et al. *Obesity*. 2018. 3. Müller, et al. *Endocr Rev*. 2014. 4. Andereggen, et al. *Swiss Med Wkly*. 2018. 5. Beckhaus, et al. *EJE*. 2023. 6. Kayadjanian et al., *JCEM*. 2023. 7. Roth, et al. *JCM*. 2015. 8. Pereira, et al. *Clin Endocrinol*. 2005.

Injury to the Hypothalamus May Lead to Acquired Hypothalamic Obesity Through Potential Disruption of MC4R Signaling Pathway[1–3]

Deficiency in α–melanocyte-stimulating hormone (α-MSH)



α-MSH, α–melanocyte-stimulating hormone; AgRP, agouti-related peptide; LEPR, leptin receptor; MC4R, melanocortin-4 receptor; POMC, proopiomelanocortin.

1. Abuzzahab, et al. *Horm Res Paediatr*. 2019. 2. Roth. *Front Endocrinol*. 2011. 3. Roth, et al. *Metabolism*. 2010.
4. Dimitri. *Front Endocrinol*. 2022. 5. Baldini, et al. *J Endocrinol*. 2019. 6. Hochberg, et al. *Obes Rev*. 2010. 7. Roth, et al. *Obesity*. 2011.

Introduction Treatment of Acquired HO – Current Status

- Acquired HO: accelerated and sustained weight gain following hypothalamic injury[1]
- Obesity treatments, including lifestyle interventions and obesity drug interventions, have often failed in the past to achieve sustained weight loss[2-3]
- A deficiency in α-melanocyte stimulating hormone (α-MSH) signaling can lead to hyperphagia, decreased energy expenditure, and the accelerated weight gain[4-8]
- Setmelanotide, an analogue of α-MSH, has demonstrated consistent and clinically significant reductions in body mass index in phase 2 and 3 studies of patients with acquired HO[9,10]

α-MSH, α–melanocyte-stimulating hormone; HO, hypothalamic obesity.

1. Roth, et al. *Diabetes Obes Metab* 2024. 2. Dimitri, et al. *JES*. 2024. 3. Van Roessel, et al. *Clin Nutr*. 2024. 4. Abawi, et al. *Front Endocrinol*. 2022. 5. Holmer, et al. *JCEM.* 2010. 6. Shoemaker, et al. *JCEM.* 2023. 7. Sohn et al. *Cell*. 2013. 8. Wu, et al. *Neuroendocrinology*. 2023. 9. Roth, et al. *Lancet D&E*. 2024. 10. Phillips SA, et al. Presented at ENDO 2025, July 12-14, San Francisco, CA.

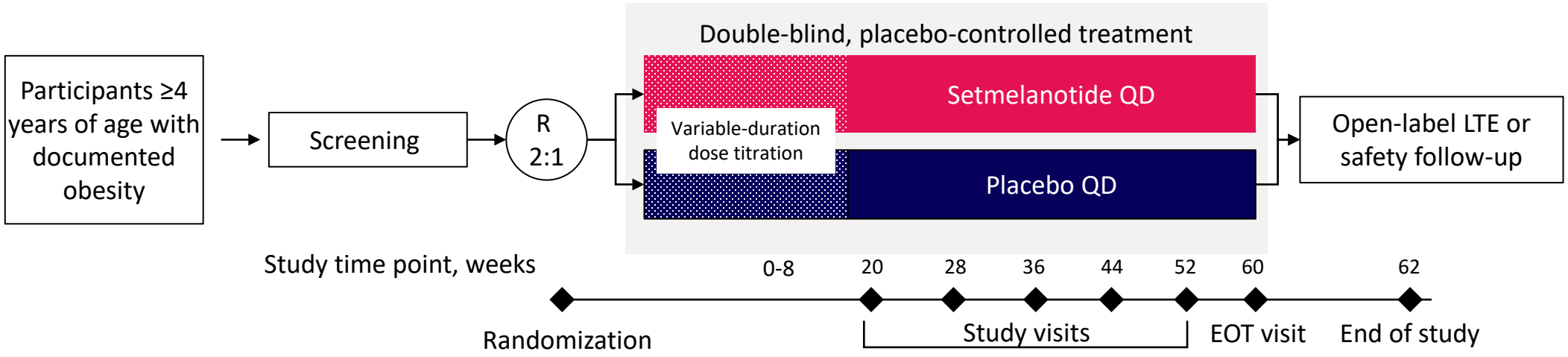
Glucagon-like Peptide-1 Receptor Agonist (GLP-1 RA) Use in Acquired HO

- Although there are no approved therapies for acquired HO, GLP-1 RA therapies have been used[1-5]
- In the international Phase 3 TRANSCEND trial of setmelanotide in acquired HO, participants were permitted to enroll if they had received a prior GLP-1 RA and had not recently lost weight
  - Participants were allowed to continue GLP-1 RA treatment on a stable dose to be continued throughout the trial
- We performed a *post hoc* analysis of the efficacy of setmelanotide in participants who received concomitant GLP-1 RAs

GLP-1 RA, glucagon-like peptide-1 receptor agonist; HO, hypothalamic obesity.

1. Roth, et al. *Diabetes Obes Metab*. 2021. 2. Gatta-Cherifi, et al. *EJE*. 2023. 3. Svendstrup, et al. *Pituitary*. 2024.
4. Wang, et al. *Clin Endocrinol.* 2025. 5. Dimitri, et al. *J Endocr Soc*. 2024.

Design of Phase 3 “TRANSCEND” Trial
Setmelanotide in Acquired Hypothalamic Obesity (NCT05774756)



Primary efficacy endpoint

- Mean percent change in BMI from baseline at 52 weeks on therapeutic regimen, setmelanotide vs placebo

BMI, body mass index; EOT, end of treatment; LTE, long-term extension; QD, once daily; R, randomization.

Baseline Participant Demographics

	Setmelanotide (n=81)	Placebo (n=39)
Age, mean ± SD (range), y	**19.2 ± 13.0 (4-65)**	**21.4 ± 13.8 (4-66)**
Age <18 y, n (%)	48 (59.3)	23 (59.0)
Age ≥18 y, n (%)	33 (40.7)	16 (41.0)
Sex, n (%)		
Female	45 (55.6)	27 (69.2)
Male	36 (44.4)	12 (30.8)
Weight, mean (95% CI), kg	**92.9 (84.4-101.4)**	**94.1 (81.5-106.7)**
In those ≥18 y	115.6 (103.6-127.6)	124.2 (106.7-141.7)
BMI, mean (95% CI), kg/m^2	**35.7 (33.7-37.8)**	**36.8 (33.8-39.8)**
Participants ≥18 years, kg/m^2	40.1 (36.7-43.6)	43.5 (38.5-48.4)
BMI Z score, 4 to <18 y, mean (95% CI)	**3.72 (3.19-4.25)**	**3.37 (2.81-3.93)**
%BMI95, 4 to <18 y, mean (95% CI)	**132.3 (124.0-140.7)**	**128.6 (118.8-138.5)**
Waist circumference (95% CI), cm	**106.6 (101.8-111.4)**	**108.6 (102.6-114.7)**
Maximal daily hunger score, mean (n; 95% CI)	**6.77 (57; 6.15-7.38)**	**7.23 (24; 6.34-8.13)**
Prior GLP-1 RA therapy, n (%)	**10 (12.3)**	**6 (15.4)**
Prior and concomitant GLP-1 RA therapy	**9 (11.1)**	**6 (15.4)**

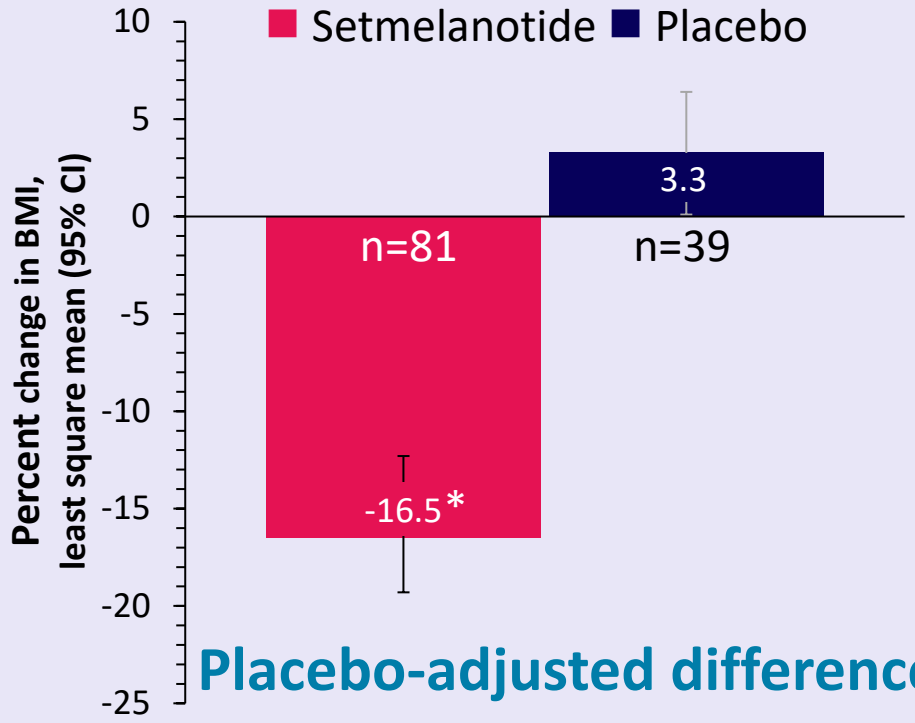
%BMI95, percent of the body mass index 95th percentile; BMI, body mass index; CDC, Centers for Disease Control and Prevention; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SD, standard deviation; y, year.

Baseline Participant Demographics (Cont)

	Setmelanotide (n=81)	Placebo (n=39)
Tumor/damage type, n (%)		
Craniopharyngioma	63 (77.8)	30 (76.9)
Glioma	4 (4.9)	3 (7.7)
Astrocytoma	3 (3.7)	3 (7.7)
Germinoma	5 (6.2)	1 (2.6)
Hamartoma	1 (1.2)	1 (2.6)
Other and non–tumor-related	5 (6.2)	1 (2.6)
Tumor treatment, n (%)		
Hypothalamic surgery for lesion removal	73 (90.1)	35 (89.7)
Radiotherapy	39 (48.1)	21 (53.8)
Chemotherapy	18 (22.2)	8 (20.5)
Hypothalamic involvement, n (%)		
Bilateral	53 (65.4)	26 (66.7)
Unilateral	7 (8.6)	2 (5.1)
Unknown	21 (25.9)	10 (25.6)
Missing	0	1 (2.6)

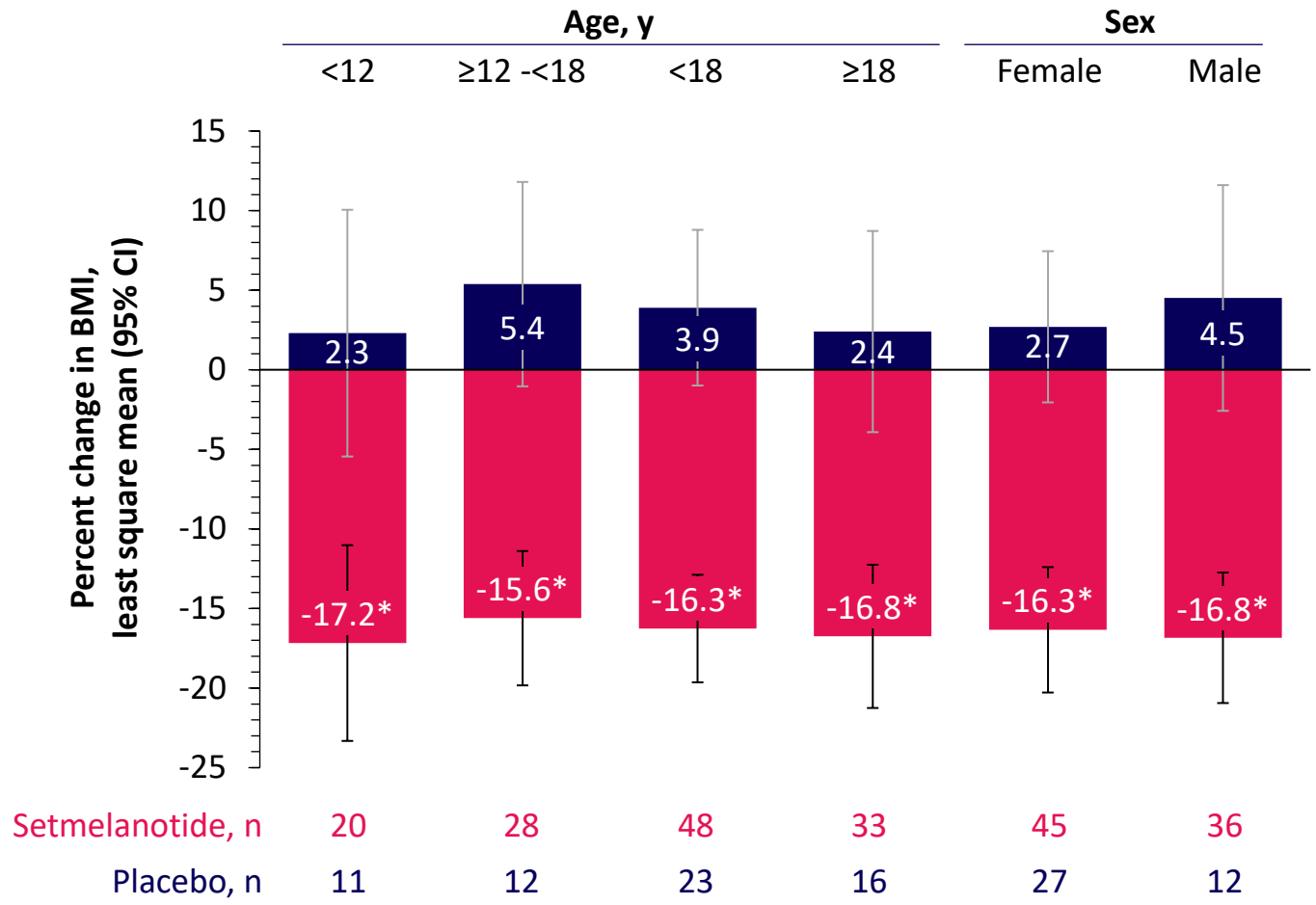
Significant Reduction in BMI With Setmelanotide at Week 52, and Consistent Response Across Subgroups

Primary Endpoint



Placebo-adjusted difference

-19.8%



*P<0.0001 vs placebo.

BMI, body mass index; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; y, year.

Prior and Concomitant GLP-1 RA Use

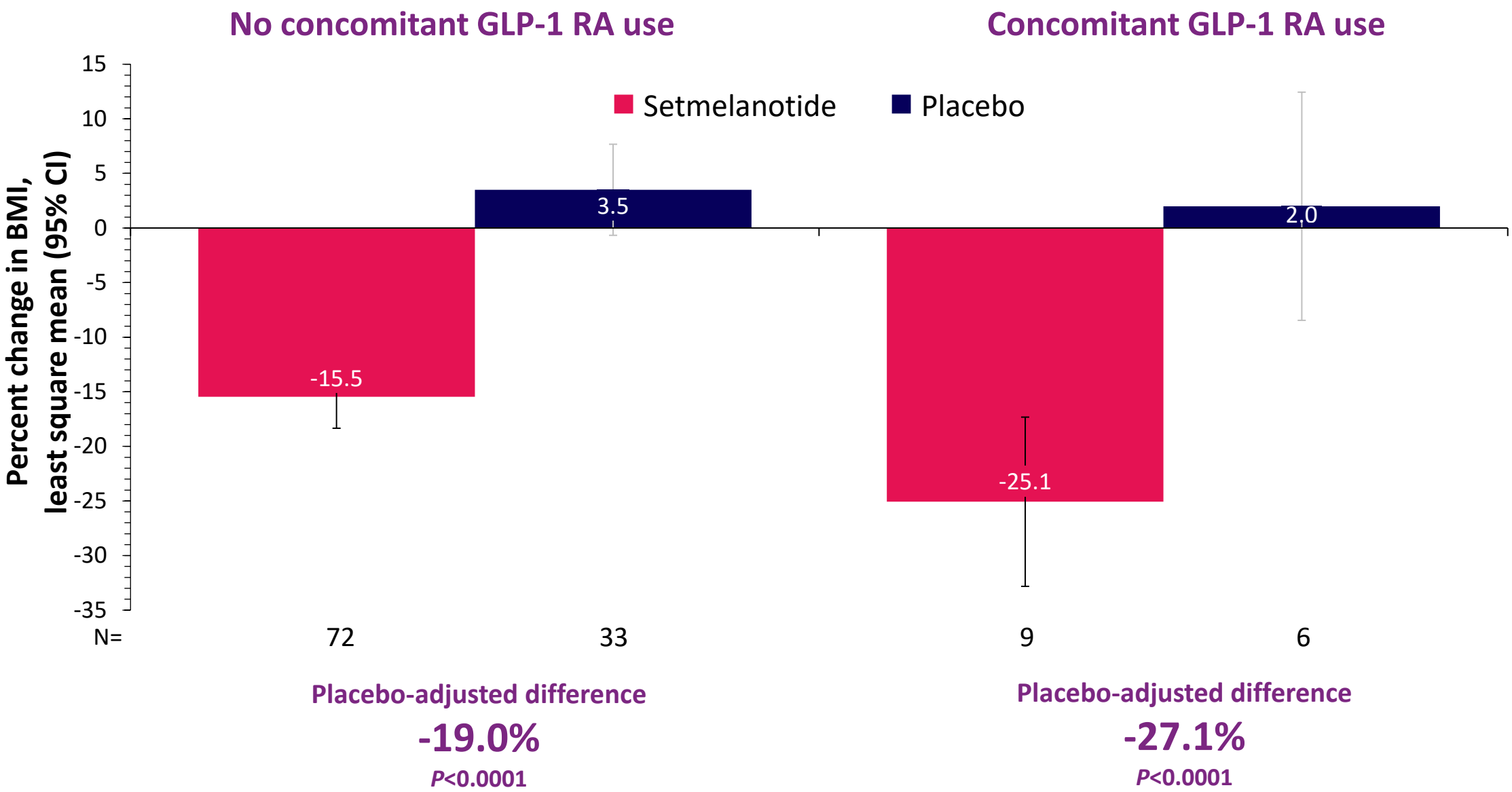
- Participants could be enrolled if they received a prior GLP-1 RA and had not experienced weight loss >2% (adults aged ≥18 years) or BMI reduction >2% (children and adolescents aged 4 to <18 years) in the preceding 3 months; no GLP-1 RAs were initiated during the trial
  - Participants could receive GLP-1 RAs on trial if the regimen and/or dose were stable and they were to be continued throughout the trial

n (%)	GLP-1 RAs received before trial (Overall; N=120)	Ongoing GLP-1 RAs received during trial (Setmelanotide; n=81)	Ongoing GLP-1 RAs received during trial (Placebo; n=39)
Liraglutide	18 (15.0)	**2 (2.5)**	**0**
Semaglutide	17 (14.2)	**5 (6.2)**	**5 (12.8)***
Tirzepatide	4 (3.3)	**2 (2.5)**	**1 (2.6)***
Exenatide	3 (2.5)	**0**	**0**
Dulaglutide	1 (0.8)	**0**	**1 (2.6)**
Total GLP-1 RAs, n	**43**	**9**	**7**

- Thirty-one participants received ≥1 GLP-1 RAs prior to the trial, of whom, **15 (9 setmelanotide, 6 placebo) received a concomitant GLP-1 RA during the trial**
- Ten participants had received ≥2 GLP-1 RAs before the start of the trial

BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist.
*One participant in the placebo group received two concomitant GLP-1 RAs (semaglutide and tirzepatide).

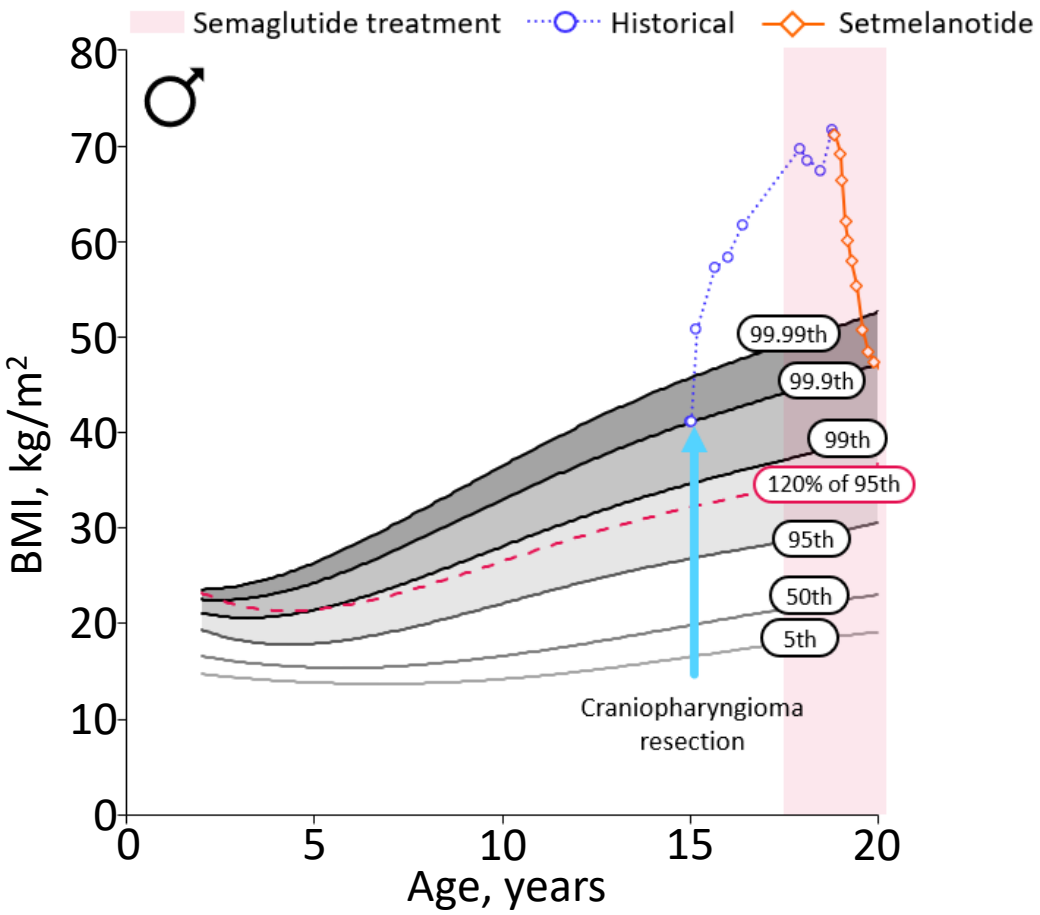
Significant BMI Reductions Observed in Participants With and Without Concomitant Use of GLP-1 RA



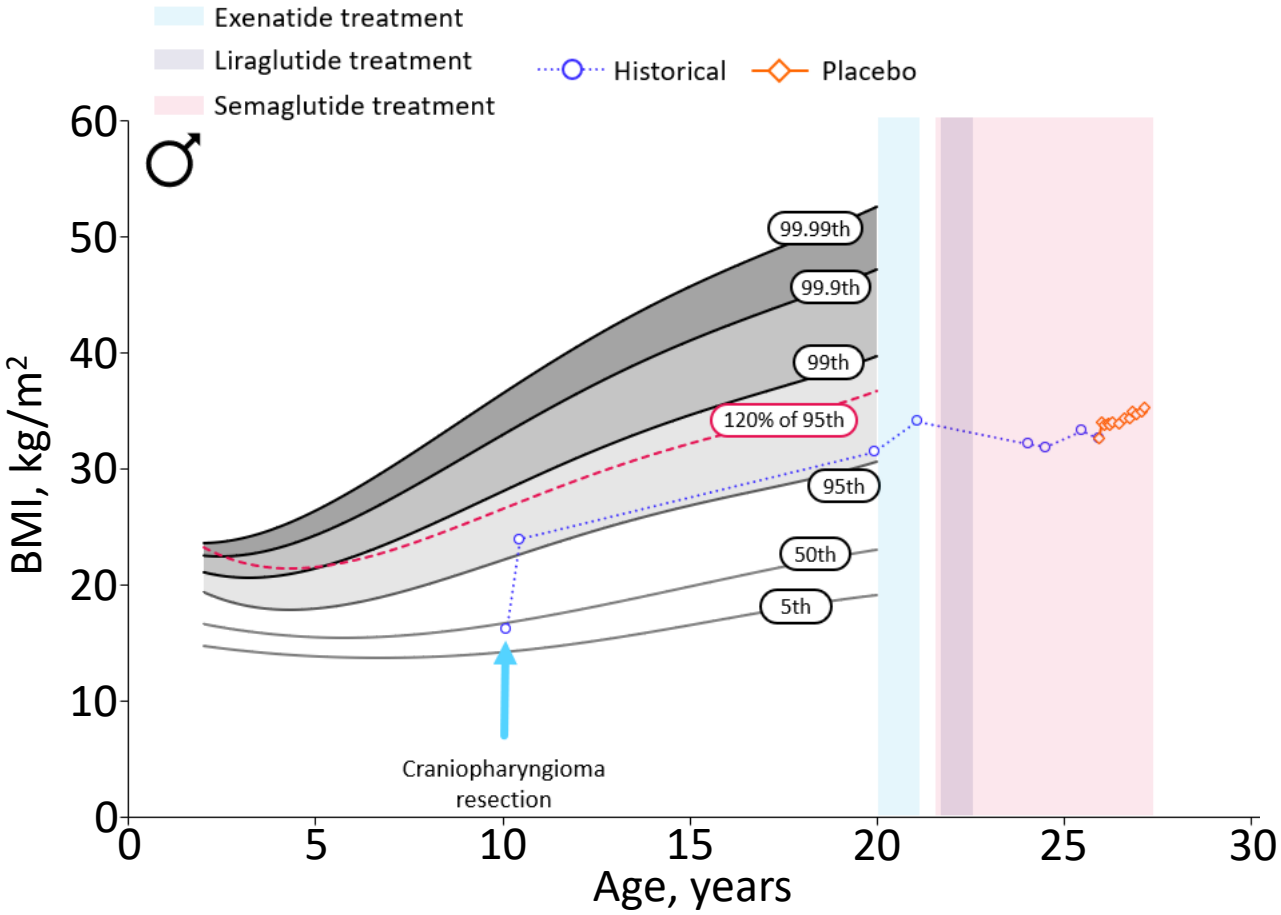
BMI, body mass index; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Participants with Concomitant GLP-1 RA: BMI Over Time

Setmelanotide



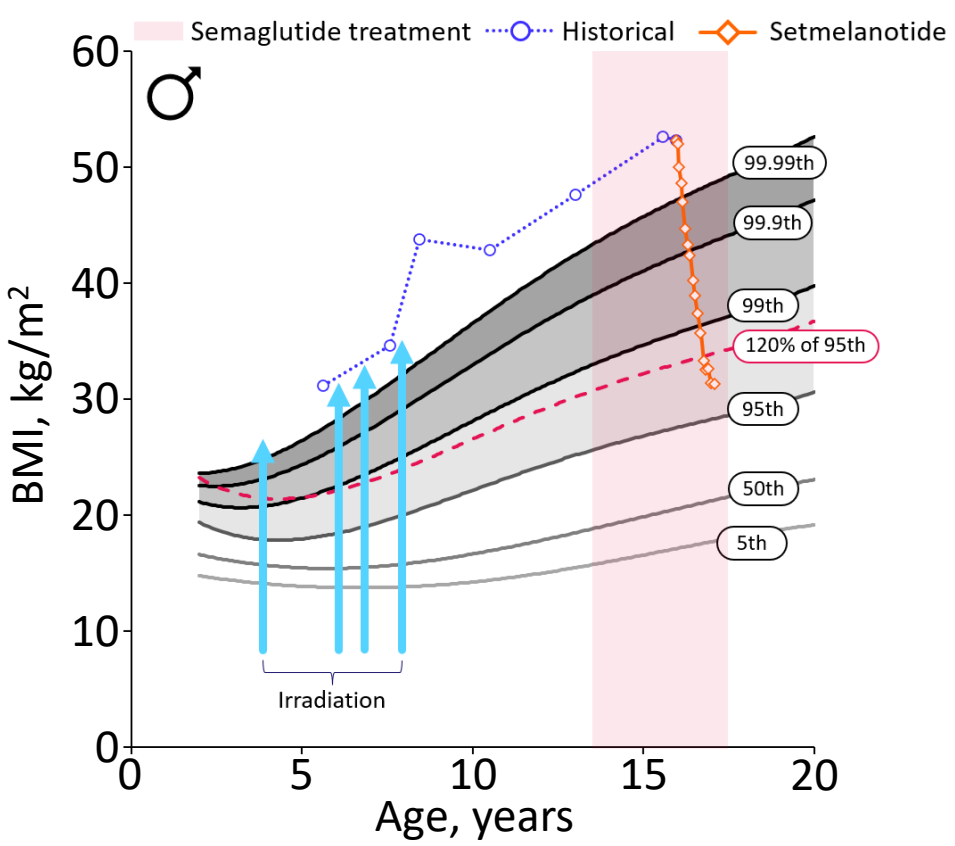
Placebo



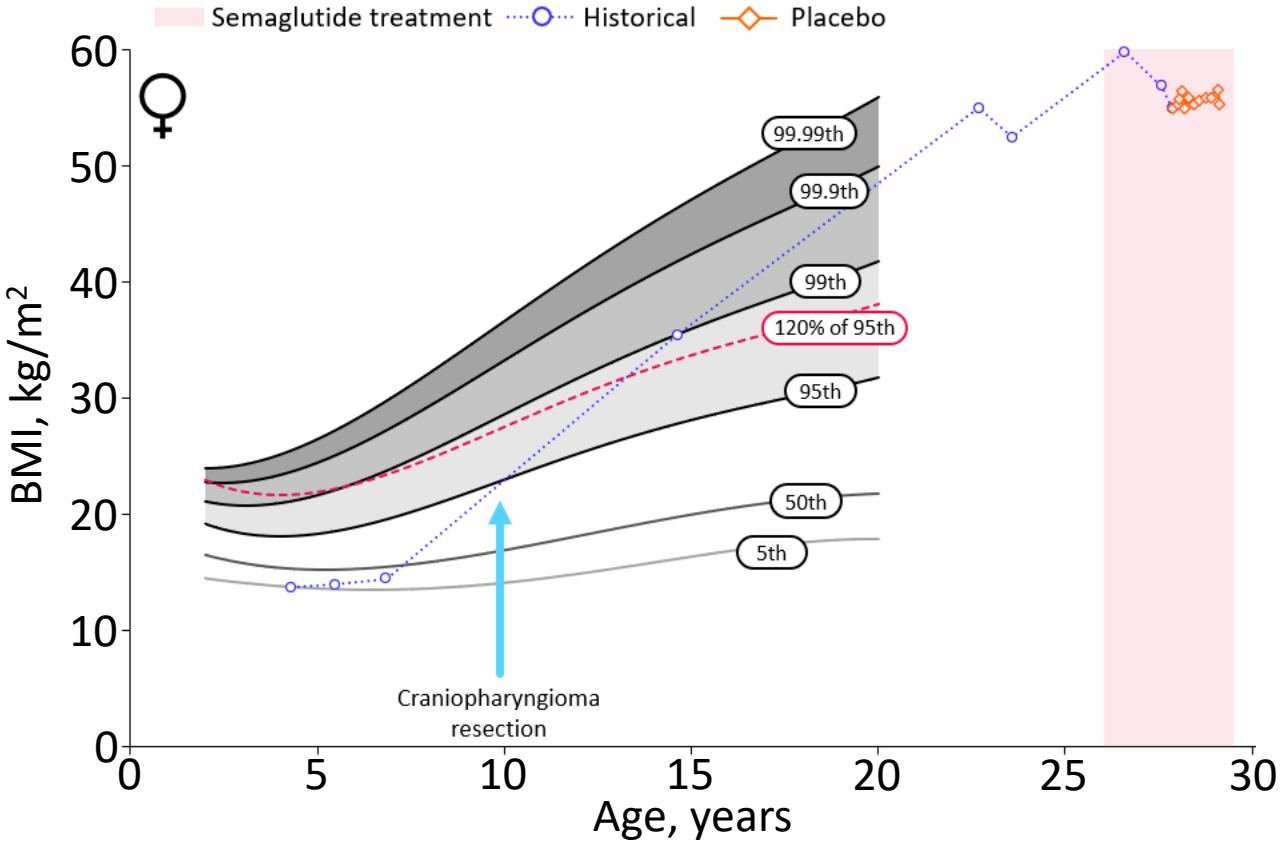
BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

Participants with Concomitant GLP-1 RA: BMI Over Time

Setmelanotide



Placebo



BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist.

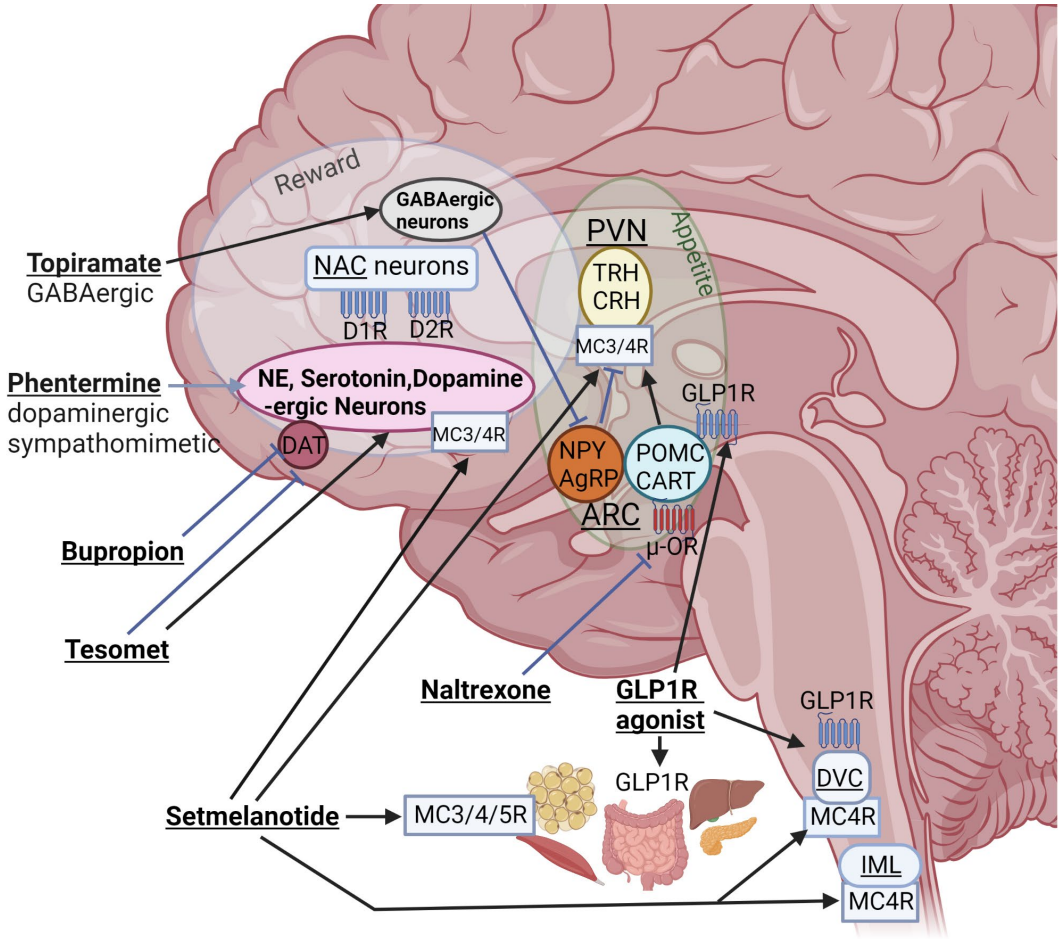
Setmelanotide Was Generally Well Tolerated With No New AE Signals

	Setmelanotide (n=81)	Placebo (n=39)	Overall (N=120)
≥1 AE of any cause	81 (100.0)	35 (89.7)	116 (96.7)
≥1 Drug-related AE	71 (87.7)	26 (66.7)	97 (80.8)
≥1 Serious AE	23 (28.4)	3 (7.7)	26 (21.7)
≥1 Drug-related serious AE	1 (1.2)	0	1 (0.8)
≥1 AE that resulted in death	1 (1.2)	0	1 (0.8)
≥1 AE leading to study drug withdrawal	6 (7.4)	3 (7.7)	9 (7.5)
≥1 AE leading to study discontinuation	4 (4.9)	0	4 (3.3)
Most common (≥20% in setmelanotide arm)			
Skin hyperpigmentation	45 (55.6)	3 (7.7)	48 (40.0)
Nausea	41 (50.6)	12 (30.8)	53 (44.2)
Headache	31 (38.3)	12 (30.8)	43 (35.8)
Vomiting	32 (39.5)	7 (17.9)	39 (32.5)
Diarrhea	19 (23.5)	8 (20.5)	27 (22.5)
Injection site reaction	19 (23.5)	9 (23.1)	28 (23.3)

- One serious AE was considered related to the study drug (setmelanotide): hypernatremia (sodium levels 150-158 mmol/L [normal upper limit 145 mmol/L]); resolved after 2 days with treatment
- There was 1 death due to seizures in a participant with a history of seizure disorder, which was not considered related to the study drug
- Safety was generally consistent with previously reported AEs in other clinical trials

AE, adverse event.

Interactions of Different Anti-Obesity Agents with Appetite and Reward Pathways Involving Melanocortin Signaling[1]



- Even if mediobasal hypothalamic structures such as the arcuate nucleus (ARC) and para-ventricular nucleus (PVN) are damaged, these drugs can interact with peripheral or brain receptors outside of hypothalamic structures[1]

μ-OR, mu-opioid receptor; AgRP, agouti-related peptide; ARC, arcuate nucleus; CART, cocaine and amphetamine regulated transcript; CRH, corticotropin-releasing hormone; DAT, dopamine active transporter; D1/2R, dopamine-1/2 receptor; DVC, dorsal vagal complex of brainstem; GABA, gamma-aminobutyric acid; GLP1R, glucagon-like peptide-1 receptor; IML, intermediolateral nucleus; MC3/4/5R, melanocortin-3/4/5 receptor; NAC, nucleus accumbens; NE, norepinephrine; NPY, neuropeptide Y; POMC, proopiomelanocortin; TRH, thyrotropin-releasing hormone.

Blue: stimulatory receptors. Red: inhibitory receptors.

1. Roth & Zenno. *Front Endocrinol.* 2023.

Conclusions

- The consistent response to setmelanotide, an analogue of endogenous α-MSH, suggests impaired signaling through the MC4R pathway is responsible for the development of acquired HO
- The potentially greater response in participants on concomitant GLP-1 RAs, but who were not losing weight at study entry, highlights the importance of first correcting the deficiency in MC4R signaling
- Once the α-MSH hormonal deficiency has been corrected, the patient may have a restored ability to respond to other anti-obesity medications including GLP-1 RAs

α-MSH, α–melanocyte-stimulating hormone; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HO, hypothalamic obesity; MC4R, melanocortin-4 receptor.

Thank you

- We would like to thank the participants, caregivers, and the TRANSCEND Trial Group, without whom this trial could not have been completed

Country	Primary Investigator(s)	Advisory & Support Staff
Canada	Jill Hamilton	Fardowsa Abdi
Germany	Guenter Stalla	Johanna Faust; Yu-Mi Lee; Anette Heinrichs; Evelyn Asbach
	Hermann L. Müller Carsten Friedrich	Kristina Maul
	Jens Aberle	Madlen Pionke
	Martin Wabitsch	Christian Denzer; Martin Heni; Pauline Kleger
Japan	Hiraku Ono	
	Keisuke Nagasaki	Chizuko Nakamura
	Tomohiro Tanaka	Katsushi Takeda
	Hiroshi Arima	Mariko Sugiyama
	Tsuyoshi Isojima	Yuri Mukoyama
Netherlands	Hanneke M. van Santen	Evelien de Vos-Kerkhof; Nathalie Doelman-Oldenburger
UK	Mehul Dattani	Olamide Alimi; Hoong Wei Gan; Manuela Cerbone
	Zainaba Mohamed	Emma Parry
	Thozhukat Sathyapalan	Lee Rollins; Lisa Baldwin

Country	Primary Investigator(s)	Advisory & Support Staff
USA	Ashley Shoemaker	Jennifer Leshko
	Christian L. Roth	Anna Zenno; Stephanie Purdy; Tiffany Hawkins
	Hussein Abdullatif	Pamela Turner
	Jennifer L. Miller	Lauren Harvey
	Joan C. Han	Gabrielle Jonny
	Katie Larson Ode	Emma Carlson
	Luma Ghalib	Aleitha Gates Hangil Kim
	Margaret Stefater-Richards	Allison Bernique; Andrea Hale; Kiana Summers; Nicole Doble
	M. Jennifer Abuzzahab	Brittany Machus
	Megan M. Kelsey	Carolyn Mulney; Christina Chambers; Kathleen Dorris; Matthew Brien
	Reema Habiby	Isabella McLaughlin; Sarayu Ratnam
	Ryan Morgan	Chalimar Rojo
	Shana E. McCormack	Anna Dedio; Julia Crowley; Kristin Wade; Isabel Chacko; Rachana Shah
	Susan A. Phillips	Michael Gottschalk; Marla Hashiguchi; Rose Manrique
	Vanita R. Aroda	Carolian M. Apovian; Grace Ordonez; John W. Ostrominski; Lee-Shing Chang; Milan Rancic
	Vidhu V. Thaker	Annelise Babcock; AnnMarie Sykes; Ella John; Ilene Fennoy; Molly Nguyen

Rhythm Pharmaceuticals
Alicia Darragh, Alicia Fiscus, Bon Lam, Brendan Lanoue, Cecilia Scimia, Cecily Citino, Charlotte Patterson, Evan Chen, Gerhard Askamp, Guojun Yuan, Jennifer Crowley-Bartoshevich, Jieruo Liu, Jill Garrison, Johanna Karas, Kristoffer Myczek, Michael Craig, Nicolas Touchot, Riddhi Shah, Robyn Neitzschman, Shuang Hu

Scan here for a copy of this presentation: