Onset of Common Adverse Events With Setmelanotide in Acquired Hypothalamic Obesity

#B3

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Introduction

- Acquired hypothalamic obesity (aHO) is characterized by accelerated and sustained weight gain following injury to the hypothalamus, caused by suprasellar tumors (or their treatment), traumatic brain injury, and/or inflammation, which can lead to hyperphagia, energy imbalance, and obesity[1-4]
- Hypothalamic damage can impair the melanocortin-4 receptor (MC4R) pathway, which regulates hunger, satiety, and energy expenditure, and lead to aHO[4-6]
- In the international, placebo-controlled Phase 3 trial of the MC4R agonist setmelanotide in participants with aHO (NCT05774756), the primary endpoint of percent change in body mass index (BMI) at Week 52 was met:
  - Participants who received setmelanotide achieved a mean 16.5% reduction in BMI, compared with the placebo group who experienced a mean 3.3% increase, yielding a placebo-adjusted difference of −19.8%

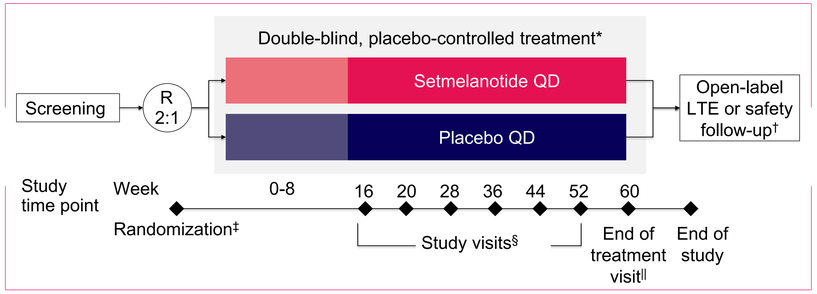
Objectives

- To investigate the timing of the onset of common adverse events (AEs) in the Phase 3 trial of setmelanotide in aHO

Methods

- Participants aged ≥4 years with BMI ≥95th percentile (for those aged 4 to <18 years) or BMI ≥30 kg/m^2 (for those aged ≥18 years) with aHO following hypothalamic tumor, lesion, or injury were included
- Participants were randomized 2:1 to setmelanotide (0.5 mg subcutaneously once daily, titrated up to 1.5-3.0 mg once daily based on age, weight, and tolerability) or placebo for up to 60 weeks (Figure 1)
- Safety data were collected for the duration of the trial, and the timing of the onset (of each event per month) of the most common AEs occurring in ≥20% of overall participants was evaluated
  - More than 1 event may have been reported for one patient

Figure 1. Study Design



LTE, long-term extension; QD, once daily; R, randomization. *The initial dose of 0.5 mg was escalated in increments of 0.5 to 1.0 mg until the participant reached an individual therapeutic regimen based on age, weight, and tolerability. †Participants who completed the trial were eligible to participate in an open-label LTE trial; the safety follow-up visit was required only for participants who prematurely discontinued treatment or those who completed the trial but did not enroll in the LTE. ‡Baseline was defined as the last available measurement before randomization. §Visits completed in clinic or at home via telehealth. ‖In-clinic visit.

Results

Participant Demographics and Baseline Clinical Characteristics

- Overall, 120 participants were enrolled in the pivotal cohort, and 81 and 39 participants received setmelanotide and placebo, respectively
- Participant demographics and baseline clinical characteristics were generally similar between the treatment groups (Table 1)

Overall Safety

- An AE was reported for 100% of participants receiving setmelanotide versus 89.7% of participants receiving placebo (Table 2)
  - The most common AEs associated with setmelanotide treatment were skin hyperpigmentation, nausea, vomiting, headache, injection site reactions, and diarrhea
    - With the exception of skin hyperpigmentation and injection site reactions, common AEs in the setmelanotide group had a reported median duration of <30 days (Table 2)
  - For participants who received setmelanotide and experienced a common AE, ≥75% of those participants reported AEs that were mild in severity

Timing of Onset of Most Common AEs

- The most common AEs predominantly occurred early after the start of treatment with setmelanotide, with the highest occurrence of AEs reported during Month 1 (Figure 2)
  - Reports of new AEs markedly declined in subsequent months

Figure 2. Onset Frequency of the Most Common AEs (Occurring in ≥20% in the Setmelanotide Group) by Month

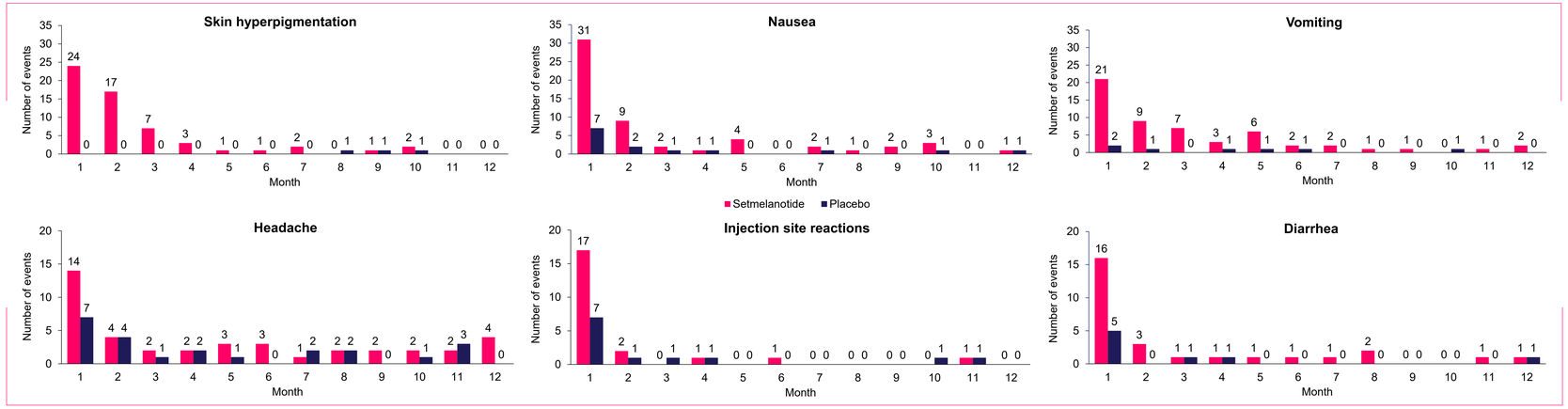


Table 1. Participant Demographics and Baseline Clinical Characteristics

	Setmelanotide (n=81)	Placebo (n=39)
Age, mean±SD (range), y	19.2±13.0 (4-65)	21.4±15.5 (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)
Race, n (%)		
White	66 (81.5)	34 (87.2)
Black or African American	6 (7.4)	0
Asian	3 (3.7)	0
Other	6 (7.4)	5 (12.8)
Ethnicity, n (%)		
Hispanic or Latino	7 (8.6)	7 (17.9)
Not Hispanic or Latino	73 (90.1)	32 (82.1)
Unknown	1 (1.2)	0
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)†
Weight, mean (SD), kg	92.9 (38.5)	94.1 (38.8)
In participants aged ≥18 y, kg	115.6 (33.8)	124.2 (32.9)
BMI, mean (SD), kg/m^2	35.7 (9.2)	36.8 (9.3)
In participants aged ≥18 y, kg/m^2	40.1 (9.8)	43.5 (9.3)
BMI Z score in participants aged 4 to <18 y, mean (SD)‡	3.72 (1.81)	3.37 (1.29)
Percentage of the 95th percentile of BMI in participants aged 4 to <18 y, mean (SD)§	132.3 (28.9)	128.6 (22.7)
Waist circumference, mean (SD), cm	106.6 (21.7)	108.6 (18.8)
Maximal daily hunger score, mean (n; SD)¶	6.77 (57; 2.32)	7.23 (24; 2.11)

BMI, body mass index; CI, confidence interval; SD, standard deviation.
*Arachnoid cyst, heterogeneous mass in the suprasellar region involving the hypothalamus and optic chiasm, mature teratoma (not classified as tumor by the investigators given the benign course and the differentiated cell type), cavernous hemangioma (not classified as tumor by the investigators given it was considered a vascular malformation), and either craniopharyngioma or astrocytoma (not classified as tumor by the investigators given uncertainty of diagnosis).
†Hypothalamic glioma pilocytic astrocytoma (not classified as tumor by the investigators given the differentiated cell type).
‡BMI Z score calculated according to the World Health Organization 2007 method.
§Percentage of the 95th percentile of BMI calculated according to the Centers for Disease Control and Prevention 2022 method.
¶Weekly average of daily scores; 11-point scale, where 0 = "not hungry at all" and 10 = "hungriest possible."

Table 2. Safety

Number of participants (% of participants)	Setmelanotide (n=81)		Placebo (n=39)	
AEs	81 (100)		35 (89.7)	
AE leading to treatment discontinuation	6 (7.4)		3 (7.7)	
Any AE leading to study discontinuation	4 (4.9)		0	
Serious AEs	23 (28.4)		3 (7.7)	
AE resulting in death on study	1 (1.2)*		0	
AE in ≥20% in the setmelanotide group		Median duration, days		Median duration, days
Skin hyperpigmentation	45 (55.6)	410.0	3 (7.7)	130.0
Nausea	41 (50.6)	29.0	12 (30.8)	3.0
Vomiting	32 (39.5)	2.0	7 (17.9)	2.0
Headache	31 (38.3)	9.5	12 (30.8)	2.0
Injection site reaction	19 (23.5)	73.0	9 (23.1)	275.5
Diarrhea	19 (23.5)	3.0	8 (20.5)	3.0
AE related to treatment†	71 (87.7)		26 (66.7)	
Serious AE related to treatment†	1 (1.2)‡		0	

AE, adverse event.
*One death (because of seizure in a participant with a preexisting seizure disorder) occurred during the study in the setmelanotide group and was considered unrelated to treatment.
†Relatedness to treatment was assessed by the investigator.
‡There was one serious treatment-related adverse event (investigator assessed) reported in the setmelanotide group: hypernatremia due to drug-induced vomiting and an inability to tolerate desmopressin in a participant with arginine vasopressin deficiency; after 2 days, setmelanotide was reinitiated concomitant with discharge from the hospital.

Conclusions

- The onset of the most common AEs, including skin hyperpigmentation, nausea, vomiting, headache, injection site reactions, and diarrhea, was generally highest during the first month of treatment with setmelanotide
  - These results highlight that the onset of these common AEs declines over time with ongoing treatment, and that if these AEs do occur, their onset is generally earlier, their duration is generally <30 days, and they are mild in severity
  - Skin hyperpigmentation was a frequent and persistent AE for participants throughout the study, consistent with that observed in previous trials of setmelanotide
- The timing and frequency of AEs were consistent with other trials of setmelanotide in patients with aHO and rare MC4R pathway–associated diseases

Conflict of Interest: Please add authors conflict of interest here. SEM receives research support from the Friedreich Ataxia Research Alliance and National Institutes of Health; and received funding to conduct industry-supported trials from Chiesi and Rhythm Pharmaceuticals, Inc. SAP has received institutional funding for clinical trials and received payment for educational lectures from Rhythm Pharmaceuticals, Inc. and consulting fee from Resolute Bio and Anjarity Pharmaceuticals. HMvS is a local primary investigator of clinical trials funded by Rhythm Pharmaceuticals, Inc.; received funding from Novo Nordisk, Pfizer, and Rhythm Pharmaceuticals, Inc. for the organization of the ESPE Science Symposium and 6th Craniopharyngioma Post-graduate Course; received reimbursement for travel expenses for scientific meetings from Rhythm Pharmaceuticals, Inc.; and received funding for research projects from Pfizer and Rhythm Pharmaceuticals, Inc. JH receives unrestricted research funds from the SickKids University of Toronto Mead Johnson Chair in Nutritional Science; received institutional funding to conduct industry-sponsored clinical trials from Eli Lilly, Novo Nordisk, and Rhythm Pharmaceuticals, Inc.; and received consulting honoraria from Rhythm Pharmaceuticals, Inc and Novo Nordisk. AHS has received institutional funding for clinical trials sponsored by Aardvark Therapeutics, Eli Lilly, Novo Nordisk, Rhythm Pharmaceuticals, Inc., and Soleno Therapeutics; and received consulting honoraria from Rhythm Pharmaceuticals, Inc. and Soleno Therapeutics. MJA receives institutional research support from Ascendis, Lumos, Medtronic, Rhythm Pharmaceuticals, Inc., and Soleno; and received consulting/speaking fees from Ascendis, DayOne, Endo, Eton, Neurocrine, Novo Nordisk, Rezolute, and Rhythm Pharmaceuticals, Inc. MW receives funding from the Federal Ministry of Research, Technology and Space (Bundesministerium für Forschung, Technologie und Raumfahrt, BMFTR) as part of the German Center for Child and Adolescent Health (DZKJ) under the funding code 01GL2407A; received consulting and lecture fees from Chiesi, InfectoPharm, Merck Serono, Novo Nordisk, and Rhythm Pharmaceuticals, Inc.; and is chair of the Metabolic Unit at Boehringer Ingelheim Ulm UniversityBioCenter (BIU). MD is a local primary investigator of clinical trials funded by Rhythm Pharmaceuticals, Inc.; received lecture fees from Neurocrine and Novo Nordisk; and received consulting fees from Besins, Pfizer, and Sandoz. TT has received honoraria from Eli Lilly Japan K.K., Mitsubishi Tanabe Pharma Corporation, Novo Nordisk Pharma Ltd., and Rhythm Pharmaceuticals, Inc. JG, CS, and GY are employees and may hold stock options in Rhythm Pharmaceuticals, Inc. HLM has received reimbursement for scientific meetings (participation and travel expenses) and honoraria from Rhythm Pharmaceuticals, Inc.; and is supported for the KRANIOPHARYNGEOM studies by a grant from the German Childhood Cancer Foundation, Bonn, Germany (H.L.M., DKS2014.13). CLR is supported by grants from the National Institutes of Health (award numbers R21HD115119, R01DK135125, R01DK098466, and R01DK135211); and is on the advisory board of Rhythm Pharmaceuticals, Inc. JLM has received funding from Harmony Biosciences, Rhythm Pharmaceuticals, Inc., Soleno Therapeutics, TRYP Therapeutics, and Aardvark Therapeutics, and is on the advisory board for Bright Minds.

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Writing and editorial assistance for this poster was provided by Fingerpaint Medical and funded by Rhythm Pharmaceuticals, Inc.

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