Timing of Onset of Adverse Events With Setmelanotide, an MC4R Agonist, in Patients With Severe Obesity Due to LEPR or POMC Deficiency

##

Karine Clément, MD[1,2]; Erica van den Akker, MD[3]; Gregory Gordon, MD[4]; Guojun Yuan, PhD[4]; Peter Kühnen, MD[5]

[1]Assistance Publique Hôpitaux de Paris, Nutrition Department, Pitié-Salpêtrière Hospital, Paris, France; [2]Sorbonne Université, INSERM, NutriOmics Research Unit, Paris, France; [3]Division of Pediatric Endocrinology, Department of Pediatrics, Sophia Children's Hospital and Obesity Center CGG, Erasmus University Medical Center, Rotterdam, The Netherlands; [4]Rhythm Pharmaceuticals, Inc., Boston, MA, USA; [5]Institute for Experimental Pediatric Endocrinology, Charité Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany

Presenting Author:
Karine Clément
karine.clement2@gmail.com

Summary

- **The onset of adverse events (AEs) of special interest was generally highest during the first month of treatment with setmelanotide in participants with obesity due to proopiomelanocortin (POMC)/proprotein convertase subtilisin/kexin type 1 (PCSK1) or leptin receptor (LEPR) deficiency receiving ≥1 year of treatment**
- **Fewer AEs of special interest occurred during each month following Month 1**
- **Apart from hyperpigmentation disorders, all AEs of special interest resolved quickly after onset**

Introduction

- Rare genetic diseases of obesity are often driven by pathogenic gene variants in the melanocortin 4 receptor (MC4R) pathway[1]
- Treatment with the MC4R agonist setmelanotide demonstrated clinically significant reductions in body weight and hunger after 1 year in Phase 3 trials of participants with obesity due to POMC, PCSK1, or LEPR deficiency[2]
  - The results of these pivotal trials led to the approval by the US Food and Drug Administration of setmelanotide for chronic weight management in individuals with POMC, PCSK1, or LEPR deficiency[3]
- AEs of special interest, defined as those related to treatment-emergent AEs (TEAEs) commonly occurring with setmelanotide in clinical trials, potential mechanistic-related events, or other events associated with background disease, include hyperpigmentation disorders, disturbances in sexual arousal, nausea, vomiting, and injection site reactions (ISRs)[2,4,5]

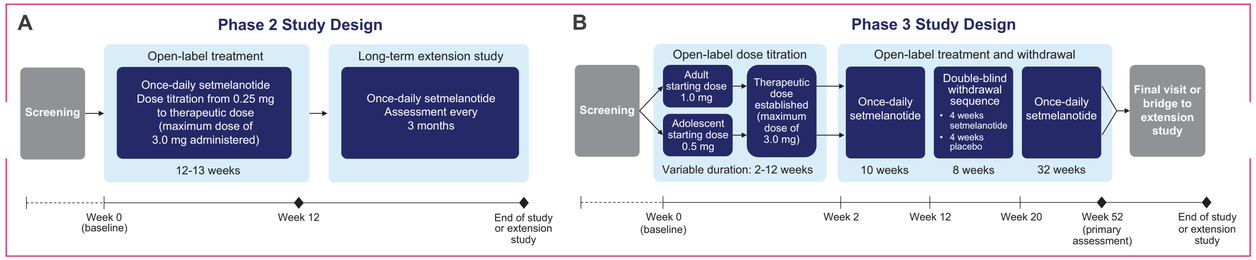
Objective

- To assess the timing of the onset of AEs of special interest in participants with obesity due to POMC, PCSK1, or LEPR deficiency treated with setmelanotide

Methods

- The timing of AE onset with setmelanotide was evaluated in a pooled set of trial participants with POMC, PCSK1, or LEPR deficiency who received setmelanotide in clinical trials
- A Phase 2 investigator-initiated (Charité Universitätsmedizin Berlin) trial evaluated setmelanotide in participants aged ≥18 years with obesity (body mass index [BMI] >30 kg/m^2) and POMC, PCSK1, or LEPR deficiency (RM-493-011 [ClinicalTrials.gov identifier: NCT02507492]; Figure 1A)[4-6]
- Two Phase 3 trials evaluated setmelanotide in participants aged ≥6 years with obesity (BMI ≥30 kg/m^2 in adults; weight >97th percentile for age in children and adolescents) and POMC, PCSK1, or LEPR deficiency (RM-493-012 [ClinicalTrials.gov identifier: NCT02896192] and RM-493-015 [ClinicalTrials.gov identifier: NCT03287960]; Figure 1B)[2,7,8]
- AEs were assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events
- Select AEs of special interest were evaluated on the basis of preferred terms (nausea, vomiting) and grouped terms (hyperpigmentation disorders, disturbances in sexual arousal, ISRs)
  - Hyperpigmentation disorders preferred terms were skin hyperpigmentation, melanocytic naevus, skin discoloration, and ephelides
  - Disturbances in sexual arousal preferred terms were spontaneous penile erection (males), erection increased (males), and disturbance in sexual arousal (females)
  - ISR preferred terms were injection site erythema, pruritus, induration, pain, bruising, edema, reaction, and swelling

Figure 1. Study design of the Phase 2 investigator-initiated trial **(A)** and Phase 3 trials **(B)** of setmelanotide in participants with POMC, PCSK1, or LEPR deficiency.



In the Phase 3 trials, the last 2 weeks of the dose titration phase were considered the first 2 weeks of the open-label treatment phase. LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type1; POMC, proopiomelanocortin.

Results

Participant Disposition and Overall Safety

- As of November 10, 2020, 35 participants were enrolled and included across the 3 trials (Table 1)
  - POMC: n=15; PCSK1: n=2; LEPR: n=18
- Daily setmelanotide doses ranged from 0.25 to 3.0 mg

Table 1. Participant Disposition

Study status	Participants with POMC, PCSK1, or LEPR deficiency, n (%) (N=35)
Ongoing	2 (5.7)
Completed	25 (71.4)
Discontinued	8 (22.9)
Protocol deviation	3 (8.6)
Protocol violation	1 (2.9)
AE	1 (2.9)
Death	1 (2.9)[a]
Lost to follow-up	1 (2.9)
Other	1 (2.9)

[a]One participant with LEPR deficiency participating in one of the Phase 3 trials died as a result of injuries sustained as a passenger in an automobile accident occurring at approximately study week 36; the death was considered to be unrelated to the study drug. AE, adverse event; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin.

- Each participant experienced at least 1 TEAE, with the most common being skin hyperpigmentation (85.7%), injection site erythema (68.6%), nausea (57.1%), and headache (51.4%)
- During setmelanotide treatment, 18 serious AEs occurred, none of which were interpreted as related to the study drug

Rates of AEs of Special Interest

- The most common AEs of special interest are shown in Table 2

Table 2. Rates of Commonly Occurring AEs of Special Interest

	Participants with POMC, PCSK1, or LEPR deficiency, n (%) (N=35)
ISRs[a]	31 (88.6)
Skin hyperpigmentation	30 (85.7)
Nausea	20 (57.1)
Vomiting	10 (28.6)
Disturbances in sexual arousal[a]	6 (17.1)

AE, adverse event; ISR, injection site reaction; LEPR, leptin receptor; PCSK1, proprotein convertase subtilisin/kexin type 1; POMC, proopiomelanocortin. [a]Represents system/class grouped term.

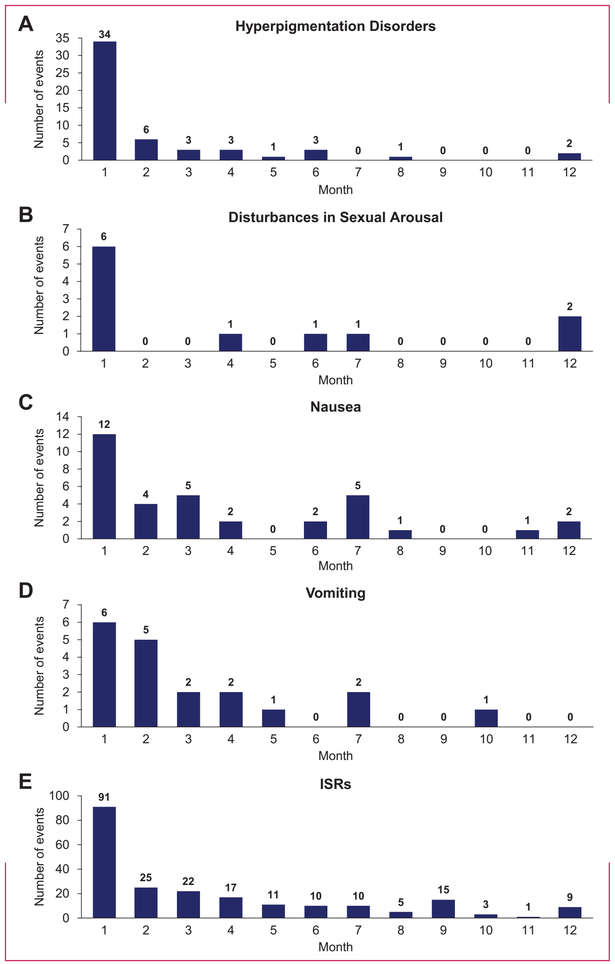
Timing of Onset of AEs of Special Interest

- The majority of hyperpigmentation disorders (34 of 53 events [64.2%]) and disturbances in sexual arousal (6 of 11 events [54.6%]) had an onset during Month 1 after starting setmelanotide treatment (Figure 2A and 2B)
  - Following onset, skin hyperpigmentation continued for the duration of setmelanotide treatment; disturbances in sexual arousal resolved quickly
- The onsets of nausea and vomiting were most frequent during Month 1 of treatment (nausea: 12 of 34 events [35.3%]; vomiting: 6 of 19 events [31.6%]) (Figure 2C and 2D)
  - Events of nausea and vomiting were typically of short duration following onset
- ISRs were reported throughout the trial, with 41.6% (91 of 219 events) having an onset within the first month of treatment (Figure 2E)
  - Following onset, ISRs typically resolved quickly
- A slight increase in onset of nausea and vomiting was observed at Month 7, which may have been associated with participants in the Phase 3 trials resuming setmelanotide treatment following placebo withdrawal in Month 5

Acknowledgments: This study was sponsored by Rhythm Pharmaceuticals, Inc. Assistance with preparation of this poster was provided under the direction of the authors by Rhyomi Sellnow, PhD, and David Boffa, ELS, of MedThink SciCom and funded by Rhythm Pharmaceuticals, Inc.

References: 1. Huvenne et al. *Obes Facts.* 2016;9:158-173. **2.** Clément et al. *Lancet Diabetes Endocrinol.* 2020;8:960-970. **3.** Imcivree. Prescribing Information. Rhythm Pharmaceuticals, Inc.; 2020. **4.** Kühnen et al. *N Engl J Med.* 2016;375:240-246. **5.** Clément et al. *Nat Med.* 2018;24:551-555. **6.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02507492. Updated February 22, 2016. Accessed February 19, 2021. **7.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT02896192. Updated January 27, 2021. Accessed February 19, 2021. **8.** ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03287960. Updated January 27, 2021. Accessed February 19, 2021.

Figure 2. Onset of the AEs of special interest hyperpigmentation disorders **(A)**, disturbances in sexual arousal **(B)**, nausea **(C)**, vomiting **(D)**, and ISRs **(E)** by treatment month.



Months are defined as 30-day periods. AE, adverse event; ISR, injection site reaction.