Trial of a Once-Weekly Setmelanotide Formulation in Patients With Obesity

Annette Valles-Sukkar, Guojun Yuan, Murray Stewart
Rhythm Pharmaceuticals, Inc., Boston, MA, USA

Presenting Author:
Annette Valles-Sukkar
avallessukkar@rhythmtx.com

Summary

- **In this Phase 1b trial, a once-weekly, long-acting formulation of the melanocortin-4 receptor (MC4R) agonist setmelanotide demonstrated similar safety, pharmacokinetics (PK), and weight loss benefits as once-daily (QD) injections in healthy volunteers with obesity**
- **Overall, these data support further investigation of once-weekly (QW) setmelanotide in individuals with rare genetic diseases of obesity**

Introduction

- Many patients with rare genetic diseases of obesity experience early-onset, severe obesity and hyperphagia due to variants in one of multiple genes in the MC4R pathway[1,2]
- QD subcutaneous setmelanotide is approved for chronic weight management in patients with obesity due to proopiomelanocortin, proprotein convertase subtilisin/kexin type 1, or leptin receptor deficiency[3]
- Weekly dosing of injected therapies may improve adherence compared with daily dosing[4]
- A long-acting formulation of setmelanotide using FluidCrystal® technology with QW administration is being investigated as an alternative to the QD formulation

Objectives

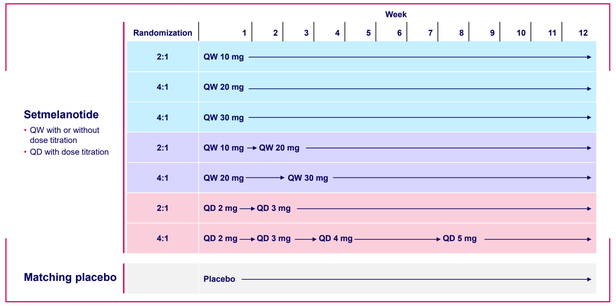
- To evaluate the safety, PK, and efficacy of a long-acting QW formulation of setmelanotide compared with QD setmelanotide injections in healthy volunteers with obesity

Methods

Study Design

- This Phase 1b randomized, double-blind, placebo-controlled trial compared the safety, PK, and efficacy of QW and QD setmelanotide or matching placebo for 12 weeks (Figure 1)

Figure 1. Study design.



QD, once daily; QW, once weekly.

Eligibility Criteria

- Healthy volunteers aged 18 to 55 years with body mass index (BMI) ≥35 kg/m^2 were eligible
  - Inclusion criteria were updated from BMI ≥40 kg/m^2 in a November 2019 amendment
- Key exclusion criteria included clinically significant physical or laboratory abnormalities; suicidal ideations, behaviors, or attempts; significant dermatologic findings; history of cancer; bariatric surgery in the last 12 months; or history of renal insufficiency (creatinine clearance rate <60 mL/min)

Endpoints and Assessments

- The primary endpoints were body weight change from baseline at Week 12 and the frequency and severity of treatment-emergent adverse events (TEAEs)
- The PK of QW and QD setmelanotide was the secondary endpoint
- Changes in hunger scores were evaluated as an exploratory endpoint

Results

Participant Disposition and Characteristics

- In total, 103 participants received setmelanotide (QW, n=48; QD, n=29) or placebo (n=26); 82 of 103 participants (79.6%) completed the study
- Mean (standard deviation [SD]) age of participants was 40.2 (8.4) years; mean (SD) weight and BMI were 126.0 (21.0) kg and 45.5 (5.8) kg/m^2, respectively

Safety of QW Setmelanotide

- The overall rates of TEAEs and TEAEs of interest were similar between QW and QD setmelanotide (Table); no serious TEAEs occurred
- Of 249 reported injection site reactions, 247 (≥99%) were classified as mild

PK Analysis of QW and QD Setmelanotide

- Peak setmelanotide concentration was numerically higher with QD setmelanotide (mean [SD] range, 38.0 [6.5] to 51.5 [11.6] ng/mL) compared with QW (mean [SD] range, 13.4 [3.97] to 35.2 [11.3] ng/mL)
- Week-12 mean trough setmelanotide plasma concentration was comparable between the pooled QW (mean [SD] range, 2.63 [1.46] to 10.2 [3.44] ng/mL) and QD (mean [SD] range, 6.48 [6.90] to 7.71 [7.84] ng/mL) formulations
- All 3 doses of QW setmelanotide demonstrated a consistent 24-hour PK range (Figure 2)
- Setmelanotide was consistently detected over the course of 7 days following QW dosing at Week 12, with mean plasma concentrations in the pooled QW population of 19.7, 14.6, 10.7, and 8.7 ng/mL at 24, 48, 72, and 168 hours following the dose, respectively

Setmelanotide QW Effect on Weight

- Participants achieved similar weight loss at Week 12 with QW setmelanotide (Figure 3)
- All dose levels of QW setmelanotide and the QD setmelanotide regimen titrated to 5 mg resulted in statistically significant differences in weight loss compared with placebo at Week 12 (P<0.05; Figure 3)
- No statistically significant differences were observed in percent change in "most hunger" scores at Week 12 between the QW and QD setmelanotide formulations and placebo

Conclusions

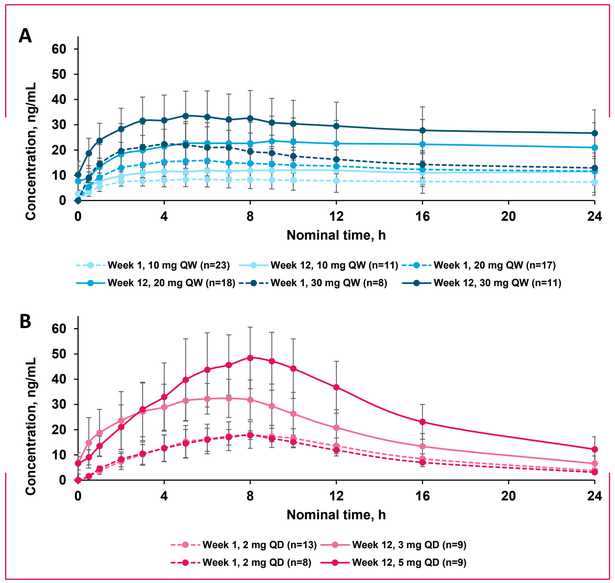
- The safety profile of QW setmelanotide was similar to that of the QD formulation
- In healthy volunteers, peak and trough QW setmelanotide concentrations were generally consistent with the concentrations of the efficacious QD formulation
- Weight and hunger change at Week 12 was comparable between QW and QD setmelanotide

Table. Safety Summary

	Participants							
	10 mg QW (n=12)	20 mg QW (n=8)	30 mg QW (n=8)	10 mg/20 mg QW (n=12)	20 mg/30 mg QW (n=8)	2 mg/3 mg QD (n=13)	2 mg/3 mg/ 4 mg/5 mg QD (n=16)	Placebo (n=26)
TEAEs, n (%)	12 (100)	8 (100)	8 (100)	12 (100)	8 (100)	13 (100)	16 (100)	22 (84.6)
TEAEs leading to study drug withdrawal, n (%)	0	1 (12.5)	1 (12.5)	0	1 (12.5)	4 (30.8)	2 (12.5)	0
TEAEs of interest, n (%)								
Injection site reaction	10 (83.3)	0	1 (12.5)	11 (91.7)	3 (37.5)	7 (53.8)	9 (56.3)	18 (69.2)
Skin hyperpigmentation	11 (91.7)	6 (75.0)	6 (75.0)	10 (83.3)	5 (62.5)	10 (76.9)	13 (81.3)	4 (15.4)
Nausea	4 (33.3)	7 (87.5)	6 (75.0)	3 (25.0)	5 (62.5)	6 (46.2)	9 (56.3)	3 (11.5)
Vomiting	3 (25.0)	4 (50.0)	3 (37.5)	3 (25.0)	1 (12.5)	2 (15.4)	2 (12.5)	2 (7.7)
Headache	1 (8.3)	5 (62.5)	6 (75.0)	2 (16.7)	2 (25.0)	3 (23.1)	1 (6.3)	5 (19.2)

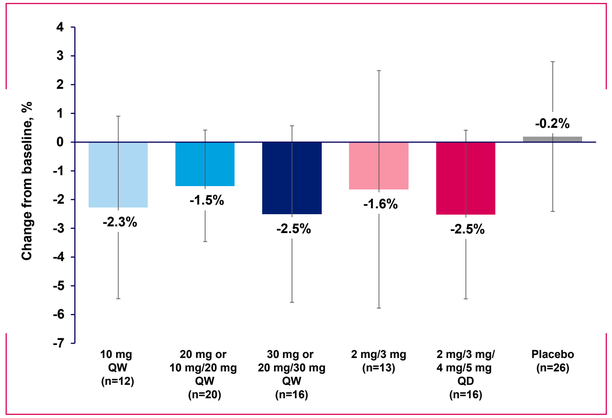
QD, once daily; QW, once weekly; TEAE, treatment-emergent adverse event.

Figure 2. Setmelanotide plasma concentrations over 24 hours in healthy volunteers who received **(A)** QW or **(B)** QD setmelanotide at Week 1 (dashed line) or Week 12 (solid line).



Error bars are the standard deviation. QD once daily; QW, once weekly.

Figure 3. Weight loss at Week 12 with QW or QD setmelanotide compared with placebo.



Cohorts were pooled on the basis of the highest final setmelanotide dose. Error bars are the standard deviation. QD, once daily; QW, once weekly.

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.** Yazdi et al. *PeerJ*. 2015;3:e856. **3.** Markham. *Drugs*. 2021;81:397-403. **4.** Qiao et al. *Diabetes Metab Syndr Obes*. 2016;9:201-205.