Design of a Phase 1 Trial of Once-Weekly RM-718, a Selective Melanocortin-4 Receptor Agonist, in Patients With General or Hypothalamic Obesity

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Summary

- **This first-in-human, first-in-patient Phase 1 trial (NCT06239116) will evaluate the safety, tolerability, and pharmacokinetics (PK) of once-weekly (QW) RM-718—a selective melanocortin-4 receptor (MC4R) agonist with potential to avoid melanocortin-1 receptor (MC1R)–related hyperpigmentation—in individuals with general obesity and patients with acquired hypothalamic obesity (HO)**
- **The trial is underway, with the first participant dosed in March 2024**

Introduction

- Hypothalamic injury can impair MC4R pathway signaling, resulting in HO, which is often refractory to traditional off-label therapies[1,2]
- The selective, once-daily MC4R agonist setmelanotide reduced weight and hunger in a Phase 2 trial of patients with acquired HO; however, skin hyperpigmentation via residual MC1R activation was a frequently reported adverse event[3-5]
- RM-718, which was formulated for QW dosing, is a highly selective MC4R agonist in development with similar in vitro potency for MC4R as setmelanotide with potential to avoid MC1R-related hyperpigmentation[6]
- We present the design of a first-in-human, first-in-patient Phase 1 trial of RM-718 QW in individuals with general obesity or patients with acquired HO

Objective

- This 3-part, first-in-human, first-in-patient Phase 1 trial (NCT06239116) will evaluate the safety, tolerability, and PK of RM-718 QW in individuals with general obesity or patients with acquired HO

Methods

Participants and eligibility criteria

- Part A of the trial will enroll ~36 participants with general obesity, part B will enroll ~30 participants with obesity, and part C will enroll ~24 patients with acquired HO (Table 1)

Table 1. Key Eligibility Criteria

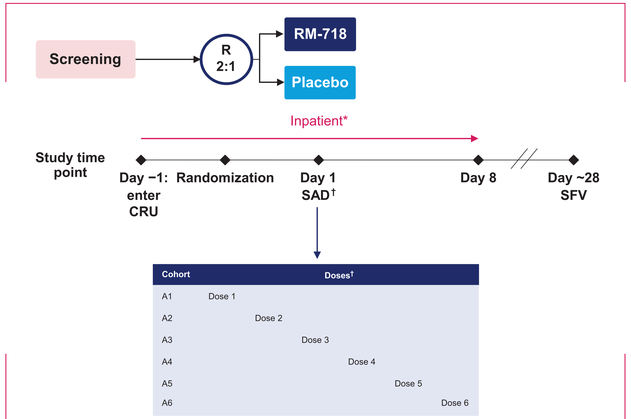
	Key inclusion criteria	Key exclusion criteria
Parts A and B	• Aged 18 to 55 years • BMI ≥30 kg/m^2	• Clinically significant abnormalities on screening laboratory tests or physical (eg, skin) examination as determined by the investigator • Active or history of any notable medical condition
Part C	• Aged ≥12 to 65 years • BMI ≥30 kg/m^2 (in those aged ≥18 years) or ≥95th percentile (in those aged ≥12 to <18 years) • Documented evidence of acquired HO	• Diagnosis of PWS or ROHHADNET syndrome • Bariatric surgery within 2 years • Weight loss >2% (in those aged ≥18 years) or BMI reduction >2% (in those aged ≥12 to <18 years) within 3 months and/or antiobesity medications for treatment of obesity*
Parts A, B, and C	• NA	• Abnormal ECG • HbA_{1c} >6.5% • GFR <90 mL/min/1.73 m^2 • Participation in a clinical trial within 3 months or 5 half-lives before the first dose of study drug

*Use of medications associated with weight loss that are taken for treatment of comorbidities are allowed if the regimen/dose has been stable for ≥3 months before randomization, the patient has not experienced weight loss (aged ≥18 years) or BMI reduction (aged ≥12 to <18 years) >2% within 3 months, and the patient intends to maintain the regimen/dose throughout the course of the trial. BMI, body mass index; ECG, electrocardiogram; GFR, glomerular filtration rate; HbA_{1c}, glycated hemoglobin; HO, hypothalamic obesity; NA, not applicable; PWS, Prader-Willi syndrome; ROHHADNET, rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation, neuroendocrine tumor.

Study design

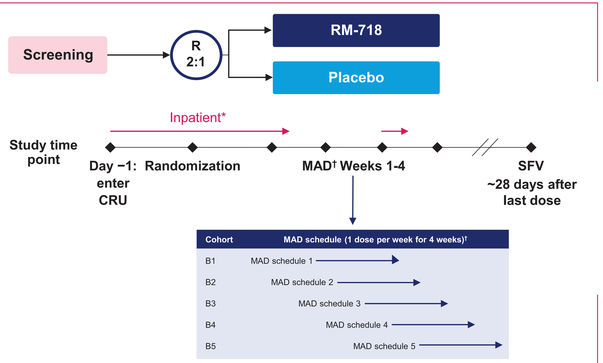
- Parts A and B will evaluate single (part A) or multiple ascending doses (MAD; part B) of RM-718 QW or placebo in individuals with obesity; part C will assess open-label MAD of RM-718 QW in patients with acquired HO
  - In part A, ~6 single-ascending dose cohorts (6 participants per cohort) will be randomized 2:1 to receive a single dose of RM-718 or placebo; in the first cohort, safety, tolerability, and PK in the first 2 participants will determine dosing for the remaining 4, and initiation of cohorts and dosing thereafter will be based on the safety, tolerability, and PK in ≥4 participants in the preceding cohort (Figure 1)
  - In part B, ~5 cohorts (6 participants per cohort) will be randomized 2:1 to receive MAD of RM-718 QW or placebo for 4 weeks; doses will be based on the safety, tolerability, and PK in part A (Figure 2)
  - In part C, ~3 cohorts (4 participants aged approximately ≥12 to <18 years and 4 participants aged ≥18 years per cohort) will receive MAD of RM-718 QW for 4 weeks; doses will be based on the safety, tolerability, and PK from parts A and B (Figure 3)

Figure 1. Part A: SAD in individuals with general obesity.



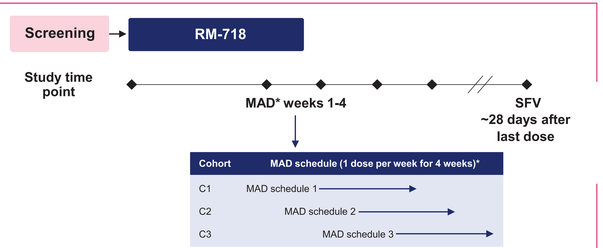
*Vital signs, pharmacokinetics, and injection sites will be monitored during the inpatient period. Participants with clinically significant adverse events or abnormalities may be asked to remain in the CRU until resolution. †In cohort A1, safety, tolerability, and pharmacokinetics in the first 2 participants will determine dosing for the remaining 4. Initiation of subsequent cohorts and ascending doses per cohort will be based on the safety, tolerability, and pharmacokinetics in ≥4 participants in the preceding cohort. CRU, clinical research unit; R, randomized; SAD, single-ascending dose; SFV, safety follow-up visit.

Figure 2. Part B: MAD in individuals with general obesity.



*Vital signs, pharmacokinetics, injection sites, and continuous electrocardiograms will be monitored during inpatient periods on Days −1, 1, 2, 22, and 23. Participants with clinically significant adverse events or abnormalities may be asked to remain in the CRU until resolution. †Doses will be based on the safety, tolerability, and pharmacokinetics in part A. CRU, clinical research unit; MAD, multiple-ascending doses; R, randomized; SFV, safety follow-up visit.

Figure 3. Part C: MAD in patients with HO.



*Doses will be based on the safety, tolerability, and pharmacokinetics in parts A and B. Vital signs, pharmacokinetics, injection sites, hunger scores, and Symptoms of Hyperphagia questionnaire responses will be recorded during clinic visits throughout the study. HO, hypothalamic obesity; MAD, multiple-ascending doses; R, randomized; SFV, safety follow-up visit.

Endpoints and analysis

- Endpoints will include safety (adverse events, laboratory parameters, vital signs, electrocardiograms, and ambulatory blood pressure monitoring), tolerability, PK, and pharmacodynamics (Table 2) and will be analyzed using descriptive statistics

Table 2. Study Endpoints

Primary	Secondary	Exploratory
Number with TEAEs, including severity and ISRs, as well as changes in laboratory parameters, vital signs, ECG, heart rate, and physical examination findings (parts A, B, and C) Ambulatory blood pressure monitoring (parts B and C)	PK parameters (parts A, B, and C), including: – AUC_{tau} – C_{avg} – C_{max} – C_{max} (t_{max}) – C_{min} – C_{min} (t_{min}) – C_{trough}	• ECG parameters (parts A and B) • PD (part C) – Change from baseline to Week 4 in weight, BMI, waist circumference, BMI Z score (in participants aged ≥12 to <18 years), hunger score, and Symptoms of Hyperphagia total score • Change in proteomic biomarkers from baseline to Week 4 (part C)

AUC_{tau}, area under the concentration-time curve from time zero to the end of the dosing interval; BMI, body mass index; C_{avg}, average drug concentration; C_{max}, maximum drug concentration; C_{max} (t_{max}), time to reach C_{max}; C_{min}, minimum drug concentration; C_{min} (t_{min}), time to reach C_{min}; C_{trough}, trough concentration; ECG, electrocardiogram; ISR, injection site reaction; PD, pharmacodynamics; PK, pharmacokinetics; TEAE, treatment-emergent adverse event.

Conclusions

- This Phase 1 trial will be the first-in-human and first-in-patient study to examine dosing, safety, and tolerability in individuals with general obesity and acquired HO with the MC1R-sparing, highly selective MC4R agonist RM-718, which includes the convenience of QW dosing and potential to avoid hyperpigmentation
- Results will provide valuable information on RM-718 QW treatment in patients with acquired HO, which will inform future development of RM-718 QW for rare MC4R pathway diseases, including acquired HO and rare genetic obesities

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References: 1. Abuzzahab et al. *Horm Res Pediatr*. 2019;91:128-136. **2.** Erfurth. *Neuroendocrinology*. 2020;110:767-779. **3.** Roth et al. Presented at: ObesityWeek®; November 1-4, 2022; San Diego, CA. **4.** IMCIVREE® [package insert]. Boston, MA: Rhythm Pharmaceuticals, Inc.; 2022. **5.** Collet et al. *Mol Metab*. 2017;6:1321-1329. **6.** Data on file, Rhythm Pharmaceuticals, Inc.