National Institute of Diabetes and Digestive and Kidney Diseases

A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Effect of a Melanocortin Receptor 4 (MC4R) Agonist, RM-493, on Resting Energy Expenditure (REE) in Obese Subjects

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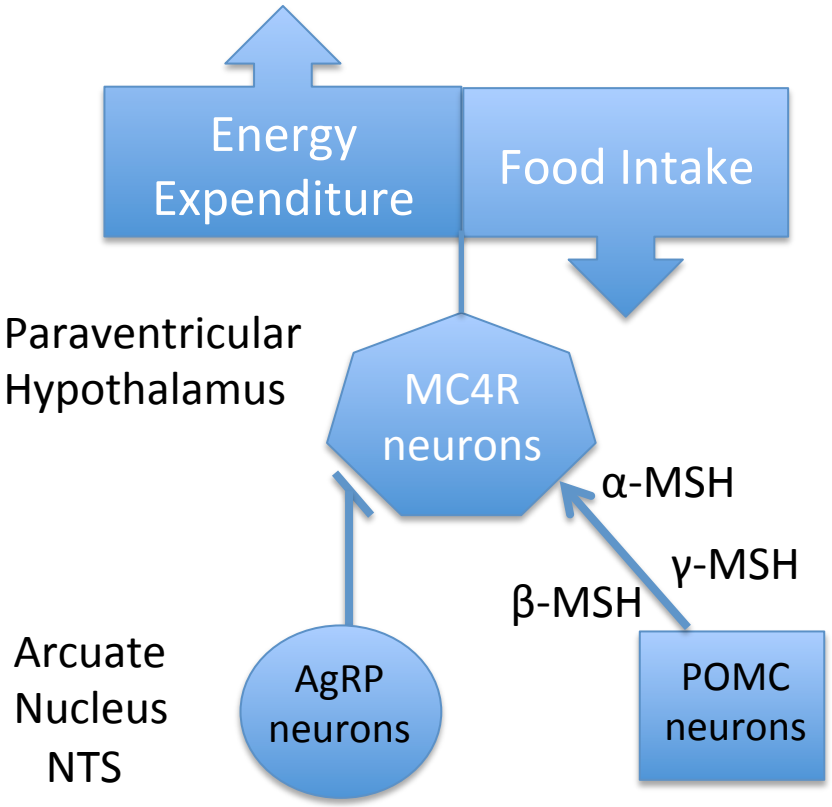
Disclosures

Hillori Connors, Keith Gottesdiener and Lex Van der Ploeg are employees of Rhythm Pharmaceuticals, a privately held Biotechnology company which is developing RM-493 for the treatment of obesity.

Rhythm Pharmaceuticals provided study drug and placebo and provided funding for genotyping and pharmacokinetic data.

The Central Melanocortin (MC) System Serves a Critical Role in the Maintenance of Body Weight

The MCs, the agouti-related proteins and their receptors (MCRs) integrate neural, metabolic and hormonal signals that control energy homeostasis



The MCRs have diverse expression and binding profiles, in the central nervous system and systemically.

MC1R: skin pigmentation
MC2R: HPA axis
MC3R: energy homeostasis
MC4R: energy homeostasis
erectile activity
MC5R: sebaceous gland secretion

RM-493, a Small Peptide MC4R Agonist; Reduced Body Weight & Improved Insulin Sensitivity in Nonclinical Models of Obesity

RM-493 (formerly BIM-22493) binds hMC4R with high affinity and is potent in activating MC4R.

	cAMP, EC_{50} (nM)				
	MC1	**MC2**	**MC3**	**MC4**	**MC5**
RM-493	5.8	>1000	5.3	0.27	1600

- Acute reduction of food intake in wild-type and MC3R KO but not MC4R KO female mice (Kumar et al. *Peptides* 30:1892-1900, 2009).
- Chronic RM-493 treatment resulted in 13% weight loss in obese rhesus over 8 weeks without adverse cardiovascular effects.
  - Food intake reduced initially and returned to baseline levels
  - Energy expenditure increased over the treatment period measured by double labeled water (Kievit et al. *Diabetes* 62:490–497, 2013).

Hypothesis: Acute Administration of RM-493 Increases Resting Energy Expenditure (REE)

Randomized, double-blind, placebo-controlled, 2-period crossover study of healthy weight stable subjects aged 18 to 50 y & BMI 30 to 40 kg/m^2

Exclusions: hypertension, diabetes, recent illness or surgery, prescription drug use or personal or family history of melanoma or dysplastic nevi

PRIMARY ENDPOINT

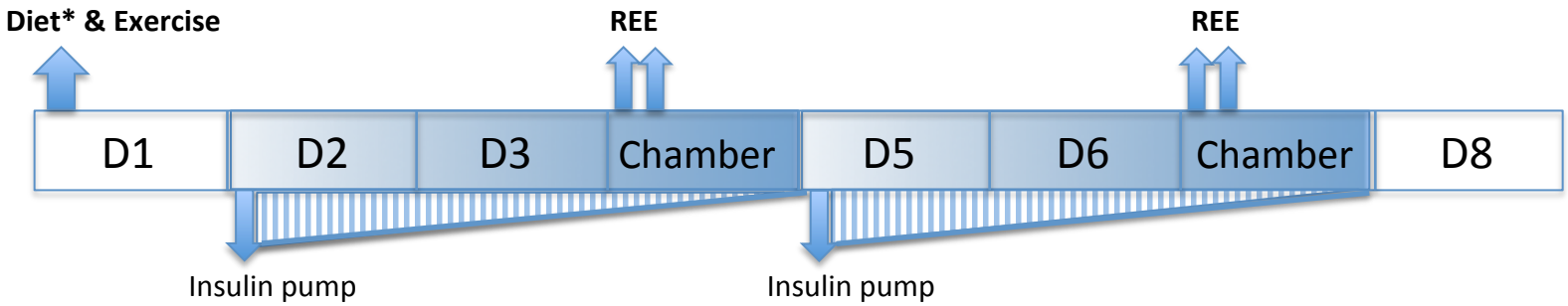
REE: Average REE measured during two 30 minute periods in the metabolic chamber (room calorimeter). Subjects were fasting, awake, still, semi-recumbent, and wearing hospital scrubs.

SECONDARY ENDPOINT

TEE: Total energy expenditure (TEE) measured in the metabolic chamber.

Study Design: Two Period Crossover

Fixed dose of RM-493 1 mg/24 hours or placebo sc



* weight maintenance diet 50% carbohydrate, 30% fat, 20% protein

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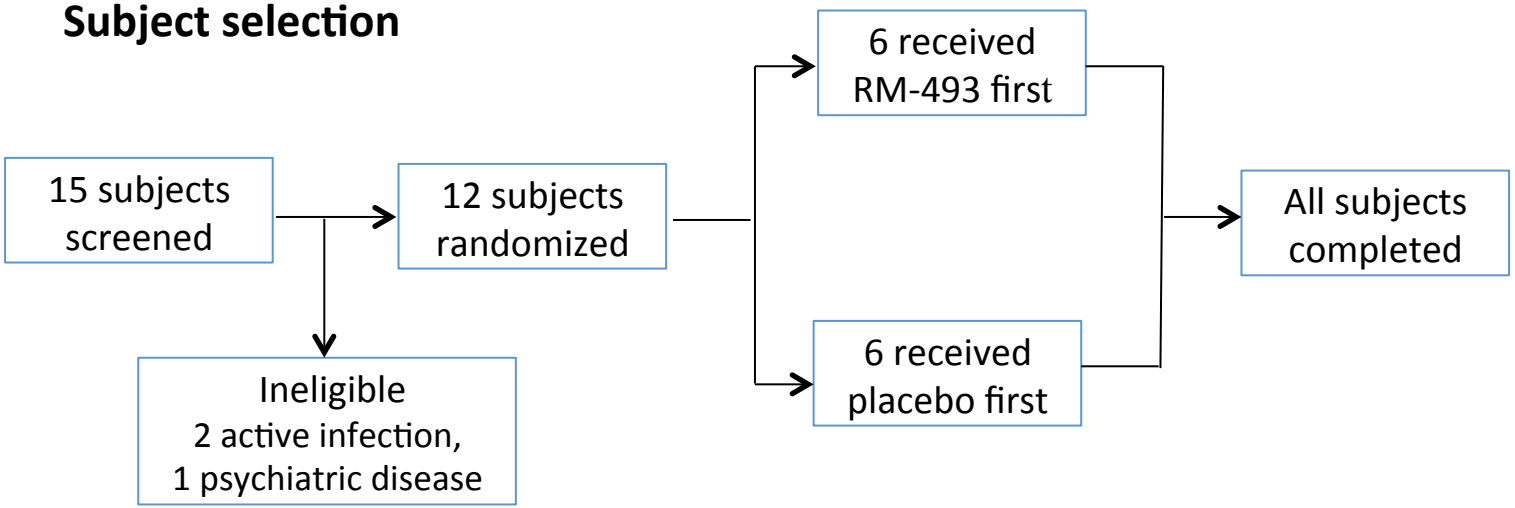
Subject selection



Statistical Analysis

- All results are expressed as the unadjusted mean (SD).
- REE, TEE, and components of TEE: sleep EE, thermic effect of food, exercise EE, and Respiratory Quotient (RQ) to assess substrate oxidation were analyzed using paired t-test
- Biochemical and hormone levels were analyzed by mixed model regression adjusting for baseline
- p values are not adjusted for multiplicity.

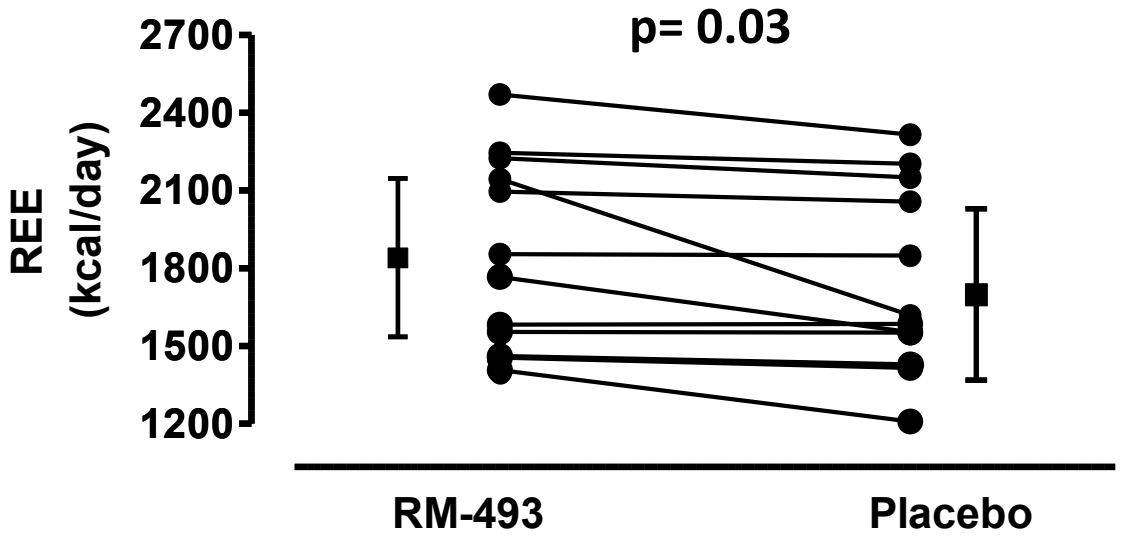
Characteristics of Healthy Obese Cohort

- **N=12; 50% female**
- **9 African American, 3 Caucasian (1 Hispanic)**
- **None had loss of function MC4R variants associated with obesity**

	Mean	(SD)
Age (*yr*)	**34.9**	(11.3)
BMI (*kg/m^2*)	**35.7**	(2.9)
Systolic BP (*mmHg*)	**115**	(13)
Diastolic BP (*mmHg*)	**62**	(11)
Heart rate (*bpm*)	**64**	(10)
Glucose (*mg/dl*)	**91**	(6)
Insulin (*mcU/ml*)	**18**	(11)
Hemoglobin A1c (*%*)	**5.5**	(0.3)
Cholesterol (*mg/dl*)	**163**	(32)
HDL (*mg/dl*)	**51**	(15)
Triglycerides (*mg/dl*)	**139**	(69)

Short-term RM-493 Treatment Increases Resting Energy Expenditure

RM-493 increased REE by 6.4%
110 (SD 151) kcal/day



Individual data with treatment group mean (SD)

RM-493 Effect on Total Energy Expenditure

		RM-493		Placebo		p-value
		Mean	(SD)	Mean	(SD)	
TEE*	kcal/d	**2509**	(420)	**2457**	(399)	0.09
Components of TEE						
Sleep EE	kcal/min	**1.35**	(0.19)	**1.35**	(0.18)	0.94
Exercise EE**	kcal/min	**4.49**	(0.96)	**4.49**	(1.1)	0.99
Thermic Effect of Food	kcal/min	**1.81**	(0.31)	**1.76**	(0.33)	0.15

*Excludes 30-minute exercise period in metabolic chamber

** Excludes two subjects with inconsistent exercise effort in chamber

Short-term RM-493 Effect on Respiratory Quotient, Glucose and Lipids

	RM-493		Placebo		p-value
	Mean	(SD)	Mean	(SD)	
Respiratory Quotient	**0.83**	(0.02)	**0.85**	(0.02)	0.017
Free Fatty Acid *(µEq/L)*	**0.45**	(0.1)	**0.33**	(0.1)	0.009
Triglycerides *(mg/dL)*	**151**	(70)	**129**	(54)	0.035
Fasting Plasma Glucose *(mg/dL)*	**95**	(5.6)	**91**	(3.6)	0.003
Fasting Plasma Insulin *(mcU/mL)*	**26**	(16)	**18**	(12)	0.008

Endocrine Effects of RM-493 Treatment

	RM-493		Placebo		p-value
	Mean	(SD)	Mean	(SD)	
TSH (*mcIU/ml)*	**1.86**	(1.0)	**1.51**	(0.7)	0.01
Free T3 (*pg/ml)*	**2.6**	(0.8)	**2.5**	(0.7)	0.31
Free T4 (*ng/ml)*	**2.2**	(0.4)	**2.1**	(0.3)	0.31

No treatment effect on irisin, FGF-21, prolactin, ghrelin, urinary cortisol.

No Adverse Cardiovascular Effect Observed During RM-493 Treatment

	RM-493		Placebo		
	Mean	**(SD)**	**Mean**	**(SD)**	**p-value**
Systolic Blood Pressure *(mmHg)*	**118**	(10)	**118**	(9)	0.95
Diastolic Blood Pressure *(mmHg)*	**68**	(8)	**69**	(10)	0.31
Heart Rate *(bpm)*	**67**	(9)	**69**	(11)	0.11

Adverse Event Profile

Adverse Event	RM-493	Placebo
Headache	3	1
Arthralgia	2	-
Female genital sensitivity	2	-
Nausea	2	-
Skin darkening	1	1
Cramping	1	-
Diarrhea	1	-
Dry mouth	1	-
Fatigue	1	-
Itching	1	-
Metallic taste	1	-
Myalgia	1	-
Penile erections	1	-
Tingling	-	1
Yeast infection	-	1

Conclusions

- This is the first exploratory study reporting the effects of MC4R agonist on energy expenditure humans.
- Short-term treatment with RM-493 increased resting energy expenditure 6.4% and decreased RQ, shifting substrate oxidation from carbohydrate to fat.
- RM-493 treatment increased FFA levels likely through induction of lipolysis.
- The observed effects on glucose, insulin, triglycerides, and TSH are of uncertain clinical significance and require additional longer-term studies.

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