T-P-3134: Analysis of the Synthetic Peptide Setmelanotide (RM-493), a Melanocortin-4 Receptor (MC4R) Agonist, on Cardiovascular Parameters in Three Phase1b/2a Studies

Keith Gottesdiener, Hillori Conners, Lex Van der Ploeg, Fred Fiedorek, Michelle Hylan, William Louis*, Kenneth Lasseter**.

Affiliations: Rhythm Pharmaceuticals, MA; *Covance, TX; *Clinical Pharmacology of Miami, FL.

Abstract

The hypothalamic Leptin- Proopiomelanocortin -MC4R pathway is a critical regulator of appetite and weight regulation. The synthetic MC4R agonist peptide setmelanotide (RM-493), a first in class efficacious and well-tolerated MC4R agonist, is ideally positioned for the treatment of defects in this pathway. Several previous MC4R agonists caused significant increases in blood pressure (BP) and heart rate (HR). Preclinical evaluations supported that RM-493 did not cause such increases at doses that resulted in weight loss in a primate weight loss study. Methods: Healthy obese patients (BMI≥30 kg/m^2) were enrolled in clinical safety, tolerability and weight loss studies, where BP (systolic [S]and diastolic [D]) and heart rate (HR) were assessed in three double-blind, randomized, placebo (pbo) controlled parallel group multiple dose studies of RM-493 by 24-hour ambulatory blood pressure (24-hr ABPM) at baseline and at ~1-2 weeks postdose. 24-hr ABPM results were analyzed for each study over the full 24 hours, the daytime and nighttime intervals, for both absolute values and change from baseline compared to placebo. In addition, PK/PD (BP, HR) analyses were conducted. Results: There were 48 patients in Study 1 (32 active; 16 pbo), 25 patients in Study 2(13 active; 12 pbo), and 55 patients in Study 3 (34 active; 21 pbo), for a total of 128 patients (79 active; 49 pbo). On average, patients lost ~0.9 kg/week of placebo-subtracted weight loss at doses of 1-2 mg/day. There was little, if any evidence of BP or HR change from baseline vs pbo in any study, nor evidence of a PK/PD relationship: for example, Study 3, the largest single study (N=55) showed -1.07 mmHg (90%CI: -3.93, 1.78), -0.44 mmHg (90%CI: -2.29, 1.41), and +0.19 beats (90%CI: -3.09, 3.46) for SBP, DBP, and HR respectively. Conclusion: RM-493, an MC4R agonist that contributes to weight loss without increasing CV parameters, may represent an important therapeutic advance for the treatment of the obesity in patients with defects in the hypothalamic Leptin-POMC-MC4R pathway.

Background

A different approach to obesity drug development is to leverage new understanding of the genetic causes of severe obesity. One initial target is the hypothalamic Leptin- POMC -MC4R pathway ("MC4 Pathway"), a critical regulator of appetite and weight (Figure 1). The MC4R agonist peptide setmelanotide (RM-493) is ideally positioned to restore impaired function in this pathway, serving in essence as replacement therapy for genetic deficiencies. Setmelanotide in being studied in several, ongoing Phase 2 studies in patients with deficiencies in the MC4 pathway.

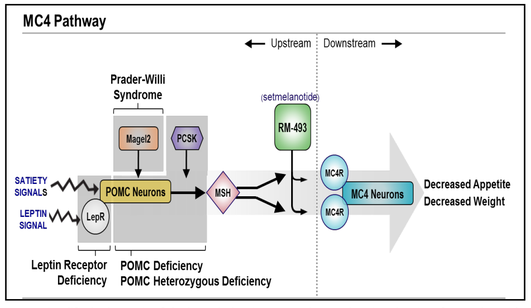


Figure 1. A simplified schematic of the hypothalamic MC4 pathway, showing the site of Setmelanotide action, as well as potential deficiencies in humans for which setmelanotide might function as replacement therapy.

Initially, MC4R agonists failed in clinical trials due to safety issues, in addition to having limited efficacy. The most significant potential safety issue was increases in HR and BP, demonstrated with LY2112688, which caused marked HR and BP increases (1). Preclinical evaluations supported that RM-493 did not cause such increases (Figure 2) at doses that resulted in marked efficacy in a primate weight loss study (2).

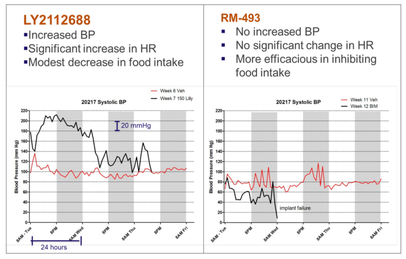


Figure 2. Head-to-head comparison of LY2112688 and RM-493 as a crossover in one obese rhesus monkey. Left: a baseline SBP tracing (red line) then superimposed SBP with treatment by LY2112688 (black line) one week later. Right: same monkey at baseline (red line) followed by the SBP tracing with treatment with RM-493 (black line; until the implanted transducer failed 24-hrs into the last tracing). Similar data was obtained for diastolic blood pressure and heart rate.

Methods: Healthy obese patients (BMI≥30 kg/m2) whose SBP, DBP, and HR were assessed by 24-hr ABPM at baseline and at ~1-4 weeks postdose in three double-blind, randomized, pbo controlled parallel group multiple dose studies of setmelanotide. 24-hr ABPM results were analyzed over 24 hours, including daytime and nighttime intervals, for both absolute values and change from baseline compared to pbo. In the Single Ascending Dose (SAD) study, frequent sitting vital signs were obtained over 24 hrs postdose in a crossover setting, one period with placebo treatment and one with setmelanotide treatment. In addition, PK/PD (BP, HR) analyses were conducted. In total, 67 patients who received placebo treatment and 92 patients who received setmelanotide were included in this analysis.

Single Ascending Dose (SAD) Study

In the SAD clinical trial (RM-493-001 study), extensive monitoring of heart rate and blood pressure did not demonstrate any notable change with setmelanotide treatment compared to a crossover period with placebo treatment (Table 1).

Cohort	Cohorts 4-8	Cohort 4	Cohort 6	Cohort 5	Cohort 7	Cohort 8
RM-493 Administration	Pooled Data	SC 24 hour Infusion				SC Injection
Dose	Pooled	0.01 mg/kg	0.02 mg/kg	0.05 mg.kg	0.1 mg/kg	0.01 mg/kg
N	22	4	4	5	5	4
DBP (mmHg)						
LS Mean (SE)	**1.0 (±1.00)**	-0.6 (±0.89)	5.3 (±2.42)	1.9 (±2.13)	-0.9 (±1.72)	-0.3 (±2.63)
95% CI	**(-1.1, 3.1)**	(-3.1, 1.9)	(-1.4, 12.0)	(-4.8, 8.7)	(-5.1, 3.3)	(-11.6, 11.1)
p-Value	**0.3445**	0.5420	0.0946	0.4290	0.6026	0.9301
SBP (mmHg)						
LS Mean (SE)	**1.6 (±1.34)**	0.2 (±1.54)	6.8 (±4.17)	2.6 (±4.14)	-1.8 (±2.25)	0.1 (±1.96)
95% CI	**(-1.2, 4.3)**	(-6.4, 6.8)	(-11.1, 24.7)	(-7.5, 12.7)	(-7.3, 3.7)	(-8.3, 8.6)
p-Value	**0.2590**	0.9235	0.2442	0.5560	0.4636	0.9511
HR (bpm)						
LS Mean (SE)	**-2.0 (±1.25)**	-4.4 (±1.64)	1.7 (±2.23)	-3.5 (±2.14)	-4.1 (±2.48)	0.8 (±2.36)
95% CI	**(-4.6, 0.5)**	(-9.0, 0.2)	(-4.5, 7.9)	(-8.7, 1.7)	(-10.1, 2.0)	(-9.4, 11.0)
p-Value	**0.1135**	0.0551	0.4931	0.1540	0.1508	0.7664

Table 1. Difference in Active versus Placebo Treatments, for Mean Change from Baseline in Vital Signs (24-Hour Average) - Both Pooled Crossover Group (outlined in red), and each Individual Cohort in the Crossover Population[1]

[1]Data is presented for the pooled Crossover Population (N=22), then for each of the individual cohorts/doses that comprise the pooled crossover population. Note Cohorts 1-3 were not crossover-cohorts, and were treated with lower doses without evidence of SBP, DBP or HR changes (data not show).
[2]For each population, 24-hour averaged change from baseline was determined, then differences in active - placebo treatment periods were compared, showing LS mean changes, 95% confidence intervals, and P-values for the difference.

Multiple Ascending Dose (MAD) Study

Similarly, in the MAD clinical trial, there was little evidence of any notable changes in cardiovascular parameters compared to placebo when assessed by 24-hr ABPM (Table 2)

Cohort	N*	Dose **	Heart Rate (bpm)				Systolic BP (mmHg)				Diastolic BP (mmHg)			
			Change from Day -1 to				Change from Day -1 to				Change from Day -1 to			
			Day 15		Day 28		Day 15		Day 28		Day 15		Day 28	
			RM493	Pbo	RM493	Pbo	RM493	Pbo	RM493	Pbo	RM493	Pbo	RM493	Pbo
1	5/3	0.01	4.49	4.06	***	***	0.35	4.55	***	***	-0.63	0.12	***	***
3	6/3	0.01	6.00	8.79	9.58	7.41	2.75	4.51	2.75	6.05	3.61	4.13	4.73	4.56
4	6/3	0.015	5.38	8.34	10.99	12.18	3.88	-8.00	4.34	-4.43	3.30	-3.68	4.44	-0.32
5	6/3	0.015	2.76	5.27	***	***	2.81	1.91			2.05	0.70	***	***
Total	23/12	All	4.66	6.62	10.29	9.80	2.45	0.74	3.55	0.81	2.08	0.32	4.59	2.12
Difference+				-1.96		0.49		1.71		2.74		1.77		2.47
Overall Difference++				-1.14						2.05				2.00

Table 2. RM-493-002 MAD study ABPM data across 4 cohorts at doses equal to, or more than doses that resulted in clinically relevant weight loss over the 14-day or 28-day treatment courses in these Phase 1b panels. *Twenty-four-hour ambulatory blood pressure measurements were taken on day -1 (baseline), as well as Days 14 (all cohorts) and Days 28 (for 28-day cohorts).*

Twelve-Week Continuous Infusion Study

In the ambulatory blood pressure sub-study (N=25) of Study RM-493-003, a 12-week continuous infusion study, there was little if any evidence of SBP, DBP or HR effects when comparing change from baseline between RM-493 and placebo treatments (Figure 3).

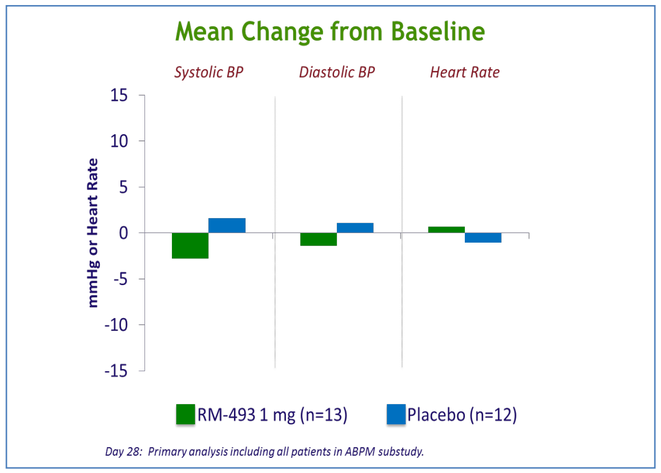


Figure 3. Mean change from baseline for SBP, DBP and HR for RM-493 treatment (green) and placebo treatment (blue) in the 24-hr ABPM sub-study[1].

[1]Two of the RM-493 treated patients had low PK measurements on the measurement day.

Twelve-Week SC Injection Study

In the ambulatory blood pressure sub-study (N=55) of Study RM-493-009, a 12-week SC injection study, there was little if any evidence of SBP, DBP or HR effects (Figure 4).

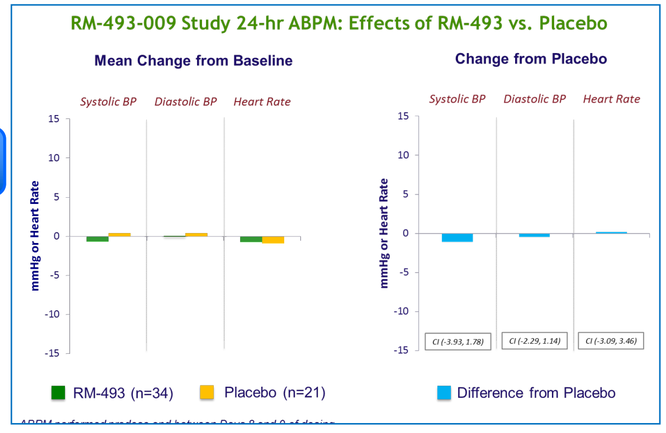


Figure 4. Mean change from baseline for SBP, DBP and HR for RM-493 treatment (green) and placebo treatment (yellow) in the 24-hr ABPM sub-study(N=55). On the right, the placebo subtracted differences (blue).

References

(1) Greenfield et al. Modulation of Blood Pressure by Central Melanocortinergic Pathways. NEJM 2009; 360 (1): 44-52.

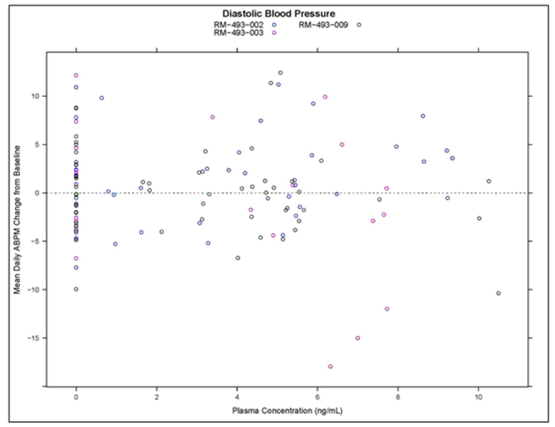
(2) Kievit. Chronic Treatment With a Melanocortin-4 Receptor Agonist Causes Weight Loss, Reduces Insulin Resistance, and Improves Cardiovascular Function in Diet-Induced Obese Rhesus Macaques. DIABETES 2013; 62: 490-497

Supported by Rhythm Pharmaceuticals

PK/PD Analysis Across 24 hour Ambulatory BP Studies

A PK/PD analysis across patients who were studied with 24-hr ABPM showed no evidence of any PK/blood pressure relationship for SBP or DBP (Figure 5; heart rate was similar, data not shown).

Mean 24-hr ABPM Diastolic BP Change from Baseline vs PK



Mean 24-hr ABPM Systolic BP Change from Baseline vs PK

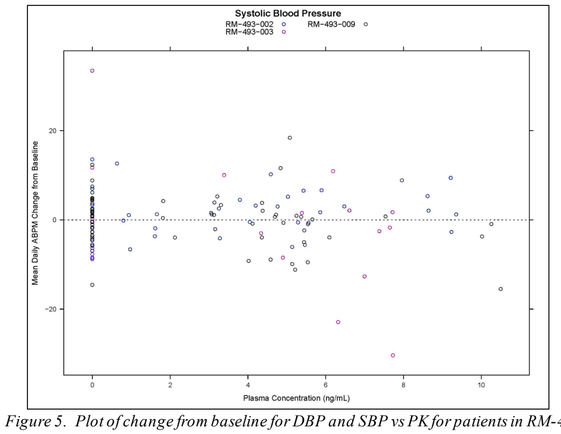


Figure 5. Plot of change from baseline for DBP and SBP vs PK for patients in RM-493 studies -002, -003 and -009. Placebo patients are indicated on the graph as 0 ng/mL)

Conclusions

- There was little, if any evidence of BP or HR change from baseline vs pbo across setmelanotide clinical studies.
- There was no evidence of a PK/PD relationship for blood pressure or heart rate.
- On average, patients lost ~0.9 kg/week of placebo-subtracted weight loss at doses of 1-2 mg/day in short-term clinical trials (data presented elsewhere).
- Setmelanotide (RM-493), an MC4R agonist that contributes to weight loss with little, if any evidence of increasing CV parameters, may represent an important therapeutic advance for the treatment of the obesity in patients with defects in the MC4 pathway.
- While the preliminary data is encouraging, there will need to be continued focus on potential cardiovascular risk until addressed in larger and longer clinical trials.