

## Effect of NPY5R Antagonist MK-0557 on Weight Regain after Very-low-calorie Diet-induced Weight Loss

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### Abstract

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**Objective:** To evaluate whether MK-0557, a highly selective, orally administered neuropeptide Y Y5 receptor antagonist, could limit weight regain after very-low-calorie diet (VLCD)-induced weight loss.

**Research Methods and Procedures:** We enrolled 502 patients 18 to 65 years of age with a BMI of 30 to 43 kg/m<sup>2</sup>. Patients were placed on a VLCD (800 kcal/d liquid diet) for 6 weeks. Patients who lost  $\geq 6\%$  of initial body weight ( $n = 359$ ) were randomized to 52 weeks of 1 mg/d MK-0557 or placebo and maintained on a hypocaloric diet (300 kcal below weight maintenance requirements).

**Results:** In randomized patients, the VLCD was associated with an average weight loss of 9.1 kg. After 12 weeks of double-blind treatment, weight began to gradually increase

for both placebo- and MK-0557-treated patients. The mean weight change (95% confidence interval) from baseline at the end of the VLCD to Week 52 was +3.1 (2.1, 4.0) and +1.5 (0.5, 2.4) kg for patients treated with placebo and MK-0557, respectively. The difference of 1.6 kg between the two groups was significant ( $p = 0.014$ ). Secondary endpoints, such as blood pressure, lipid profile, insulin, and leptin, as well as waist circumference and quality-of-life measurements, did not show significant differences between MK-0557 and placebo treatments.

**Discussion:** Although the difference in weight regain between placebo- and MK-0557-treated patients was statistically significant, the magnitude of the effect was small and not clinically meaningful. Antagonism of the neuropeptide Y Y5 receptor is not an efficacious treatment strategy for reducing weight regain after VLCD.

**Key words:** neuropeptide Y, weight maintenance, neurotransmitter, diet, neurochemistry

### Introduction

Very-low-calorie diets (VLCDs),<sup>1</sup> which provide 400 to 800 kcal/d, are an effective means of achieving rapid weight loss in the treatment of obesity. Weight loss on VLCDs averages 1.5 kg/wk, with total loss after 12 to 16 weeks of  $\sim 20$  kg (1). However, patients generally regain 40% to 50% of lost weight within 1 to 2 years if they do not receive follow-up treatment (2). Studies indicate that combining VLCD therapy with intensive behavioral modification results in more effective long-term weight loss than VLCD therapy alone (3,4). Similarly, it has been shown that adjunctive pharmacotherapy with dexfenfluramine (5,6) or

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<sup>1</sup> Nonstandard abbreviations: VLCD, very-low-calorie diet; NPY, neuropeptide Y; NPY1R, neuropeptide Y1 receptor; NPY5R, neuropeptide Y5 receptor; IGF-I, insulin-like growth factor-I; IGFBP, insulin-like growth factor binding protein; ANCOVA, analysis of covariance; CI, confidence interval.

sibutramine (7,8) may lessen the weight regain that is typically observed after VLCD therapy.

Weight regain after a VLCD likely involves a complex interplay of physiologic, genetic, and environmental factors. Among the important anabolic pathways that might be expected to favor weight regain is the central neuropeptide Y (NPY) pathway, which promotes food intake and decreases energy expenditure (9). Although NPY is produced in several brain regions, a prominent component of this anabolic pathway consists of neurons in the ventromedial part of the arcuate nucleus of the hypothalamus, which synthesize and release NPY in response to peripheral signals that reflect the body's nutritional status (10). Among the peripheral nutrient signals known to influence NPY synthesis and release are the hormones insulin, leptin, ghrelin, and peptide YY, as well as nutrients themselves (11–19). Experimental evidence suggests that NPY mediates its anabolic effects through activation of the NPY Y1 and Y5 receptors (NPY1R and NPY5R), which are expressed in adjacent hypothalamic areas and elsewhere (20–28). Although *in vitro* pharmacologic data have implicated both the NPY1R and NPY5R in mediating the anabolic actions of NPY, the relative importance of each NPY receptor subtype to these actions has been a topic of controversy (29–31). Nevertheless, it has been postulated that antagonism of the NPY5R might prove an effective method for the treatment of obesity.

MK-0557 is a potent, highly selective, orally bioavailable NPY5R antagonist, which has recently been described (32). In this study, we used MK-0557 to test the hypothesis that antagonism of the NPY5R ameliorates the weight regain typically observed after dietary intervention, such as VLCD.

## Research Methods and Procedures

### *Study Design and Subjects*

A worldwide, multicenter, double-blind, randomized, placebo-controlled clinical trial was conducted to evaluate the efficacy of MK-0557 in preventing weight regain after weight loss induced by a 6-week 800 kcal/d VLCD.

Subjects were male and female non-diabetic obese patients 18 to 65 years of age, with a BMI between 30 and 43 kg/m<sup>2</sup>. Applicants were excluded from participation if they had significant cardiovascular, pulmonary, renal, neurologic, or psychiatric disease or were taking medications that might affect body weight. Individuals who had participated in a weight loss program within 3 months of the study were also excluded. All study subjects underwent the informed consent process before any study-related procedures.

### *VLCD Program*

During the 6-week VLCD phase of the study, participants consumed 800 kcal/d provided by a liquid meal replacement (HMR800; Health Management Resources, Boston, MA,

and comparable liquid meal replacements outside of the U.S.). They also were instructed to take a daily multivitamin. The daily intake of 800 kcal was divided across five meals at the following times: breakfast (~8:00 AM), lunch (~12:00 noon), afternoon (~3:00 PM), dinner (~6:00 PM), and evening (~9:00 PM). In addition to the liquid meals, patients were told to drink at least eight glasses of water each day to maintain fluid balance. Patients met one-on-one with a registered dietitian each week during the 6-week liquid-meal replacement phase and received educational materials related to meal replacements, nutrition, behavior modification, and physical activity. One week before randomization, dietitians discussed the refeeding phase and prepared patients for adding conventional food back into their diets. The refeeding phase began at randomization and included a gradual switch from liquid meals to conventional meals over a 2-week period, as well as an increase in the patients' daily caloric intake. During the first week of refeeding, patients were instructed to consume three meals using liquid meal replacement and to include lean protein and vegetables for the balance of their meals. During the second week, two liquid meals were consumed in addition to lean protein, vegetables, fruit, and complex carbohydrates. Sample menus and guidance on counting calories were provided to each patient. During the third week after randomization, patients were instructed to discontinue liquid meal replacements altogether. For the remainder of the 52-week study period, patients met with registered/licensed dietitians and were instructed to consume a mildly hypocaloric diet (300 kcal deficit from that needed to maintain the weight recorded at the randomization visit) consisting of 55% to 60% carbohydrate, 10% to 20% protein, and ≤30% fat. Basal metabolic rate was calculated using the equation of James et al. (33). Daily energy expenditure was estimated as basal metabolic rate multiplied by an activity factor of 1.3. Patients were instructed to record food intake and physical activity using a daily diary during the 300 kcal deficit period. Patient educational materials were translated and culturally adapted for sites outside of the United States.

### *Treatment*

Patients who lost ≥6% of their baseline body weight during the VLCD phase were randomized using a computer-generated allocation schedule to either MK-0557 or placebo. Early phase clinical studies established that a 1-mg/d oral dose of MK-0557 was optimal for later phase clinical studies. Those studies included a positron emission tomography study, which indicated that a 1.25-mg/d oral dose of MK-0557 resulted in 98 ± 5% NPY5R occupancy at 24 hours, and a 12-week proof-of-concept/dose ranging study, which indicated that a 1-mg/d oral dose of MK-0557 resulted in equivalent weight loss efficacy as a 5- and 25-mg/d dose (32).

### Assessments

All patients had an initial clinical evaluation including laboratory assessment (hematology, chemistry, and urinalysis) and electrocardiogram. At baseline and during the study, the following efficacy measurements were collected: body weight, waist circumference, blood pressure, fasting lipid profile, insulin, leptin, and quality of life. A 20% increase in insulin-like growth factor-I (IGF-I) was observed in an earlier proof-of-concept/dose ranging study (32), and we, therefore, examined IGF-I and insulin-like growth factor binding protein (IGFBP)-3 in this study.

Patients were instructed to fast for at least 8 hours before the measurement of body weight. Throughout the study, weight was measured to the nearest 0.1 kg on a calibrated digital scale after subjects had voided and were wearing only a gown and underwear. Measurements were collected until three consecutive measurements did not differ by more than 0.25 kg from each other.

Height was measured without shoes at baseline to the nearest millimeter, using a stadiometer with vertical backboard, fixed floorboard, and movable headboard.

Waist circumference was measured according to the National Health and Nutrition Examination Survey III protocol using a tension-controlled measuring tape. When feasible, the same nurse or study coordinator measured the waist circumference at each visit to provide consistency. Measurements were made in duplicate at the end of normal minimal respiration.

All blood pressure measurements were taken with a mercury sphygmomanometer while patients sat in position for at least 5 minutes. Sitting systolic and diastolic blood pressures were determined by averaging three replicate measurements, obtained 1 to 2 minutes apart. The same arm was measured for all readings throughout the study.

Quality of life was assessed by the Impact of Weight on Quality of Life (34), the Medical Outcomes Trust Short Form, version 2 (35), and the EuroQoL Questionnaire (36).

### Statistical Analyses

The primary efficacy hypothesis was that, in obese patients, MK-0557 at 1 mg/d for 1 year after VLCD-induced weight loss produces less weight regain (or decreases body weight more) than treatment with placebo. The primary tolerability hypothesis was that MK-0557 was well tolerated. The secondary efficacy hypothesis was that the proportion of obese patients who maintain: 1) at least 80% of the weight loss that occurred in the VLCD period (referred to as 80% responders) is higher in patients treated with MK-0557 than those treated with placebo for 1 year; 2) the loss of at least 5% of their initial (Week -6, pre-VLCD) body weight (referred to as 5% responders) is higher in patients treated with VLCD followed by MK-0557 than those treated with VLCD followed by placebo for 1 year.

The primary analyses for the key efficacy endpoints (e.g., change in body weight) were performed on an all-patients-treated population that consisted of patients who were randomized and received at least one dose of study medication. For analyses of change from baseline, patients were required to have both a baseline and at least one post-baseline measurement. A secondary per-protocol population, consisting of patients who completed the 52 weeks of double-blind treatment with no major protocol violations (e.g., lack of compliance with study medication or procedures) was also analyzed.

The primary efficacy hypothesis was evaluated by comparing the mean change in body weight between placebo and MK-0557 using a parametric analysis of covariance (ANCOVA) model appropriate for a multicenter, parallel design. The ANCOVA model adjusted for weight loss during the VLCD, baseline body weight (post-VLCD), center, and treatment. The primary test was a two-sided  $\alpha = 0.05$  test. Least squares means, derived from the ANCOVA model, are reported. The proportion of patients who maintained the loss of at least 80% of the VLCD-induced weight loss was analyzed using logistic regression with terms for weight loss during the VLCD, baseline body weight, center, and treatment. The proportion of patients who maintained the loss of at least 5% of their Week -6 body weight was also analyzed using logistic regression. Missing data were imputed by carrying forward the last observed post-baseline measurement. A longitudinal repeated measures analysis of covariance (37) was used to assess the sensitivity of the results to this imputation technique, and a non-parametric analysis was performed to assess the sensitivity of the analysis to the assumptions of the ANCOVA model.

A post hoc analysis was performed to compute the rate of weight regain. The regain portion of the treatment period was assessed visually, and a repeated-measures ANCOVA was fit to this portion of the data, which allowed for the estimation of the rate of weight regain for each treatment.

Secondary efficacy endpoints, such as blood pressure, fasting lipid profile, etc., were analyzed using a parametric ANCOVA model that adjusted for baseline value of the endpoint, baseline body weight, VLCD-induced weight loss, center, and treatment.

An interim analysis was planned after patients completed 24 weeks of treatment. The purpose of the interim analysis was to check for futility, and there was no intent to stop the study early for positive findings because 1-year data are required for regulatory submission. Because of the interim analysis, a 0.001  $\alpha$  adjustment was made to preserve the type I error rate (38). Significance of the final results was, therefore, assessed at  $p = 0.049$ . Multiplicity among the two secondary efficacy hypotheses was controlled for by considering these hypotheses in order. The secondary hypothesis on the proportion of 80% responders was tested first. If significant at the 0.050 level, the hypothesis on the propor-

**Table 1.** Patient accounting

	<b>Total</b>		
Total patients assessed for eligibility	665		
Patients excluded at screening	163		
Patients entering VLCD phase	502		
Patients discontinued/excluded during VLCD phase	143		
Clinical adverse experiences (VLCD-related)	5		
Clinical adverse experiences (not VLCD-related)	4		
Laboratory adverse experiences	2		
Insufficient weight loss	24		
Lost to follow-up	41		
Withdrew consent	54		
Other	13		
	<b>Placebo</b>	<b>MK-0557 1 mg</b>	<b>Total</b>
Number of patients randomized	177	182	359
Patients completing 4 weeks on drug	173	168	341
Patients completing 12 weeks on drug	154	150	204
Patients completing 24 weeks on drug	144	141	285
Patients completing study (52 weeks on drug)	129	127	256
Lost to follow-up	19	20	39
Other (withdrew consent, adverse experience, patient moved, etc.)	29	35	64
Number of patients included in all patients treated	176	181	357
Number of patients included in PP	121	122	243
Patients excluded from all-patients-treated population*			
No post-baseline data	1	1	2
Patients excluded from PP population†			
No measurement available at week 52	48	55	103
Failed to achieve 6% weight loss during the VLCD‡	8	1	9
Prohibited medication use for 28 or more days	3	3	6
Pregnancy	2	2	4
Other (drug compliance, use of prohibited medication, etc.)	2	2	4

VLCD, very-low-calorie diet.

\* PP is a subset of all patients treated; therefore, patients excluded from all patients treated are also excluded from PP.

† Patient is counted only once in a category. The same patient may appear in different categories.

‡ These patients were incorrectly randomized.

PP, per-protocol.

tion of 5% responders was tested; if not, the secondary hypothesis on 5% responders was not tested.

With the planned 150 patients on MK-0557 and 150 patients on placebo, assuming a standard deviation of 6.7 kg as observed in a similarly designed 1-year study with sibutramine (7) and a level 0.049 test for the primary hypothesis, there was 90% (80%) power to detect a 2.5 (2.2 kg) difference between groups [half-width of the 95% confidence interval (CI) = 1.5 kg].

## Results

### *Patient Accounting*

Of the 665 patients screened, 163 failed screening, and 502 were enrolled in the VLCD phase of the study. Table 1 summarizes patient accounting during the study. The attrition rate during the VLCD phase was 23.7%. The two largest patient categories that discontinued during the VLCD were 54 patients (10.8%) who withdrew consent (no

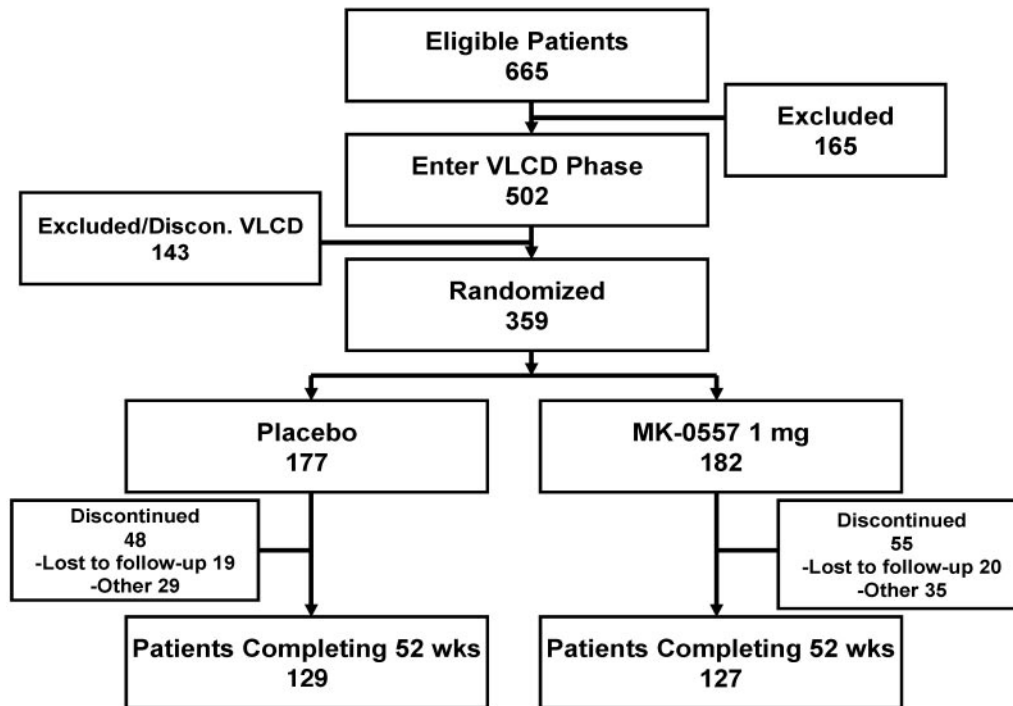


Figure 1: Patient disposition over the 52-week study of MK-0557. The “other” category of discontinued patients represents those patients who withdrew consent, moved, had an adverse experience, or discontinued for reasons other than lost to follow-up.

specific reasons offered) and 41 patients (7.9%) who were lost to follow-up. Five of the patients (0.1%) who started the VLCD phase had VLCD-related clinical adverse effects, which led to their discontinuation from the study. The clinical adverse effects included nausea, vomiting, and diarrhea. Two patients were discontinued because their liver enzyme tests (aspartate aminotransferase or alanine aminotransferase) rose to levels greater than three times the upper limit of normal. Twenty-four patients (6.3%) who completed the VLCD failed to attain a 6% weight loss and were, thus, ineligible for randomization. Of those who were enrolled in the VLCD, 359 patients lost  $\geq 6\%$  of their baseline body weight and were randomized to placebo (177 patients) or MK-0557 (182 patients).

An accounting of patients during the double-blind treatment phase of the study is also summarized in Table 1 and Figure 1. Of the 177 patients randomized to placebo, 131 (75.1%) completed 52 weeks of treatment, 19 (10.7%) were lost to follow-up, and 29 (16.4%) withdrew consent, moved, had an adverse experience, or discontinued for other reasons. Of the 182 patients randomized to MK-0557, 127 (69.8%) completed 52 weeks of treatment, 20 (11.0%) were lost to follow-up, and 35 (19.2%) withdrew consent, moved, had an adverse experience, or discontinued for other reasons.

The categorical baseline characteristics of the all patients treated population are summarized in Table 2. Approx-

mately 80% of subjects in both groups were women. The race and age distributions were similar across the placebo and active treatment groups.

### Body Weight

In the patients who were randomized, the mean (standard deviation) body weight before the VLCD was 100.0 (14.6) kg. The mean body weight after the VLCD was 90.9 (13.3) kg, which represents a  $-9.1\%$  (95% CI: 8.9, 9.3) reduction of initial body weight. Patients continued to lose weight after the VLCD phase until 12 weeks of double-blind treatment, when the weight began to increase for both placebo and MK-0557-treated patients (Figure 2).

The results after 52 weeks of treatment are summarized in Table 3. In the all-patients-treated population, the least-squares mean change from baseline (end of the VLCD) to Week 52 (CI 95%) was +3.1 (2.1, 4.0) and +1.5 (0.5, 2.4) kg for patients treated with placebo and MK-0557, respectively. The difference of 1.6 kg was statistically significant ( $p = 0.014$ ; 95% CI:  $-2.9, -0.3$  kg). Results were consistent among sex, age, and ethnic groups, baseline BMI, and degrees of VLCD-induced weight change. Significantly more patients on MK-0557, relative to placebo, maintained  $\geq 80\%$  of the weight lost during the VLCD phase (48% vs. 36%;  $p = 0.022$ ; odds ratio = 1.7, 95% CI: 1.1, 2.6) and maintained the loss of  $\geq 5\%$  of their initial body weight (62% vs. 49%;  $p = 0.006$ ; odds ratio = 1.9, 95% CI: 1.2,

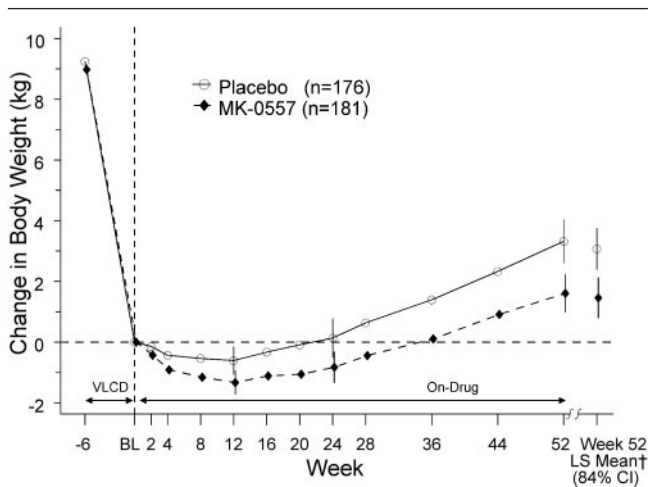
**Table 2.** Categorical baseline patient characteristics by treatment group at Week -6

Baseline demographics	Placebo (N = 176)	MK-0557 1 mg (N = 181)	Total (N = 357)
Sex			
Men	32 (18.2)	37 (20.4)	69 (19.4)
Women	144 (81.8)	144 (79.6)	288 (80.6)
Ethnic group			
White	149 (84.7)	159 (87.8)	308 (86.2)
Black	20 (11.4)	16 (8.8)	36 (10.1)
Other	7 (4.0)	6 (3.3)	13 (3.7)
Age group (years)			
<20	2 (1.1)	4 (2.2)	6 (1.7)
21 to 30	15 (8.5)	18 (9.9)	33 (9.3)
31 to 40	45 (25.6)	40 (22.1)	85 (23.9)
41 to 50	53 (30.1)	55 (30.4)	108 (30.1)
51 to 60	48 (27.3)	53 (29.3)	101 (28.4)
61 to 70	13 (7.4)	11 (6.1)	24 (6.7)

Values are n (%).

3.0). In the per-protocol patient population, the least-squares mean weight change to Week 52 was +3.6 and +1.8 kg for placebo and MK-0557, respectively. The difference of 1.8 kg was significant ( $p = 0.031$ ; 95% CI: -3.5, -0.2 kg). In these patients, the rate of weight regain be-

tween Weeks 28 and 52 was +0.145 and +0.126 kg/wk for patients on placebo and MK-0557, respectively. The difference in weight regain was not significant ( $p = 0.281$ ). Results were corroborated by repeated-measures ANCOVA and by non-parametric analyses.



**Figure 2:** Change in body weight (kilograms) over 52 weeks of treatment using last observation carried forward (all-patients-treated population). BL, baseline; LS, least squares. †LS mean estimates and 84% CI based on ANCOVA model with terms for treatment, baseline measurement, center, and run-in weight change. 84% CI on the observed means shown at Weeks 12, 24, and 52.

**Secondary Efficacy Endpoints**

Secondary efficacy endpoints are summarized in Table 4. The change in waist circumference generally mirrored the change in body weight. There was an ~8 cm decrease in waist circumference during the VLCD and a continued 1 to 2 cm decrease in the first 12 weeks of double-blind treatment. After 52 weeks of treatment, the least squares mean change from baseline was +1.5 and -0.2 cm for patients on placebo and MK-0557, respectively; the difference of -1.7 cm was significant ( $p = 0.009$ ; 95% CI: -3.0, -0.4 cm).

There were no statistically significant differences between placebo and MK-0557 in other secondary endpoints, including blood pressure, fasting lipid profile, insulin, or leptin. It is notable, however, that most of these endpoints showed substantial change during the VLCD followed by a slow rebound during the 52-week double-blind treatment phase.

**Secondary Safety Endpoints**

Among patients completing the study, IGF-I increased from the beginning of the VLCD until 12 weeks of the double-blind treatment phase, with patients on MK-0557 experiencing a slightly greater increase in IGF-I than pa-

**Table 3.** Summary statistics for the change in body weight (kilograms) at baseline and after 52 weeks of treatment

Parameter and patient population	Treatment group	Initial/ pre-VLCD mean (SD)	Randomization mean (SD)	Week 52 mean (SD)	Least squares mean change (95% CI)	Difference from Placebo	
						Least-Squares Mean Difference 95% CI	<i>p</i> -Value
Body weight (kg) All patients	Placebo	101.5 (15.3)	92.3 (13.9)	95.6 (15.7)	3.1 (2.1, 4.0)	1.6 (0.3, 2.9)	0.014
treated-LOCF	MK-0557	98.4 (13.8)	89.5 (12.7)	91.1 (14.5)	1.5 (0.5, 2.4)		
Body weight (kg) All patients	Placebo	101.5 (15.3)	92.3 (13.9)	95.6 (15.7)	4.4 (3.3, 5.5)	1.8 (0.2, 3.3)	0.023
treated-RM	MK-0557	98.4 (13.8)	89.5 (12.7)	91.1 (14.5)	2.6 (1.6, 3.7)		
Body weight (kg) Per-protocol	Placebo	101.7 (15.4)	92.3 (14.0)	94.5 (16.1)	3.6 (2.4, 4.8)	1.8 (0.2, 3.5)	0.031
	MK-0557	98.5 (13.9)	89.5 (12.8)	91.7 (14.5)	1.8 (0.6, 3.0)		

VLCD, very-low-calorie diet; SD, standard deviation; CI, confidence interval; LOCF, last observation carried forward; RM, repeated measures analysis. Based on the analysis of covariance model with terms for treatment, center, baseline body weight, and run-in weight change. In all patients treated population, missing values imputed using the last post-baseline measurement.

tients on placebo. IGF-I decreased between Weeks 12 and 24, and by Week 52, there was no significant difference in IGF-I or IGFBP-3 between treatment groups (median percentage change from baseline at Week 52 for IGF-I and IGFBP-3 was  $-1.6\%$  and  $+5.0\%$ , respectively, in the placebo group and  $+1.1\%$  and  $3.7\%$ , respectively, in the MK-0557 group).

#### Adverse Experiences

Clinical adverse experiences that occurred with an incidence  $\geq 5\%$  in any treatment group are listed in Table 5. Numerically fewer patients on MK-0557 had a clinical adverse experience, serious clinical adverse experience, or discontinued because of a clinical adverse experience. No one died during the study. Overall, MK-0557 was well tolerated.

### Discussion

The principal finding of this study is that potent pharmacologic antagonism of NPY5R was not associated with clinically meaningful prevention of weight regain after an initial loss of 9.1% of body weight achieved with a VLCD. Participants who received MK-0557 regained significantly less weight in the 1 year of treatment than did those who received placebo ( $+1.5$  vs.  $+3.1$  kg, respectively), but the difference between groups was not judged to be clinically meaningful. In comparison with currently approved medications, the efficacy of MK-0557 seems to be more com-

parable to orlistat than to sibutramine. In patients who initially lost 9.9 kg by adhering to a 1000-kcal/d diet, Hill et al. (39) found that those who received orlistat (120 mg three times a day) for the ensuing year maintained a loss of 7.2 kg at the end of this time, compared with a loss of 5.9 kg for placebo-treated patients ( $p < 0.001$ ). Thus, orlistat slowed, but did not prevent, weight regain, similar to MK-0557. In contrast, after a loss of 7.7 kg achieved with a 4-week VLCD, Apfelbaum et al. (7) found that patients who received sibutramine in the ensuing year achieved a cumulative weight loss of 12.9 kg, compared with a loss of 7.3 kg for placebo-treated patients ( $p = 0.004$ ).

Pharmacologic and neuroanatomical data have implicated NPY1R and NPY5R in feeding behavior and metabolism (20,21,24–31). MK-0557 is a highly selective NPY5R antagonist, which in preclinical studies was shown to cause significant weight loss in mice, rats, and rhesus monkeys (32). Based on weight loss efficacy observed in a 12-week proof-of-concept/dose ranging clinical study (32), clinical trials were undertaken to further evaluate the effects of MK-0557 on weight loss. In this study, we evaluated the efficacy of a MK-0557 to lessen the weight regain typically observed after dietary intervention in obese individuals.

Although a statistically significant reduction in weight regain was observed for the MK-0557-treated group compared with the placebo group, the difference was small and clinically insignificant. Nonetheless, the modest effect indicates that NPY5R indeed plays a role in human energy homeostasis. In addition, MK-0557 was also observed to be

**Table 4.** Summary statistics and analysis results of key secondary efficacy parameters (all patients treated)

Parameter	Treatment group	Initial/pre-VLCD mean (SD)	Randomization mean (SD)	Week 52 mean (SD)	Change mean (SD)	Difference from placebo	
						Least squares mean difference	95% CI
							<i>p</i>
Diastolic blood pressure (mm Hg)	Placebo	80.6 (7.9)	75.7 (8.1)	77.9 (8.8)	2.2 (9.1)	1.2 (-0.3, 2.7)	0.126
	MK-0557	79.6 (8.4)	74.7 (8.9)	76.3 (9.2)	1.6 (8.5)		
Systolic blood pressure (mm Hg)	Placebo	125.3 (14.2)	116.0 (12.2)	121.4 (14.1)	5.4 (11.6)	-0.5 (-2.9, 1.9)	0.691
	MK-0557	124.0 (13.9)	115.1 (12.8)	121.4 (14.9)	6.3 (13.5)		
Waist circumference (cm)	Placebo	109.8 (11.3)	102.2 (10.7)	103.7 (11.4)	1.5 (6.6)	1.7 (0.4, 3.0)	0.009
	MK-0557	108.5 (11.7)	99.9 (11.2)	100.0 (12.0)	0.1 (5.8)		
FPG (mg/dL)	Placebo	94.5 (10.9)	89.9 (9.9)	94.4 (12.4)	4.6 (11.5)	0.2 (-2.1, 2.4)	0.895
	MK-0557	94.4 (10.3)	91.3 (10.9)	95.0 (11.7)	3.7 (10.8)		
QUICKI	Placebo	0.33 (0.03)	0.37 (0.04)	0.35 (0.04)	-0.02 (0.04)	0.00 (-0.01, 0.01)	0.781
	MK-0557	0.34 (0.03)	0.37 (0.04)	0.35 (0.04)	-0.02 (0.04)		
Plasma HDL-C (mg/dL)	Placebo	56.1 (13.0)	48.7 (9.8)	57.2 (14.3)	18.1 (23.0)	-3.4 (-8.0, 1.2)	0.144
	MK-0557	54.5 (14.0)	47.0 (11.2)	57.2 (15.4)	22.6 (20.3)		
Non-HDL (mg/dL)	Placebo	149.3 (31.4)	118.4 (30.3)	140.4 (34.2)	21.3 (24.6)	3.0 (-1.7, 7.7)	0.214
	MK-0557	147.8 (33.1)	119.7 (30.6)	137.5 (31.3)	17.9 (24.0)		
LDL-C (mg/dL)	Placebo	121.5 (28.8)	97.7 (28.1)	116.1 (31.9)	22.0 (27.7)	2.0 (-3.2, 7.3)	0.447
	MK-0557	120.5 (29.9)	99.1 (27.7)	115.0 (28.2)	19.5 (25.9)		
Total cholesterol (mg/dL)	Placebo	205.4 (32.5)	166.9 (32.2)	197.7 (36.9)	20.0 (18.5)	2.0 (-1.5, 5.4)	0.256
	MK-0557	202.3 (34.5)	166.7 (32.6)	194.7 (34.4)	18.4 (17.2)		
Plasma triglycerides (mg/dL)	Placebo	126.0 (69.8)	93.0 (40.9)	111.0 (52.1)	9.3 (48.6)	-4.6 (-13.3, 3.8)	0.087
	MK-0557	124.0 (71.6)	96.0 (43.7)	101.0 (51.2)	10.9 (46.9)		
Fasting serum insulin (μU/mL)	Placebo	12.7 (7.0)	7.7 (5.2)	11.3 (12.6)	3.5 (12.0)	-0.6 (-3.2, 2.0)	0.633
	MK-0557	13.0 (12.1)	7.0 (5.0)	11.2 (12.1)	4.2 (11.6)		
Free serum thyroxine (ng/dL)	Placebo	1.0 (0.3)	1.1 (0.2)	. (.)	6.0 (19.2)	0.0 (-0.0, 0.0)	0.912
	MK-0557	1.0 (.)	1.1 (0.3)	1.1 (0.2)	4.4 (16.6)		
Serum IGF-I (ng/mL)	Placebo	144.6 (61.7)	150.4 (61.3)	153.1 (66.9)	11.4 (59.6)	-3.4 (-21.6, 14.9)	0.715
	MK-0557	137.8 (48.4)	152.9 (66.3)	152.4 (53.7)	14.3 (95.5)		
Serum IGFBP-3 (mg/L)	Placebo	3.05 (0.98)	2.80 (0.70)	3.02 (0.81)	11.87 (37.28)	4.27 (-4.85, 13.39)	0.357
	MK-0557	2.79 (0.72)	2.79 (0.79)	2.89 (0.82)	9.37 (47.19)		
Serum leptin (ng/mL)	Placebo	47.6 (25.0)	21.0 (15.1)	39.6 (25.5)	18.5 (17.3)	3.3 (-0.1, 6.8)	0.059
	MK-0557	42.0 (20.6)	18.2 (12.8)	32.7 (20.3)	14.5 (15.2)		
Total serum triiodothyronine (ng/dL)	Placebo	n/a	94.9 (26.1)	106.2 (27.8)	15.4 (27.0)	-1.1 (-5.9, 3.7)	0.655
	MK-0557	n/a	96.7 (26.9)	108.7 (24.0)	17.2 (26.8)		

VLCD, very-low-calorie diet; SD, standard deviation; CI, confidence interval; FPG, fasting plasma glucose; QUICKI, Quantitative Insulin Sensitivity Check Index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IGF-I, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor-binding protein 3; Triglycerides analyzed non-parametrically, median reported. SD of median computed as (Q3-Q1)/1.075. Hodges-Lehmann estimate of the median difference between treatments with a corresponding distribution-free CI based on Wilcoxon's rank sum test. Missing data imputed by last observation carried forward.

**Table 5.** Number (%) of patients with specific clinical adverse experiences (incidence  $\geq 5.0\%$  in one or more treatment groups) by system organ class

	Placebo (N = 177)		MK-0557 (N = 182)	
	n	(%)	n	(%)
Patients with no adverse experience	26	(14.7)	37	(20.3)
Patients with one or more adverse experiences	151	(85.3)	145	(79.7)
Constipation	10	(5.6)	12	(6.6)
Diarrhea	7	(4.0)	14	(7.7)
Bronchitis	12	(6.8)	14	(7.7)
Influenza	12	(6.8)	12	(6.6)
Nasopharyngitis	32	(18.1)	24	(13.2)
Sinusitis	18	(10.2)	15	(8.2)
Upper respiratory tract infection	10	(5.6)	14	(7.7)
Urinary tract infection	11	(6.2)	7	(3.8)
Arthralgia	12	(6.8)	17	(9.3)
Back Pain	21	(11.9)	15	(8.2)
Headache	17	(9.6)	13	(7.1)
Depression	6	(3.4)	10	(5.5)
Cough	5	(2.8)	12	(6.6)
Hypertension	10	(5.6)	9	(4.9)

Although a patient may have had two or more clinical adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

safe and well tolerated in this study. Of note, the small degree of efficacy of MK-0557 in preventing weight regain observed in this study is consistent with a similar degree of efficacy observed in a long-term study of the induction of weight loss (32).

Preliminary positron emission tomography and proof of concept/dose-ranging studies (32) provide strong evidence that adequate antagonism of NPY5R was achieved with the 1-mg dose of MK-0557 used in this study. Therefore, if NPY is a physiologically relevant orexigenic neuropeptide in humans, the minimal efficacy of MK-0557 observed in this study suggests that the contribution of the NPY5R to the orexigenic effects of NPY is small.

A potential explanation is that compensatory mechanisms overrode MK-0557 antagonism of NPY5R. Those mechanisms might involve compensatory NPY signaling through NPY1R or compensation through other anabolic pathways. Energy homeostasis is well recognized to involve multiple redundant anabolic and catabolic pathways, and it has been suggested that effective pharmacotherapy of obesity might require a multidrug regimen, as is commonly used for diseases such as hypertension or diabetes.

Another potential explanation relates to the importance of NPY5R itself in human energy homeostasis. Although data

support the involvement of both NPY receptor subtypes in energy homeostasis, the relative contributions of NPY1R and NPY5R to the anabolic actions of NPY have been a topic of controversy in obesity research literature. Although targeted gene deletion is often a helpful method to gain insight into a gene's participation in a physiologic process, in the case of NPY1R or NPY5R knockout mice, those studies generated seemingly paradoxical results. NPY1R<sup>-/-</sup> mice have only slightly diminished spontaneous and NPY-stimulated feeding and develop late onset mild obesity (40,41). NPY5R<sup>-/-</sup> mice feed normally and similarly develop late onset mild obesity (42). A comparison of NPY1R<sup>-/-</sup> mice and NPY5R<sup>-/-</sup> mice generated on a similar genetic background did, however, show that NPY-induced feeding was reduced in NPY1R<sup>-/-</sup> mice but not in NPY5R<sup>-/-</sup> mice (28). In addition, two recent studies failed to show an effect of highly selective NPY5R antagonists on NPY-induced food intake, although both compounds significantly suppressed feeding induced by selective NPY5R agonists (29,30). These studies could be interpreted to suggest a greater role for NPY1R in energy homeostasis compared with NPY5R. Future clinical studies with selective NPY1R antagonists will be needed to answer that question as it relates to energy balance in humans.

Several aspects of the 6-week VLCD phase of the study are worthy of note. The average weight loss of 1.5 kg/wk is consistent with that reported in the literature (1,43,44). Similarly, patients in the placebo group regained more than 40% of their weight loss in the year after treatment. This is an expected outcome in the absence of patients' receiving weight maintenance therapy (1,2). We believe that the small degree of efficacy of MK-0557 in preventing weight regain after the VLCD is independent of the type of diet provided and that similar results would have been observed with other dietary regimens that provided greater daily caloric intake and that induced more gradual rates of weight loss. We used the VLCD to induce an average loss of only 9.1 kg, rather than a reduction of 20 kg or more, as observed in many studies. Greater weight loss is associated with more rapid weight regain, which we wished to avoid in this study (45).

In summary, this study showed that potent pharmacologic antagonism of NPY5R induced significant, but not clinically meaningful, prevention of weight regain, unlike what has been observed with dexfenfluramine and sibutramine in similar trial paradigms (5–8). While this study provides support for a role of NPY5R in human energy homeostasis, a major potential implication of this study is that the relative importance of NPY5R alone in that process is small.

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### References

1. **National Task Force on the Prevention and Treatment of Obesity, National Institutes of Health.** Very low-calorie diets. *JAMA*. 1993;270:967–74.
2. **Wadden TA, Berkowitz RI.** Very low calorie diets. In: Fairburn CG, Brownell KD, eds. *Eating Disorders and Obesity: A Comprehensive Handbook*. 2nd ed. New York: Guilford Press; 2002, pp. 534–38.
3. **Wadden TA, Stunkard AJ.** Controlled trial of very low calorie diet, behavior therapy, and their combination in the treatment of obesity. *J Consult Clin Psychol*. 1986;54:482–8.
4. **Wadden TA, Sternberg JA, Letizia KA, Stunkard AJ, Foster GD.** Treatment of obesity by very low calorie diet, behavior therapy, and their combination: a five-year perspective. *Int J Obes Relat Metab Disord*. 1989;13(Suppl 2):39S–46S.
5. **Finer N, Finer S, Naoumova RP.** Drug therapy after very-low-calorie diets. *Am J Clin Nutr*. 1992;56(Suppl 1):195S–8S.
6. **Andersen T, Astrup A, Quaade F.** Dexfenfluramine as adjuvant to a low-calorie formula diet in the treatment of obesity: a randomized clinical trial. *Int J Obes Relat Metab Disord*. 1992;16:35–40.
7. **Apfelbaum M, Vague P, Ziegler O, Hanotin C, Thomas F, Leutenegger E.** Long-term maintenance of weight loss after a very-low-calorie diet: a randomized blinded trial of the efficacy and tolerability of sibutramine. *Am J Med*. 1999;106:179–84.
8. **Mathus-Vliegen EM, Balance Study Group.** Long-term maintenance of weight loss with sibutramine in a GP setting following a specialist guided very-low-calorie diet: a double-blind, placebo-controlled, parallel group study. *Eur J Clin Nutr*. 2005;59(Suppl 1):S31–8.
9. **Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG.** Central nervous system control of food intake. *Nature*. 2000;404:661–71.
10. **Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS.** Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocr Rev*. 1999;20:68–100.
11. **Schwartz MW, Sipols AJ, Marks JL, et al.** Inhibition of hypothalamic neuropeptide Y gene expression by insulin. *Endocrinology*. 1992;130:3608–16.
12. **Stephens TW, Basinski M, Bristow PK, et al.** The role of neuropeptide Y in the antiobesity action of the obese gene product. *Nature*. 1995;377:530–2.
13. **Baskin DG, Breininger JF, Schwartz MW.** Leptin receptor mRNA identifies a subpopulation of neuropeptide Y neurons activated by fasting in rat hypothalamus. *Diabetes*. 1999;48:828–33.
14. **Batterham RL, Cowley MA, Small CJ, et al.** Gut hormone PYY(3–36) physiologically inhibits food intake. *Nature*. 2002;418:650–4.
15. **Willeesen MG, Kristensen P, Romer J.** Co-localization of growth hormone secretagogue receptor and NPY mRNA in the arcuate nucleus of the rat. *Neuroendocrinology*. 1999;70:306–16.
16. **Dickson SL, Luckman SM.** Induction of c-fos messenger ribonucleic acid in neuropeptide Y and growth hormone (GH)-releasing factor neurons in the rat arcuate nucleus following systemic injection of the GH secretagogue, GH-releasing peptide-6. *Endocrinology*. 1997;138:771–7.
17. **Kumarsit E, Johnstone LE, Leng.** Actions of neuropeptide Y and growth hormone secretagogues in the arcuate nucleus and ventromedial hypothalamic nucleus. *Eur J Neurosci*. 2003;17:937–44.
18. **Lynch RM, Tompkins LS, Brooks HL, Dunn-Meynell AA, Levin BE.** Localization of glucokinase gene expression in the rat brain. *Diabetes*. 2000;49:693–700.
19. **Lam TK, Schwartz GJ, Rossetti L.** Hypothalamic sensing of fatty acids. *Nat Neurosci*. 2005;8:579–84.
20. **Gerald C, Walker MW, Criscione L, et al.** A receptor subtype involved in neuropeptide-Y-induced food intake. *Nature*. 1996;382:168–71.
21. **Hu Y, Bloomquist BT, Cornfield LJ, et al.** Identification of a novel hypothalamic neuropeptide Y receptor associated with feeding behavior. *J Biol Chem*. 1996;271:26315–9.
22. **Sawchenko PE.** Toward a new neurobiology of energy balance, appetite, and obesity: the anatomists weigh in. *J Comp Neurol*. 1998;402:435–41.
23. **Elias CF, Saper CB, Maratos-Flier E, et al.** Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. *J Comp Neurol*. 1998;402:442–59.
24. **Cowley MA, Pronchuk N, Fan W, Dinulescu DM, Colmers WF, Cone RD.** Integration of NPY, AGRP, and melanocortin signals in the hypothalamic paraventricular nucleus: evidence of a cellular basis for the adipostat. *Neuron*. 1999;24:155–63.

25. **Kishi T, Aschkenasi CJ, Choi BJ, et al.** Neuropeptide Y Y1 receptor mRNA in rodent brain: distribution and colocalization with melanocortin-4 receptor. *J Comp Neurol.* 2005;482:217–43.
26. **Cabrele C, Langer M, Bader R, et al.** The first selective agonist for the neuropeptide YY5 receptor increases food intake in rats. *J Biol Chem.* 2000;275:36043–8.
27. **Mullins D, Kirby D, Hwa J, Guzzi M, Rivier J, Parker E.** Identification of potent and selective neuropeptide Y Y(1) receptor agonists with orexigenic activity in vivo. *Mol Pharmacol.* 2001;60:534–40.
28. **Parker EM, Balasubramaniam A, Guzzi M, et al.** [D-Trp(34)] neuropeptide Y is a potent and selective neuropeptide Y Y(5) receptor agonist with dramatic effects on food intake. *Peptides.* 2000;21:393–9.
29. **Kanatani A, Mashiko S, Murai N, et al.** Role of the Y1 receptor in the regulation of neuropeptide Y-mediated feeding: comparison of wild-type, Y1 receptor-deficient, and Y5 receptor-deficient mice. *Endocrinology.* 2000;141:1011–6.
30. **Turnbull AV, Ellershaw L, Masters DJ, et al.** Selective antagonism of the NPY Y5 receptor does not have a major effect on feeding in rats. *Diabetes.* 2002;51:2441–9.
31. **Kanatani A, Ishihara A, Iwaasa H, MacNeil DJ, Fukami T.** Development of NPY antagonists and their anorectic effects. *Folia Pharmacol Japonica.* 2006;127:88–91.
32. **Erondu N, Gantz I, Musser B, et al.** Neuropeptide Y5 receptor antagonism does not induce clinically meaningful weight loss in overweight and obese Adults. *Cell Metab.* 2006;4:275–82.
33. **James WP, Avenell A, Broom J, Whitehead J.** A one-year trial to assess the value of orlistat in the management of obesity. *Int J Obes Relat Metab Disord.* 1997;21(Suppl 3):S24–30.
34. **Kolotkin RL, Head S, Hamilton M, Tse CK.** Assessing impact of weight on quality of life. *Obes Res.* 1995;3:49–56.
35. **Ware JE Jr, Sherbourne CD.** The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992;30:473–83.
36. **The EuroQol Group.** EuroQol: a new facility for the measurement of health related quality of life. *Health Policy.* 1990;16:199.
37. **Gadbury GL, Coffey CS, Allison DB.** Modern statistical methods for handling missing repeated measurements in obesity trial data: beyond LOCF. *Obes Rev.* 2003;4:175–84.
38. **Peto R.** Clinical trial methodology. *Biomedicine.* 1978;28:24–36.
39. **Hill Jo, Hauptman J, Anderson JW, et al.** Orlistat, a lipase inhibitor, for weight maintenance after conventional dieting: a 1-y study. *Am J Clin Nutr.* 1999;69:1108–16.
40. **Pedrazzini T, Seydoux J, Kunstner P, et al.** Cardiovascular response, feeding behavior and locomotor activity in mice lacking the NPY Y1 receptor. *Nat Med.* 1998;4:722–6.
41. **Kushi A, Sasai H, Koizumi H, Takeda N, Yokoyama M, Nakamura M.** Obesity and mild hyperinsulinemia found in neuropeptide Y-Y1 receptor-deficient mice. *Proc Natl Acad Sci U S A.* 1998;95:15659–64.
42. **Marsh DJ, Hollopeter G, Kafer KE, Palmiter RD.** Role of the Y5 neuropeptide Y receptor in feeding and obesity. *Nat Med.* 1998;4:718–21.
43. **Anderson JW, Konz EC, Frederich RC, Wood CL.** Long-term weight-loss maintenance: a meta-analysis of US studies. *Am J Clin Nutr.* 2001;74:579–84.
44. **Saris WH.** Very-low-calorie diets and sustained weight loss. *Obes Res.* 2001;9(Suppl):295S–301S.
45. **Wadden TA, Foster GD, Letizia KA.** One-year behavioral treatment of obesity: Comparison of moderate and severe caloric restriction and the effects of weight maintenance therapy. *J Consult Clin Psychol.* 1994;62:165–171.