This report may include approved and non-approved uses, formulations, or treatment regimens. The results reported may not reflect the overall profile of a product. Before prescribing any product mentioned in this report, healthcare professionals should consult local prescribing information for the product approved in their country.

2. Synopsis

MERCK RESEARCH LABORATORIES MK-0364 taranabant capsules Obesity	**CLINICAL STUDY REPORT SYNOPSIS**

PROTOCOL TITLE/NO.: A Phase III Randomized, Placebo-Controlled Clinical Trial to Study the Safety and Efficacy of Taranabant (MK-0364) in Obese Patients and in Overweight Patients With Obesity-Related Co-Morbidities, Followed by a 1-Year Extension — #037-10

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (72) in the United States (40), European (26), and Rest of World (6).

PRIMARY THERAPY PERIOD: 24-Oct-2006 to 22-Jan-2008. Base study completed, extension study ongoing. — **CLINICAL PHASE:** III

DURATION OF TREATMENT: 52 weeks

OBJECTIVE(S): **Primary:** In obese patients and in overweight patients with obesity-related co-morbidities, to assess the effects of 0.5, 1, or 2 mg of taranabant on: (1) body weight after 1 year of treatment; (2) safety and tolerability during base and extension studies. **Secondary:** In obese patients and in overweight patients with obesity-related co-morbidities, to assess the effects of taranabant on: (1) waist circumference at 1 year; (2) percent body fat at 1 year; (3) biochemical markers [triglycerides, HDL-C, LDL-C subclasses, non-HDL-C, LDL-C, total cholesterol, fasting insulin, insulin sensitivity, fasting plasma glucose (FPG), adiponectin and C-reactive protein (CRP)] at 1 year; (4) blood pressure at 1 year; (5) Patient-Reported Outcomes (PRO) at 1 year.

HYPOTHESES: **Primary:** In obese patients and in overweight patients with obesity-related comorbidities, 0.5, 1, or 2 mg of taranabant: (1) decreases body weight more than placebo after 1 year of treatment; (2) is well tolerated. **Secondary:** In obese patients and in overweight patients with obesity-related comorbidities, compared to placebo, 0.5, 1, or 2 mg of taranabant: (1) decreases waist circumference after 1 year of treatment, decreases percent body fat after 1 year: (2) decreases triglycerides, increases HDL-C, decreases non-HDL-C, decreases LDL-C after 1 year; (3) decreases fasting insulin, increases insulin sensitivity, decreases FPG after 1 year.

STUDY DESIGN: Double-blind, randomized, placebo-controlled. The randomization ratio was 1:1:1:2 for placebo, taranabant 0.5 mg, 1 mg, and 2 mg, respectively. The study consisted of a one-week screening period, two-week single-blind placebo run-in period, 52-week treatment period, and 4-week post-treatment follow-up period for those patients not participating in the ensuing 1-year extension. Discontinued patients were asked to continue in the study off drug.

SUBJECT/PATIENT DISPOSITION:

	Taranabant 0.5 mg (N=207)	Taranabant 1 mg (N=208)	Taranabant 2 mg (N=417)	Placebo (N=209)	Total (N=1041)
TOTAL SCREENED:					1481
SCREENING FAILURES:					440
TOTAL RANDOMIZED:	207[†]	208	417	209	1041
Male (age range in years)	71 (31 to 79)	63 (24 to 74)	151 (21 to 74)	70 (24 to 74)	355 (21 to 79)
Female (age range in years)	136 (24 to 73)	145 (25 to 75)	266 (21 to 81)	139 (24 to 77)	686 (21 to 81)
Total Treated:	206	208	417	209	1040
Patient completed base study	141 (68.4)	138 (66.3)	277 (66.4)	137 (65.6)	693 (66.6)
Patient discontinued Rx with follow up	14 (6.8)	31 (14.9)	58 (13.9)	19 (9.1)	122 (11.7)
clinical AE	11 (5.3)	20 (9.6)	46 (11.0)	8 (3.8)	85 (8.2)
lack efficacy	1 (0.5)	0 (0.0)	3 (0.7)	6 (2.9)	10 (1.0)
patient moved	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)
protocol deviation	1 (0.5)	2 (1.0)	5 (1.2)	4 (1.9)	12 (1.2)
patient discontinued for other	1 (0.5)	9 (4.3)	3 (0.7)	1 (0.5)	14 (1.3)
Patient discontinued Rx w/o follow-up	51 (24.8)	39 (18.8)	82 (19.7)	53 (25.4)	225 (21.6)
clinical AE	8 (3.9)	10 (4.8)	16 (3.8)	9 (4.3)	43 (4.1)
lack efficacy	3 (1.5)	3 (1.4)	3 (0.7)	5 (2.4)	14 (1.3)
lost to follow-up	16 (7.8)	10 (4.8)	25 (6.0)	6 (2.9)	57 (5.5)
patient moved	1 (0.5)	0 (0.0)	5 (1.2)	2 (1.0)	8 (0.8)
patient withdrew consent	19 (9.2)	14 (6.7)	27 (6.5)	29 (13.9)	89 (8.6)
protocol deviation	2 (1.0)	1 (0.5)	3 (0.7)	1 (0.5)	7 (0.7)
patient discontinued for other	2 (1.0)	1 (0.5)	3 (0.7)	1 (0.5)	7 (0.7)

[†] [redacted]

DOSAGE/FORMULATION NOS.: One of 3 doses of taranabant (0.5 mg, 1 mg, or 2 mg) or placebo was administered orally (capsules) once daily for 52 weeks total. The formulation number used for taranabant 0.5 mg was [redacted] The formulation number used for taranabant 1 mg was [redacted] The formulation number used for taranabant 2 mg was [redacted] The formulation numbers used for the matching placebo were [redacted] and [redacted] All formulations had the same image.

DIAGNOSIS/INCLUSION CRITERIA: Obese patients with body mass index (BMI) between 30 kg/m^2 and 43 kg/m^2, inclusive (BMI between 27 kg/m^2 and 43 kg/m^2, inclusive, for overweight patients with obesity-related comorbidities), who were ≥18 years old and met other entry criteria, were eligible to participate. Sites targeted the enrollment of 40% men with a minimum of 25%.

EVALUATION CRITERIA: Efficacy Measurements: Body weight, waist circumference, percent body fat (measured by dual energy x-ray absorptiometry [DXA] scans in a subset of patients), fasting serum lipid profile (triglycerides (TG), HDL-C, non-HDL-C, LDL-C , total cholesterol, and LDL-C subclasses), fasting serum insulin levels, insulin sensitivity, fasting plasma glucose (FPG), C-reactive protein (CRP), adiponectin, blood pressure and patient reported outcomes. Safety Measurements: Safety assessments included collection of adverse experiences, physical examination, vital signs, and ECGs. Depression, mood, and cognitive/neuropsychomotor function were assessed using the Patient Health Questionnaire-9 (PHQ-9), Patient Health Questionnaire (PHQ), Profile of Mood States brief form (POMSb) and Digit Symbol Substitution Test (DSST). Laboratory safety assessment included blood chemistry, hematology, and urinalysis. An external Data Safety Monitoring Committee (DSMC) was established to review and evaluate data across all studies in the Phase IIb/III program. Unblinded data were provided to the DSMC every 3 to 6 months.

STATISTICAL PLANNING AND ANALYSIS:

Efficacy: The primary weight loss hypothesis consisted of an ordered family of comparisons: mean weight loss, the proportion of patients with at least 5% weight loss (5% responders), and the proportion of patients with at least 10% weight loss (10% responders). These hypotheses were assessed by comparing the effect of each dose of taranabant to placebo on the mean change in body weight and the proportions of patients who lost ≥5% or ≥10% of their baseline body weight. Change from baseline in body weight at Week 52 was assessed by an analysis of covariance (ANCOVA) model. The model included terms for treatment, baseline body weight, weight change during run-in, and region. Treatment effects relative to placebo were estimated using least squares (LS) mean differences from the ANCOVA model. The proportions of 5% responders and 10% responders at Week 52 were evaluated by logistic regression with terms for treatment, baseline body weight, weight change during run-in and region. The primary analysis was based on the All Patients Treated (APT) population with the last observation carried forward (LOCF) method used for handling missing data. For change in body weight, sensitivity analysis using repeated measures for handling missing data was performed. Multiplicity adjustments were made for the primary and key secondary efficacy hypotheses. For the primary hypothesis, if the comparison between taranabant 2 mg and placebo was positive, then the study would be declared positive from an efficacy perspective and the secondary efficacy endpoints would be assessed as well as the other comparisons associated with the primary hypothesis. For secondary efficacy hypotheses at a particular taranabant dose, multiplicity adjustments were made within families of endpoints using a closed testing procedure. For key secondary and other secondary efficacy endpoints (including waist circumference, percent body fat, lipid parameters, glycemic parameters, blood pressure parameters, CRP and adiponectin), change or percent change at Week 52 in an endpoint was analyzed using an analysis of covariance (ANCOVA) model with terms for treatment, baseline body weight, weight change during run-in, change in parameter during run-in (as appropriate) and region. Percent changes in triglycerides, CRP and adiponectin were analyzed using non-parametric methods, and treatment effects relative to placebo were estimated based on medians of the differences. Patient-reported outcomes in efficacy measures SF36v2 and IWQoL were analyzed using

an ANCOVA model similarly. For the EQ5D, a descriptive summary was provided. Patterns of patient discontinuation were ascertained by Kaplan-Meier curves. For change in body weight, an analysis using an ITT approach that accounted for all reported data including data obtained during an off-drug follow-up period during the study were performed.

Approximately 1000 patients were expected to be randomized with ratio 1:1:1:2 into placebo, 0.5-mg, 1-mg and 2-mg groups respectively. Assuming all randomized patients were included in the analysis, the study had 90% (80%) power to detect a difference of 2.0 kg (1.7 kg) between 2-mg and placebo and 2.3 kg (2.0 kg) between 0.5-mg or 1-mg and placebo for mean change in body weight. This calculation used a standard deviation estimate of 7.2 kg with a two sided test at the 0.050 level.

Safety: Analyses were based on the All Patients as Treated (APaT) population, which included all randomized patients who were documented as receiving at least one dose of active treatment. Safety and tolerability were assessed by clinical and/or statistical review of all safety parameters, including adverse experiences, laboratory values and vital signs. A multi-tiered approach was used for the analysis of adverse experiences. Inferential p-values were obtained from analyses of pre-specified clinical adverse experiences (Tier 1) using Fisher's exact test; 95% confidence intervals (CIs) for the differences between active treatment groups and placebo were provided for adverse experiences and predefined limits of change parameters if the incidence was ≥2% in one or more treatment groups (Tier 2). For other adverse experiences (occurrence <2% in all groups), counts and percentages were tabulated. Supportive information on mood and cognitive function was obtained by analyses of the patient reported outcomes constructed from PHQ-9, POMSb, and DSST. Summary statistics over time for change from baseline in laboratory, vital signs, and ECG parameters were provided.

RESULTS:

Efficacy: *Primary Endpoints:* The primary efficacy hypothesis was met demonstrating superiority of taranabant at 0.5-mg, 1-mg, and 2-mg doses over placebo in achieving weight loss at Week 52. Statistical significance was reached for all of the pre-specified comparisons from the ordered family of primary comparisons, results are summarized below.

Body Weight Endpoints at Week 52
All Patients Treated Population

Change in body weight from baseline at Week 52					
Treatment	N	Mean Change (SD)	LS Means[†] (95% CI)	LS Mean[†] Difference From Placebo (95% CI)	p-Value
Taranabant 0.5 mg	197	-5.4 (7.2)	-5.0 (-5.9, -4.0)	-3.5 (-4.8, -2.3)	<0.001
Taranabant 1 mg	203	-5.3 (6.4)	-5.2 (-6.2, -4.2)	-3.8 (-5.0, -2.5)	<0.001
Taranabant 2 mg	411	-6.7 (6.8)	-6.4 (-7.2, -5.7)	-5.0 (-6.1, -3.9)	<0.001
Placebo	206	-1.7 (5.9)	-1.4 (-2.4, -0.5)	-	-
[†]: Least Squares (LS) Means based on an ANCOVA with terms for treatment, region, baseline body weight, and run-in weight change.					

Number (%) of patients who lost ≥5% of baseline body weight at Week 52				
Treatment	N	Number (%) of Responders	Adjusted Odds Ratio[‡] (95% CI)	p-Value
Taranabant 0.5 mg	197	87 (44.2)	2.5 (1.6, 3.8)	<0.001
Taranabant 1 mg	203	92 (45.3)	2.7 (1.8, 4.2)	<0.001
Taranabant 2 mg	411	218 (53.0)	3.7 (2.5, 5.4)	<0.001
Placebo	206	50 (24.3)	-	-
Number (%) of patients who lost ≥10% of baseline body weight at Week 52				
Taranabant 0.5 mg	197	42 (21.3)	3.4 (1.8, 6.4)	<0.001
Taranabant 1 mg	203	37 (18.2)	3.0 (1.6, 5.7)	<0.001
Taranabant 2 mg	411	115 (28.0)	5.1 (2.9, 9.1)	<0.001
Placebo	206	15 (7.3)	-	-
[‡]: Compared to placebo and based on a logistic regression model with terms for treatment, region, baseline body weight, and run-in weight change.				

Body Weight-Related Key Secondary Endpoints: The key secondary hypothesis that assessed the effect of taranabant at 0.5-mg, 1-mg, and 2-mg doses over placebo after 52 weeks of treatment in decreasing waist circumference was met for all doses of taranabant. In addition, the key secondary hypothesis that treatment with taranabant decreases percent body fat was met for 2-mg, but not 1-mg and 0.5-mg. Details are provided below.

Body Weight-Related Key Secondary Endpoints at Week 52
All Patients Treated Population

Change from Baseline	Treatment	N	Mean Change (SD)	LS Mean (95% CI)	LS Mean Difference From Placebo (95% CI)	p-Value
Waist Circumference (cm) †	Taranabant 0.5 mg	176	-6.0 (7.5)	-5.6 (-6.6, -4.5)	-2.5 (-3.9, -1.1)	<0.001
	Taranabant 1 mg	180	-6.2 (6.4)	-5.7 (-6.7, -4.6)	-2.6 (-4.0, -1.2)	<0.001
	Taranabant 2 mg	365	-7.5 (7.4)	-6.9 (-7.7, -6.1)	-3.9 (-5.1, -2.7)	<0.001
	Placebo	176	-3.6 (7.7)	-3.0 (-4.1, -1.9)	-	-
Percent Body Fat ‡	Taranabant 0.5 mg	47	-2.9 (3.7)	-3.0 (-4.1, -2.0)	-0.6 (-2.1, 0.9)	0.426
	Taranabant 1 mg	37	-3.0 (3.6)	-2.8 (-4.0, -1.6)	-0.4 (-2.0, 1.2)	0.642
	Taranabant 2 mg	97	-4.2 (4.2)	-4.2 (-4.9, -3.5)	-1.8 (-3.1, -0.5)	0.008
	Placebo	42	-2.4 (3.1)	-2.4 (-3.5, -1.3)	-	-

†: Least Squares (LS) Means based on an ANCOVA with terms for treatment, region, baseline value, baseline body weight, and run-in weight change.
‡: Percent body fat is measured by DXA in a subset of patients from US sites that are eligible to perform such evaluation. The analysis is based on all valid data with full body views obtained at baseline and at study endpoint. Least squares (LS) means based on analysis of covariance with terms for treatment, baseline value, baseline body weight, run-in weight change. Region is not included in the model since DXAs were conducted only at selected sites in the US.

Early Responders: Weight loss efficacy and waist circumference at Week 52 were explored in a post-hoc analysis in the early responder and early non-responder subgroups defined by whether or not patients lost at least 1.5 kg of their baseline body weight at Week 4. The proportions of early responders were 43.9%, 45.5%, 61.3% and 31.0% for the 0.5-mg, 1-mg, 2-mg and placebo groups, respectively. Compared with placebo, the proportion of early responders at Week 4 was significantly higher in patients treated with taranabant (Fishers exact test $p<0.010$ for 0.5-mg, 1-mg or 2-mg). The LS means for change (kg) in body weight at Week 52 in the early responders were -8.2, -8.0, -8.7 and -4.6 for the 0.5-mg, 1-mg, 2-mg and placebo groups, respectively. The LS means for change (kg) in body weight at Week 52 in the early non-responders were -2.2, -2.6, -2.8 and 0.2 for the 0.5-mg, 1-mg, 2-mg and placebo groups, respectively. The LS means for change (cm) in waist circumference at Week 52 in the early responders were -7.5, -7.5, -8.4 and -5.6 for the 0.5-mg, 1-mg, 2-mg and placebo groups; and the LS means for change (cm) in waist circumference at Week 52 in the early non-responders were -4.2, -4.0, -4.4 and -1.7 for the 0.5-mg, 1-mg, 2-mg and placebo groups, respectively.

Lipid-Related Key Secondary Endpoints: Statistically significant decreases in TG at Week 52 were seen for taranabant 1-mg and 2-mg ($p\leq0.038$) but not 0.5-mg when compared with placebo. Increases in HDL-C at Week 52 were seen in all treatment groups but the differences were not statistically significant compared with placebo. Treatment effects on non-HDL-C and LDL-C at Week 52 were not formally tested due to multiplicity control. Nominally significant p-values showed that, compared with placebo: (1) the 0.5-mg, 1-mg and 2-mg groups had smaller increases in non-HDL-C at Week 52 (nominal $p\leq0.015$) (2) the 0.5-mg group had smaller increases in LDL-C at Week 52 (nominal $p=0.045$).

Glycemia-Related Key Secondary Endpoints: Treatment effects on fasting plasma insulin, insulin sensitivity, or fasting plasma glucose at Week 52 were not statistically significant for 0.5-mg, 1-mg or 2-mg compared with placebo.

Other Secondary Endpoints: Consistent with findings from the primary comparison of change in body weight, effects on weight loss as measured by percent change in body weight at Week 52 were statistically significant in favor of 0.5-mg, 1-mg and 2-mg groups (nominal $p<0.001$) when compared with placebo. Effects on diastolic or systolic blood pressure at Week 52 were not statistically significant for 0.5-mg, 1-mg or 2-mg groups compared with placebo. At Week 52, compared with placebo, the 0.5-mg, 1-mg and 2-mg groups had greater improvement in CRP (nominal $p\leq0.001$) and that the 1-mg and 2-mg groups had greater improvement in serum adiponectin (nominal $p=0.003$, 1-mg and 2-mg). Compared with placebo, the 0.5-mg, 1-mg and 2-mg groups had smaller increases in TC (nominal $p\leq0.048$) at Week 52.

Safety: The table below summarizes the clinical adverse experiences for the 0.5-mg, 1-mg, and 2-mg and placebo groups over 52 weeks.

Clinical Adverse Experience Summary
(Treatment Phase Over 52 Weeks) All Patients as Treated Population

	Taranabant 0.5 mg (N = 206)		Taranabant 1 mg (N = 208)		Taranabant 2 mg (N = 417)		Placebo (N = 209)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With one or more adverse experiences	167	(81.1)	164	(78.8)	352	(84.4)	169	(80.9)
With no adverse experience	39	(18.9)	44	(21.2)	65	(15.6)	40	(19.1)
With drug-related adverse experiences†	53	(25.7)	78	(37.5)	160	(38.4)	47	(22.5)
With serious adverse experiences	18	(8.7)	17	(8.2)	25	(6.0)	16	(7.7)
With serious drug-related adverse experiences	2	(1.0)	1	(0.5)	2	(0.5)	2	(1.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	19	(9.2)	30	(14.4)	62	(14.9)	17	(8.1)
Discontinued due to drug-related adverse experiences	13	(6.3)	25	(12.0)	50	(12.0)	10	(4.8)
Discontinued due to serious adverse experiences	2	(1.0)	2	(1.0)	3	(0.7)	3	(1.4)
Discontinued due to serious drug-related adverse experiences	1	(0.5)	1	(0.5)	2	(0.5)	1	(0.5)

† Determined by the investigator to be possibly, probably or definitely drug related.

Tier I adverse experiences were prespecified based on adverse experiences that were identified in previous taranabant studies and/or deemed potentially related to the CB1R mechanism. Tier I adverse experiences followed the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. The Tier 1 adverse experiences were analyzed at the level of preferred terms and system organ classes (SOCs). Tier 1 SOCs included: the Gastrointestinal (GI) Disorders, expanded Nervous System Disorders (Nervous System Disorders SOC plus hypoesthesia facial, amaurosis fugax, vision blurred, scotoma, blindness, altered visual depth perception, photopsia, and diplopia), Psychiatric Disorders plus irritability, Skin and Subcutaneous Disorders minus hypoesthesia facial, and Vascular Disorders SOCs.

The incidences of adverse experiences within the GI Disorders SOC were significantly higher in the 2-mg group compared with the placebo group (p=0.023). The incidences of nausea and diarrhea were significantly higher in the 2-mg group compared with the placebo group (p=0.017). GI-related adverse experiences were predominantly mild to moderate in intensity, resolved, and led to few discontinuations.

The incidences of adverse experiences within the expanded Nervous System Disorders SOC in the taranabant groups were generally comparable with the placebo group. The incidence of adverse experiences in the dizziness/dizziness postural was significantly higher in the 2-mg group compared with the placebo group (p=0.006). Expanded Nervous System Disorder adverse experiences were predominantly mild to moderate in intensity, resolved, and led to few discontinuations.

The incidences of adverse experiences within the Psychiatric Disorders SOC plus irritability were significantly higher in the taranabant 1-mg and 2-mg groups compared with the placebo group (p=0.008 and p=0.002 for the 1-mg and 2-mg groups versus placebo, respectively). The incidence of adverse experiences within the Psychiatric Disorders SOC plus irritability in the 0.5-mg group was not statistically different from the placebo group. The incidences of adverse experiences of irritability for all dose groups were significantly higher ($p \leq 0.035$) than placebo. The incidence of aggression, anger in the 2-mg group was higher than placebo (p=0.036). Adverse experiences within the Psychiatric Disorders SOC plus irritability were generally mild to moderate in intensity and single episodes. Discontinuations due adverse experiences in the Psychiatric SOC plus irritability were similar between the taranabant groups and the placebo group. Adverse experiences in the Psychiatric Disorders SOC plus irritability resolved in the majority of patients

There was one adverse experience of suicidal ideation in each of the taranabant dose groups (0.5 mg, 1 mg, and 2 mg) and none in the placebo group. These single episodes were mild or moderate in intensity and lasted 1 minute for the patient in the 1-mg group, and 19.0 and 82.0 days for the patients in the 0.5-mg and 2-mg group, respectively. The patient with suicidal ideation in the 0.5-mg group discontinued due to the adverse experience.

In patients with a history of psychiatric disorders, there was a numerically higher incidence of adverse experiences in taranabant and placebo groups compared with patients with no psychiatric history in the same treatment group.

The PHQ-9 was incorporated into the protocol as a screening and monitoring tool to assess depression-related mood changes and suicidal ideation. Mean baseline PHQ-9 scores were similar across the treatment groups. All treatment groups (including placebo) had small increases in PHQ-9 scores. The changes from baseline in PHQ-9 scores in taranabant groups were similar to placebo. Question 9 of the PHQ-9 assessed possible suicidal ideation by asking if the patient had "Thoughts that you would be better off dead or of hurting yourself in some way?". The percentages of patients with a positive score for question 9 of the PHQ-9 were low and similar across the treatment groups.

The incidences of adverse experiences within the Skin and Subcutaneous Disorders SOC minus hypoaesthesia facial in the taranabant dose groups were comparable with the placebo group.

The incidences of adverse experiences within the Vascular Disorders SOC in the in the 3 taranabant dose groups were comparable with the placebo group. The incidence of flushing, hot flush was significantly higher in the taranabant 2-mg group compared with the placebo group.

No clinically significant changes were observed in any of the laboratory safety parameters measured. There were few laboratory adverse experiences. The number (proportion) of patients with a laboratory adverse experience was higher in the taranabant 0.5-mg group (4.7%) compared with the placebo group (1.0%).

Laboratory Adverse Experience Summary
(Treatment Phase Over 52 Weeks) All Patients as Treated Population

	Taranabant 0.5 mg (N = 206)		Taranabant 1 mg (N = 208)		Taranabant 2 mg (N = 417)		Placebo (N = 209)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With at least one lab test postbaseline	191		196		393		196	
With one or more adverse experiences	9	(4.7)	3	(1.5)	8	(2.0)	2	(1.0)
With no adverse experience	182	(95.3)	193	(98.5)	385	(98.0)	194	(99.0)
With drug-related adverse experiences[†]	4	(2.1)	2	(1.0)	0	(0.0)	0	(0.0)
With serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[†] Determined by the investigator to be possibly, probably or definitely drug related.

[‡] The percent = number of patients within the laboratory adverse experience category / number of patients with one or more laboratory tests postbaseline.

CONCLUSIONS:

In overweight and obese patients:

1. Treatment with taranabant at 0.5 mg, 1 mg, and 2 mg for 52 weeks results in a statistically significant and clinically meaningful dose-dependent reduction in body weight and waist circumference compared with placebo. Weight loss after 4 weeks of treatment is a good predictor of Week 52 weight loss response.
2. Treatment with taranabant 2 mg results in a statistically significant reduction in total body adipose tissue compared with placebo at 52 weeks.
3. Treatment with taranabant 1 mg and 2 mg results in a statistically significant improvement in triglycerides compared with placebo at 52 weeks.
4. Treatment with taranabant 1 mg and 2 mg is associated with a higher incidence of psychiatric-related adverse experiences. Treatment with taranabant (all doses) is associated with a higher incidence of irritability. Psychiatric-related adverse experiences are mild to moderate in intensity, resolve, and do not lead to discontinuation in the majority of patients. The incidences of psychiatric-related adverse experiences are similar in early responders and early non-responders, and both groups have adverse experience profiles that are similar to the overall study population.
5. Treatment with taranabant 2 mg is associated with a higher incidence of gastrointestinal disorders SOC, dizziness grouping, and flushing/hot flush adverse experiences that are primarily mild to moderate in intensity and single episodes. These adverse experiences resolve and do not lead to discontinuation in the majority of patients.
6. Treatment with taranabant is not associated with significant laboratory safety test abnormalities compared with placebo.

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