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 2-Year Study (1-Year Weight Loss Followed by 1-Year Prevention of Weight Regain) to Assess the Safety, Tolerability and Efficacy of MK-0364 in Obese Patients	#014
INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (84) in the United States and Canada (33), Europe (36) and Rest of the World (15)	
PRIMARY THERAPY PERIOD: 17-Aug-2005 to 12-Feb-2008. Study extension is ongoing.	**CLINICAL PHASE:** III

DURATION OF TREATMENT: 104 weeks

OBJECTIVE(S): Primary: In obese patients: (1) to assess the safety and tolerability of taranabant during base and extension studies; (2) to assess the effects of 52 weeks of treatment with taranabant 4 mg, relative to placebo, on body weight; (3) after treatment with taranabant 6 mg, to assess the effect of 1 year of treatment with taranabant 2 mg on prevention of weight regain, relative to placebo. Secondary: In obese patients: (1) to assess the effect of 52 weeks of treatment with taranabant 4 mg, relative to placebo, on: (a) waist circumference; (b) metabolic syndrome; (c) biochemical markers (triglycerides, HDL-C, non-HDL-C, LDL-C, total cholesterol, fasting insulin, fasting plasma glucose, and insulin sensitivity); (d) blood pressure; (e) patient-reported outcomes (quality-of-life and health economic assessments); (2) after treatment with taranabant 6 mg, to assess the effect of 52 weeks of treatment with taranabant 2 mg, relative to placebo, on: (a) waist circumference; (b) metabolic syndrome; (c) biochemical markers (triglycerides, HDL-C, non-HDL-C, LDL-C, total cholesterol, fasting insulin, fasting plasma glucose, and insulin sensitivity); (d) blood pressure; (e) patient-reported outcomes (quality-of-life and health economic assessments); (3) in patients who experienced weight loss on taranabant 6 mg, to assess the effects of taranabant 2 mg after 52 weeks on: (a) proportion who maintain ≥75% of the weight loss induced by taranabant 6 mg; (b) proportion who maintain the loss of ≥5% of their initial body weight.

HYPOTHESES: Primary: (1) Taranabant 4 mg decreases body weight more than placebo over 52 weeks of treatment; (2) After treatment with taranabant 6 mg, taranabant 2 mg prevents weight regain (or decreases body weight) more than placebo over 52 weeks of treatment after switching to taranabant 2 mg; (3) Taranabant is well tolerated. Secondary: *After 52 weeks of treatment, taranabant 4 mg, compared to placebo:* (1) Decreases waist circumference; decreases the proportion of patients with metabolic syndrome; (2) Decreases triglycerides, increases HDL-C, decreases non-HDL-C, decreases LDL-C; (3) Decreases fasting insulin, increases insulin sensitivity, decreases FPG. *In patients who lose weight when administered taranabant 6 mg, after 52 weeks of treatment with taranabant 2 mg, as compared to placebo:* (4) Increases the proportion of patients who maintain ≥75% of the weight loss induced by taranabant 6 mg; increases the proportion of patients who maintain the loss of ≥5% of their initial body weight.

STUDY DESIGN: Double-blind, randomized, placebo-controlled. The randomization ratio for Protocol 014-00 was 1:1:1:1:1:1 for placebo/placebo, taranabant 4 mg/taranabant 4 mg, taranabant 6 mg/placebo, taranabant 6 mg/taranabant 2 mg, taranabant 6 mg/taranabant 4 mg, or taranabant 6 mg/taranabant 6 mg, respectively, with the change in dose occurring at 52 weeks (Visit 16) of treatment. The base study consisted of a one-week screening, two-week single-blind placebo run-in period, 104-week treatment period, and a 28-day post-treatment follow-up. Diet (25% hypocaloric) and exercise counseling were initiated at the start of the placebo run-in period and continued throughout the study. Following a scheduled review of unblinded data from the Phase IIb/III studies that included taranabant 2 mg, 4 mg, and 6 mg, the Data Safety Monitoring Committee (DSMC) observed that there was no significant benefit/risk advantage of continuing the 6-mg dose in the program. Patients on the 6-mg dose were switched to placebo or 2 mg at the first dose change visit (first scheduled visit that occurred at or after Visit 10 [Week 28] following IRB/ERC approval of Amendment 014-05. Patients on the 4-mg and placebo doses also underwent a mock dose switch to maintain blinding at the first dose change visit. Because of the varying duration of exposure to the 6-mg dose, this group was not included in the efficacy analyses. Efficacy data from this group after the dose switch were analyzed for weight maintenance. Safety data for the 6-mg group for the period prior to the dose switch were examined in the *Pre-switch population,* for the period after the dose switch in the *Post-switch population*, and for the entire period of the study in the *Overall population*. Safety data for 4-mg and placebo groups prior to the first dose change visit were examined in the *Pre-switch population*, and over the entire period of the study in the *Overall population*. Amendment/Extension 014-10 included a 1-year extension to the base study and a revision to the study design to discontinue the 4-mg dose. All patients on 4 mg were switched to 2 mg in a blinded fashion at the second dose change visit (first scheduled visit that occurred at or after Visit 20 [Week 68] following IRB/ERC approval of Amendment/Extension 014-10 and availability of drug supply via IVRS). The majority of patients in the 4-mg group completed the base study (104 weeks) on 4 mg (except for 39 patients who switched to the 2-mg dose). Of note, extension data will be reported in a separate CSR. Discontinued patients were allowed to continue in the study off-drug.

SUBJECT/PATIENT DISPOSITION:

	Taranabant 4 mg/2 mg (N=434)	Taranabant 6 g / 2 mg (N=1297)	Taranabant 6 mg / Placebo (N=432)	Placebo (N=431)	Total (N=2594)
SCREENED					4450
SCREENING FAILURES					1856
RANDOMIZED	434	1297	432	431	2594
Male (age range)	180 (19-76)	558 (18-87)	207 (19-76)	200 (18-81)	1145 (18-87)
Female (age range)	254 (20-84)	739 (18-79)	225 (21-79)	231 (19-86)	1449 (18-86)
PRE-TREATMENT†	n =1	n =0	n =0	n =0	n =1
Patient discontinued without follow-up	1	0	0	0	1
lost to follow-up	1	0	0	0	1
TREATMENT	n =433	n =1297	n =432	n =431	n =2593
Patient completed base study	219 (50.5)	646 (49.8)	226 (52.3)	225 (52.2)	1316 (50.7)
Patient discontinued Rx and has follow up	51 (11.8)	126 (9.7)	35 (8.1)	26 (6.0)	238 (9.2)
clinical adverse experience	34 (7.8)	83 (6.4)	22 (5.1)	13 (3.0)	152 (5.9)
lack efficacy	2 (0.5)	6 (0.5)	2 (0.5)	3 (0.7)	13 (0.5)
lost to follow-up	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
patient moved	3 (0.7)	1 (0.1)	0 (0.0)	1 (0.2)	5 (0.2)
patient withdrew consent	1 (0.2)	5 (0.4)	3 (0.7)	3 (0.7)	12 (0.5)
protocol deviation	4 (0.9)	12 (0.9)	3 (0.7)	2 (0.5)	21 (0.8)
laboratory adverse experience	0 (0.0)	3 (0.2)	1 (0.2)	0 (0.0)	4 (0.2)
patient discontinued for other	7 (1.6)	15 (1.2)	4 (0.9)	4 (0.9)	30 (1.2)
Patient discontinued Rx without follow-up	163 (37.6)	525 (40.5)	171 (39.6)	180 (41.8)	1039 (40.1)
clinical adverse experience	66 (15.2)	242 (18.7)	79 (18.3)	33 (7.7)	420 (16.2)
lack efficacy	4 (0.9)	4 (0.3)	2 (0.5)	9 (2.1)	19 (0.7)
lost to follow-up	25 (5.8)	65 (5.0)	24 (5.6)	28 (6.5)	142 (5.5)
patient moved	6 (1.4)	17 (1.3)	2 (0.5)	4 (0.9)	29 (1.1)
patient withdrew consent	53 (12.2)	174 (13.4)	56 (13.0)	100 (23.2)	383 (14.8)
protocol deviation	7 (1.6)	13 (1.0)	3 (0.7)	0 (0.0)	23 (0.9)
laboratory adverse experience	0 (0.0)	3 (0.2)	0 (0.0)	2 (0.5)	5 (0.2)
patient discontinued for other	2 (0.5)	5 (0.4)	4 (0.9)	4 (0.9)	15 (0.6)

† [redacted]
This table is based on the first status from patient status data. [redacted]

DOSAGE/FORMULATION NOS.: Patients were to take one capsule daily (timing of dose was not specified by protocol) for 104 weeks. The formulation numbers used for taranabant 2 mg were [redacted] The formulation numbers used for taranabant 4 mg were [redacted] The formulation numbers used for taranabant 6 mg were [redacted] The formulation numbers used for the matching placebo were [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 those with obesity-related comorbidities), and ≥18 years old who met other entry criteria were eligible to participate. Sites targeted enrollment of 40% male patients and a minimum of 50% of patients with metabolic syndrome.

EVALUATION CRITERIA: **EFFICACY MEASUREMENTS:** Body weight, waist circumference, blood pressure, fasting serum lipid profile (triglycerides, HDL-C, non-HDL-C, LDL-C, total cholesterol), fasting serum insulin levels, insulin sensitivity, fasting plasma glucose (FPG), and questionnaires to assess patient-reported outcomes (quality-of-life and health economic assessments); plasma and serum samples were archived for possible subsequent assay of additional metabolic biomarkers. **SAFETY MEASUREMENTS:** Clinical evaluation included assessment of adverse experiences, laboratory values (hematology, chemistry, and urinalysis), ECG, and vital signs. Depression, suicidal ideation or behavior, mood, and cognitive/neuropsychomotor function were assessed using standard instruments. 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 are being provided to the DSMC every 3 to 6 months.

STATISTICAL PLANNING AND ANALYSIS: **EFFICACY:** The change in body weight was assessed as the mean change in body weight from baseline (Week 0) to Week 52, as well as the proportion of patients who lost at least 5% or 10% of their baseline (Week 0) body weight at Week 52. For the 4-mg treatment group, change in body weight from baseline to Week 52 was the primary endpoint. For patients treated initially with 6 mg, followed by 2 mg or placebo, change in body weight 52 weeks after the dose switch was another primary endpoint. The primary efficacy hypothesis that taranabant 4 mg would decrease body weight more than placebo was assessed using an analysis of covariance (ANCOVA) model on the change in body weight from baseline (Week 0) to Week 52. The ANCOVA model included terms for treatment, region, baseline body weight, and weight change during run-in. The proportions of patients who lost ≥5% (5% responders) or ≥10% (10% responders) of their baseline (Week 0) body weight at Week 52 were assessed using a logistic regression model with terms for treatment, region, baseline (Week 0) body weight, and weight change during run-in. The hypothesis that taranabant 2 mg would prevent weight regain was assessed with a similar ANCOVA model, on the change in body weight 52 weeks after the time of dose switch except that the covariates for weight change during run-in and baseline (Week 0) body weight were replaced by weight change induced by 6 mg up to the time of switch in dose and body weight at the time of switch respectively. Only patients who lost weight with taranabant 6 mg were included to assess this weight regain hypothesis. Using the appropriate metric of change or percent change, similar ANCOVA (or a nonparametric equivalent when appropriate) models (described above) were used to compare the treatment groups for secondary efficacy endpoints (e.g., waist circumference, lipid and glucose variables). The proportion of patients who had metabolic syndrome at Week 52 was assessed by comparing taranabant 4 mg with placebo using a logistic model with terms for treatment, region, baseline (Week 0) body weight, weight change during run-in, and baseline (Week 0) value. The proportion of patients who had metabolic syndrome 52 weeks after the dose switch from 6 mg to either 2 mg or placebo was analyzed in the same way as above with the model terms for treatment, region, body weight at time of switch, weight change induced by 6 mg, and metabolic syndrome value at time of switch. The proportions of patients maintaining at least 75% of the weight loss induced by 6 mg after 52 weeks of treatment with 2 mg or placebo were also summarized. For the comparison of 2 mg to placebo in the proportion of patients maintaining the loss of 5% of their initial (Week 0) body weight, a logistic model was used in the analysis.

Note that this analysis included only those patients who lost at least 5% of their baseline (Week 0) body weight while on 6 mg.

All Patients Treated (APT) population was the primary analysis population. Per-Protocol (PP) completer population was also used as a secondary analysis population for the analyses of the primary and some other key efficacy variables.

This study allowed for following patients who have formally discontinued the test drug. Data collected after patients discontinued from treatment were not included in the primary analysis; an analysis that included any available data collected after a patient discontinued test drug was also performed. The primary approach to handling missing data was the last observation carried forward (LOCF) method for the comparisons of: (1) taranabant 4 mg versus placebo in Year 1, and (2) taranabant 2 mg versus placebo 52 weeks after the dose switch from 6 mg to either 2 mg or placebo. A longitudinal repeated measures approach was used as a sensitivity analysis to estimate the treatment effects on primary endpoints.

Multiplicity adjustments were made for the primary and secondary efficacy hypotheses. The primary hypothesis was considered satisfied (and the study declared positive) if the comparison between taranabant 4 mg and placebo at Week 52 was significant. The hypothesis of the ability of taranabant 2 mg to prevent the regain of weight loss induced by 6 mg was assessed after the comparison of taranabant 4 mg versus placebo at Week 52. For secondary efficacy hypotheses, multiplicity adjustments were made using a closed ordered testing procedure within each family of secondary endpoints.

With 400 patients randomized to each treatment group of taranabant 4 mg and placebo, this study had 90% (80%) power to detect a difference of 1.7 (1.4) kg in the change in body weight from baseline (Week 0) to Week 52. For the assessment of weight maintenance (i.e., taranabant 2 mg versus placebo), assuming 240 patients on placebo and 720 patients on 2 mg, this study had 90% (80%) power for detecting a difference of 2.5 (2.2) kg in the change in body weight 52 weeks after the dose switch.

SAFETY: As a consequence of the discontinuation of the 6-mg and 4-mg doses while the study was ongoing, the safety of taranabant has been examined in the following populations: The *Pre-switch population* describes the safety experiences for patients randomized to taranabant 4 mg or placebo until they underwent the first dose change visit, and for patients randomized to taranabant 6 mg until their dose was switched to taranabant 2 mg or placebo. The *Post-switch population* describes the safety experiences for patients originally randomized to taranabant 6 mg, during the 52 weeks after their dose was switched to taranabant 2 mg or placebo. The *Overall population* describes the safety experiences for patients over 104 weeks. Four treatment groups are described in this population: taranabant 4 mg/2 mg; taranabant 6 mg/2 mg; taranabant 6 mg/placebo; and placebo.

The safety and tolerability were assessed by clinical and/or statistical review of all safety parameters, including adverse experiences, laboratory values and vital signs; data were analyzed for the *Pre-switch* and *Post-switch populations* and tabulated for the *Overall population*. The analysis of adverse experiences followed a multi-tiered approach. For pre-specified adverse experiences (Tier 1), inferential tests using Fisher's exact test and 95% CIs (based upon Wilson's score method) between placebo and each of the doses of taranabant were provided. When proportions of patients with specific Tier 1 adverse experiences in each of the active treatment groups compared with the placebo group were tested using Fisher's exact test and found to have a p-value that was ≤ 0.05, then the incidence is referred to as being either "*significantly higher*" or "*significantly lower*." Ninety-five percent confidence intervals were computed for adverse experiences with an incidence $\geq 2\%$ and are provided to help identify between-group differences that may be clinically meaningful. Given the many different clinical and laboratory adverse experience terms assessed, chance alone would likely lead to the identification of specific adverse experiences in which the confidence interval around the between-group difference excludes "0". The following terminology will be used to describe clinically relevant adverse experiences that occur more or less often in taranabant groups compared with placebo. If the 95% CI for the difference excludes "0" the adverse experience will be

described as having a *higher or lower* incidence compared to placebo. Where incidences are numerically different and the 95% CI includes "0" or when groups are not formally compared but differences between groups might be clinically meaningful, e.g. differences between the incidences of adverse experiences in the 4-mg and 6-mg groups, the adverse experience will be described as having a *numerically higher* or *numerically lower* incidence compared with placebo.

Supportive information on mood and cognitive function was obtained by analyses of the following patient-reported outcomes: Patient Health Questionnaire-9 (PHQ-9), Profile of Mood States brief form (POMSb), and Digit Symbol Substitution Test (DSST). Summary statistics over time for change from baseline (Week 0 or time of switch to 2 mg or placebo) for laboratory values, vital signs, and ECG parameters are provided.

RESULTS: EFFICACY: Results related to primary efficacy endpoints based on the All Patients Treated (APT) population are provided below. Treatment comparisons of taranabant 4 mg to placebo from baseline (Week 0) at Week 52 for all primary efficacy endpoints (change from baseline in body weight, and 5% and 10% responders at Week 52) were statistically significant and satisfied the multiplicity control.

Summary of Body Weight Results at Week 52
(All Patients Treated Population, Last Observation Carried Forward)

Change in body weight (kg) from baseline (Week 0) at Week 52				
Treatment	**N**	**Mean Change (SD)**	**LS Mean† Difference From Placebo (95% CI)**	**p-Value**
Taranabant 4 mg	422	-8.2 (6.8)	-5.8 (-6.6, -5.0)	<0.001
Placebo	423	-2.4 (5.6)	-	-
†: Least Squares Means based on an ANCOVA with terms for treatment, region, baseline (Week 0) body weight, run-in weight change.				

Number (%) of patients who lost ≥ 5% of baseline (Week 0) body weight at Week 52				
Treatment	**N**	**Count (%) of Responders**	**Adjusted Odds Ratio‡ (95% CI)**	**p-Value**
Taranabant 4 mg	422	280 (66.4)	6.5 (4.8, 8.9)	<0.001
Placebo	423	107 (25.3)	-	-
Number (%) of patients who lost ≥ 10% of baseline (Week 0) body weight at Week 52				
Taranabant 4 mg	422	156 (37.0)	6.2 (4.2, 9.2)	<0.001
Placebo	423	40 (9.5)	-	-
‡: Compared to placebo and based on a logistic regression model with terms for treatment, region, baseline (Week 0) body weight, run-in weight change.				

Patients who lost weight with taranabant 6 mg and were switched from taranabant 6 mg to either 2 mg or placebo showed significantly less weight regain in the taranabant 2 mg group compared with placebo.

Analysis of Change in Body Weight (kg) From the Time of Switch to 52 Weeks After Dose Switch to Taranabant 2 mg or Placebo
(All Patients as Treated Population, Patients Who Lost Weight With 6 mg, Using Last Observation Carried Forward)

Treatment	N	Mean Change (SD)	LS Mean† Difference From Placebo (95% CI)	p-Value
Taranabant 2 mg	820	2.8 (4.6)	-3.5 (-4.2, -2.9)	<0.001
Placebo	265	6.2 (5.3)	-	-

†: Least Squares Means based on analysis of covariance with terms for treatment, body weight at time of switch, region, weight change induced by 6 mg.
Note: Missing values imputed using the last post-baseline measurement after switch in dose to 2 mg or placebo

The results of the key secondary endpoints included in the secondary hypotheses are described below. Significant improvements in waist circumference, metabolic syndrome, triglycerides, HDL-C, non-HDL-C, fasting serum insulin (FSI), QUICKI, and FPG at Week 52 were observed in taranabant 4 mg compared with placebo. Significant treatment effect was not observed between taranabant 4 mg and placebo for LDL-C at Week 52

Summary of Key Secondary Endpoints for the Comparison of Taranabant 4 mg vs. Placebo
(All Patients Treated Population, Last Observation Carried Forward)

Variables at Week 52	Treatment	N	Mean Change (SD)	LS Mean Difference† From Placebo (95% CI)	p-Value
Change in Waist Circumference (cm) †	Taranabant 4 mg	399	-8.0 (7.4)	-3.9 (-4.7, -3.0)	<0.001
	Placebo	385	-4.0 (6.0)		
Percent Change in TG‡	Taranabant 4 mg	410	-1.0 (42.1)	-14.7 (-19.7 , -9.9)	<0.001
	Placebo	397	13.0 (45.6)		
Percent Change in HDL-C	Taranabant 4 mg	410	14.4 (21.4)	5.4 (2.9, 7.8)	<0.001
	Placebo	397	9.1 (18.5)		
Percent Change in non-HDL-C	Taranabant 4 mg	410	-0.4 (19.7)	-3.8 (-6.2, -1.3)	0.003
	Placebo	397	4.5 (19.7)		
Percent change in LDL-C	Taranabant 4 mg	410	0.9 (24.7)	-0.2 (-3.2, 2.9)	0.903
	Placebo	397	1.8 (23.5)		
Change in FSI (µIU/mL)	Taranabant 4 mg	400	-1.4 (9.4)	-2.7 (-4.4, -1.0)	0.002
	Placebo	390	1.5 (14.7)		
Change in QUICKI	Taranabant 4 mg	399	0.008 (0.025)	0.007 (0.003, 0.010)	<0.001
	Placebo	383	0.001 (0.025)		
Change in FPG (mg/dL)	Taranabant 4 mg	411	-0.6 (10.2)	-1.5 (-2.8, -0.3)	0.013
	Placebo	397	1.5 (9.7)		

†: Least Squares (LS) Mean differences based on an ANCOVA with terms for treatment, region, baseline (Week 0) value, baseline (Week 0) body weight, change in parameter during run-in (except waist, FSI, QUICKI) and run-in weight change.
‡: For TG, median change and median difference are presented.

Number (%) of Patients with Metabolic Syndrome at Week 52				
Treatment	**N**	**Count (%) of Metabolic Syndrome Patients**	**Adjusted Odds Ratio‡ (95% CI)**	**p-Value**
Taranabant 4 mg	401	146 (36.4)	0.6 (0.4, 0.8)	<0.001
Placebo	387	174 (45.0)	-	-
‡: Compared to placebo and based on a logistic regression model with terms for treatment, region, baseline (Week 0) body weight, run-in weight change, baseline (Week 0) metabolic syndrome value..				

A small proportion of patients maintained at least 75% of the weight loss (induced by 6 mg) 52 weeks after the dose switch to taranabant 2 mg and no patient maintained at least 75% of the weight loss (induced by 6 mg) 52 weeks after the dose switch to placebo. Inferential testing could not be performed here. Among 5% responders with taranabant 6 mg, a numerically greater proportion of patients maintained the loss of at least 5% of their initial (Week 0) body weight 52 weeks after switching to taranabant 2 mg compared with patients switching to placebo. Due to multiplicity adjustment, no formal testing was performed for the patients who maintained at least 5% loss of their initial (Week 0) body weight after 52 weeks of treatment with taranabant 2 mg compared with placebo among patients who were 5% responders with the taranabant 6 mg.

Number (%) of Patients Who Maintained ≥75% of the Weight Loss Induced by 6 mg After 52 Weeks of Treatment with 2 mg or Placebo (All Patients Treated Population, Patients Who Lost Weight with 6 mg, Using Last Observation Carried Forward)

Treatment	N	Count (%) of Responders
Taranabant 2 mg	820	14 (1.7)
Placebo	265	0 (0.0)
Note: Missing values imputed using the last post-baseline measurement after switch in dose to 2 mg or placebo.		

Number (%) of Patients Who Maintained ≥5% Loss of the Initial (Week 0) Body Weight After 52 Weeks of Treatment with 2 mg or Placebo (All Patients Treated Population, Patients Who Lost ≥ 5% of the Initial (Week 0) Body Weight with 6 mg, Using Last Observation Carried Forward))

Treatment	N	Count (%) of Responders
Taranabant 2 mg	722	527 (73.0)
Placebo	228	128 (56.1)
Note: Missing values imputed using the last post-baseline measurement after switch in dose to 2 mg or placebo.		

SAFETY: Safety experiences (summaries of clinical, laboratory, and Tier 1 adverse experiences) are presented for the following previously-described populations: *Pre-switch*, *Post-switch*, and *Overall*. In general, interpretation of adverse experiences did not change when investigator-assigned causality was considered. Summaries of the clinical and laboratory adverse experiences for the *Pre-switch population* are presented below.

For the *Pre-switch population*, serious adverse experiences labeled as drug-related by investigators were reported for 2 (0.5%), 13 (0.8%), and 1 (0.2%) patient(s) in the 4-mg, 6-mg, and placebo groups, respectively. For patients in the 4-mg group, the adverse experiences of asthenia (1 patient) and

depression (1 patient) were reported as serious and drug-related. For patients in the 6-mg group, the adverse experiences of myocardial infarction (1 patient), ventricular extrasystoles (1 patient), diarrhea and vomiting (2 patients), irritability (1 patient), convulsion (1 patient), dizziness (1 patient), headache (1 patient), hypoesthesia (1 patient), vasovagal syncope (1 patient), anxiety (1 patient), depressed mood (1 patient) depression (1 patient), and cutis laxa (1 patient) were reported as serious and drug-related. For patients in the placebo group, adverse experiences of urticaria and angioedema (1 patient) were reported as serious and drug-related.

Prespecified (Tier 1) adverse experiences included adverse experiences within the following system organ classes (SOCs) GI Disorders, expanded Nervous System Disorders, Psychiatric Disorders plus Irritability, Skin and Subcutaneous Tissue Disorders, and Vascular Disorders.

In the *Pre-switch population*, treatment with taranabant was associated with a significant increase in GI-related adverse experiences, specifically, nausea, diarrhea, and vomiting. There did not appear to be a dose-related increase in the incidence of GI-related adverse experiences between the 4-mg and 6-mg groups. The majority of these adverse experiences were mild or moderate in intensity, and relatively few patients discontinued from the study due to GI-related adverse experiences.

In the *Pre-switch population*, treatment with taranabant was associated with a significant increase in nervous system-related adverse experiences, specifically, for the sensory grouping. There did not appear to be a dose-dependent increase in nervous-related adverse experiences between the 4-mg and 6-mg groups. Adverse experiences in the expanded Nervous System Disorders SOC were predominantly mild to moderate in intensity. Discontinuations due to nervous system-related adverse experiences were numerically higher in the taranabant treatment groups compared with the placebo group.

Clinical Adverse Experience Summary
(Treatment Phase - Pre-Switch)
All Patients as Treated Population

	Taranabant 4 mg (N = 433)		Taranabant 6 mg / 2 mg (N = 1297)		Taranabant 6 mg / Placebo (N = 432)		Placebo (N = 431)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With one or more adverse experiences	370	(85.5)	1112	(85.7)	379	(87.7)	340	(78.9)
With no adverse experience	63	(14.5)	185	(14.3)	53	(12.3)	91	(21.1)
With drug-related adverse experiences†	258	(59.6)	804	(62.0)	287	(66.4)	154	(35.7)
With serious adverse experiences	25	(5.8)	81	(6.2)	18	(4.2)	20	(4.6)
With serious drug-related adverse experiences	2	(0.5)	11	(0.8)	2	(0.5)	1	(0.2)
Who died	0	(0.0)	1	(0.1)	1	(0.2)	1	(0.2)
Discontinued due to adverse experiences	77	(17.8)	268	(20.7)	91	(21.1)	37	(8.6)
Discontinued due to drug-related adverse experiences	61	(14.1)	220	(17.0)	82	(19.0)	24	(5.6)
Discontinued due to serious adverse experiences	5	(1.2)	22	(1.7)	4	(0.9)	7	(1.6)
Discontinued due to serious drug-related adverse experiences	2	(0.5)	8	(0.6)	2	(0.5)	1	(0.2)

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

In the *Pre-switch population*, treatment with taranabant was associated with an increased incidence of psychiatric-related adverse experiences. Adverse experiences in the depression grouping, and specific

adverse experiences of irritability, and anxiety, and the combined adverse experiences of depressed mood and depressed symptoms had the highest incidence with rates that were comparable in the taranabant groups and statistically higher compared with the placebo group. Incidences for the anxiety grouping, and the combined adverse experiences of depression and major depression were numerically higher in the 4-mg group and statistically higher in the 6-mg group compared with placebo.

In the *Pre-switch population*, adverse experiences in the Psychiatric Disorders SOC plus irritability were predominantly mild to moderate in intensity. Psychiatric-related adverse experiences were the most common adverse experiences for which patients discontinued study drug, with adverse experiences in the depression grouping being the most frequent. The incidences of discontinuations due to psychiatric-related adverse experiences were statistically higher (approximately 2 to 3 times higher) in the 4-mg and 6-mg groups compared with the placebo group.

In the *Pre-switch population*, adverse experiences of suicidal behavior or completed suicides were not reported; suicide ideation (self-reported, non-elicited) was reported for 5 patients (2 in the 4-mg group, 3 in the 6-mg group, and 0 in the placebo group). Positive responses to PHQ-9 question 9 (which actively probes for suicidal ideation) were reported for 2.7%, 3.9%, and 2.1% in the 4-mg, 6-mg, and placebo groups, respectively.

In the *Pre-switch population*, treatment with taranabant was associated with a significantly higher incidence of skin and subcutaneous tissue-related adverse experiences, specifically, hyperhidrosis and adverse experiences in the pruritus grouping. These adverse experiences were mild to moderate in intensity, and led to few discontinuations.

In the *Pre-switch population*, treatment with taranabant was associated with a significantly higher incidence of vascular disorder-related adverse experiences, specifically the combined adverse experiences of flushing and hot flush. These adverse experiences were mild to moderate in intensity, and led to few discontinuations.

Laboratory Adverse Experience Summary
(Treatment Phase - Pre-Switch)
All Patients as Treated Population

	Taranabant 4 mg (N = 433)		Taranabant 6 mg / 2 mg (N = 1297)		Taranabant 6 mg / Placebo (N = 432)		Placebo (N = 431)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With at least one lab test postbaseline	411		1232		413		400	
With one or more adverse experiences	19	(4.6)	42	(3.4)	14	(3.4)	14	(3.5)
With no adverse experience	392	(95.4)	1190	(96.6)	399	(96.6)	386	(96.5)
With drug-related adverse experiences[†]	3	(0.7)	13	(1.1)	2	(0.5)	6	(1.5)
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)	4	(0.3)	1	(0.2)	1	(0.3)
Discontinued due to drug-related adverse experiences	0	(0.0)	3	(0.2)	1	(0.2)	1	(0.3)
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.

During the *Post-switch* period, serious adverse experiences considered by the investigator to be drug-related were reported for 1 patient in the 2-mg group (pulmonary embolus) and 2 patients in the placebo group (1 with convulsion and 1 with an incomplete abortion).

During the *Post-switch* period, with the exception of significantly higher incidences of nervous system-related and psychiatric-related adverse experiences in the 2-mg group, incidences of other Tier 1 adverse experiences were comparable between the 2-mg and placebo groups.

For the *Overall population*, summaries of clinical and laboratory adverse experiences demonstrated that for the taranabant 4-mg and placebo groups few treatment emergent adverse experiences were reported after the *Pre-switch* period, while for the 6-mg/2-mg and 6-mg/placebo groups the summaries represent a combination of the adverse experiences reported in the *Pre-switch* and *Post-switch* periods.

For the *Overall population,* the serious drug-related adverse experiences reported over the 104 weeks of the study include 1 additional patient with an adverse experience of atrial flutter in the 4-mg group that was not captured in the *Pre-switch population*. For the other treatment groups, the *Overall population* represents the combination of the serious drug-related adverse experiences captured in the *Pre-switch* and *Post-switch populations*.

For the *Overall population*, the incidences of Tier 1 adverse experiences for patients in the 6-mg/2-mg and 6-mg/placebo groups represent an aggregate of experiences captured over the course of 104 weeks (i.e. *Pre-switch* and *Post-switch populations)*. For the 4-mg/2-mg and placebo groups the Tier 1 adverse experiences captured over the course of 104 weeks include those adverse experiences that were reported after the first dose change visit.

CONCLUSIONS

In overweight and obese patients, in conjunction with diet and exercise, 52 weeks of:

1. Treatment with taranabant 4 mg results in a statistically significant and clinically meaningful reduction in body weight compared with placebo.
2. Treatment with taranabant 2 mg results in a statistically significant and clinically meaningful prevention of weight regain, after initial weight loss induced by taranabant 6 mg compared with placebo.
3. Treatment with taranabant 4 mg results in a statistically significant and clinically meaningful reduction in waist circumference compared with placebo.
4. Treatment with taranabant 4 mg is associated with improvements in triglycerides, HDL-C, non-HDL-C, fasting plasma glucose, fasting serum insulin, QUICKI, and metabolic syndrome compared with placebo.
5. Treatment with taranabant 4 and 6 mg is associated with a significant increase in the incidence of psychiatric-related adverse experiences, most commonly irritability, depressed mood or depressive symptoms, anxiety grouping and insomnia grouping compared with placebo.
6. Treatment with taranabant 4 mg and 6 mg is associated with increased incidences of GI-related (most commonly, nausea, diarrhea, and vomiting), nervous system-related (most commonly, adverse experiences in the sensory grouping), skin and subcutaneous tissue-related (pruritus and hyperhidrosis), and vascular-related (flushing or hot flush) adverse experiences compared with placebo.
7. Treatment with taranabant 2 mg, 4 mg, and 6 mg is not associated with significant laboratory safety test abnormalities compared with placebo.
8. Treatment with taranabant 2 mg after inducing weight loss with taranabant 6 mg is associated with numerically increased incidence of nervous system-related and psychiatric-related adverse experiences compared with placebo.

In overweight and obese patients, in conjunction with diet and exercise, 104 weeks of:

1. Treatment with taranabant is associated with numerically increased incidence of adverse experiences compared with placebo with a profile similar to that observed during the *Pre-switch* period.

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