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 to Assess the Efficacy, Safety, and Tolerability of Taranabant (MK-0364) in Obese Patients Followed by a 1-Year Extension #015

INVESTIGATORS/STUDY CENTERS: Multicenter (122) in the United States and Canada (68), Europe (33), and Rest of the World (21)

PUBLICATION: I Gantz, et al. A two-year study to assess the efficacy, safety and tolerability of taranabant in obese patients: 52 week results. Presented at American College of Cardiology 2008 Chicago, IL; Abstract 1021-220.

PRIMARY THERAPY PERIOD: 15-Aug-2005 to 08-Jan-08; Extension study is ongoing

CLINICAL PHASE: III

DURATION OF TREATMENT: The duration of this study is 104 weeks. This clinical study report (CSR) addresses endpoints in Year 2. A separate CSR was written for data from Week 0 through Week 52.

OBJECTIVES: Primary: In obese patients, (1) to assess the effects of taranabant 2 mg or 4 mg after 1 year of treatment on body weight; (2) to assess the safety and tolerability of taranabant during base and extension studies. Secondary: In obese patients, to assess the effects of 2 mg taranabant on: (1) body weight after 2 years of treatment; (2) waist circumference at 1 year and 2 years; (3) percent body fat at 6 months; (4) biochemical markers [triglycerides, HDL-C, non-HDL-C, LDL-C, total cholesterol, fasting insulin, insulin sensitivity, fasting plasma glucose (FPG)] at 1 year; (5) proportion of patients with metabolic syndrome after 1 year and 2 years of treatment; (6) blood pressure at 1 year; (7) Patient-Reported Outcomes (PRO) at 1 year; (8) After treatment with taranabant 6 mg, to assess the effect of treatment with taranabant 2 mg, relative to placebo after 52 weeks post dose change, on (a) body weight; (b) waist circumference; (c) metabolic syndrome; (d) biochemical markers (triglycerides, HDL-C, non-HDL-C, LDL-C, total cholesterol, fasting insulin, insulin sensitivity and fasting plasma glucose). In obese patients, to assess the effects of 4 mg taranabant on:(1) waist circumference at 1 year; (2) percent body fat at 6 months; (3) biochemical markers [triglycerides, HDL-C, non-HDL-C, LDL-C, total cholesterol, fasting insulin, insulin sensitivity, fasting plasma glucose (FPG)] at 1 year; (4) proportion of patients with metabolic syndrome after 1 year of treatment; (5) blood pressure at 1 year; (6) Patient-Reported Outcomes (PRO) at 1 year.

HYPOTHESES: Primary: In obese patients: (1) 1 year of treatment with 2 mg or 4 mg of taranabant decreases body weight more than placebo; (2) taranabant is well tolerated. Secondary: In obese patients, compared to placebo, 2 mg of taranabant: (1) decreases waist circumference after 1 year of treatment, decreases percent body fat after 6 months, decreases body weight after 2 years of treatment in those patients who complete one year of treatment, decreases the proportion of patients with the metabolic syndrome after 1 year of treatment; (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; (4) 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. In obese patients, compared to placebo, 4 mg of taranabant (1) decreases waist circumference after 1 year of treatment, decreases percent body fat after 6 months, decreases the proportion of patients with the metabolic syndrome after 1 year of treatment; (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 FOR YEARS 1 and 2: This is a double-blind, randomized, placebo-controlled study. In the original study design, patients were randomized to 1 of 5 treatment groups; placebo or taranabant 2-mg, 4-mg, 6-mg fixed, or titrated up to 6 mg (2/4/6-mg at 2 week intervals during the first 4 weeks of the double-blind treatment period) with a randomization ratio of 2:2:2:3:3, respectively. Patients were to be maintained on their initial dose assignments (no dose changes) throughout the 2 years of the study. However, following a scheduled review of unblinded data in June, 2006, the Data Safety

Monitoring Committee (DSMC) recommended, based on their assessment of the risk/benefit ratio of the 6-mg dose, that the 6-mg dose should be discontinued. In response to the DSMC recommendation, Merck & Co., Inc. made a decision to re-randomize patients on 6 mg taranabant to 2 mg taranabant or placebo in a 2:1 ratio, respectively, in a blinded fashion. Patients originally randomized to 2 mg and 4 mg taranabant continued on the same dose as initially planned (although they had a dose change visit to maintain blinding). Design changes and modification of objectives due to the elimination of the 6-mg dose were encompassed in Amendment 015-05 (effective date: 20-Jul-2006). The dose change was performed at the next scheduled visit following ERC/IRB approval of Amendment 015-05, which occurred at or after Visit 10 (Week 24). Based on an assessment by Merck & Co., Inc. of the risk/benefit ratio of the 4 mg dose in June 2007, the 4-mg dose was discontinued. Patients on 4 mg taranabant were switched to a 2 mg taranabant in a blinded fashion. Design changes and modification of objectives due to the elimination of the 4-mg dose are encompassed in Amendment/Extension 015-10, which also initiated a 1-year extension to the 2-year base study. In this study, diet (25% hypocaloric) and exercise counseling were initiated at the start of a 2-week placebo run-in period and continued throughout the study. Patients discontinued from study drug were allowed to participate in the study off study drug.

SUBJECT/PATIENT DISPOSITION:

Overall Disposition of Patients Over Two Years of Treatment
(Week 0 through Week 104)

	Taranabant 2 mg	Taranabant 4 mg	Taranabant 6 mg/2 mg †	Taranabant 6 mg/placebo ‡	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
SCREENED						4105
SCREENED FAILURES						1603
RANDOMIZED	414	415	836	420	417	2502
Male (age range)	167 (20-76)	156 (22-77)	351 (20-75)	164 (18-75)	184 (20-84)	1022 (18-84)
Female (age range)	247 (18-74)	259 (19-76)	485 (18-81)	256 (18-77)	233 (19-76)	1480 (18-81)
PATIENT COMPLETED STUDY (104 WEEKS)	202 (48.8)	200 (48.2)	396 (47.4)	182 (43.3)	197 (47.2)	1177 (47.0)
PATIENT DISCONTINUED RX AND HAS A FOLLOW-UP	43 (10.4)	53 (12.8)	76 (9.1)	56 (13.3)	32 (7.7)	260 (10.4)
Clinical adverse experience	26 (6.3)	31 (7.5)	52 (6.2)	39 (9.3)	13 (3.1)	161 (6.4)
Lack of efficacy	2 (0.5)	4 (1.0)	3 (0.4)	1 (0.2)	7 (1.7)	17 (0.7)
Lost to follow-up	0 (0.0)	0 (0.0)	1 (0.1) §	1 (0.2) ‖	1 (0.2) ¶	3 (0.1)
Patient moved	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)
Patient withdrew consent	0 (0.0)	0 (0.0)	1 (0.1)	2 (0.5)	1 (0.2)	4 (0.2)
Protocol deviation	7 (1.7)	3 (0.7)	1 (0.1)	4 (1.0)	2 (0.5)	17 (0.7)
Laboratory adverse experience	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.0)
Patient discontinued for other	8 (1.9)	15 (3.6)	18 (2.2)	7 (1.7)	8 (1.9)	56 (2.2)
PATIENT DISCONTINUED RX W/O FOLLOW-UP	169 (40.8)	162 (39.0)	364 (43.5)	182 (43.3)	188 (45.1)	1065 (42.6)
Clinical adverse experience	47 (11.4)	67 (16.1)	149 (17.8)	78 (18.6)	34 (8.2)	375 (15.0)
Lack of efficacy	8 (1.9)	3 (0.7)	8 (1.0)	4 (1.0)	19 (4.6)	42 (1.7)
Lost to follow-up	32 (7.7)	21 (5.1)	60 (7.2)	31 (7.4)	32 (7.7)	176 (7.0)
Patient moved	5 (1.2)	4 (1.0)	10 (1.2)	6 (1.4)	7 (1.7)	32 (1.3)
Patient withdrew consent	67 (16.2)	58 (14.0)	124 (14.8)	56 (13.3)	79 (18.9)	384 (15.3)
Protocol deviation	4 (1.0)	5 (1.2)	5 (0.6)	4 (1.0)	9 (2.2)	27 (1.1)
Laboratory adverse experience	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)	3 (0.1)
Patient discontinued for other	2 (0.5)	1 (0.2)	6 (0.7)	1 (0.2)	2 (0.5)	12 (0.5)
Terminated by sponsor	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.0)
Site terminated	3 (0.7)	3 (0.7)	1 (0.1)	2 (0.5)	4 (1.0)	13 (0.5)

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

† Patients originally randomized to 6-mg fixed or 6-mg titrated (2/4/6-mg) dose and re-randomized to 2-mg dose.
‡ Patients originally randomized to 6-mg fixed or 6-mg titrated (2/4/6-mg) dose and re-randomized to placebo.
[redacted]

Disposition of Patients in Second Year of Treatment
Who Completed First Year of Treatment
(Week 52 to Week 104)

Status	Taranabant 2 mg (N=270) † n (%)	Taranabant 4 mg (N=264) † n (%)	Placebo (N=254) † n (%)	Total (N=788) † n (%)
PATIENT COMPLETED STUDY (104 WEEKS)	202 (74.8)	200 (75.8)	198 (78.0)	600 (76.1)
PATIENT DISCONTINUED RX AND HAS A FOLLOW-UP	23 (8.5)	27 (10.2)	11 (4.3)	61 (7.7)
Clinical adverse experience	14 (5.2)	11 (4.2)	3 (1.2)	28 (3.6)
Lack of efficacy	2 (0.7)	3 (1.1)	2 (0.8)	7 (0.9)
Patient withdrew consent	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Protocol deviation	2 (0.7)	0 (0.0)	0 (0.0)	2 (0.3)
Patient discontinued for other	5 (1.9)	13 (4.9)	5 (2.0)	23 (2.9)
PATIENT DISCONTINUED RX W/O FOLLOW-UP	45 (16.7)	37 (14.0)	45 (17.7)	127 (16.1)
Clinical adverse experience	7 (2.6)	5 (1.9)	3 (1.2)	15 (1.9)
Lack of efficacy	2 (0.7)	0 (0.0)	4 (1.6)	6 (0.8)
Lost to follow-up	13 (4.8)	7 (2.7)	15 (5.9)	35 (4.4)
Patient moved	1 (0.4)	3 (1.1)	2 (0.8)	6 (0.8)
Patient withdrew consent	18 (6.7)	18 (6.8)	15 (5.9)	51 (6.5)
Protocol deviation	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.1)
Laboratory adverse experience	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)
Patient discontinued for other	0 (0.0)	1 (0.4)	1 (0.4)	2 (0.3)
Site terminated	3 (1.1)	3 (1.1)	4 (1.6)	10 (1.3)

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

If IRB/ERC approval of the amendment/extension occurred prior to the completion of the base study, patients on taranabant 4 mg were down dosed to 2 mg

† Of the 788 patients (270 in the 2-mg group, 264 in the 4-mg group, and 254 in the placebo group) who completed Year 1 and entered Year 2, 768 patients (264 patients in the 2 mg group, 260 patients in the 4 mg group, and 244 patients in the placebo group) took a dose of study drug in the second year and were included in the Year 2 safety assessment.

DOSAGE/FORMULATION NOS.: Original Design: Placebo or taranabant 2, 4, or 6 mg, or taranabant 6-mg titrated dose administered orally (capsules) once daily. First revised Design: Placebo, or taranabant 2 mg or 4 mg, administered orally (capsules) once daily. Second revised Design: Placebo or taranabant 2 mg, administered orally (capsules) once daily. 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 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 meet other entry criteria will be eligible to participate. Sites targeted the enrollment of 40% male patients and a minimum of 50% patients with metabolic syndrome.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Body weight, metabolic syndrome, waist circumference, blood pressure, fasting plasma lipid profile (triglycerides, HDL-C, non-HDL-C, LDL-C, total cholesterol), fasting insulin, insulin sensitivity, FPG, and PRO by questionnaires (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; laboratory assessment (hematology, chemistry, and urinalysis); ECG. 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 committee every 3 to 6 months.

STATISTICAL PLANNING AND ANALYSIS:

EFFICACY: The approaches to the primary efficacy hypothesis of body weight after 52 weeks of treatment and any other Year 1 analyses are detailed in a separate Clinical Study Report (CSR). This report addresses the efficacy results in the second year (Year 2). There were two body weight efficacy hypotheses in Year 2 of this study, both of which were secondary hypotheses. The first secondary hypothesis was that treatment with 2 mg taranabant would demonstrate statistically significant weight loss from baseline (Week 0) compared with placebo at Week 104. The ANCOVA model used to assess this included terms for treatment, baseline body weight, weight change during the 2-week run-in period, and region. The second hypothesis was that in patients treated during Year 1 with 6 mg taranabant (and subsequently switched to 2 mg taranabant or placebo), that treatment with 2 mg taranabant would prevent weight regain more than placebo after 52 weeks of treatment post the dose change. The ANCOVA model for the second hypothesis included terms for treatment, region, baseline body weight, weight change during treatment with 6 mg taranabant instead of weight change during the 2-week run-in period. The proportion of obese patients who lost ≥5% or ≥10% of their baseline body weight at Week 104 was assessed using a logistic model with terms for treatment, baseline body weight, weight change during the 2-week run-in period and region. The primary analysis population was an all-patients-treated (APT) population, which includes all randomized patients who have a baseline value, received at least one dose of randomized treatment, and have at least one post baseline measurement. In addition, for the assessment of the treatment effect of 2 mg or 4 mg of taranabant at Week 104, patients had to complete Week 52 on treatment, begin the second year on treatment and have at least one post-Week 52 measurement. Using the appropriate metric of change or percent change, a similar ANCOVA (or a nonparametric equivalent when appropriate) was used to compare the treatment groups for secondary efficacy endpoints (e.g., waist circumference, lipid and glucose variables). The proportion of patients meeting criteria for metabolic syndrome at Week 104 was assessed by comparing the taranabant 2 mg and 4 mg groups with placebo using a logistic model with terms for treatment, weight change during the 2-week run-in period, region and baseline metabolic syndrome status. This study allowed for following patients after having formally discontinued the test drug. Data collected after patients discontinued from treatment was not included in the primary analysis; an analysis that includes data collected after a patient discontinued was also performed. The primary approach to handling missing data was the last observation carried forward (LOCF) method in Year 2. A longitudinal repeated measures approach was used as a sensitivity analysis to estimate the treatment effects.

SAFETY: The safety and tolerability throughout 104 weeks was assessed by clinical and/or statistical review of all safety parameters, including adverse experiences, laboratory values, vital signs and ECG parameters. The analysis of adverse experiences followed a multitiered 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 the placebo group and each of the taranabant dose groups were provided.

Ninety-five percent confidence intervals were computed for adverse experiences with an incidence ≥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 2- and 6-mg groups, the adverse experience will be described as having a *numerically higher* or *numerically lower* incidence compared with placebo. 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*."

RESULTS:

EFFICACY: Treatment with 2 mg or 4 mg taranabant (in conjunction with diet and exercise) led to a statistically significant reduction in body weight at Week 104 compared with placebo. Based on last observation carried forward (LOCF) analysis of the all-patients-treated (APT) population who finished Year 1 and entered Year 2, the treatment effect of the 4-mg group was approximately 24% greater than that observed in the 2-mg group. For the per-protocol completers population, the treatment effect of the 4-mg group was similar to that observed in the 2-mg dose. Weight loss reached a plateau at approximately 36-40 weeks in Year 1, after which some weight regain occurred. The slopes of the weight loss curves after Year 1 were similar among all treatment groups suggesting a similar rate of weight regain. A significantly greater reduction in mean waist circumference (a surrogate of intraabdominal fat mass) was also observed in the 2-mg and 4-mg groups compared with the placebo group at Week 104.

The percentage of patients who lost at least 5% of their baseline body weight (5% responders) at Week 104 was significantly higher in the 2-mg and 4-mg groups compared with the placebo group. The percentage of 5% responders in the taranabant groups was approximately 2 times greater than that observed in the placebo group (59.6% and 64.8% in the 2-mg and 4-mg groups, respectively, versus 30.3% for the placebo group). The percentage of patients who lost at least 10% of their baseline body weight (10% responders) after 104 weeks was significantly higher in the 2-mg and 4-mg groups compared with the placebo group. The percentage of 10% responders in the taranabant groups was 33.0% and 37.9% for the 2-mg and 4-mg groups, respectively, versus 13.4% for the placebo group.

The results demonstrated significantly decreased weight regain in the patients treated with 6 mg (fixed or titrated) and switched to 2 mg compared to those switched to placebo. Therefore, the secondary efficacy hypothesis related to prevention of weight regain was met.

Taranabant treatment for 104 weeks (in conjunction with diet and exercise) led to statistically significant reductions in TG and increases in HDL-C in the 2-mg and 4-mg groups compared with the placebo group. A statistically significant reduction in TG and increase in HDL-C were also observed in the 6-mg/2-mg group compared with the 6-mg/Pbo group. No significant differences in non-HDL-C were observed in the 2-mg and 4-mg groups compared with the placebo group. Similarly, no significant difference in non-HDL-C was observed for the 6-mg/2mg group compared with the 6-mg/Pbo group. Changes in LDL-C from baseline at Week 104 were comparable in the 2-mg, 4-mg and placebo groups. There were no significant differences in LDL-C in the 6-mg/2-mg group compared with the 6-mg/Pbo group 52 weeks after the 6-mg dose change.. Changes in total cholesterol from baseline at Week 104 were comparable in the 2-mg, 4-mg and placebo groups and there was no difference in total cholesterol in the 6-mg/2-mg group compared with the 6-mg/Pbo group after the 6-mg dose change.

Taranabant treatment (in conjunction with diet and exercise) led to no significant differences in FPG, FSI or insulin sensitivity (calculated by quantitative insulin sensitivity check index or QUICKI) in the 2-mg and 4-mg groups compared with the placebo group. The differences in FPG, FSI and QUICKI between the 6-mg/2-mg group and 6-mg/Pbo group 52 weeks after the switch from 6 mg taranabant were not statistically significant.

Taranabant treatment led to no significant effect on systolic or diastolic blood pressure (BP) from baseline at Week 104 in the taranabant 2-mg and 4-mg groups compared with the placebo group. Similarly, there were no significant differences in systolic and diastolic BP in the 6-mg/2-mg and 6-mg/Pbo groups 52 weeks after the switch from 6 mg taranabant. There were no meaningful changes in the pulse rate over time in any treatment group.

The proportion of patients meeting criteria for the metabolic syndrome in the 2-mg and 4-mg groups after 104 weeks of treatment with taranabant were lower compared with the placebo group. However, the proportions in all treatment groups (including placebo) increased slightly from Week 52 to Week 104.

SAFETY: Summaries of clinical and laboratory adverse experiences are provided below for patients who completed Year 1 and entered Year 2.

A total of 788 patients (270 in the 2 mg group, 264 in the 4 mg group, and 254 in the placebo group) completed Year 1 and entered Year 2 of the study. Of these 788 patients, 768 patients (264 patients in the 2-mg group, 260 patients in the 4-mg group, and 244 patients in the placebo group) took a dose of study drug in the second year and were included in the Year 2 safety assessment.

Clinical Adverse Experience Summary
(Treatment Phase From Week 52 Up to Week 104) All Patients as Treated Population

	Taranabant 2 mg (N = 264)		Taranabant 4 mg (N = 260)		Placebo (N = 244)	
	N	(%)	N	(%)	n	(%)
Number (%) of patients:						
With one or more adverse experiences	189	(71.6)	193	(74.2)	192	(78.7)
With no adverse experience	75	(28.4)	67	(25.8)	52	(21.3)
With drug-related adverse experiences†	25	(9.5)	38	(14.6)	18	(7.4)
With serious adverse experiences	16	(6.1)	17	(6.5)	11	(4.5)
With serious drug-related adverse experiences	1	(0.4)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	11	(4.2)	11	(4.2)	3	(1.2)
Discontinued due to drug-related adverse experiences	9	(3.4)	7	(2.7)	2	(0.8)
Discontinued due to serious adverse experiences	1	(0.4)	2	(0.8)	0	(0.0)
Discontinued due to serious drug-related adverse experiences	1	(0.4)	0	(0.0)	0	(0.0)

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

Laboratory Adverse Experience Summary
(Treatment Phase From Week 52 Up to Week 104) All Patients as Treated Population

	Taranabant 2 mg (N = 264)		Taranabant 4 mg (N = 260)		Placebo (N = 244)	
	n	(%)	n	(%)	n	(%)
Number (%) of patients:						
With at least one lab test postbaseline	264		260		244	
With one or more adverse experiences	7	(2.7)	11	(4.2)	8	(3.3)
With no adverse experience	257	(97.3)	249	(95.8)	236	(96.7)
With drug-related adverse experiences†	2	(0.8)	2	(0.8)	1	(0.4)
With serious adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
With serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Who died	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	1	(0.4)	0	(0.0)	0	(0.0)
Discontinued due to drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to serious adverse experiences	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)

† 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.

Introduction

The summary of safety in this synopsis will primarily focus on adverse experiences during Year 2 and focuses on Tier I adverse experiences. Year 1 adverse experiences are described in the Year 1 CSR. Adverse experiences which occurred in Year 1 and Year 2 (*Overall treatment population)* are briefly summarized in this synopsis and discussed in Section 12.

Adverse experiences initiated after Week 52 in patients who were randomized in Year 1 to placebo or taranabant 2 mg or 4 mg who continued in the study in Year 2 are summarized in the *Second year of treatment (2 mg, 4 mg and placebo only) population.* Adverse experiences initiated after dose change to 2 mg taranabant or placebo in patients who were randomized to fixed or titrated 6 mg taranabant in Year 1 are summarized in the *Post-switch population*.

Tier 1 adverse experiences are adverse experiences which occur with increased incidences in patients taking taranabant or those adverse experiences that are of potential interest based on the CB1R mechanism. Tier 1 adverse experiences include adverse experiences in the Gastrointestinal (GI) Disorders, Nervous System Disorders, Psychiatric Disorders, Skin and Subcutaneous Tissue Disorders and Vascular Disorders System Organ Classes (SOCs). SOC adverse experience terminology follows Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. In the ensuing description, the term "grouping" refers to MedDRA preferred terms that describe clinically related adverse experiences.

Second year of treatment (2 mg, 4 mg and placebo only) population

The incidences of adverse experiences within the GI Disorders SOC in the *Second year of treatment (2 mg, 4 mg and placebo only) population* were statistically significantly lower in the 2-mg and numerically lower in the 4-mg group compared with the placebo group. The incidences of the adverse experiences of nausea, vomiting and frequent bowel movements were comparable in the 2-mg and placebo groups; incidences in the 4-mg group were numerically higher compared with the 2-mg and placebo groups. The incidences of the adverse experience of diarrhea were numerically lower in the 4-mg and the 2-mg group compared with the placebo group.

The majority of adverse experiences in the GI Disorders SOC were single episodes, which were mild to moderate in intensity and of limited duration GI-related adverse experiences mostly occurred as single episodes in 64.4%, 60.3% and 69.4% of patients in the 2-mg, 4-mg and placebo groups, respectively; while 2 episodes occurred in 22.2%, 27.6% and 21.0% of patients in the 2-mg, 4-mg and placebo groups, respectively. Discontinuations due to GI-related adverse experiences were infrequent during Year 2 (1 patient in the 2-mg group and 2 patients in the 4-mg group discontinued due to the adverse experience of nausea and 1 patient in the 4-mg group discontinued due to the adverse experience of diarrhea).

The incidence of adverse experiences in the expanded Nervous System Disorders SOC (i.e. Nervous System Disorders SOC plus hypoesthesia facial, amaurosis fugax, vision blurred, scotoma, blindness, altered visual depth perception, photopsia, diplopia) in the 2-mg and 4-mg group was numerically higher compared with the placebo group. The incidences of adverse experiences in the dizziness, sedation and motor groupings were comparable in the 2-mg, 4-mg groups and placebo groups. The incidences of adverse experiences in the cognition grouping were comparable in the 2-mg and placebo groups; incidences in the 4-mg group were numerically higher compared with the placebo group. The incidences of adverse experiences in the sensory grouping were numerically higher in the 2-mg and 4-mg groups compared with the placebo groups. There was 1 report of an adverse experience in the syncope grouping in the 2-mg group and 2 reports in the 4-mg group (none were reported in the placebo group).

No significant differences were detected by the Digit Symbol Substitution Test in the mean changes from baseline in the cognitive/neuropsychomotor skills between taranabant and placebo groups.

Adverse experiences in the expanded Nervous System Disorders SOC were predominantly mild to moderate in intensity, single episodes, which had a median duration of 14 and 27 days in the 2-mg and 4-mg groups, respectively, compared to 8 days in the placebo group. There were no discontinuations due to nervous system-related adverse experiences in the 2-mg and placebo groups; 1 patient in the 4-mg group discontinued due to the adverse experience of presyncope.

The incidences of adverse experiences in the Psychiatric disorders SOC plus irritability were numerically higher in the 2-mg and 4-mg groups compared with the placebo group. Incidences of adverse experiences in the affect, depression, anxiety and insomnia groupings were comparable in the 2-mg and placebo groups; incidences of adverse experiences in these groupings were numerically higher in the 4-mg compared with the placebo group. The incidence of the combined adverse experiences depression, major depression was comparable in the 2-mg and placebo groups; the incidence in the 4-mg group was numerically higher compared with the placebo group. The incidence of the combined adverse experiences of depressed mood, depressive symptom was numerically higher in the 2-mg group compared with the placebo group; however, the incidence in the 4-mg group was comparable the placebo group. The adverse experiences of irritability and anxiety were comparable in the 2-mg and placebo groups; incidences in the 4-mg group were numerically higher compared with the 2-mg and placebo groups. There were no reports of the combined adverse experiences of aggression, anger in the placebo group; 1/270 patients in the 2-mg group and 4/264 patients in the 4-mg group reported aggression or anger.

There were no significant differences compared to placebo in mean changes from baseline in any POMSb domains including Anger-Hostility, Confusion-Bewilderment, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety or Vigor-Activity.

There was 1 self-report of suicidal ideation in the 4-mg group. Positive responses to Patient Health Questionnaire-9 (PHQ-9) question #9, which probes suicidal ideation, were reported by 4.9% of the 2-mg group, 2.5% of the 4-mg group and 2.2% of the placebo group during Year 2. There were no cases of suicidal behavior and no suicide deaths in the study.

Adverse experiences in the Psychiatric Disorders SOC plus irritability were mild to moderate in intensity, predominantly occurred as single episodes, and had median durations ranging from approximately 2-4 months in the 2-mg and 4-mg groups (median duration tended to be longer in the placebo group). Discontinuations due to psychiatric-related adverse experiences were low during Year 2 (8/270 patients in the 2-mg group, 5/264 in the 4-mg group and 4/254 in the placebo group); the majority of discontinuations were due to adverse experiences in the depression grouping.

The incidences of adverse experiences in the Skin and Subcutaneous Tissue Disorders SOC minus hypoesthesia facial were comparable in the 2-mg and placebo groups and significantly higher in the 4-mg group compared with the placebo group. The incidences of the adverse experience of hyperhidrosis were comparable in the 2-mg, 4-mg and placebo groups. The incidences of the adverse experiences in the pruritus grouping were numerically higher in the 2-mg and 4-mg groups compared with the placebo group.

Adverse experiences in the Skin and Subcutaneous Tissue Disorders SOC minus hypoesthesia facial were mild to moderate in intensity, primarily occurred as single episodes, with a median duration of approximately 1-2.5 months. There were no discontinuations in the 2-mg and 4-mg groups due to adverse experiences in the in this SOC (one patient in the placebo group discontinued due to the adverse experience of pruritus generalized).

The incidence of adverse experiences in the Vascular Disorders SOC was numerically lower in the 2-mg group compared with the incidences in the placebo and 4-mg groups; incidences in the placebo and 4-mg groups were comparable. The Tier 1 adverse experience in this SOC was the combined adverse experiences of flushing, hot flush. The incidence of the combined adverse experiences flushing, hot flush was numerically lower in the 2-mg group compared with the incidences in the placebo and 4-mg groups; incidences in the placebo and 4-mg groups were comparable.

Adverse experiences in the Vascular Disorders SOC were mild to moderate in intensity, were single episodes, with a variable duration (1 to 6 months) and no patient discontinued due to these adverse experiences.

Post-switch Population

In the *Post-switch population* there were no significant differences in the incidences of adverse experiences between the 6-mg/Pbo and 6-mg/2-mg groups (the groups that constitute the *Post-switch population*), with the exception of the adverse experience of anxiety, which was significantly higher in the 6-mg/Pbo group compared with the 6-mg/2-mg group. An examination of new psychiatric and neurological adverse experiences in the 3 month periods prior to and after the dose change from 6 mg taranabant to 2 mg taranabant or placebo did not show an increase in adverse experiences post-switch, suggesting that there is no "withdrawal" effect with respect to psychiatric or neurological adverse experiences.

No significant differences were detected by the Digit Symbol Substitution Test in the mean changes from baseline in the cognitive/neuropsychomotor skills in the 6-mg/2-mg and 6-mg/Pbo groups.

The POMSb questionnaire did not detect significant differences in mean changes from baseline for the 5 of the 6 domains, including Anger-Hostility, Depression-Dejection, Fatigue-Inertia, Tension-Anxiety or Vigor-Activity. There was a significant difference in the mean change from baseline in the Confusion-Bewilderment domain in the 2-mg group compared with the placebo.

There were no statistically significant differences in the change from baseline in the Patient Health Questionnaire-9 (PHQ-9) at Week 104 between the 6-mg/2-mg and 6-mg/Pbo groups. Positive responses to PHQ-9 question #9, which probes suicidal ideation, were reported by 1.1% in the 6-mg/2-mg group and 1.0% in the 6-mg/Pbo group during Year 2. There were no cases of suicidal behavior and no suicide deaths in the study. [redacted] It was retrospectively learned that the patient had a history of 2 previous suicide attempts prior to entering the study.

Overall Treatment Population

A review of adverse experiences in Year 1 and Year 2 indicates that, in general, the safety profile of taranabant was unchanged in the 2-mg, 4-mg and placebo groups over the 2-year period of the study. The incidences of adverse experiences in the GI Disorders, expanded Nervous System Disorders, Psychiatric Disorders plus irritability, Skin and Subcutaneous Disorders, and Vascular Disorders SOCs during Year 2 were numerically lower when compared to Year 1 in the taranabant 2-mg and 4-mg groups. Similarly, incidences in the placebo groups of adverse experiences in these SOCs were comparable or numerically lower during Year 2 compared with Year 1. There were no suicide deaths in any treatment group during Year 1 or Year 2 of the study.

Laboratory Safety Parameters

There were no significant differences in cardiovascular adverse experiences or ECG parameters between treatment groups. No clinically significant changes were observed in the laboratory safety parameters measured in this study. There were few laboratory adverse experiences, serious laboratory adverse experiences or patients discontinued from the study due to laboratory adverse experiences.

CONCLUSIONS: In overweight and obese patients: **Efficacy:** (1) Treatment with taranabant 2 mg or 4 mg for 104 weeks results in a statistically significant and clinically meaningful reduction in body weight compared to placebo. The 4-mg dose is associated with a modest increase in efficacy compared with the 2-mg dose. (2) After 52 weeks of treatment with taranabant 6 mg, treatment with taranabant 2 mg is associated with less weight regain during Year 2 than treatment with placebo. (3) Treatment with taranabant for 104 weeks is associated with improvements in metabolic parameters, including a reduction in waist circumference and serum triglycerides, an increase in HDL-C, and improvement in insulin sensitivity. **Safety:** *During Year 2* (4) Treatment with 2 mg and 4 mg taranabant is associated with an increased incidence of psychiatric-related adverse experiences, most commonly irritability, nervousness, anxiety, and those in the depression grouping. In general, psychiatric-related adverse experiences are mild to moderate in intensity and in the majority of cases do not require discontinuation from therapy. (5) Treatment with 2 mg taranabant is not associated with an increased incidence of nervous system-related adverse experiences. Treatment with 4 mg taranabant is associated with an increased incidence of nervous system-related adverse experiences belonging to the cognitive disorder and sensory groupings. In general, nervous system-related adverse experiences are mild to moderate in intensity, of limited duration and do not require discontinuation from drug therapy. (6) Treatment with 4 mg taranabant is associated with an increased incidence of the GI-related adverse experiences of nausea, vomiting, and diarrhea; incidences of these GI-related adverse experiences are not increased with 2 mg taranabant. These adverse experiences are generally mild to moderate in intensity and do not require discontinuation from drug therapy. (7) Treatment with 2 mg and 4 mg taranabant is associated with an increased incidence of the combined adverse experiences of pruritus, pruritus generalized. These adverse experiences are generally mild to moderate in intensity and do not require discontinuation from drug therapy. (8) Treatment with 2 mg and 4 mg taranabant is not associated with significant laboratory safety test abnormalities compared with placebo. *Overall (Week 0 to Week 104)* (9) The safety profile of 2 mg and 4 mg taranabant is characterized by adverse experiences in the psychiatric, neurological, gastrointestinal, skin, and vascular organ systems. The safety profile of 2 mg and 4 mg taranabant does not meaningfully change with continued treatment over 104 weeks.

AUTHORS:

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