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 soft gel capsules Weight Loss in Overweight and Obese patients With T2DM	**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 Overweight and Obese Patients With Type 2 Diabetes Mellitus (T2DM) Followed by a 1-Year Extension #011

INVESTIGATOR(S)/STUDY CENTER(S): Multicenter (60 sites) in the United States and Canada (20), Europe (16) and Rest of the World (24)

PRIMARY THERAPY PERIOD: 21-Nov-2006 to 20-May-2008 (A 1-Year extension of this study is ongoing) **CLINICAL PHASE:** III

DURATION OF TREATMENT: This is a 52-week study followed by a 52-week extension. This clinical study report presents data from Week 0 through Week 52. The primary efficacy objectives were assessed at Week 36.

OBJECTIVE(S): Primary: In patients with T2DM and a body mass index (BMI) between 27 kg/m^2 and 43 kg/m^2, inclusive, to assess the effects of taranabant on: (1) body weight after 36 weeks of treatment; (2) hemoglobin A1c (HbA_{1c}) after 36 weeks of treatment; (3) safety and tolerability of taranabant. Secondary: In patients with T2DM and a body mass index (BMI) between 27 kg/m^2 and 43 kg/m^2, inclusive, to assess the effects of taranabant on: (1) body weight after 24 and 52 weeks; (2) HbA_{1c} after 24 and 52 weeks; (3) fasting plasma glucose (FPG), insulin and insulin sensitivity after 24, 36, and 52 weeks; (4) biochemical markers [triglycerides (TG), HDL-C, non-HDL-C, LDL-C, total cholesterol (TC), adiponectin, and C-reactive protein (CRP)] after 24, 36, and 52 weeks; (5) body weight and HbA_{1c} in subgroups of patients not on anti-hyperglycemic therapy or on metformin monotherapy at randomization; (6) waist circumference after 24, 36, and 52 weeks; (7) blood pressure after 24, 36, and 52 weeks; (8) the proportion of patients requiring glycemic rescue therapy after 24, 36, and 52 weeks; (9) quality-of-life and health economic patient-reported outcomes (PRO) after 24, 36, and 52 weeks.

HYPOTHESES: **Primary:** In patients with T2DM and a BMI between 27 kg/m^2 and 43 kg/m^2, inclusive: (1) taranabant 0.5-, 1-, or 2-mg decreases body weight more than placebo after 36 weeks of treatment; (2) taranabant 0.5-, 1-, or 2-mg decreases HbA_{1c} more than placebo after 36 weeks of treatment; (3) taranabant is well tolerated. **Secondary:** In patients with T2DM and a BMI between 27 kg/m^2 and 43 kg/m^2, inclusive, taranabant at the 0.5-, 1-, or 2-mg dose: (1) decreases body weight more than placebo after 24 or 52 weeks of treatment; (2) reduces HbA_{1c} more than placebo after 24 or 52 weeks of treatment of treatment; (3) reduces FPG, reduces insulin and increases insulin sensitivity more than placebo after 24, 36, or 52 weeks of treatment; (4) decreases TG, increases HDL-C, decreases non-HDL-C, decreases LDL-C after 24, 36, or 52 weeks of treatment.

STUDY DESIGN: Double-blind, randomized, placebo-controlled. The randomization ratio for this protocol was 1:1:1:1 for taranabant 0.5 mg, taranabant 1 mg, taranabant 2 mg, and placebo, respectively. Patients were stratified by the use of metformin at baseline. The study consisted of a 1-week screening period, a 2-week single-blind placebo run-in period, a 52-week treatment period, and a 28-day follow-up period. Diet (25% hypocaloric) and exercise counseling were initiated at the start of the placebo run-in period and continued throughout the study. Discontinued patients were allowed to continue in the study off study drug.

Subject/Patient Disposition Over 36 Weeks and 52 Weeks:

	Taranabant 0.5 mg	Taranabant 1 mg	Taranabant 2 mg	Placebo	Total
Screened					1556
Screening Failures:					933
Randomized:	155	157	155	156	623
Male (age range, years)	67 (31-73)	67 (35-75)	69 (31-72)	74 (20-74)	277 (20-75)
Female (age range, years)	88 (20-72)	90 (28-72)	86 (29-75)	82 (27-74)	346 (20-75)
Pre-Treatment†	n =0	n =0	n =1	n =0	n =1
Discontinued	0	0	1	0	1
	n (%)	n (%)	n (%)	n (%)	n (%)
Treatment	n =155	n =157	n =154	n =156	n =622
Completed 36 weeks	123 (79.4)	118 (75.2)	122 (78.7)	123 (78.8)	486 (78.0)
Treatment					
Discontinued over 36 weeks	32 (20.6)	39 (24.8)	32 (20.6)	33 (21.2)	136 (21.8)
Patient discontinued Rx with follow up	8 (5.2)	9 (5.8)	7 (4.5)	7 (4.5)	35 (5.6)
Patient discontinued Rx without follow up	24 (15.5)	23 (14.8)	23 (14.8)	26 (16.7)	101 (16.2)
Clinical AE	9 (5.8)	16 (10.2)	8 (5.1)	9 (5.8)	42 (6.7)
Lack efficacy	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Lost to follow-up	8 (5.2)	10 (6.4)	11 (7.1)	12 (7.7)	41 (6.6)
Pat. moved	3 (1.9)	1 (0.6)	2 (1.3)	2 (1.3)	8 (1.3)
Pat. withdrew consent	9 (5.8)	8 (5.1)	8 (5.2)	5 (3.2)	30 (4.8)
Protocol dev	0 (0.0)	0 (0.0)	1 (0.6)	2 (1.3)	3 (0.5)
Laboratory AE	1 (0.6)	1 (0.6)	0 (0.0)	1 (0.6)	3 (0.5)
Discont. for other	2 (1.2)	2 (1.3)	2 (1.2)	2 (1.2)	8 (1.3)
Completed 52 weeks	116 (74.8)	112 (71.3)	117 (75.5)	114 (73.1)	459 (73.7)
Treatment					
Discontinued over 52 weeks	39 (25.2)	45 (28.7)	37 (23.9)	42 (26.9)	163 (26.2)
Patient discontinued Rx with follow up	9 (5.8)	14 (8.9)	10 (6.5)	8 (5.1)	41 (6.6)
Patient discontinued Rx without follow up	30 (19.4)	31 (19.7)	27 (17.4)	34 (21.8)	122 (19.6)
Clinical AE	11 (7.1)	19 (12.1)	10 (6.4)	10 (6.4)	50 (8.0)
Lack efficacy	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	1 (0.2)
Lost to follow-up	10 (6.5)	9 (5.7)	11 (7.1)	14 (9.0)	44 (7.1)
Pat. moved	4 (2.6)	4 (2.5)	2 (1.3)	2 (1.3)	12 (1.9)
Pat. withdrew consent	9 (5.8)	9 (5.7)	9 (5.8)	10 (6.4)	37 (5.9)
Protocol dev	1 (0.6)	0 (0.0)	1 (0.6)	2 (1.3)	4 (0.7)
Laboratory AE	1 (0.6)	1 (0.6)	1 (0.6)	2 (1.2)	5 (0.8)
Discont. for other	3 (1.9)	2 (1.3)	3 (1.9)	2 (1.2)	10 (1.6)

† Randomized patients who did not take any post-randomization study medication.

Table based on first patient discontinuation status or status at Week 36 / Week 52 visit, whichever occurred first.

[redacted]

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

DIAGNOSIS/INCLUSION CRITERIA: Patients with T2DM (≥18 and ≤75 years of age), either not on antihyperglycemic medication or on a stable dose of metformin (≥1500 mg/day). The HbA_{1c} had to be ≥7.0% and ≤10.0% and the BMI had to be ≥27 kg/m^2 and ≤ 43 kg/m^2. If patients met these criteria, in addition to other entry criteria they were eligible to participate.

EVALUATION CRITERIA:

EFFICACY MEASUREMENTS: Body weight, HbA_{1c}, waist circumference, FPG, insulin and insulin sensitivity, fasting lipid profile (TG, HDL-C, non-HDL-C, LDL-C, TC), adiponectin, CRP, blood pressure, proportion of patients requiring glycemic rescue therapy, quality-of-life and health economic patient reported outcomes.

SAFETY MEASUREMENTS: Safety assessments included collection of adverse experiences, physical examination, vital signs, and electrocardiogram (ECG). Laboratory safety assessment included blood chemistry, hematology, urinalysis, and urine pregnancy testing (in women of child bearing potential). Depression, mood, and cognitive/neuropsychomotor function were assessed with standard questionnaires (Patient Health Questionnaire-9 [PHQ-9], Profile of Mood States brief form [POMSb], and Digit Symbol Substitution Test [DSST]). 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 primary efficacy endpoints of change from baseline in body weight and change from baseline in HbA_{1c} at Week 36 were assessed by analysis of covariance (ANCOVA) models including terms for treatment, baseline HbA_{1c}, baseline body weight, weight change during the run-in period, baseline anti-hyperglycemic treatment (metformin or not currently on antihyperglycemic therapy), and region. In addition, the proportion of patients who lost ≥5% of their baseline body weight (5% weight loss responders) and the proportion of patients who lost ≥10% of their baseline body weight (10% weight loss responders) at Week 36 were analyzed using logistic models with the same terms as used in the ANCOVA model for primary endpoints. Key secondary efficacy endpoints, including change from baseline in glycemic parameters (FPG, fasting insulin, insulin sensitivity) and percent change from baseline in lipid parameters (triglycerides, HDL-C, non-HDL-C, LDL-C) at Week 36, were analyzed using ANCOVA models with terms for treatment, baseline parameter value, change in the parameter during the run-in (if available), baseline HbA_{1c}, baseline anti-hyperglycemic treatment, baseline body weight, change in weight during the run-in, and region. In particular, percent change in triglycerides was assessed non-parametrically using Tukey's normalized scores of the change in triglycerides. Other secondary efficacy endpoints include change from baseline in body weight, HbA_{1c}, 5% weight loss responders, 10% weight loss responders, glycemic parameters, and lipid profile parameters at Week 24 and Week 52, percent change from baseline in body weight at Weeks 24, 36, and 52, proportions of patients who had an HbA_{1c} <7% or <6.5% at Weeks 24, 36, and 52, proportion of patients requiring glycemic rescue therapy at Weeks 24, 36, and 52, and change from baseline in waist circumference, blood pressure, CRP, adiponectin, scores on patient-reported quality of life outcomes, and health economic assessment at Weeks 24, 36, and 52. Change or percent change (as appropriate) in these secondary variables was analyzed using an ANCOVA model with terms for treatment, baseline HbA_{1c}, baseline body weight, baseline parameter value, change in parameter during the run-in (if available), change in weight during the run-in, baseline anti-hyperglycemic treatment (metformin or not currently on antihyperglycemic therapy), and region.

Randomization of approximately 600 patients consisting of men (minimum 25%; targeting 40%) and women was planned for this study. Patients were stratified based on presence or absence of metformin therapy at baseline and were randomized to 1 of 3 doses of taranabant (0.5 mg, 1 mg, or 2 mg) or placebo within each stratum in a 1:1:1:1 ratio, resulting in approximately 150 patients randomized to each of the 4 treatment arms. Assuming a standard deviation of 6.5 kg for mean weight change from baseline at Week 36 and a standard deviation of 1.15% for mean change in HbA_{1c} at Week 36, the study had 90% (80%) power to detect a difference of 2.4 (2.1) kg in mean change from baseline in body weight at Week 36, and a difference of 0.43% (0.37%) in mean change from baseline in HbA_{1c}. For subgroups defined by metformin or drug-naïve strata, the study had 90% (80%) power to detect a difference of 3.8 (3.3) kg in mean change from baseline in body weight at Week 36, and a difference of 0.69% (0.59%) in mean change from baseline in HbA_{1c}.

SAFETY: Safety and tolerability were assessed by a review of all safety parameters including adverse experiences, clinical and laboratory safety parameters, mood and cognition function, and ECG data. Changes in Profile of Mood States brief form (POMSb), Digit Symbol Substitution Test (DSST), and PHQ-9 were also assessed. Comparisons of proportions of patients with laboratory values exceeding predefined limits of change were performed. A tiered approach was used for the analysis of adverse experiences: for prespecified (Section 4.4.1 of the statistical analysis plan [SAP]) Tier 1 adverse experiences (gastrointestinal [GI], nervous system, psychiatric, skin and subcutaneous, and vascular disorders), inferential p-values were obtained based on differences in proportions of patients with an event using Fisher's exact test. In addition, confidence intervals (CIs) for the between-group differences between placebo and each dose of taranabant were computed using Wilson's Score method. For Tier 2 adverse experiences (specified as adverse experiences with an incidence ≥2% in 1 or more treatment groups), the proportion of patients with the adverse experience in the active versus placebo groups was compared using 95% CIs. All other adverse experiences (Tier 3) were tabulated. All patients had a 28-day posttreatment follow-up after cessation of study medication and were monitored for serious and non-serious adverse experiences. The primary analysis included safety data during the active treatment period prior to rescue. Secondary analyses included all safety data regardless of discontinuation of study drug or initiation of rescue therapy and all safety data regardless of discontinuation of study drug, but excluding data after initiation of rescue therapy.

Ninety-five percent CIs 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 CI 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 the adverse experience will be described as having a numerically higher or numerically lower incidence compared with placebo.

RESULTS:

EFFICACY: For the endpoints described in the primary hypotheses and related endpoints of interest, results are displayed in the table below. The changes from baseline in body weight at Week 36 induced by taranabant 0.5 mg, 1 mg, and 2 mg were significantly greater than placebo. The reductions of HbA_{1c} from baseline induced by taranabant 1 mg and 2 mg were significantly greater than placebo, while the reduction induced by taranabant 0.5 mg was not significantly different from placebo. At Week 36 the proportions of 5% and 10% weight loss responders in the taranabant 1-mg and 2-mg groups were significantly greater than in the placebo group. The proportion of patients with an HbA_{1c} <7% at Week 36 was significantly greater compared to placebo in the taranabant 1-mg and 2-mg groups. The proportion of patients with an HbA_{1c} <6.5% at Week 36 was significantly greater in the taranabant 2-mg group compared to placebo.

Body Weight and HbA_{1c} Related Endpoints
All Patients Treated Population

Change from baseline in body weight (kg) at Week 36				
Treatment Group	N	LS Mean	LS Mean Difference from Placebo (95% CI)	p-Value
Taranabant 0.5 mg	149	-3.7	-1.2 (-2.1, -0.3)	0.008
Taranabant 1 mg	155	-4.5	-2.0 (-2.8, -1.1)	<0.001
Taranabant 2 mg	149	-5.1	-2.6 (-3.5, -1.7)	<0.001
Placebo	154	-2.5	-	-
Number (%) of patients who lost ≥5% of baseline body weight at Week 36				
Treatment Group	N	Number (%) of responders	Adjusted Odds Ratio from Logistic Model (95% CI)	p-Value
Taranabant 0.5 mg	149	54 (36.2)	1.5 (0.9, 2.5)	0.116
Taranabant 1 mg	155	74 (47.7)	2.4 (1.5, 3.9)	<0.001
Taranabant 2 mg	149	80 (53.7)	3.0 (1.8, 4.9)	<0.001
Placebo	154	44 (28.6)	-	-
Number (%) of patients who lost ≥10% of baseline body weight at Week 36				
Treatment Group	N	Number (%) of responders	Adjusted Odds Ratio from Logistic Model (95% CI)	p-Value
Taranabant 0.5 mg	149	10 (6.7)	1.4 (0.5, 3.9)	0.465
Taranabant 1 mg	155	18 (11.6)	2.8 (1.1, 6.7)	0.026
Taranabant 2 mg	149	22 (14.8)	3.5 (1.5, 8.3)	0.005
Placebo	154	8 (5.2)	-	-
Change from HbA_{1c} (%) at Week 36				
Treatment Group	N	LS Mean	LS Mean Difference from Placebo (95% CI)	p-Value
Taranabant 0.5 mg	141	-0.47	-0.08 (-0.29, 0.14)	0.484
Taranabant 1 mg	150	-0.68	-0.29 (-0.50, -0.08)	0.007
Taranabant 2 mg	144	-0.71	-0.31 (-0.52, -0.10)	0.003
Placebo	149	-0.40	-	-
Number (%) of patients with HbA_{1c} <7% at Week 36				
Treatment Group	N	Number (%) of responders	Adjusted Odds Ratio from Logistic Model (95% CI)	p-Value
Taranabant 0.5 mg	141	58 (41.1)	1.4 (0.8, 2.5)	0.183
Taranabant 1 mg	150	70 (46.7)	2.0 (1.2, 3.4)	0.013
Taranabant 2 mg	144	71 (49.3)	2.3 (1.3, 3.9)	0.003
Placebo	149	52 (34.9)	-	-
Number (%) of patients with HbA_{1c} <6.5% at Week 36				
Treatment Group	N	Number (%) of responders	Adjusted Odds Ratio from Logistic Model (95% CI)	p-Value
Taranabant 0.5 mg	141	31 (22.0)	1.6 (0.8, 3.0)	0.150
Taranabant 1 mg	150	30 (20.0)	1.4 (0.7, 2.6)	0.318
Taranabant 2 mg	144	36 (25.0)	1.8 (1.0, 3.4)	0.057
Placebo	149	26 (17.4)	-	-
Note: Missing values imputed using the last post-baseline measurement. CI = Confidence Interval; LS = Least Squares.				

Other Efficacy Endpoints: All treatment groups in the early responder subgroup (patients who lost at least 1.5 kg of their baseline body weight at Week 4) lost more weight, had greater proportions of 5% and 10% weight loss responders, and had a greater reduction in HbA_{1c} at Week 36 and Week 52. Treatment with taranabant 0.5 mg, 1 mg, and 2 mg led to a statistically significant decrease in waist circumference and a statistically significant reduction in FPG compared with placebo at Week 36. An increase in insulin sensitivity from baseline was observed for all taranabant doses, the difference compared with the placebo group was statistically significant for the taranabant 2-mg group. For lipid parameters, a significant decrease in TGs compared with the placebo group was observed for all taranabant groups, for HDL-C a significantly larger increase in the taranabant 2-mg group compared with the placebo group was observed at Week 36. For blood pressure, small numerical decreases were observed in the taranabant groups, but the differences compared with the placebo group were not significant. CRP levels decreased significantly in the taranabant 1-mg and 2-mg groups compared with the placebo group at Week 36. The analyses of the primary endpoints body weight and HbA_{1c} at Week 52 confirmed the results observed at Week 36.

SAFETY: The safety analysis focused on the 52-week treatment period. The overall incidence of clinical adverse experiences is shown in the table below. The incidences of serious clinical adverse experiences were low and comparable in all taranabant groups and the placebo group. The incidences of drug-related serious clinical adverse experiences were similar in the placebo group and the taranabant 0.5-mg group and slightly higher in the taranabant 1-mg and 2-mg groups.

There were no meaningful changes in any laboratory measures. No serious laboratory adverse experiences were reported. One (1) patient in each treatment group discontinued due to a laboratory adverse experience: One (1) patient in the 0.5-mg group and 1 patient in the 1-mg group were discontinued due to alanine aminotransferase increase. One (1) patient in the 2-mg taranabant group was discontinued due to absolute neutrophil and white blood cell count decrease and 1 patient in the placebo group was discontinued due to fasting blood glucose increase.

Clinical Adverse Experience Summary
Treatment Phase - Excluding data after initiation of glycemic rescue therapy (Over 52 weeks)
All Patients as Treated Population

	Taranabant 0.5 mg (N = 155)		Taranabant 1 mg (N = 157)		Taranabant 2 mg (N = 154)		Placebo (N = 156)	
	n	(%)	n	(%)	n	(%)	n	(%)
Number (%) of patients:								
With one or more adverse experiences	108	(69.7)	106	(67.5)	100	(64.9)	89	(57.1)
With no adverse experience	47	(30.3)	51	(32.5)	54	(35.1)	67	(42.9)
With drug-related adverse experiences†	20	(12.9)	36	(22.9)	35	(22.7)	24	(15.4)
With serious adverse experiences	8	(5.2)	10	(6.4)	10	(6.5)	5	(3.2)
With serious drug-related adverse experiences	1	(0.6)	2	(1.3)	3	(1.9)	1	(0.6)
Who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Discontinued due to adverse experiences	10	(6.5)	17	(10.8)	9	(5.8)	10	(6.4)
Discontinued due to drug-related adverse experiences	7	(4.5)	8	(5.1)	9	(5.8)	4	(2.6)
Discontinued due to serious adverse experiences	2	(1.3)	5	(3.2)	3	(1.9)	4	(2.6)
Discontinued due to serious drug-related adverse experiences	1	(0.6)	2	(1.3)	3	(1.9)	1	(0.6)

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

Laboratory Adverse Experience Summary
Treatment Phase - Excluding data after initiation of glycemic rescue therapy (Over 52 weeks)
All Patients as Treated Population

	Taranabant 0.5 mg (N = 155)		Taranabant 1 mg (N = 157)		Taranabant 2 mg (N = 154)		Placebo (N = 156)	
	n	(%)‡	n	(%)‡	n	(%)‡	n	(%)‡
Number (%) of patients:								
With at least one lab test postbaseline	149		154		149		154	
With one or more adverse experiences	27	(18.1)	17	(11.0)	9	(6.0)	24	(15.6)
With no adverse experience	122	(81.9)	137	(89.0)	140	(94.0)	130	(84.4)
With drug-related adverse experiences†	2	(1.3)	2	(1.3)	1	(0.7)	1	(0.6)
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	1	(0.7)	1	(0.6)	1	(0.7)	1	(0.6)
Discontinued due to drug-related adverse experiences	1	(0.7)	1	(0.6)	1	(0.7)	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.

Tier 1 adverse experiences included adverse experiences in the GI Disorders, Nervous System Disorders, Psychiatric Disorders, Skin and Subcutaneous Tissue Disorders, and Vascular Disorders System Organ Classes (SOCs). SOC adverse experience terminology follows the current version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of the analysis. The term "grouping" refers to MedDRA preferred terms that describe clinically related adverse experiences.

The incidences of adverse experiences within the GI Disorders SOC were numerically higher in all taranabant treatment groups compared with the placebo group. For the specific adverse experiences nausea, vomiting, and diarrhea, numerically higher incidences were observed in all taranabant groups compared with the placebo group. The incidences of nausea in the 2-mg taranabant group and the incidence of diarrhea in the 0.5-mg taranabant group were statistically significantly higher compared with placebo. In general, adverse experiences within the GI Disorders SOC were predominantly mild to moderate in intensity and were mostly single episodes, and resolved either during continued treatment or after discontinuation (>80% of all GI-related adverse experiences resolved in all treatment groups). The incidence of discontinuations due to GI-related adverse experiences was low and similar in the taranabant groups and the placebo group.

The incidences of adverse experiences within the Nervous System Disorders SOC were higher in the taranabant 1-mg and 2-mg groups and numerically higher in the taranabant 0.5-mg group compared with the placebo group. However, for the prespecified expanded Nervous System Disorder SOC numerically higher incidences of adverse experiences were observed in the taranabant groups compared with the placebo group but the differences were not statistically significant. Numerically

higher incidences for all taranabant groups compared with the placebo group were observed for adverse experiences within the dizziness grouping and the sensory disorder grouping. The adverse experiences of dizziness were single episodes and mostly mild to moderate in intensity. All adverse experiences of dizziness resolved and only 1 patient discontinued due to an adverse experience of dizziness. For adverse experiences in the sensory disorder grouping the reported intensities in the taranabant groups were mild to moderate and no event led to discontinuation. Adverse experiences within this grouping in the taranabant groups resolved in most cases.

The incidences of adverse experiences within the Psychiatric Disorders SOC plus irritability were significantly higher in the 1-mg taranabant groups compared with the placebo group and borderline significantly higher for the 2-mg taranabant group. However, similar incidences compared with the placebo group were observed in the taranabant 0.5-mg group.

The incidence of adverse experiences in the depression grouping was significantly higher in the 2-mg group compared with the placebo group and numerically higher in the 1-mg group, whereas the adverse experiences in the depression grouping were rare and similar in the taranabant 0.5-mg group and the placebo group. Adverse experiences of depression were mostly mild to moderate in intensity, mostly patients experiencing single episodes. Resolution of the adverse experiences within the depression grouping occurred in most patients in the taranabant groups. The only adverse experience of suicidal ideation was reported for 1 patient in the placebo group in this study.

The higher incidence of irritability in the 1-mg group was statistically significant and the incidences in the 0.5-mg and 2-mg groups were numerically higher compared with the placebo group. The intensities of the adverse experiences of irritability were mostly mild to moderate. One (1) patient in the 1-mg group experienced severe irritability, but no serious adverse experience of irritability was reported. One (1) patient in the 0.5-mg group and 1 patient in the 1-mg group discontinued due to this adverse experience. Resolution of the adverse experience of irritability occurred in most patients in the taranabant groups.

The incidences of adverse experiences in the altered affect grouping, nervousness, anxiety grouping, anxiety, anxiety disorder, panic disorder, panic attack, and in the insomnia grouping were similar between the taranabant groups and the placebo group.

The incidences of adverse experiences within the Skin and Subcutaneous Tissue Disorders SOC minus hypoaesthesia facial were similar between the taranabant groups and the placebo group. For the specific adverse experience of pruritus generalized, a higher incidence was observed in the taranabant 0.5-mg group compared with the placebo group. However, the incidences of the combined adverse experiences pruritus and pruritus generalized were not statistically different between any taranabant group and the placebo group. The intensities of the adverse experiences of pruritus and pruritus generalized were mostly mild and occurred as a single episode. Two (2) patients in the 0.5-mg group discontinued due to an adverse experience of pruritus/pruritus generalized. Resolution of the adverse experiences of pruritus and pruritus generalized occurred in all patients in the taranabant groups.

The incidences of adverse experiences in the Vascular Disorders SOC were low and comparable in the taranabant groups and the placebo group.

For Tier 1 adverse experiences, including psychiatric disorders, the incidences were similar in the early responders (subgroup of patients who lost at least 1.5 kg of their baseline body weight at Week 4) and in early non-responders.

No meaningful differences between the taranabant groups and the placebo group in laboratory or ECG safety parameters were observed.

CONCLUSIONS:

In overweight and obese patients with type 2 diabetes mellitus and inadequate glycemic control on diet and exercise alone or on metformin monotherapy:

1. At Week 36, treatment with taranabant 0.5 mg, 1 mg, and 2 mg results in a statistically significant reduction in body weight and waist circumference compared with placebo. Weight loss after 4 weeks of treatment is a good predictor of Week 36 and Week 52 weight loss response.

2. At Week 36, treatment with taranabant 1 mg and 2 mg results in a statistically significant reduction in HbA_{1c} compared with placebo. Weight loss after 4 weeks of treatment is a good predictor of the reduction in HbA_{1c} at Week 36 and Week 52.

3. At Week 36, treatment with taranabant 0.5 mg, 1 mg, and 2 mg results in a statistically significant reduction in FPG compared with placebo.

4. At Week 36, treatment with taranabant 0.5 mg, 1 mg, and 2 mg results in a statistically significant improvement in triglycerides. Treatment with taranabant 1 mg and 2 mg result in a statistically significant improvement in CRP and treatment with taranabant 2 mg results in a statistically significant improvement in insulin sensitivity and HDL-C.

5. At Week 52 of treatment taranabant 1 mg is associated with a significantly higher incidence of psychiatric-related adverse experiences compared with placebo. Taranabant 2 mg is associated with a numerically higher incidence of psychiatric-related adverse experiences compared with placebo. For taranabant 0.5 mg, the incidence of psychiatric-related adverse experiences is similar to placebo, except for irritability which has a numerically higher incidence compared to placebo. The most commonly reported psychiatric-related adverse experiences are irritability and adverse experiences in the depression grouping. In general, psychiatric-related adverse experiences are mild to moderate in intensity and resolve either during continued treatment or after discontinuation from drug therapy.

6. At Week 52 of treatment taranabant 0.5 mg, 1 mg, and 2 mg are associated with an increased incidence of GI related adverse experiences (nausea, diarrhea, and vomiting) and Nervous System related adverse experiences (dizziness and adverse experiences in the sensory disorder grouping) compared with placebo. These adverse experiences are primarily mild to moderate in intensity, single episodes and lead to few discontinuations.

7. The adverse experience profile of taranabant is similar in early responders and non-responders.

8. Treatment with taranabant over 52 weeks is not associated with significant laboratory safety test abnormalities compared with placebo.

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