PFIZER INC.

These results are supplied for informational purposes only.
Prescribing decisions should be made based on the approved package insert.
For publications based on this study, see associated bibliography.

PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: None/CP-945,598

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NCT NO.: NCT00396448

PROTOCOL NO.: A5351019

PROTOCOL TITLE: A 2-Year, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Long-Term Efficacy and Safety of CP-945,598 in the Treatment of Obese Subjects

Study Centers: 62 centers in 11 countries Argentina (6), Australia (6), Chile (3), France (6), Germany (6), Republic of Korea (4), Mexico (1), Spain (5), Sweden (3), United Kingdom (6), and the United States (16).

Study Initiation and Termination Dates: 19 February 2007 to 11 February 2009

(Pfizer decided to discontinue this study, and the CP-945,598 development program, based on changing regulatory perspectives of the risk/benefit profile of the CB1 class of drugs and the likely resulting new regulatory requirements for approval)

Phase of Development: Phase 3

Study Objectives:

Co-Primary Objectives:

Determine the effect of CP-945,598 on:

- Percent change in body weight at Year 1;
- Proportion of subjects who lose 5% of body weight at Year 1.

Secondary Clinical Objectives

Determine the effect of CP-945,598 on:

- Percent change in body weight at Year 2;
- Proportion of subjects who lose 10% body weight at Year 1;

- Changes in waist circumference at Year 1;
- Changes in high-density lipoprotein (HDL) and triglycerides at Year 1.

Secondary Patient Reported Outcome Objectives

Determine the effect of CP-945,598 on Changes in Patient Reported Outcome Scales at 1 Year:

- --Uncontrolled Eating (from the Three Factor Eating Questionnaire R 21) and;
- --Power of Food (from the Power of Food Scale, USA or AMOTPIOTFE, ex USA).

Exploratory Objectives

- Evaluate the safety and tolerability of CP-945,598 in a 2-year outpatient setting.
- Explore the effect of CP-945,598 on:
  - Pharmacodynamic (PD) measurements including glucose, insulin, total cholesterol, low-density lipoprotein-cholesterol (LDL-C), HDL-C, triglycerides, apolipoprotein AI (Apo-AI), apolipoprotein B (Apo-B), number and size of LDL particles, adiponectin, and high sensitivity C-reactive protein (hsCRP);
  - Waist circumference;
  - Proportion of subjects who lose 5 and 10% body weight;
  - Sun/Artificial light related adverse event (AE) monitoring;
  - Prevalence of metabolic syndrome;
  - Patient Reported Outcomes;
  - Characterize the pharmacokinetics (PK) of CP-945,598 in the target population including an assessment of covariate effects by population PK modeling.
- Explore PK/PD relationships between CP-945,598 exposure and changes in body weight, and other selected secondary endpoints as permitted by the data.

Note: Pfizer decided to discontinue this study, and the CP-945,598 development program, based on changing regulatory perspectives of the risk/benefit profile of the CB-1 class of drugs and the likely resulting new regulatory requirements for approval. Therefore, only the results for the co-primary objectives and the safety and tolerability assessments were reported.

METHODS

Study Design: This was designed to be a 2-year, double-blind, placebo-controlled, 3-arm, parallel-group, multicenter study of CP-945,598 for the assessment of weight loss and weight maintenance.

Approximately 1200 subjects were to have been randomly assigned to receive either 10 mg or 20 mg once daily (QD) of CP-945,598, or placebo for 2 years using a 1:1.5:1 randomization ratio, respectively. Additionally, all subjects were asked to follow a nonpharmacological weight loss program.

An additional research component, involving collection of biological samples for de-identified genetic analysis, was also planned. Subjects could have participated in the study without having to participate in the pharmacogenomics component; the exception was Korean subjects, who did not have the option of providing samples for pharmacogenomics.

Number of Subjects (Planned and Analyzed): Planned enrollment was 1200 subjects; a total of 1663 subjects were screened, and 1253 subjects were randomized and treated:

Diagnosis and Main Criteria for Inclusion: Subjects were males and females aged 18 to 70 years, inclusive, with a body mass index (BMI) of ≥30 kg/m^2 for subjects without comorbidities and ≥27 kg/m^2 for subjects with comorbidities (treated or untreated hypertension and/or treated or untreated dyslipidemia). Hypertension was defined as systolic blood pressure (BP) ≥140 and/or diastolic BP ≥90 mm Hg and/or the subject was on antihypertensive medication. Dyslipidemia was defined as LDL-C not at goal according to local guidelines and/or, triglycerides ≥150 mg/dL and/or HDL-C <40 mg/dL and/or the subject was on any antidyslipidemic medication. Women of childbearing potential were allowed to participate but must have had a negative serum pregnancy test, and if not surgically sterile or postmenopausal, had to agree to use effective contraception during the study (as defined in their respective country). Oral contraceptive use was permitted if used for at least 3 months before starting study medication.

Study Treatment: Subjects were randomly assigned to receive either 10 mg or 20 mg QD of CP-945,598 or placebo for 2 years (using a 1:1.5:1 randomization ratio, respectively). In addition to CP-945,598 or placebo treatment assignments, all subjects were placed on a standardized nonpharmacological weight loss program comprised of diet, physical activity, and behavioral modification advice.

Investigator site personnel administered study medication in the morning to all subjects on the Day 1 visit. Trial medication was taken orally. On the remaining days, subjects self-administered their study medication in the morning on an outpatient basis, without

regard to the timing of breakfast, except for visits specified in the protocol as predose visits. It was recommended that the study medication be taken with water.

Pfizer supplied CP-945,598 as 5 and 15 mg tablets and matching placebo in 40 count bottles. All subjects received 3 bottles in order to maintain the blind. Subjects took 1 tablet from each bottle on a daily basis. All doses were administered using a double-dummy technique. Subjects brought any unused study medication to specific study visits, and the number of tablets were counted to assess compliance.

Efficacy Evaluations: Body weight (the primary efficacy endpoint) was recorded while the subject was wearing only light indoor clothing and no shoes. Pockets were emptied and heavy jewelry, hats, etc. were removed prior to weighing. Body weight was measured using calibrated scales, at approximately the same time and under standardized conditions at every visit. Measurements were recorded to one decimal place.

Pharmacokinetic, Pharmacodynamic, and Metabolic Evaluations and De-identified Genotyping: Blood samples (7 mL) to provide approximately 3 mL of serum for pharmacokinetic analysis were to have been collected at Months 1, 12, and 24 at 0 hours (just prior to dosing). Samples were collected prior to the morning dose for analysis of trough levels at Months 2 and 3. Postdose samples were to have been collected at Month 2 at 2 to 6 hours and at Month 3 at 6 to 12 hours. At each of these visits (Months 2 and 3), 2 PK samples were to have been obtained from each subject, separated by at least 30 minutes.

For PD assays, blood was to have been collected for analysis of fasting plasma glucose, insulin, and lipid profile at Baseline (Day 1) and at Months 6, 12, 18, and 24. Additionally, it was planned to collect blood samples for analysis of adiponectin, hsCRP, Apo-AI, Apo-B, and number and size of LDL particles at baseline (Day 1) and at Months 12 and 24.

It was planned to evaluate the prevalence of metabolic syndrome based on the collection of clinical data at baseline (Day 1) and at the end of Years 1 and 2. Metabolic syndrome was defined according to the most recent accepted guidelines at the time of analysis.

A 9 mL blood sample for the de-identified genotyping was to have been collected at Randomization (Day 1). The goals of the genotyping evaluations were:

- If individuals had an unexpected/unusual response or if analyses revealed populations of ‘responders’ and ‘non-responders’ or variation in PK data, the intention was to use these samples to examine the genetic basis of such responses. Genes that could have been examined include those encoding the target protein of CP-945,598 (ie, CB-1 receptor), other proteins involved in signal transduction pathways as well as proteins involved in the disposition, metabolism, and elimination of CP-945,598 (such as CYP3A5). In addition, other genes could have been selected based upon current literature knowledge.
- To examine the contribution of genetic variation to the development of obesity and related conditions. Samples from this study, as well as other

obesity collections, may be used for candidate gene or whole genome association studies to identify or confirm disease-susceptibility loci.

Participation in this component of the study was voluntary.

Results for the PK, PD, metabolic, and genotyping evaluations are not summarized in this synopsis report but may be summarized separately.

Safety Evaluations: Safety and tolerability were assessed using monitoring of AEs, vital signs measurements (BP and pulse rate), clinical laboratory measurements, and 12-lead electrocardiograms (ECGs).

In order to determine if there were any effects in response to sun exposure during CP-945,598 treatment, subjects were asked at each clinic visit whether they had experienced any sun- or artificial light-related AEs. Examples of events of interest in this area included: erythema, sun burn, and urticaria.

Statistical Methods: The Full Analysis Set (FAS) was defined as the set of subjects who took at least 1 dose of assigned study medication, had a valid baseline measurement and at least 1 valid posttreatment weight measurement. This was the set of subjects used for the primary significance tests. The Per Protocol Completers (PPC) were protocol-adherent subjects who correctly completed approximately 12 months of treatment for the 1-Year analyses and/or approximately 24 months of treatment for the 2-Year analyses. Subjects who, either for reasons of personal choice or medical necessity, discontinued study medication were invited to continue participating in the study by undergoing study tests and measurements; this was the off-drug, in-study subset (ODIS). A subject was considered to be a 5% 'responder' at Year 1 or Year 2 if they made the endpoint visit within the weight determination window associated with that visit, and the weight recorded at that visit was at least 5% less than their baseline weight.

There were 2 analyses of the primary co-objectives of the existence and magnitude of treatment effects on weight loss. The prespecified primary comparison was between the 20 mg treatment group and the placebo control group.

For one analysis, a linear model was used to fit by ordinary least squares to the percent change from baseline data of the FAS subset using last observation carried forward (LOCF) at the 1-Year time point.

In the other analysis, the frequency of 5% response at the 1-Year time point was compared to the frequency in the control group by means of the Cochran-Mantel-Haenszel (CMH) method (using the FAS LOCF subset).

An important secondary analysis for both testing and estimation of weight loss treatment effects was conducted by fitting a repeated measures analysis model to the observed data of the FAS.

The magnitude of the treatment effects were also estimated using the linear model, and using the Per Protocol Completers subset.

As a "worst-case analysis", the frequencies of 5% response at 1-Year in the data set formed by combining the FAS with the ODIS data and imputing any missing data as 'failure' were compared using the CMH.

RESULTS

Subject Disposition and Demography: A total of 1663 subjects were screened, and 1253 subjects were randomized and treated: 360 to 10 mg CP-945,598, 534 to 20 mg CP-945,598, and 359 to placebo (Table 1). A total of 1240 subjects (356 10 mg CP-945,598; 529 20 mg CP-945,598; and 355 placebo) were included in the FAS. At Month 12, a total of 945 subjects (264 10 mg CP-945,598; 405 20 mg CP-945,598; and 276 placebo) were evaluated for body weight. At Month 20 (study termination), a total of 71 subjects (19 10 mg CP-945,598; 30 20 mg CP-945,598; and 22 placebo) were evaluated for body weight.

Table 1. Subject Disposition

	Number (%) of Subjects		
	10 mg CP-945,598	**20 mg CP-945,598**	**Placebo**
Screened	1663		
Assigned to treatment	360	534	359
Treated	360	534	359
Completed[a]	0	0	0
Discontinued[a]	360 (100)	534 (100)	359 (100)
Subject died	1 (0.3)	0	0
Unrelated adverse events	2 (0.6)	3 (0.6)	1 (0.3)
Related adverse events	6 (1.7)	7 (1.3)	2 (0.6)
Lost to follow-up	34 (9.4)	47 (8.8)	34 (9.5)
Other reasons (unrelated)	4 (1.1)	7 (1.3)	11 (3.1)
Other reasons (related) [a]	280 (77.8)	415 (77.7)	272 (75.8)
Subject withdrew[b]	33 (9.2)	55 (10.3)	39 (10.9)
Analyzed for safety			
Adverse events	359 (99.7)	533 (99.8)	359 (100.0)
Laboratory analyses	324 (90.0)	478 (89.5)	315 (87.7)
Full Analysis Set[c]	356 (98.9)	529 (99.1)	355 (98.9)
Per Protocol Completers at 1 Year	225 (62.5)	341 (63.9)	236 (65.7)
Number (%) of subjects evaluable for weight at Month 12	264 (73.3)	405 (75.8)	276 (76.9)

[a]Study was terminated.
[b]A total of 127 subjects were considered to have discontinued study treatment; 104 subjects discontinued due to adverse events. Of these, 21 subjects discontinued the study and 83 subjects were off drug, in study (ODIS).
[c]All subjects dosed and having had at least 1 valid postdose weight determination

The majority of subjects in this study were female (1000, 79.8%). Among the female subjects, 58.4% were premenopausal. The mean ages were 45.4, 45.6, and 46.1 years for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 18 to 70 years overall). The mean baseline weight was 102.0 kg, 103.3 kg, and 102.0 kg (range: 61.4 to 197.3 kg overall) for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups,

respectively. Mean BMI was 37.5 kg/m^2, 37.2 kg/m^2, and 37.2 kg/m^2 for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 26.8 to 76.1 kg/m^2 overall). Mean height was 164.8 cm, 166.4 cm, and 165.4 cm for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 141.0 to 200.5 cm overall).

Efficacy Results: A summary of the results for the primary efficacy variable, change in body weight from Baseline to Month 12, is provided in Table 2. Mean body weight at Baseline was comparable across the treatment groups, ranging from 101.9 to 103.1 kg. At Month 12 (LOCF), weight loss was observed in all treatment groups: 5.8% in the CP-945,598 10 mg group, 6.6%, in the CP-945,598 20 mg treatment group, and 4.4% for placebo. The mean percent weight loss for the 10 mg and 20 mg CP-945,598 dose groups was statistically significantly greater than placebo ($p=0.0043$ and $p<0.0001$, respectively; also significant for the repeated measures analysis.

Table 2. Summary of Body Weight at Baseline and Percent Change at Month 12, Full Analysis Set

Study Visit	Statistic	CP-945,598 10 mg	CP-945,598 20 mg	Placebo
Baseline (Day 1)	N	355	529	355
	Mean (SD)	101.98 (20.47)	103.10 (20.52)	101.88 (21.43)
	95% CI	(99.85, 104.12)	(101.35, 104.86)	(99.64, 104.12)
Week 2	N	347	512	348
	Mean (SD)	-1.67 (1.38)	-1.92 (1.48)	-1.19 (1.55)
	95% CI	(-1.82, -1.53)	(-2.05, -1.80)	(-1.35, -1.02)
Month 1	N	331	503	344
	Mean (SD)	-2.70 (2.00)	-3.12 (1.93)	-2.14 (2.01)
	95% CI	(-2.92, -2.49)	(-3.29, -2.95)	(-2.35, -1.93)
Month 2	N	318	475	332
	Mean (SD)	-4.02 (3.01)	-4.78 (2.89)	-3.18 (2.98)
	95% CI	(-4.35, -3.69)	(-5.04, -4.52)	(-3.50, -2.86)
Month 3	N	311	464	315
	Mean (SD)	-5.20 (3.86)	-5.94 (3.70)	-3.83 (3.85)
	95% CI	(-5.63, -4.77)	(-6.28, -5.60)	(-4.26, -3.41)
Month 4	N	293	441	301
	Mean	-5.83 (4.66)	-6.73 (4.34)	-4.46 (4.54)
	95% CI	(-6.36, -5.29)	(-7.13, -6.32)	(-4.98, -3.95)
Month 5	N	287	428	296
	Mean (SD)	-6.35 (5.29)	-7.28 (5.01)	-4.92 (5.05)
	95% CI	(-6.96, -5.73)	(-7.75, -6.80)	(-5.49, -4.34)
Month 6	N	272	413	286
	Mean	-6.86 (5.88)	-7.80 (5.45)	-5.27 (5.51)
	95% CI	(-7.56, -6.15)	(-8.33, -7.28)	(-5.91, -4.63)
Month 8	N	264	403	271
	Mean (SD)	-7.13 (6.52)	-7.66 (6.34)	-5.22 (6.25)
	95% CI	(-7.92, -6.34)	(-8.28, -7.04)	(-5.97, -4.47)
Month 10	N	254	378	249
	Mean (SD)	-6.87 (7.23)	-7.96 (6.69)	-5.54 (6.23)
	95% CI	(-7.77, -5.98)	(-8.63, -7.28)	(-6.31, -4.76)
Month 12	N	233	350	242
	Mean (SD)	-7.30 (7.81)	-8.05 (7.14)	-5.62 (6.51)
	95% CI	(-8.31, -6.29)	(-8.80, -7.30)	(-6.45, -4.80)
Month 12 LOCF	N	355	529	355
	Mean (SD)	-5.83 (7.04)	-6.56 (6.72)	-4.40 (6.22)
	95% CI	(-6.57, -5.10)	(-7.13, -5.98)	(-5.05, -3.75)
			Treatment Comparison	
			LS Mean (SE)	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		-1.43 (0.50)	(-2.42,-0.45)	0.0043
	20 mg CP-945,598 vs placebo		-2.14 (0.46)	(-3.04,-1.25)	<0.0001

Body weight was measured in kilograms.
SD = standard deviation; CI = confidence interval; LOCF = last observation carried forward; LS Mean = least squares mean; vs = versus; SE = standard error; N = number of subjects

Results were similar for the FAS with ODIS set.

Analysis of the Per Protocol Completers demonstrated larger mean percent decreases from Baseline than were observed for the FAS. Mean body weight at Baseline was comparable

across the treatment groups, ranging from 101.7 to 102.8 kg. At Month 12, the observed mean percent decreases in body weight were: 7.5% for the CP-945,598 10 mg group, 8.2% for the 20 mg group, and 5.8% for placebo. The mean percent weight loss for the 10 mg and 20 mg CP-945,598 dose groups was statistically significantly greater than placebo (p=0.011 and p=0.0001, respectively).

The proportions of subjects with at least a 5% decrease in weight at the end of 1 year of treatment were 44.2% (95% confidence interval [CI]: 39.1, 49.4) for the 10 mg CP-945,598 group; 51.6% (95% CI: 47.3, 55.9) for the 20 mg CP-945,598 group; and 34.4% (95% CI: 29.4, 39.3) for the placebo group (FAS LOCF). The difference between the 10 mg and 20 mg CP-945,598 dose groups and placebo was significant (p=0.0072 and p<0.0001, respectively). The odds ratios for the 10 mg and 20 mg CP-945,598 dose groups were 1.51 and 2.04, respectively. The proportions were lower for the FAS with ODIS set (worst case analysis), ranging from 31.8% for placebo to 44.8% for the 20 mg CP-945,598 group and higher for the Per Protocol Completers, ranging from 44.5% for placebo to 62.8% for the 20 mg CP-945,598 group. The differences between the CP-945,598 dose groups and placebo were significant for ODIS and the Per Protocol Completers.

Safety Results:

Adverse Events

A total of 96 subjects experienced serious AEs (SAEs): 27 (7.5%) in the 10 mg CP-945,598 group, 45 (8.4%) in the 20 mg CP-945,598 group, and 24 (6.7%) in the placebo group. Overall, a total of 104 subjects were discontinued from treatment due to AEs, of which 83 subjects were ODIS and 21 subjects were discontinued from the study (see following discussion of discontinuations due to AEs): 32 (8.9%) in the 10 mg CP-945,598 group, 51 (9.6%) in the 20 mg CP-945,598 group, and 21 (5.8%) in the placebo group. A total of 217 subjects had temporary discontinuations of study drug due to AEs: 64 (17.8%) in the 10 mg CP-945,598 group, 105 (19.7%) in the 20 mg CP-945,598 group, and 48 (13.4%) in the placebo group. One subject, in the CP-945,598 10 mg group, died on Day 385 of a myocardial infarction that the investigator considered to be not related to study drug.

A summary of the incidence of treatment-emergent AEs is presented by treatment in Table 3.

Table 3. Treatment-Emergent Adverse Events- All Causalities and Treatment Related

	Number (%) of Subjects		
	10 mg CP-945,598	**20 mg CP-945,598**	**Placebo**
All causalities			
Subjects evaluable for adverse events	360	534	359
Number of adverse events	1430	2083	1277
Subjects with adverse events	317 (88.1)	469 (87.8)	313 (87.2)
Subjects with serious adverse events	27 (7.5)	45 (8.4)	24 (6.7)
Subjects with severe adverse events	35 (9.7)	57 (10.7)	31 (8.6)
Subjects discontinued due to adverse events[a]	32 (8.9)	51 (9.6)	21 (5.8)
Subjects with dose reduced or temporary discontinuation due to adverse events	64 (17.8)	105 (19.7)	48 (13.4)
Treatment related			
Number of treatment-related adverse events	402	701	304
Subjects with treatment-related adverse events	174 (48.3)	296 (55.4)	152 (42.3)
Subjects with treatment-related serious adverse events	4 (1.1)	6 (1.1)	1 (0.3)
Subjects with severe treatment-related adverse events	9 (2.5)	23 (4.3)	6 (1.7)
Subjects discontinued due to treatment-related adverse events[a]	21 (5.8)	38 (7.1)	13 (3.6)
Subjects with dose reduced or temporary discontinuation due to treatment-related adverse events	36 (10.0)	54 (10.1)	24 (6.7)

Except for the Number of Adverse Events, subjects are counted only once per treatment in each row.
[a]Based on Adverse Event page of the Case Report Form.

The AEs that were experienced by more than 5% of subjects during any treatment are summarized in Table 4. The most frequently reported AEs were nasopharyngitis, diarrhea, nausea, headache, back pain, and upper respiratory tract infection.

Table 4. Treatment-Emergent Adverse Events Reported for 5% or More Subjects in a Treatment Group – All Causalities

System Organ Class Preferred Term	Number (%) of Subjects 10 mg CP-945,598 N=360	 20 mg CP-945,598 N=534	 Placebo N=359
Gastrointestinal Disorders			
Constipation	16 (4.4)	25 (4.7)	23 (6.4)
Diarrhea	53 (14.7)	97 (18.2)	29 (8.1)
Nausea	45 (12.5)	90 (16.9)	25 (7.0)
General Disorders and Administrative Site Conditions			
Fatigue	14 (3.9)	28 (5.2)	19 (5.3)
Irritability	16 (4.4)	36 (6.7)	12 (3.3)
Infections and Infestations			
Bronchitis	15 (4.2)	28 (5.2)	19 (5.3)
Influenza	15 (4.2)	26 (4.9)	20 (5.6)
Nasopharyngitis	84 (23.3)	125 (23.4)	80 (22.3)
Upper respiratory tract infection	27 (7.5)	46 (8.6)	33 (9.2)
Injury, Poisoning and Procedural Complications			
Fall	18 (5.0)	17 (3.2)	18 (5.0)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	30 (8.3)	32 (6.0)	33 (9.2)
Back pain	46 (12.8)	49 (9.2)	41 (11.4)
Pain in extremity	12 (3.3)	12 (2.2)	19 (5.3)
Nervous System Disorders			
Dizziness	27 (7.5)	42 (7.9)	22 (6.1)
Headache	57 (15.8)	60 (11.2)	39 (10.9)
Psychiatric Disorders			
Anxiety	21 (5.8)	41 (7.7)	22 (6.1)
Depressed mood	18 (5.0)	26 (4.9)	13 (3.6)
Insomnia	21 (5.8)	24 (4.5)	13 (3.6)

Depressed mood was reported for slightly higher proportions of subjects in the CP-945,598 10 mg and 20 mg groups (5.0% and 4.9%, respectively) compared with placebo (3.6%), and the AE of depressed mood was considered treatment-related in similar proportions of subjects (3.1% and 3.4% in the CP-945,598 10 mg and 20 mg groups, respectively; 2.8% of placebo). Insomnia was more frequent in the CP-945,598 10 mg and 20 mg groups (5.8% and 4.5%, respectively) compared with placebo (3.6%). When analyzed by relatedness to treatment, insomnia was more frequent in the CP-945,598 10 mg group (4.2%) compared with the 20 mg group (2.6%) and placebo (2.2%).

Suicidal ideation was reported for 9 subjects (5 in the CP-945,598 20 mg group, and 2 each in the 10 mg and placebo groups) and was considered related to treatment for 3 of the subjects in the CP-945,598 20 mg group only; 1 of these subjects made a suicide attempt.

All other treatment-related nervous system and psychiatric events, other than headache, were reported in less than 5% of subjects in any treatment group.

The most frequently reported treatment-related AEs were nausea, diarrhea, and headache. Treatment-related nausea was reported more frequently in the CP-945,598 10 and 20 mg groups (9.4% and 13.7%, respectively) compared with placebo (5.0%). A similar trend was observed for treatment-related diarrhea, with the most frequent occurrence in the CP-945,598 10 mg and 20 mg groups (9.2% and 13.3%, respectively), compared with placebo (3.1%). Headache occurred among similar proportions of subjects in the CP-945,598 10 mg and 20 mg and placebo groups (8.3%, 6.2%, and 5.6%, respectively).

The majority of reported SAEs were unrelated to study drug but were related to the subject's underlying disease. Of the 96 subjects who experienced SAEs, 11 subjects had SAEs that were considered related to treatment: 4 subjects in the CP-945,598 10 mg group (squamous cell carcinoma, abnormal liver function test, rheumatoid arthritis, and squamous cell skin carcinoma in 1 subject each); 6 subjects in the CP-945,598 20 mg group (anxiety in 2 subjects; suicide attempt, depression, panic attack, sinusitis aspergillus, and gastroesophageal reflux disease in 1 subject each); and 1 subject in the placebo group (macular edema and optic neuritis).

A total of 21 subjects were discontinued from the study due to AEs (ie, does not include ODIS subjects): 8 subjects in the CP-945,598 10 mg group, 10 subjects in the CP-945,598 20 mg group, and 3 subjects in the placebo group. Of these, 15 subjects discontinued due to treatment-related AEs: 6 subjects in the CP-945,598 10 mg group, 7 subjects in the CP-945,598 20 mg group, and 2 subjects in the placebo group. The most frequently reported treatment-related AE leading to discontinuation was irritability in 2 subjects (1 in the CP-945,598 10 mg group and 1 in the CP-945,598 20 mg group). The AE of depression resulted in discontinuation for 1 subject in the CP-945,598 10 mg group and depressed mood resulted in discontinuation for 1 subject in the placebo group.

A total of 217 subjects had dose reductions or temporary discontinuations of study drug due to AEs. These AEs were considered related to study drug in 114 subjects: 36 subjects (10.0%) in the CP-945,598 10 mg group, 54 subjects (10.1%) in the CP-945,598 20 mg group, and 24 subjects (6.7%) in the placebo group.

No consistent treatment- or dose-related changes in clinical laboratory results, vital signs measurements, or ECG readings were observed.

Patient Health Questionnaires (Generalized Anxiety Disorder-7 [GAD-7] for anxiety and Patient Health Questionnaire-9 [PHQ-9] for depression) were utilized at multiple timepoints for assessment of psychiatric status. The proportions of subjects in each treatment group who had a total score of 10 or more on the GAD-7 at any time were 42 subjects (12.0%) in the CP-945,598 10 mg group, 77 subjects (14.8%) in the CP-945,598 20 mg group, and 38 subjects (10.8%) in the placebo group.

The proportions of subjects who endorsed item #9 (regarding suicidality) on the PHQ-9 questionnaire were higher in the CP-945,598 treatment groups: 11 subjects (3.2%) in the CP-945,598 10 mg group; 21 subjects (4.0%) in the CP-945,598 20 mg group; and 3 subjects (0.8%) in the placebo group.

CONCLUSIONS:

- For the 12-month LOCF analysis, weight loss was observed in all treatment groups: 5.8% in the CP-945,598 10 mg group, 6.6%, in the CP-945,598 20 mg treatment group, and 4.4% for placebo. The mean percent weight loss for the 10 mg and 20 mg CP-945,598 dose groups was statistically significantly greater than placebo ($p=0.0043$ and $p<0.0001$). Results were similar for the FAS with ODIS analysis; analysis of the Per Protocol Completers demonstrated larger mean percent decreases from Baseline than were observed for the FAS.

- The proportions of subjects with at least a 5% decrease in weight were 44.2% (95% CI: 39.1, 49.4) for the 10 mg CP-945,598 group; 51.6% (95% CI: 47.3, 55.9) for the 20 mg CP-945,598 group; and 34.4% (95% CI: 29.4, 39.3) for the placebo group. The difference between the 10 mg and 20 mg CP-945,598 dose groups and placebo was significant ($p=0.0072$ and $p<0.0001$, respectively). The odds ratios for the 10 mg and 20 mg CP-945,598 dose groups were 1.51 and 2.04, respectively. The differences between the CP-945,598 dose groups and placebo were significant for ODIS and the Per Protocol Completers.

- The CP-945,598 10 mg and 20 mg doses were safe and well-tolerated, although gastrointestinal events (primarily nausea and diarrhea), which were considered related to CP-945,598 treatment, were more frequent in the CP-945,598 treatment groups.

- No clinically meaningful trends with regards to treatment-related changes in clinical laboratory results, vital signs measurements, or ECGs were observed.

- Depression and depressed mood were reported as AEs more frequently in the CP-945,598 treatment groups compared with placebo and resulted in discontinuation for 2 subjects overall (1 of whom was treated with placebo). Four subjects in the 20 mg group reported SAEs related to anxiety or depression judged to be related to study medication; these AEs were not considered serious in any other treatment groups. Results for the PHQ-9, Item 9, were consistent with a higher incidence of suicidal ideations in the CP-945,598 treatment groups (3.2% to 4.0% endorsed Item 9 at some time) compared with placebo (0.8%).