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.: NCT00483171

PROTOCOL NO.: A5351028

PROTOCOL TITLE: A 15-Month, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Long-Term Efficacy and Safety of CP-945,598 in Prevention of Weight Regain in Obese Subjects

Study Centers: This study was conducted in 26 centers in 5 countries: Australia (5), Denmark (4), The Netherlands (4), South Africa (4), and the United States (9).

Study Initiation and Termination Dates: 18 January 2008 to 7 January 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 CB-1 class of drugs and the likely resulting new regulatory requirements for approval)

Phase of Development: Phase 3

Study Objectives:
Primary

- To determine the long term efficacy of CP-945,598 in prevention of weight regain in obese or overweight subjects over 12 months after previous weight loss (WL) induced by an 8-week low-calorie diet (LCD)

Secondary

To determine the effect of CP-945,598 at the end of the 12-month treatment period on:

- The proportion of subjects maintaining at least 25%, 50%, 75% or 100% of their initial weight loss achieved during the LCD;
- Changes in waist circumference;
- Changes in triglycerides and high-density lipoprotein (HDL).

- Changes in Patient-Reported Outcome Scales:
  - Uncontrolled Eating (from the Three Factor Eating Questionnaire R 21);
  - Power of Food (from the Power of Food Scale, USA or AMOTPIOTFE, ex USA).

Exploratory and Safety

Explore the effect of CP-945,598 on:

- Electrocardiograms;
- Urine and blood safety laboratory tests;
- Vital signs;
- Pharmacodynamic measurements including fasting insulin, fasting plasma glucose, adiponectin;
- Lipid panel: total cholesterol, low-density lipoprotein (LDL), HDL, triglycerides;
- Trough serum concentrations of CP-945,598;
- Generalized Anxiety Disorder-7 items (GAD-7) and Patient Health Questionnaire-9 items (PHQ-9);
- Columbia Suicide-Severity Rating Scale (C-SSRS);
- Adverse events (AEs);
- Sun/artificial light-related AEs;
- Patient reported outcomes scales; and
- The effect of CP-945,598 on Resting Metabolic Rate (RMR) and Resting Energy Expenditure (REE) (sub-study only).

Note: As described below, development of CP-945,598 was discontinued. This study was stopped prior to completion of the primary objective of measuring weight regain over 12 months; therefore, no subjects completed the protocol. The primary efficacy result of weight regain could not be calculated, but a brief summary of change in body weight following the 8-week LCD period and the results for the primary safety evaluations are summarized.

METHODS

Study Design: This was designed to be a 15-month, double-blind, placebo-controlled, 3-arm, parallel group multicenter study of CP-945,598 for the assessment of weight regain prevention. Subjects were to undergo an intensive 2-month LCD weight loss period. During this period, all subjects were placed on an LCD of 800 to 1000 kcal/day. Subjects who lost ≥5% of their initial body weight were randomly assigned to receive CP-945,598 either 10 mg once daily (QD) or 20 mg QD, or placebo, for 12 months. Additionally, all subjects were

asked to follow a nonpharmacological weight loss program during the 12-month period. A follow-up visit was to occur no more than 30 days after Month 12.

A research component involving collection of biological samples for de-identified genetic analysis was also included in the study protocol. This pharmacogenomics component was optional for subjects participating in this study. No data from this analysis are available at this time.

Number of Subjects (Planned and Analyzed): Planned enrollment was 850 subjects; a total of 1105 subjects were screened, 794 entered the 8-week LCD period, 699 subjects were randomized, and 698 were randomized and treated.

Diagnosis and Main Criteria for Inclusion: Subjects were males and females aged 18 to 70 years, inclusive, with either a body mass index (BMI) of ≥30 kg/m^2 for subjects without comorbidities or ≥27 kg/m^2 for those with comorbidities (treated or untreated hypertension or dyslipidemia, or both).

Women of childbearing potential were allowed to participate in the study but must have had a negative serum pregnancy test, and if not surgically sterile or postmenopausal, had to agree to use effective contraception (based on the judgment of the investigator or designated associate) throughout the study. Oral contraceptive use was permitted if used for at least 3 months prior to starting study drug.

Study Treatment: Subjects were randomly assigned to receive CP-945,598 10 mg or 20 mg, or placebo using a 2:2:3 randomization ratio. Subjects were initially enrolled into the weight loss period of the study. All subjects who completed this period with a weight loss of at least 5% were randomized into the 12-month treatment phase.

All study drug was taken orally in the morning, without regard to the timing of the meal.

In addition to drug treatment or placebo, all subjects were placed on a nonpharmacological weight loss program comprised of an energy-deficit diet, physical activity, and behavioral and lifestyle advice. All subjects were provided with a comprehensive manual describing the program (The Diet and Exercise Guidebook [DEG]) and worked with a health care professional with experience in weight counseling.

Pfizer supplied CP-945,598 as 5 mg and 15 mg tablets and matching placebo in 40-count bottles. All subjects received 3 bottles in order to maintain the blind, and all doses were administered using a double-dummy technique.

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. As the study was terminated prior to reaching the efficacy endpoint, only a summary of weight loss at the last evaluation is presented.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Evaluations: Blood was collected for analysis of fasting plasma glucose, insulin, adiponectin, and lipid profile (HDL, LDL, triglycerides, and total cholesterol) during the study.

Blood samples (7 mL) to provide 3 mL of serum for pharmacokinetics (PK) trough value analysis were to be taken at Months 6 and 12 at 0 hours (just prior to dosing).

Subjects who voluntarily participated in the genomics portion of the study provided a 9-mL blood sample at Randomization (Day 1).

Results for the PK, pharmacodynamics, 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 (blood pressure and pulse rate), clinical laboratory measurements, and 12-lead electrocardiograms (ECGs). Subjects were asked to complete the GAD-7 for anxiety and the PHQ-9 for depression at multiple timepoints for assessment of psychiatric status. Results for the CNS evaluations are not summarized in this synopsis report.

Statistical Methods: The primary efficacy endpoint was prospectively defined as regain in body weight, defined as the change in body weight from Baseline (Day 1, Randomization) to Week 52, expressed as a percentage of the weight lost during the low calorie diet. As no subjects completed the full year of randomized treatment following the 8-week LCD period, the primary endpoint was not analyzed.

The Full Analysis Set (FAS), defined as all randomized subjects who received at least 1 dose of study treatment, had a valid baseline measurement, and at least 1 valid scheduled postrandomization measurement of body weight, was to have been the population for the primary treatment comparisons. Subjects who, either for personal reasons or medical necessity discontinued taking study drug were invited to continue participating in the study by undergoing the remaining study tests and measurements. This was considered the Off-Drug, In-Study (ODIS) subset.

Summary statistics for weight changes from baseline by time in study for the FAS population population are presented, as is a summary of changes from baseline to their last observation regardless of the time in study.

RESULTS

Subject Disposition and Demography: A total of 1105 subjects were screened, 794 entered the 8-week LCD period, 699 subjects were randomized, and 698 were treated: 201 with CP-945,598 10 mg, 297 with CP-945,598 20 mg, and 200 with placebo (Table 1). A total of 690 subjects (199 CP-945,598 10 mg; 293 CP-945,598 20 mg; and 198 placebo) were included in the FAS. As this study was prematurely terminated, no subject was evaluated for change in body weight at the end of Year 1.

Table 1. Subject Disposition

	Number (%) of Subjects		
	10 mg CP-945,598	**20 mg CP-945,598**	**Placebo**
Screened	1105		
Assigned to treatment	201	298	200
Treated	201	297	200
Completed[a]	0	0	0
Discontinued[a]	201 (100.0)	297 (99.7)	200 (100.0)
Unrelated adverse events[b]	1 (0.5)	0	0
Related adverse events[b]	4 (2.0)	5 (1.7)	0
Lost to follow-up	6 (3.0)	9 (3.0)	6 (3.0)
Other reasons (unrelated)	3 (1.5)	1 (0.3)	1 (0.5)
Other reasons (related)[a]	179 (89.1)	264 (88.9)	180 (90.0)
Subject no longer willing to participate	8 (4.0)	18 (6.1)	13 (6.5)
Analyzed for safety			
Adverse events	201 (100.0)	296 (99.3)	199 (99.5)
Laboratory analyses	184 (91.5)	264 (88.6)	179 (89.5)
Never ODIS	179	255	182
Ever ODIS	22	42	18
Full Analysis Set[c]	199	293	198
Per Protocol Completers at 1 Year[a]	0	0	0

[a]Study was terminated; no subject completed 12 months of treatment.
[b]Discontinued from study; does not include additional 36 subjects summarized in Table 1 who were off-drug, in study (ODIS).
[c]Defined as all subjects dosed and having had at least 1 valid postdose weight determination

The majority of subjects in this study were female (530, 75.8%). Among the female subjects, 59.1% were premenopausal. The mean ages were 46.8, 46.4, and 47.8 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 105.5 kg, 107.7 kg, and 105.2 kg for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 65.6 to 307.0 kg overall). Mean BMI was 36.8 kg/m^2, 37.7 kg/m^2, and 37.1 kg/m^2 for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 27.5 to 83.8 kg/m^2 overall; the highest BMI value was attributed to a male subject who was 191.4 cm tall and weighed 307 kg).

Efficacy Results: Due to cancellation of the CP-945,598 development program and the early termination of this study, the primary efficacy variable of weight regain at 12 months could not be analyzed. Mean body weight at Baseline for the treatment period (ie, following completion of the 8-week LCD period) was comparable across the treatment groups, ranging from 95.2 to 97.5 kg. Continued weight loss was observed for both CP-945,598 dose groups at all of the evaluation time points. At the last observation, mean % weight loss was highest in the CP-945,598 10 mg group (2.9%) compared with 2.5% in the CP-945,598 20 mg group, and 2.0% in the placebo group.

Safety Results: A total of 19 subjects experienced serious AEs (SAEs): 5 (2.5%) in the CP-945,598 10 mg group, 7 (2.4%) in the CP-945,598 20 mg group, and 7 (3.5%) in the placebo group. Overall, a total of 46 subjects were discontinued from treatment due to AEs: 16 (8.0%) in the CP-945,598 10 mg group, 25 (8.4%) in the CP-945,598 20 mg group, and 5 (2.5%) in the placebo group, of which 36 subjects were ODIS and 10 subjects were discontinued from the study (see following discussion of discontinuations due to AEs). A total of 65 subjects had temporary discontinuations of study drug due to AEs: 14 (7.0%) in the CP-945,598 10 mg group, 35 (11.8%) in the CP-945,598 20 mg group, and 16 (8.0%) in the placebo group. No subjects died during this study.

A summary of the incidence of treatment-emergent AEs is presented by treatment group in Table 2.

Table 2. 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	201	297	200
Number of adverse events	355	650	323
Subjects with adverse events	145 (72.1)	221 (74.4)	132 (66.0)
Subjects with serious adverse events	5 (2.5)	7 (2.4)	7 (3.5)
Subjects with severe adverse events	21 (10.4)	24 (8.1)	17 (8.5)
Subjects discontinued due to adverse events[a]	16 (8.0)	25 (8.4)	5 (2.5)
Subjects with dose reduced or temporary discontinuation due to adverse events	14 (7.0)	35 (11.8)	16 (8.0)
Treatment related			
Number of treatment-related adverse events	171	330	152
Subjects with treatment-related adverse events	87 (43.3)	156 (52.5)	71 (35.5)
Subjects with treatment-related serious adverse events	0	2 (0.7)	0
Subjects with treatment-related severe adverse events	10 (5.0)	16 (5.4)	6 (3.0)
Subjects discontinued due to treatment-related adverse events[a]	11 (5.5)	22 (7.4)	5 (2.5)
Subjects with dose reduced or temporary discontinuation due to treatment-related adverse events	10 (5.0)	29 (9.8)	7 (3.5)

Except for the Number of Adverse Events, subjects are counted only once per treatment in each row.
[a]Includes subjects who discontinued the study and the additional 36 subjects who were off-drug, in study (ODIS).

The AEs that were experienced by more than 5% of subjects during any treatment are summarized in Table 3. The most frequently reported AEs were headache, nausea, and diarrhea.

Table 3. 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=201	 20 mg CP-945,598 N=297	 Placebo N=200
Gastrointestinal Disorders			
Diarrhea	17 (8.5)	30 (10.1)	5 (2.5)
Nausea	19 (9.5)	39 (13.1)	11 (5.5)
General Disorders and Administration Site Conditions			
Irritability	6 (3.0)	22 (7.4)	7 (3.5)
Infections and Infestations			
Nasopharyngitis	14 (7.0)	18 (6.1)	11 (5.5)
Nervous System Disorders			
Dizziness	11 (5.5)	14 (4.7)	6 (3.0)
Headache	19 (9.5)	30 (10.1)	22 (11.0)
Psychiatric Disorders			
Insomnia	6 (3.0)	15 (5.1)	5 (2.5)
Skin and Subcutaneous Tissue Disorders			
Pruritus	6 (3.0)	15 (5.1)	4 (2.0)

Insomnia was reported most frequently in the CP-945,598 20 mg group (5.1%) compared with 3.0% in the 10 mg group and 2.5% in the placebo group and was considered related to treatment in the majority of cases (2.5% and 4.4% in the CP-945,598 10 mg and 20 mg dose groups, respectively, and 1.5% for placebo). Pruritus was also reported most frequently in the CP-945,598 20 mg group (5.1%) compared with 3.0% in the 10 mg group and 2.0% in the placebo group and was considered related to treatment in the majority of cases (3.0% and 4.4% in the CP-945,598 10 mg and 20 mg dose groups, respectively, and 1.5% for placebo).

Depression was reported for <5% of subjects in all treatment groups but occurred in more subjects in the CP-945,598 10 mg and 20 mg groups (2.5% and 1.7%, respectively) compared with no subjects taking placebo, and was considered treatment-related for the majority of cases (2.0% and 1.3% in the CP-945,598 10 mg and 20 mg groups, respectively).

Suicidal ideation was reported for <2% of subjects in any treatment group, but was reported for 5 subjects overall (1 in the CP-945,598 10 mg group and 4 subjects in the 20 mg group) and was considered treatment-related for 4 of those subjects: 1 in the CP-945,598 10 mg group, 3 in the CP-945,598 20 mg group. No subject made an actual suicide attempt.

The most frequently reported treatment-related AEs were nausea and diarrhea. Treatment-related nausea was reported more frequently in the CP-945,598 10 and 20 mg groups (6.5% and 11.8%, 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 (6.5% and 8.4%, respectively), compared with placebo (1.0%).

The majority of the reported SAEs were considered not related to study drug but were related to subjects' underlying disease. Of the 19 subjects who experienced SAEs, 2 subjects (both

in the CP-945,598 20 mg group) had SAEs considered related to study treatment. One subject experienced spontaneous abortion after 36 days of treatment and 1 subject experienced global amnesia and dyspnea.

A total of 10 subjects were discontinued from the study due to AEs (ie, does not include ODIS subjects): 5 subjects each in the CP-945,598 10 mg and 20 mg groups. Of these, 9 subjects discontinued due to treatment-related AEs: 4 subjects in the CP-945,598 10 mg group and 5 subjects in the CP-945,598 20 mg group. The most frequently reported treatment-related AEs leading to discontinuation were irritability (2 subjects, 1 in each CP-945,598 dose group), and headache (2 subjects, 1 in each CP-945,598 dose group). The AE of suicidal ideation resulted in discontinuation for 1 subject in the CP-945,598 20 mg group.

A total of 65 subjects had dose reductions or temporary discontinuations of study drug due to AEs. These AEs were considered related to study drug in 46 subjects: 10 subjects (5.0%) in the CP-945,598 10 mg group, 29 subjects (9.8%) in the CP-945,598 20 mg group, and 7 subjects (3.5%) in the placebo group.

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

Conclusions:

- This study was discontinued, and the efficacy endpoint of weight regain during the 12 months following completion of an 8-week weight loss period without the use of the study drug cannot be analyzed. However, for the last observation analysis, mean weight loss was observed in all treatment groups (2.9% in the CP-945,598 10 mg group, 2.5% in the CP-945,598 20 mg group, and 2.0% for placebo), as has been observed for protocols A5351019, A5351022, and A5351025.

- 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 was reported as an AE in the CP-945,598 10 mg and 20 mg treatment groups (2.5% and 1.7%, respectively) and for no subjects in the placebo group. No subjects were discontinued for depression; however, 1 subject in the CP-945,598 20 mg group discontinued due to suicidal ideation. Two subjects (both in the CP-945,598 20 mg group) had SAEs that were considered by the investigator to be related to treatment: spontaneous abortion in 1 subject and dyspnea and global amnesia in 1 subject.