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

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NCT NO.: NCT00391196

PROTOCOL NO.: A5351022

PROTOCOL TITLE: A 1-Year, Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Evaluate the Efficacy and Safety of CP-945,598 in the Treatment of Overweight, Oral Agent-Treated Subjects with Type 2 Diabetes Mellitus

Study Centers: This study was conducted in 11 countries (90 centers): Argentina (3), Australia (5), Brazil (6), Canada (7), Czech Republic (5), Germany (6), Mexico (5), Slovakia (4), Sweden (2), United Kingdom (6), and the United States (41).

Study Initiation and Termination Dates: 28 November 2006 to 20 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 CB1 class of drugs and the likely resulting new regulatory requirements for approval.)

Phase of Development: Phase 3

Study Objectives:
Primary Objective

- Determine in overweight/obese subjects with type 2 diabetes mellitus whether body weight could be made significantly lower by treatment with CP-945,598 compared to treatment with placebo.

Secondary Clinical Objectives

- Determine in overweight/obese subjects with type 2 diabetes mellitus whether hemoglobin A_{1c} (HbA_{1c}) could be made significantly lower by treatment with CP-945,598 compared to treatment with placebo;
- Determine the effect of CP-945,598 at 1 year on:
    - Proportion of subjects who lost 5% and 10% body weight;

- Proportion of subjects with HbA_{1c} <6.5;
- Proportion of subjects with HbA_{1c} <7.0;
- Change from baseline waist circumference;
- Change from baseline fasting triglyceride and high density lipoproteins (HDL) concentrations.

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 [in the USA] or AMOTPIOTFE [outside of the USA])

Exploratory Objectives

- Evaluate the safety and tolerability of CP-945,598 in a 1-year outpatient setting;
- Explore the effect of CP-945,598 on:
  - Change from baseline fasting plasma glucose;
  - Change from baseline postprandial glucose determined from oral glucose tolerance tests (OGTT) in a subset of subjects;
  - Fasting and postprandial insulin concentrations determined from OGTT in a subset of subjects;
  - Protocol-defined hypoglycemia event rates and percentage of subjects with hypoglycemic events;
  - 7-point home glucose profiles in a subset of subjects;
  - Additional pharmacodynamic (PD) biomarkers: total cholesterol, low density lipoproteins (LDL), adiponectin, tumor necrosis factor-alpha (TNF-α), and high sensitivity C-reactive Protein (hsCRP);
  - Patient reported outcomes subscales not identified above as a secondary Patient Reported Outcome;
  - Prevalence of metabolic syndrome;

- Homeostasis model assessment (HOMA-IR=fasting insulin × fasting glucose/22.5);
- Background sulfonylurea (SU) or meglitinide (MEG) dose reductions in subjects taking these medications;
- Percentage of subjects who required additional diabetes pharmacotherapy because they met protocol criteria for inadequate glycemic control;
- Patient Health Questionnaire-9 (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) scores;
- Columbia Suicide Severity Rating Scale (C-SSRS)
- Sun/Artificial light-related adverse event (AE) monitoring

- 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 indices of glycemic control, body weight, and other selected efficacy/safety endpoints as permitted by the data.

Note: Only the primary objective of weight loss; the secondary objectives of proportion of subjects who lost 5% of body weight at Month 12, the proportions of subjects with HbA_{1c} <6.5 and <7.0, and results of the GAD-7 and PHQ-9 questionnaires; and the safety evaluations were summarized for this discontinued study.

METHODS

Study Design: This was designed to be a 1-year, double blind, placebo-controlled, 3-arm, parallel-group, multicenter study of CP-945,598 for the assessment of weight loss and glycemic control.

It was planned to enroll approximately 900 subjects, who were randomly assigned to receive CP-945,598 10 mg QD (once daily), CP-945,598 20 mg QD, or placebo to be taken in conjunction with their pre-existing oral anti-diabetes therapy, which could have included any locally approved sulfonylurea (SU), metformin (Met), thiazolidinediones (TZD - rosiglitazone or pioglitazone), sitagliptin, MEG (repaglinide or nateglinide), or alpha-glucosidase inhibitors (AGI - acarbose or miglitol). These agents could have been used as monotherapy or in certain combinations defined in the protocol. All subjects were asked to follow a nonpharmacological weight loss program.

Pre-existing anti-diabetes medicine regimens were managed during the study using protocol-specified criteria.

An additional research component involving collection of biological samples for de-identified genetic analysis was also included in the protocol. This pharmacogenomics

component was optional for subjects participating in this trial. No data from this analysis are available at this time.

Number of Subjects (Planned and Analyzed): Planned enrollment was 900 subjects; 1919 subjects were screened; 975 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion: Subjects were males and females aged 18 to 70 years, inclusive, with a body mass index (BMI) of 27 to 50 kg/m^2 inclusive, and with type 2 diabetes mellitus as defined by the American Diabetes Association for at least 4 months. Subjects were on stable oral anti-diabetes regimens (no changes in agents or doses for at least 4 months prior to study start) consisting of any locally approved SU, Met, TZD, sitagliptin, MEG, or AGI. These agents could have been used as monotherapy or in combinations defined in the protocol. Subjects were to have had screening HbA_{1c} values of between 6.5% and 10%, inclusive, fasting plasma glucose ≤ 270 mg/dL (15 mmol/L), and had documentation of an appropriate ophthalmologic exam (including dilated examination of the fundus) by a qualified health care professional, during the 12 months prior to randomization. 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 one of the following regimens: CP-945,598 10 mg QD, CP-945,598 20 mg QD, or placebo. Subjects were also placed on an identical nonpharmacological weight loss program comprised of an energy-deficit diet appropriate for subjects with diabetes, physical activity, and behavioral and lifestyle 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 was 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 pill 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: For the primary endpoint (change in body weight) and secondary endpoints relating to changes in body weight, body weight was measured while the subject was wearing only light indoor clothing and no shoes, using calibrated scales, at approximately the same time and under standardized conditions at every visit.

HbA_{1c} was measured by a central laboratory using an assay certified by the National Glycohemoglobin Standardization Program (DCCT-consistent).

It was planned for the prevalence of metabolic syndrome to be determined based on clinical data collected at baseline and at the end of Year 1, where metabolic syndrome would be defined according to accepted guidelines at the time of analysis. Due to termination of the program, this assessment will not be performed.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Evaluations: Blood was collected for analysis of lipid profiles (fasting triglycerides, HDL, LDL, total cholesterol), adiponectin, TNF-α, and hsCRP during the study. Only lipid profiles were collected at Screening. Subjects were to have fasted for at least 10 hours prior to sample collection.

Blood samples (7 mL) to provide approximately 3 mL of serum for PK analysis (trough values) were collected at predose on Day 1 (Baseline), and at Months 1 and 12 at 0 hours (just prior to dosing). Additional samples for the randomized sparse sampling PK analysis were collected at Month 2 at 2 to 6 hours postdose and at Month 5 at 6 to 12 hours postdose.

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

Results for the pharmacokinetic, pharmacodynamic, 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 [BP] and pulse rate), clinical laboratory measurements, and 12-lead electrocardiograms (ECGs).

All subjects were provided with a new glucose test meter, along with all supplies needed for home glucose monitoring throughout the study and were asked to measure their glucose whenever hypoglycemic symptoms occurred. Monitoring of the central nervous system (CNS) was also performed via self assessments. Subjects were asked to complete Patient Health Questionnaires (GAD-7 for anxiety and PHQ-9 for depression) as subjective measures of anxiety and depression.

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: For this synopsis report, results for the following endpoints are summarized using the described methods. Test statistics, p-values, and estimates were based on linear contrasts between treatment levels of Least Squares Means calculated from linear models that contained treatment group, diabetes regimen, and baseline value unless otherwise indicated.

- The primary efficacy endpoint of percent change from baseline (as a percentage of baseline) in body weight measured after 1 year of treatment was established by means of tests of the null hypothesis of no treatment effect carried out at the 0.05 (2-sided) level of significance comparing the 20 mg treatment group to the control group. The Full Analysis Set (FAS), defined as all subjects dosed and having at least 1 valid

postdose weight determination, was the subject subset for the primary significance tests for the weight loss objective. Last Observation Carried Forward (LOCF) was used to impute data for those subjects missing the 1-year time points. The Per Protocol Completers analysis set was comprised of all subjects who correctly completed 12 months of treatment and had a 1-year weight measurement. 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). The FAS with ODIS set included all measurements collected while the subjects were ODIS, whereas the FAS analysis excluded those measurements.

- The secondary analysis of HbA_{1c} was carried out by fitting linear models. The baseline HbA_{1c} was defined as the average of the Screening and predose Day 1 HbA_{1c} values. The parameters of interest were the contrasts of the expected values for the treatments at 1 year as estimated by this model.

- A repeated measures analysis was performed for weight and HbA_{1c}. The model contained treatment, occasion, treatment by occasion interaction, anti-diabetes regimen, and baseline value of the analysis variable as fixed independent predictors; and a term for subject as a random effect.

- The proportion of subjects who lost 5% of their body weight was summarized. The odds ratios to the placebo group were estimated based on the inverse-(asymptotic) variance weighted linear combination of the estimators for the log odds ratios within strata defined by anti-diabetes regimen. Missing responses were imputed as "failure" in the worst case analysis conducted for the FAS with ODIS whereas LOCF was used for the FAS analysis.

- Results for the GAD-7 and PHQ-9 scores were analyzed as described above for the primary efficacy variable. There were 4 variables:

  GAD-7 Total, total derived from the first 7 questions
  GAD-7 How Difficult question, the overall summary question
  PHQ-9 Total, derived from the first 9 questions
  PHQ-9, Item 9 (suicidality)

RESULTS

Subject Disposition and Demography: A total of 1919 subjects were screened, and 975 subjects were randomized and treated: 318 to CP-945,598 10 mg, 320 to CP-945,598 20 mg, and 337 to placebo. A total of 963 subjects (315 CP-945,598 10 mg; 314 CP-945,598 20 mg; and 334 placebo) were included in the FAS. At Month 12, a total of 652 subjects (223 CP-945,598 10 mg; 212 CP-945,598 20 mg; and 217 placebo) were evaluated for body weight.

Table S1. Subject Disposition

	Number (%) of Subjects		
	CP-945,598 10 mg	**CP-945,598 20 mg**	**Placebo**
Screened	1919		
Assigned to treatment	318	320	337
Treated	318	320	337
Completed	187 (58.8)	174 (54.4)	172 (51.0)
Discontinued	131 (41.2)	146 (45.6)	165 (49.0)
Subject died	0	0	1 (0.3)
Unrelated adverse events	2 (0.6)	2 (0.6)	4 (1.2)
Related adverse events	3 (0.9)	11 (3.4)	3 (0.9)
Lost to follow-up	26 (8.2)	22 (6.9)	31 (9.2)
Other reasons (unrelated)	9 (2.8)	12 (3.8)	18 (5.3)
Other reasons (related)[b]	68 (21.4)	74 (23.1)	83 (24.6)
Subject withdrew[c]	23 (7.2)	25 (7.8)	25 (7.4)
Analyzed for safety			
Adverse events	318 (100)	320 (100)	337 (100)
Laboratory analyses	314 (98.7)	310 (96.9)	329 (97.6)
Full Analysis Set[a]	315	314	334
Per Protocol Completers at 1 Year	156	127	144
Number (%) of subjects evaluable for weight at Month 12	223 (70.1)	212 (66.3)	217 (64.4)

[a]Defined as all subjects dosed and having had at least 1 valid postdose weight determination
[b]Study was discontinued
[c]Subjects were off-drug, in-study; these 73 subjects and the 25 subjects who discontinued due to unrelated and related adverse events comprise the 98 total subjects who discontinued.

The majority of subjects in this study were female (564, 57.8%) (Table S2). Among the female subjects, 26.2% were premenopausal. The mean ages were 54.7, 54.8, and 55.2 years for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 22 to 71 years overall). The mean baseline weight was 105.1 kg, 101.6 kg, and 102.5 kg (range: 59.2 to 170.1 kg overall) for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively. Mean BMI was 37.1 kg/m^2, 36.3 kg/m^2, and 36.3 kg/m^2 for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 26.3 to 50.9 kg/m^2 overall). Mean height was 168.1 cm, 167.1 cm, and 167.8 cm for the CP-945,598 10 mg, CP-945,598 20 mg, and placebo groups, respectively (range: 144 to 197 cm overall).

Table S2. Demographic Characteristics

Demographic Characteristic	Number (%) of Subjects		
	CP-945,598 10 mg N = 318	CP-945,598 20 mg N = 320	Placebo N = 337
Sex			
Male	138	130	143
Female	180	190	194
Premenopausal	51	45	52
Postmenopausal	129	145	142
Age (years)			
18 - 44	46 (14.5)	40 (12.5)	39 (11.6)
45 - 64	231 (72.6)	231 (72.2)	252 (74.8)
≥65	41 (12.9)	49 (15.3)	46 (13.6)
Mean (SD)	54.7 (9.1)	54.8 (8.9)	55.2 (8.8)
Range	23-70	22-71	23-70
Race			
White	246 (77.4)	238 (74.4)	252 (74.8)
Black	29 (9.1)	32 (10.0)	39 (11.6)
Asian	7 (2.2)	3 (0.9)	6 (1.8)
Other	36 (11.3)	47 (14.7)	40 (11.9)
Weight (kg)			
Mean (SD)	105.1 (19.4)	101.6 (19.3)	102.5 (20.0)
Range	65.5-165.3	64.1-166.9	59.2-170.1
Body Mass Index (kg/m^2)			
Mean (SD)	37.1 (5.6)	36.3 (5.4)	36.3 (5.5)
Range	27.0-50.9	26.3-49.3	27.0-50.0
Height (cm)			
Mean (SD)	168.1 (10.3)	167.1 (10.0)	167.8 (10.1)
Range	145.0-197.0	144.0-198.0	146.0-197.0

SD = standard deviation; Body Mass Index = body weight/$(\text{height} \times 0.01)^2$

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 S3. Mean body weight at Baseline was comparable across the treatment groups, ranging from 101.3 to 104.7 kg. At Month 12, weight loss was observed in all treatment groups (range: decreases of 2.8% to 6.2%); the largest decrease from Baseline (6.2%) was in the CP-945,598 20 mg treatment group. Similar results were observed for the LOCF analysis, with weight loss ranging from 2.3% to 5.2%, with the largest decrease in the CP-945,598 20 mg treatment group. The mean percent weight loss for both CP-945,598 dose groups was statistically significantly greater than placebo ($p<0.0001$).

Table S3. 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	315	314	334
	Mean (SD)	104.69 (19.34)	101.29 (19.32)	102.45 (20.06)
	95% CI	(102.54, 106.83)	(99.14, 103.43	(100.29, 104.61)
Week 2	N	310	309	323
	Mean (SD)	-1.45 (1.37)	-1.80 (1.46)	-0.87 (1.53)
	95% CI	(-1.60, -1.30)	(-1.97, -1.64)	(-1.04, -0.70)
Month 1	N	310	299	324
	Mean (SD)	-2.33 (1.70)	-2.71 (1.83)	-1.55 (1.69)
	95% CI	(-2.52, -2.14)	(-2.92, -2.50)	(-1.73, -1.36)
Month 2	N	291	291	308
	Mean (SD)	-3.41 (2.63)	-3.95 (2.54)	-2.05 (2.50)
	95% CI	(-3.71, -3.10)	(-4.24, -3.66)	(-2.33, -1.77)
Month 3	N	283	277	293
	Mean (SD)	-4.23 (3.28)	-4.86 (3.16)	-2.69 (2.93)
	95% CI	(-4.62, -3.85)	(-5.24, -4.49)	(-3.02, -2.35)
Month 4	N	270	264	279
	Mean	-4.76 (3.80)	-5.38 (3.75)	-2.77 (3.60)
	95% CI	(-5.22, -4.31)	(-5.83, -4.92)	(-3.20, -2.35)
Month 5	N	258	256	267
	Mean (SD)	-5.20 (4.36)	-5.75 (4.19)	-2.92 (3.93)
	95% CI	(-5.73, -4.66)	(-6.27, -5.24)	(-3.40, -2.45)
Month 6	N	253	251	253
	Mean	-5.51 (4.79)	-6.26 (4.65)	-3.17 (4.27)
	95% CI	(-6.11, -4.92)	(-6.84, -5.69)	(-3.70, -2.65)
Month 9	N	238	233	240
	Mean (SD)	-5.65 (5.24)	-6.24 (5.41)	-3.03 (4.70)
	95% CI	(-6.32, -4.98)	(-6.94, -5.54)	(-3.63, -2.44)
Month 11	N	210	208	224
	Mean (SD)	-5.05 (5.10)	-6.08 (5.84)	-2.78 (4.60)
	95% CI	(-5.75, -4.36)	(-6.87, -5.28)	(-3.38, -2.17)
Month 12	N	196	183	195
	Mean (SD)	-4.76 (5.21)	-6.21 (5.75)	-2.80 (4.92)
	95% CI	(-5.50, -4.03)	(-7.05, -5.37)	(-3.49, -2.10)
Month 12 LOCF	N	315	314	334
	Mean (SD)	-4.47 (5.19)	-5.19 (5.13)	-2.28 (4.34)
	95% CI	(-5.04, -3.89)	(-5.76, -4.62)	(-2.74, -1.81)
			Treatment Comparison	
			LS Mean (SE)	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		-2.15 (0.39)	(-2.90,-1.39)	<0.0001
	20 mg CP-945,598 vs placebo		-2.87 (0.39)	(-3.63,-2.12)	<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

Results were similar for the FAS with ODIS set.

Analysis of the Per Protocol Completers demonstrated slightly larger mean percent decreases from Baseline than were observed for the FAS (Table S4). Mean body weight at Baseline

was comparable across the treatment groups, ranging from 101.6 to 104.8 kg. At Month 12, the observed mean percent decreases in body weight ranged from 3.3% to 6.4%, with the largest decrease in the CP-945,598 20 mg treatment group. The mean percent weight loss for both CP-945,598 dose groups was statistically significantly greater than placebo (p=0.006 and p<0.0001, respectively for CP-945,598 10 mg and CP-945,598 20 mg, compared with placebo).

Table S4. Summary of Body Weight at Baseline and Percent Change at Month 12, Per Protocol Completers Set

Study Visit	Statistic	CP-945,598 10 mg	CP-945,598 20 mg	Placebo
Baseline (Day 1)	N	156	127	144
	Mean (SD)	104.83 (17.92)	101.55 (20.10)	101.71 (20.40)
	95% CI	(102.00, 107.67)	(98.02, 105.08)	(98.35, 105.07)
Week 2	N	153	127	140
	Mean (SD)	-1.57 (1.41)	-1.91 (1.35)	-1.16 (1.54)
	95% CI	(-1.79, -1.34)	(-2.15, -1.67)	(-1.41, -0.90)
Month 1	N	156	126	143
	Mean (SD)	-2.48 (1.60)	-3.00 (1.82)	-1.82 (1.59)
	95% CI	(-2.73, -2.23)	(-3.32, -2.68)	(-2.08, -1.56)
Month 2	N	153	127	142
	Mean (SD)	-3.60 (2.63)	-4.10 (2.51)	-2.63 (2.27)
	95% CI	(-4.02, -3.18)	(-4.54, -3.66)	(-3.01, -2.26)
Month 3	N	155	125	142
	Mean (SD)	-4.23 (3.39)	-5.23 (3.13)	-3.21 (2.91)
	95% CI	(-4.77, -3.69)	(-5.79, -4.68)	(-3.69, -2.73)
Month 4	N	154	124	142
	Mean (SD)	-4.87 (3.73)	-5.84 (3.81)	-3.45 (3.59)
	95% CI	(-5.46, -4.27)	(-6.51, -5.16)	(-4.04, -2.85)
Month 5	N	153	123	141
	Mean (SD)	-5.36 (4.38)	-6.23 (4.25)	-3.71 (3.95)
	95% CI	(-6.06, -4.66)	(-6.99, -5.47)	(-4.37, -3.05)
Month 6	N	154	124	139
	Mean (SD)	-5.49 (4.66)	-6.69 (4.72)	-3.88 (4.28)
	95% CI	(-6.23, -4.75)	(-7.53, -5.86)	(-4.60, -3.16)
Month 9	N	155	124	140
	Mean (SD)	-5.58 (5.05)	-6.63 (5.39)	-3.58 (4.82)
	95% CI	(-6.38, -4.78)	(-7.59, -5.67)	(-4.38, -2.77)
Month 11	N	152	123	138
	Mean (SD)	-5.14 (5.09)	-6.33 (5.78)	-3.21 (4.76)
	95% CI	(-5.95, -4.32)	(-7.37, -5.30)	(-4.01, -2.41)
Month 12	N	156	127	144
	Mean (SD)	-5.00 (5.24)	-6.41 (5.64)	-3.30 (4.99)
	95% CI	(-5.83, -4.18)	(-7.40, -5.42)	(-4.13, -2.48)
			Treatment Comparison	
			LS Mean (SE)	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		-1.70 (0.62)	(-2.91,-0.49)	0.006
	20 mg CP-945,598 vs placebo		-3.11 (0.65)	(-4.38,-1.83)	<0.0001

Body weight was measured in kilograms.
SD = standard deviation; CI = confidence interval; LS Mean = least squares mean; vs = versus; SE = standard error

The proportions of subjects with at least a 5% decrease in weight at the end of 1 year of treatment were 33.7% (95% CI: 28.4, 38.9) for the CP-945,598 10 mg group; 44.6% (95% CI: 39.1, 50.1) for the CP-945,598 20 mg group; and 22.2% (95% CI: 17.7, 26.6) for the placebo group (Table S5, FAS LOCF). The difference between the CP-945,598 dose groups and placebo was significant (p=0.001 and p<0.0001, respectively for CP-945,598 10 mg and CP-945,598 20 mg, compared with placebo), and the odds ratios for both CP-945,598 dose groups were 1.82 and 2.86, respectively for 10 mg and 20 mg vs. placebo. The proportions were slightly lower for the FAS with ODIS set (worst case analysis), ranging from 18.3% for placebo to 33.8% for the CP-945,598 20 mg group and higher for the PP set, ranging from 32.6% for placebo to 60.6% for the CP-945,598 20 mg group. However, for the PP analysis, the difference between the 10 mg dose group and placebo was not significant (p=0.1952).

Table S5. Summary of Proportion of Subjects with at Least Five Percent Weight Loss at Month 12: FAS, FAS with ODIS, and Per Protocol Completers Sets

Study Visit	Statistic	CP-945,598 10 mg	CP-945,598 20 mg		Placebo
Full Analysis Set					
Month 12	N	196	183		195
	n (%)	71 (36.2)	102 (55.7)		57 (29.2)
	95% CI	(29.5, 43.0)	(48.5, 62.9)		(22.8, 35.6)
Month 12 LOCF	N	315	314		334
	n (%)	106 (33.7)	140 (44.6)		74 (22.2)
	95% CI	(28.4, 38.9)	(39.1, 50.1)		(17.7, 26.6)
			Treatment Comparison		
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.82	(1.27, 2.59)	0.001[a]
	20 mg CP-945,598 vs placebo		2.86	(2.02, 4.05)	<0.0001[b]
Full Analysis Set with ODIS (Worst Case Analysis)					
Month 12	N	315	314		334
	n (%)	79 (25.1)	106 (33.8)		61 (18.3)
	95% CI	(20.3, 29.9)	(28.5, 39.0)		(14.1, 22.4)
			Treatment Comparison		
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.54	(1.05, 2.26)	0.0263[c]
	20 mg CP-945,598 vs placebo		2.27	(1.56, 3.29)	<0.0001[d]
Per Protocol Completers					
Month 12	N	156	127		144
	n (%)	59 (37.8)	77 (60.6)		47 (32.6)
	95% CI	(30.2, 45.4)	(52.1, 69.1)		(25.0, 40.3)
			Treatment Comparison		
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.39	(0.84 , 2.30)	0.1952[e]
	20 mg CP-945,598 vs placebo		3.17	(1.88 , 5.32)	<0.0001[f]

FAS = Full Analysis Set; ODIS = off-drug in study; LOCF = last observation carried forward; CI = confidence interval; LS Mean = least squares mean; vs = versus

[a]Breslow-Day Homogeneity Test = 0.1752
[b]Breslow-Day Homogeneity Test = 0.6168
[c]Breslow-Day Homogeneity Test = 0.7497
[d]Breslow-Day Homogeneity Test = 0.4036
[e]Breslow-Day Homogeneity Test = 0.4596
[f]Breslow-Day Homogeneity Test = 0.0280

A summary of the results for changes in HbA_{1c} from Baseline to Month 12 is provided in Table S6. Mean HbA_{1c} values at Baseline were comparable across the treatment groups, ranging from 7.56% to 7.62%. Mean decreases of 0.38% were observed as early as Month 1 in all treatment groups. For the placebo group, the mean changes from baseline never exceeded 0.45% at any time point. At Month 12, the largest decrease from Baseline (0.71%) was in the CP-945,598 20 mg treatment group. Similar results were observed for the LOCF analysis, with decreases ranging from 0.33% (placebo) to 0.61% (CP-945,598 20 mg). The mean decreases in HbA_{1c} for both CP-945,598 dose groups were statistically significantly greater than placebo (p=0.0188 and p=0.0003, respectively for CP-945,598 10 mg and CP-945,598 20 mg, compared with placebo; also significant for the repeated measures analysis).

Table S6. Summary of HbA_{1c} at Baseline and 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	312	309	329
	Mean (SD)	7.62 (0.87)	7.60 (0.83)	7.56 (0.89)
	95% CI	(7.53, 7.72)	(7.51, 7.69)	(7.47, 7.66)
Month 1	N	306	304	326
	Mean (SD)	-0.38 (0.50)	-0.38 (0.49)	-0.38 (0.47)
	95% CI	(-0.44, -0.33)	(-0.44, -0.33)	(-0.43, -0.33)
Month 3	N	284	279	291
	Mean (SD)	-0.56 (0.84)	-0.60 (0.76)	-0.45 (0.78)
	95% CI	(-0.66, -0.46)	(-0.69, -0.51)	(-0.54, -0.36)
Month 6	N	259	258	263
	Mean (SD)	-0.64 (0.91)	-0.65 (0.92)	-0.36 (0.90)
	95% CI	(-0.75, -0.53)	(-0.76, -0.54)	(-0.47, -0.25)
Month 9	N	238	236	243
	Mean (SD)	-0.65 (0.98)	-0.72 (0.89)	-0.33 (0.95)
	95% CI	(-0.77, -0.52)	(-0.83, -0.61)	(-0.45, -0.21)
Month 12	N	207	197	209
	Mean (SD)	-0.62 (1.07)	-0.71 (0.94)	-0.39 (0.95)
	95% CI	(-0.77, -0.48)	(-0.85, -0.58)	(-0.52, -0.26)
Month 12 LOCF	N	312	309	329
	Mean (SD)	-0.53 (1.02)	-0.61 (0.92)	-0.33 (0.93)
	95% CI	(-0.65, -0.42)	(-0.71, -0.51)	(-0.43, -0.23)
			Treatment Comparison	
			LS Mean (SE)	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		-0.17 (0.07)	(-0.31,-0.03)	0.0188
	20 mg CP-945,598 vs placebo		-0.26 (0.07)	(-0.40,-0.12)	0.0003

HbA_{1c} = hemoglobin A1c; SD = standard deviation; CI = confidence interval; LOCF = last observation carried forward; LS Mean = least squares mean; vs = versus; SE = standard error

Results were similar for the FAS with ODIS analysis.

Results for the Per Protocol Completers were larger mean decreases from Baseline than were observed for the FAS (Table S7). HbA_{1c} values at Baseline were comparable across the treatment groups, ranging from 7.57% to 7.63%. At Month 12, the observed mean decreases in HbA_{1c} ranged from 0.39 to 0.79, with the largest decrease in the CP-945,598 20 mg treatment group. The mean decreases for both CP-945,598 dose groups were statistically

significantly greater than placebo, p=0.0395 and p=0.0004, respectively for CP-945,598 10 mg and CP-945,598 20 mg, compared with placebo.

Table S7. Summary of HbA_{1c} at Baseline and Change at Month 12, Per Protocol Completers Set

Study Visit	Statistic	CP-945,598 10 mg	CP-945,598 20 mg	Placebo
Baseline (Day 1)	N	156	127	144
	Mean (SD)	7.60 (0.87)	7.57 (0.79)	7.63 (0.88)
	95% CI	(7.46, 7.73)	(7.43, 7.71)	(7.49, 7.78)
Month 1	N	154	127	143
	Mean (SD)	-0.45 (0.46)	-0.43 (0.40)	-0.41 (0.45)
	95% CI	(-0.53, -0.38)	(-0.50, -0.36)	(-0.49, -0.34)
Month 3	N	155	127	142
	Mean (SD)	-0.56 (0.84)	-0.66 (0.76)	-0.46 (0.80)
	95% CI	(-0.69, -0.43)	(-0.79, -0.52)	(-0.59, -0.33)
Month 6	N	153	127	141
	Mean (SD)	-0.63 (0.90)	-0.80 (0.93)	-0.45 (0.85)
	95% CI	(-0.77, -0.48)	(-0.96, -0.63)	(-0.59, -0.31)
Month 9	N	154	126	141
	Mean (SD)	-0.62 (0.95)	-0.81 (0.92)	-0.37 (1.01)
	95% CI	(-0.77, -0.47)	(-0.97, -0.65)	(-0.54, -0.21)
Month 12	N	153	123	139
	Mean (SD)	-0.61 (1.07)	-0.79 (0.96)	-0.39 (1.00)
	95% CI	(-0.78, -0.44)	(-0.97, -0.62)	(-0.55, -0.22)
			Treatment Comparison	
			LS Mean (SE)	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		-0.23 (0.11)	(-0.46,-0.01)	0.0395
	20 mg CP-945,598 vs placebo		-0.43 (0.12)	(-0.66,-0.19)	0.0004

HbA_{1c} = hemoglobin A1c; SD = standard deviation; CI = confidence interval; LOCF = last observation carried forward; LS Mean = least squares mean; vs = versus; SE = standard error

The proportions of subjects with HbA_{1c} <6.5% at the end of 1 year of treatment are summarized for the FAS, FAS with ODIS, and PP analysis sets in Table S8. For the CP-945,598 10 mg group, the proportions ranged from 21.0% (FAS with ODIS) to 29.5% (FAS). For the CP-945,598 20 mg group, the proportions ranged from 26.8% (FAS with ODIS) to 42.3% (PP). For placebo, the proportions ranged from 16.1% (FAS with ODIS) to 23.4% (FAS). For the CP-945,598 20 mg group, the difference from placebo was statistically significant (p<0.003) for the FAS with ODIS and PP analysis sets. For the FAS (LOCF) analysis, the p-value was 0.065. The difference between the CP-945,598 10 mg group and placebo was not statistically significant (p>0.08) for the PP analysis.

Table S8. Summary of Proportion of Subjects with HbA_{1c} <6.5% at Month 12: FAS, FAS with ODIS, and Per Protocol Completers Sets

Study Visit	Statistic	CP-945,598 10 mg	CP-945,598 20 mg		Placebo
Full Analysis Set					
Month 12	N	207	197		209
	n (%)	61 (29.5)	74 (37.6)		49 (23.4)
	95% CI	(23.3, 35.7)	(30.8, 44.3)		(17.7, 29.2)
Month 12 LOCF	N	312	309		329
	n (%)	80 (25.6)	92 (29.8)		74 (22.5)
	95% CI	(20.8, 30.5)	(24.7, 34.9)		(18.0, 27.0)
			Treatment Comparison		
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.21	(0.83, 1.77)	0.3289[a]
	20 mg CP-945,598 vs placebo		1.42	(0.96, 2.08)	0.0652[b]
Full Analysis Set with ODIS (Worst Case Analysis)					
Month 12	N	314	310		329
	n (%)	66 (21.0)	83 (26.8)		53 (16.1)
	95% CI	(16.5, 25.5)	(21.8, 31.7)		(12.1, 20.1)
			Treatment Comparison		
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.42	(0.94, 2.16)	0.0902[c]
	20 mg CP-945,598 vs placebo		1.81	(1.19, 2.76)	0.0027[d]
Per Protocol Completers					
Month 12	N	153	123		139
	n (%)	45 (29.4)	52 (42.3)		29 (20.9)
	95% CI	(22.2, 36.6)	(33.5, 51.0)		(14.1, 27.6)
			Treatment Comparison		
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.55	(0.87, 2.73)	0.0835[e]
	20 mg CP-945,598 vs placebo		2.88	(1.58, 5.25)	0.0003[f]

FAS = Full Analysis Set; ODIS = off-drug in study; LOCF = last observation carried forward; CI = confidence interval; LS Mean = least squares mean; vs = versus; HbA_{1c} = hemoglobin A1c
[a]Breslow-Day Homogeneity Test = 0.7238
[b]Breslow-Day Homogeneity Test = 0.2758
[c]Breslow-Day Homogeneity Test = 0.7588
[d]Breslow-Day Homogeneity Test = 0.2347
[e]Breslow-Day Homogeneity Test = 0.3538
[f]Breslow-Day Homogeneity Test = 0.0895

The proportions of subjects with HbA_{1c} <7% at the end of 1 year of treatment are summarized for the FAS, FAS with ODIS, and PP analysis sets in Table S9. For the CP-945,598 10 mg group, the proportions ranged from 39.8% (FAS with ODIS) to 56.9% (PP). For the CP-945,598 20 mg group, the proportions ranged from 42.3% (FAS with ODIS) to 61.0% (PP). For placebo, the proportions ranged from 33.7% (FAS with ODIS) to 48.3% (FAS). For the CP-945,598 20 mg group, the difference from placebo was statistically significant ($p \leq 0.02$) for the FAS with ODIS and PP analysis sets. For the FAS (LOCF) analysis, the p-value was 0.193. The difference between the CP-945,598 10 mg group and placebo was not statistically significant ($p > 0.13$) for the PP analysis.

Table S9. Summary of Proportion of Subjects with HbA_{1c} <7% at Month 12: FAS, FAS with ODIS, and Per Protocol Completers Sets

Study Visit	Statistic	CP-945,598 10 mg	CP-945,598 20 mg	Placebo
Full Analysis Set				
Month 12	N	207	197	209
	n (%)	116 (56.0)	117 (59.4)	101 (48.3)
	95% CI	(49.3, 62.8)	(52.5, 66.2)	(41.6, 55.1)
Month 12 LOCF	N	312	309	329
	n (%)	160 (51.3)	158 (51.1)	154 (46.8)
	95% CI	(45.7, 56.8)	(45.6, 56.7)	(41.4, 52.2)
			Treatment Comparison	
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.17	(0.83, 1.64)	0.3939
	20 mg CP-945,598 vs placebo		1.25	(0.88, 1.77)	0.1933
Full Analysis Set with ODIS (Worst Case Analysis)				
Month 12	N	314	310	329
	n (%)	125 (39.8)	131 (42.3)	111 (33.7)
	95% CI	(34.4, 45.2)	(36.8, 47.8)	(28.6, 38.8)
			Treatment Comparison	
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.29	(0.91, 1.82)	0.1558
	20 mg CP-945,598 vs placebo		1.47	(1.04, 2.09)	0.0223
Per Protocol Completers				
Month 12	N	153	123	139
	n (%)	87 (56.9)	75 (61.0)	63 (45.3)
	95% CI	(49.0, 64.7)	(52.4, 69.6)	(37.0, 53.6)
			Treatment Comparison	
			Odds Ratio	**95% CI**	**p-value**
	10 mg CP-945,598 vs placebo		1.50	(0.89, 2.52)	0.1373
	20 mg CP-945,598 vs placebo		1.95	(1.11, 3.44)	0.0105

FAS = Full Analysis Set; ODIS = off-drug in study; LOCF = last observation carried forward; CI = confidence interval; LS Mean = least squares mean; vs = versus; HbA_{1c} = hemoglobin A1c
[a]Breslow-Day Homogeneity Test = 0.2465
[b]Breslow-Day Homogeneity Test = 0.4942
[c]Breslow-Day Homogeneity Test = 0.6010
[d]Breslow-Day Homogeneity Test = 0.6282
[e]Breslow-Day Homogeneity Test = 0.3208
[f]Breslow-Day Homogeneity Test = 0.1776

Safety Results: A total of 51 subjects experienced serious AEs (SAEs): 14 (4.4%) in the CP-945,598 10 mg group, 17 (5.3%) in the CP-945,598 20 mg group, and 20 (5.9%) in the placebo group. Overall, a total of 98 subjects were discontinued from treatment due to AEs: 26 (8.2%) in the CP-945,598 10 mg group, 45 (14.1%) in the CP-945,598 20 mg group, and 27 (8.0%) in the placebo group, of which 73 were ODIS and 25 subjects were discontinued from the study (see following discussion of discontinuations due to AEs). A total of 99 subjects had temporary discontinuations of study drug due to AEs: 37 (11.6%) in the CP-945,598 10 mg group, 44 (13.8%) in the CP-945,598 20 mg group, and 18 (5.3%) in the placebo group. One subject, in the placebo group, died 40 days after the start of treatment due to unrelated causes (autopsy revealed evidence of hypertensive and atherosclerotic disease).

A summary of the incidence of treatment-emergent AEs is presented by treatment in Table S10.

Table S10. Treatment-Emergent Adverse Events- All Causalities and Treatment Related

	Number (%) of Subjects		
	CP-945,598 10 mg	CP-945,598 20 mg	Placebo
All causalities			
Subjects evaluable for adverse events	318	320	337
Number of adverse events	1079	1217	1042
Subjects with adverse events	266 (83.6)	269 (84.1)	263 (78.0)
Subjects with serious adverse events	14 (4.4)	17 (5.3)	20 (5.9)
Subjects with severe adverse events	44 (13.8)	43 (13.4)	38 (11.3)
Subjects discontinued due to adverse events[a]	26 (8.2)	45 (14.1)	27 (8.0)
Subjects with dose reduced or temporary discontinuation due to adverse events	37 (11.6)	44 (13.8)	18 (5.3)
Treatment related			
Number of treatment-related adverse events	361	466	269
Subjects with treatment-related adverse events	159 (50.0)	165 (51.6)	125 (37.1)
Subjects with treatment-related serious adverse events	0	2 (0.6)	0
Subjects with severe treatment-related adverse events	10 (3.1)	19 (5.9)	3 (0.9)
Subjects discontinued due to treatment-related adverse events[a]	19 (6.0)	37 (11.6)	16 (4.7)
Subjects with dose reduced or temporary discontinuation due to treatment-related adverse events	22 (6.9)	31 (9.7)	7 (2.1)

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; includes subjects who were off-drug, in study.

The AEs that were experienced by more than 5% of subjects during any treatment are summarized in Table S11. The most frequently reported AEs were hypoglycemia, diarrhea, and nausea.

Table S11. Treatment-Emergent Adverse Events Reported for 5% or More Subjects in a Treatment Group – All Causalities

System Organ Class Preferred Term	Number (%) of Subjects CP-945,598 10 mg N=318	 CP-945,598 20 mg N=320	 Placebo N=337
Gastrointestinal Disorders			
Constipation	11 (3.5)	13 (4.1)	17 (5.0)
Diarrhea	46 (14.5)	51 (15.9)	33 (9.8)
Nausea	45 (14.2)	65 (20.3)	18 (5.3)
Vomiting	19 (6.0)	27 (8.4)	7 (2.1)
General Disorders and Administration Site Conditions			
Fatigue	12 (3.8)	15 (4.7)	19 (5.6)
Irritability	13 (4.1)	16 (5.0)	12 (3.6)
Infections and Infestations			
Influenza	26 (8.2)	18 (5.6)	15 (4.5)
Nasopharyngitis	40 (12.6)	24 (7.5)	42 (12.5)
Sinusitis	17 (5.3)	19 (5.9)	14 (4.2)
Upper respiratory tract infection	30 (9.4)	32 (10.0)	38 (11.3)
Urinary tract infection	9 (2.8)	11 (3.4)	17 (5.0)
Metabolism and Nutrition Disorders			
Hypoglycemia	79 (24.8)	86 (26.9)	90 (26.7)
Musculoskeletal and Connective Tissue Disorders			
Back pain	15 (4.7)	12 (3.8)	17 (5.0)
Arthralgia	21 (6.6)	28 (8.8)	23 (6.8)
Nervous System Disorders			
Dizziness	16 (5.0)	14 (4.4)	17 (5.0)
Headache	26 (8.2)	28 (8.8)	27 (8.0)
Psychiatric Disorders			
Anxiety	20 (6.3)	27 (8.4)	17 (5.0)
Depression	25 (7.9)	24 (7.5)	15 (4.5)

As summarized in Table S11, hypoglycemia was reported for approximately 25% of all subjects in all treatment groups. The hypoglycemia was considered treatment-related for approximately half of those subjects (range: 11.3% to 12.5%). Treatment-related diarrhea was reported at similar rates in the CP-945,598 groups (9.4% to 11.3%) and less frequently in the placebo group (5.0%). A similar trend was observed for treatment-related nausea, with the most frequent occurrence in the CP-945,598 20 mg group (15.6%), a slightly lower rate in the CP-945,598 10 mg group (10.1%), and the lowest frequency in the placebo group (3.6%).

Depressed mood/depression was reported for approximately 8% of subjects in the CP-945-598 dose groups and was considered related to treatment in 6.6% of subjects in the CP-945,598 10 mg group, 7.2% of subjects in the CP-945,598 20 mg group, and 3.9% of subjects treated with placebo). Headache, which was reported for approximately 8% of subjects in all treatment groups, was considered related to treatment for 3.5% of subjects in the CP-945,598 10 mg group, 5.0% of subjects in the CP-945,598 20 mg group, and 3.3% of subjects treated with placebo. All other nervous system and psychiatric events that were

considered treatment-related were reported in less than 5% of subjects in any treatment group. Suicidal ideation was reported for 10 subjects and considered related to treatment for 7 of these subjects: 1 subject in the CP-945,598 10 mg group and 3 subjects each in the CP-945,598 20 mg and placebo groups. Suicidal depression was reported for 1 subject; this subject was in the placebo group. Treatment-related insomnia was reported for 25 subjects: 11 subjects in the CP-945,598 20 mg group, 9 subjects in the placebo group, and 5 subjects in the CP-945,598 10 mg group.

The majority of reported SAEs were unrelated to study drug but were related to the subject's underlying disease. Of the 51 subjects who experienced SAEs, 2 subjects, both in the 20 mg CP-945,598 group, had SAEs that were considered related to treatment. One subject experienced a spontaneous abortion on Day 76 of study treatment and 1 subject experienced serious suicidal ideation. Subject 10831005, a 38-year-old female at a study site in Mexico, had a positive pregnancy test on Day 76. The last day of her most recent menstrual period had been approximately 7 weeks earlier. Study drug and antidiabetic treatment (glyburide) were stopped. Five days later, the subject experienced a spontaneous abortion and was treated with endouterine manual aspiration. A relationship between the study drug and the event could not be completely excluded but also cannot be confirmed. Subject 10381029, a 52-year-old male at a study site in the United States with a previous history of mild depression, anxiety and insomnia, experienced moderate depression and suicidal ideation on Day 5. Study drug was discontinued, and he was treated with alprazolam. Both SAEs resolved without sequelae.

A total of 25 subjects were discontinued from the study due to AEs (ie, does not include ODIS subjects; see the footnote in Table S1): 5 subjects in the CP-945,598 10 mg group, 13 subjects in the CP-945,598 20 mg group, and 7 subjects in the placebo group. Of these, 17 subjects discontinued due to treatment-related AEs: 3 subjects in the CP-945,598 10 mg group, 11 subjects in the CP-945,598 20 mg group, and 3 subjects in the placebo group. The most frequently reported treatment-related AE leading to discontinuation was depression/depressed mood in 4 subjects: 1 in the CP-945,598 10 mg group; 2 in the CP-945,598 20 mg group; and 1 in the placebo group. None of the treatment-related AEs leading to discontinuation were SAEs.

A total of 99 subjects had dose reductions or temporary discontinuations of study drug due to AEs; these AEs were considered related to study drug in 60 subjects, of which 53 subjects had been treated with CP-945,598. In the 10 mg CP-945,598 group, the most frequently reported related AE leading to a temporary discontinuation of study drug was depression/depressed mood (7 subjects). In the 20 mg CP-945,598 group, the most frequently reported related AE leading to a temporary discontinuation of study drug was nausea (10 subjects).

Overall, protocol-defined hypoglycemic AEs were reported for 50 subjects (15.7%) in the 10 mg CP-945,598 group, 56 subjects (17.5%) in the 20 mg CP-945,598 group, and 47 subjects (13.9%) in the placebo group. The overall crude event rates (total number of events/total subject-months of treatment) were highest for placebo (0.060) and lowest for the CP-945,598 10 mg group (0.037); the crude event rate was 0.049 for the CP-945,598 20 mg group. These events were considered to be severe in 1 subject in each treatment group.

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

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 56 subjects (18%) in the 10 mg CP-945,598 group, 44 subjects (14.4%) in the 20 mg CP-945,598 group, and 29 subjects (8.9%) in the placebo group.

The proportions of subjects who endorsed item #9 on the PHQ-9 questionnaire were similar across the treatment groups: 12 subjects (3.9%) in the 10 mg CP-945,598 group; 15 subjects (4.9%) in the 20 mg CP-945,598 group; and 12 subjects (3.7%) in the placebo group.

CONCLUSIONS:

- For the 12-month LOCF analysis, where weight loss ranged from 2.3% to 5.2%, with the largest decrease in the CP-945,598 20 mg treatment group, the mean percent weight loss for both CP-945,598 dose groups was statistically significantly greater than placebo ($p<0.0001$). Results were similar for the FAS with ODIS analysis; analysis of the Per Protocol Completers demonstrated slightly 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 33.7% (95% CI: 28.4, 38.9) for the CP-945,598 10 mg group; 44.6% (95% CI: 39.1, 50.1) for the CP-945,598 20 mg group; and 22.2% (95% CI: 17.7, 26.6) for the placebo group. The difference between the CP-945,598 dose groups and placebo was statistically significant ($p=0.001$ and $p<0.0001$, respectively for CP-945,598 10 mg and CP-945,598 20 mg, compared with placebo). The proportions were slightly lower for the FAS with ODIS set (worst case analysis), and higher for the PP set.

- The proportions of subjects with HbA_{1c} <6.5% ranged from 21.0% to 29.5% for the CP-945,598 10 mg group, from 26.8% to 42.3% for the CP-945,598 20 mg group, and from 16.1% to 23.4% for placebo for the FAS, FAS with ODIS, and PP datasets. The difference from placebo was statistically significant ($p<0.003$) for all 3 datasets for the CP-945,598 20 mg group. The difference between the CP-945,598 10 mg group and placebo was not statistically significant ($p>0.08$) for the PP analysis. The proportions of subjects with HbA_{1c} <7% ranged from 39.8% to 56.9% for the CP-945,598 10 mg group, from 42.3% to 61.0% for the CP-945,598 20 mg group, and from 33.7% to 48.3% for placebo for the FAS, FAS with ODIS, and PP datasets. For the CP-945,598 20 mg group, the difference from placebo was statistically significant ($p\leq0.02$) for the FAS with ODIS and PP analysis sets. The difference between the CP-945,598 10 mg group and placebo was not statistically significant ($p>0.13$) for the PP analysis.

- The CP-945,598 10 mg and 20 mg doses were safe and well-tolerated, although mild to moderate gastrointestinal events (primarily nausea) were considered related to CP-945,598 treatment.

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

- Hypoglycemia occurred at similar rates across all 3 treatment groups.

- One female subject experienced a spontaneous abortion during treatment with CP-945,598 20 mg; a relationship to treatment has to be considered possible, but is not conclusively established.

- Although, depression (and depressed mood) resulted in temporary discontinuation of study treatment more frequently in the CP-945,598 dose groups compared with placebo, results for subject questionnaires evaluating emotional well-being indicated no difference between the 3 treatment groups. Adverse events related to anxiety or depression were reported in a higher proportion of subjects treated with CP-945,598 than among subjects treated with placebo.