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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: CE-326,597

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS:

NATIONAL CLINICAL TRIAL NO.: NCT00542009

PROTOCOL NO.: A7211005

PROTOCOL TITLE: A 12-Week, Phase 2a, Randomized, Subject and Investigator Blinded, Placebo-Controlled Trial to Evaluate the Safety, Tolerability and Efficacy of CE-326,597 on Glucose Control and Body Weight in Overweight Adult Subjects With Type 2 Diabetes Mellitus

Study Center(s): A total of 53 sites had drug shipped for the purposes of conducting this study; of these, a total of 50 sites randomized at least 1 subject in the study. Three sites had drug shipped but did not randomize any subject into the study. Among the 50 sites that randomized at least 1 subject, were: Mexico (3 sites), Bulgaria (4 sites), Spain (3 sites), India (5 sites), Canada (5 sites), and the USA (30 sites).

Study Initiation and Completion Dates: 03 December 2007 to 25 November 2008

Phase of Development: Phase 2a

Study Objectives:

Primary objectives:

- To estimate the magnitude of change in glycosylated hemoglobin (HbA1c) with a range of oral doses of CE-326,597 administered over 12 weeks in overweight and obese adult subjects with Type 2 diabetes mellitus (T2DM) either treatment naïve or on stable (up to 2) oral, anti-diabetic agents.

- To estimate the magnitude of weight loss with a range of oral doses of CE-326,597 administered over 12 weeks in overweight and obese adult subjects with T2DM either treatment naïve or on stable (up to 2) oral, anti-diabetic agents.

Secondary objectives:

- To estimate the magnitude of change in post-prandial glucose and insulin area under the curve (AUC) following a mixed meal tolerance test (MMTT) with a range of oral

doses of CE-326,597 in overweight and obese adult subjects with T2DM either treatment naïve or on stable (up to 2) oral, anti-diabetic agents.

- To evaluate the safety and tolerability of a range of oral doses of CE-326,597 administered over 12 weeks in overweight and obese adult subjects with T2DM either treatment naïve or on stable (up to 2) oral, anti-diabetic agents, including use of a focused evaluation of gastrointestinal (GI)-related adverse events (AEs) and episodes of hypoglycemia, as well as assessment of cholelithiasis/cholecystolithiasis.

- To characterize the pharmacokinetics (PK) of CE-326,597 in overweight and obese adult subjects with T2DM either treatment naïve or on stable (up to 2) oral, anti-diabetic agents, including assessment of covariate effects via a population PK modeling approach; and to explore PK/pharmacodynamic (PD) relationships between CE-326,597 exposure and changes in HbA1c and body weight, and selected secondary endpoints, as permitted by the data.

METHODS

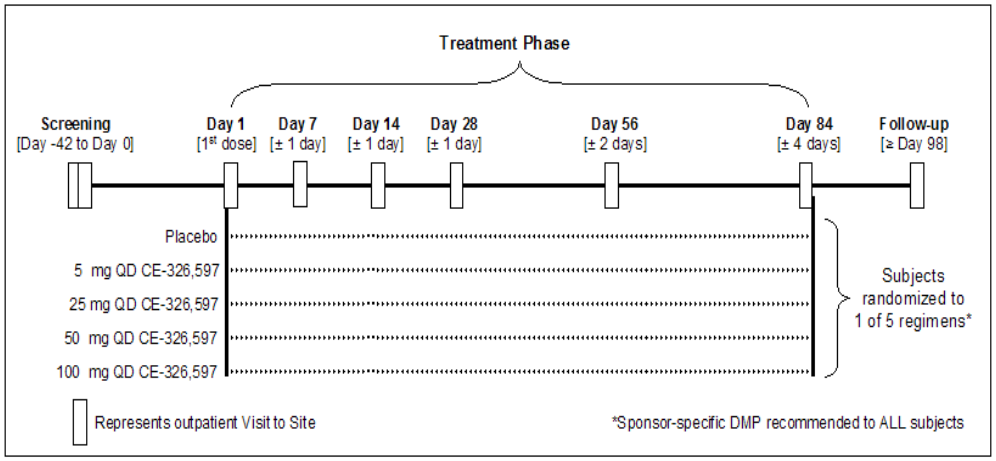
Study Design: This was a randomized, subject- and investigator-blinded, placebo-controlled, 5-arm (4 active doses plus placebo) study. It included a total of up to 9 outpatient visits (excluding screening) to the clinical research site. Total participation in the study for each subject, exclusive of the screening period, was approximately 14 weeks.

MMTT was undertaken prior to dosing on Day 1 and Day 28 visits; a minimum of 75 subjects had to complete the MMTT assessments.

The study was designed to over-enroll subjects by approximately 20% due to the anticipated dropout; subjects withdrawn were not replaced.

A schematic of the study is presented in Table S1.

Table S1. Study Schematic



Number of Subjects (Planned and Analyzed): The study planned to enroll at least 200 subjects at approximately 45 sites to ensure a minimum of 165 subjects (n = 33 per arm) completed the study. A total of 252 subjects were assigned to and received treatment.

Diagnosis and Main Criteria for Inclusion: Subjects must have had a diagnosis of T2DM and have either been treatment naïve or taking (up to 2) oral anti-diabetic agents, except thiazolidinediones (TZDs), for the management of T2DM; must have been between the ages of 18 to 65 years, inclusive, and females were limited to those who were of non-childbearing potential; had body mass index (BMI) ≥26.6 kg/m^2 and ≤45.5 kg/m^2 at screening; were medically stable with no overt complications due to T2DM (eg, subjects were excluded for moderate to severe renal impairment, severe retinopathy or neuropathy, history of stroke/transient ischemic attack, unstable angina, or myocardial infarction within 1-year of screening). Evidence of cholelithiasis on screening ultrasound or history of biliary disease were deemed exclusionary. Subjects had to have HbA1c ≥6.5% and ≤10%, fasting plasma glucose levels <270 mg/dL, and no abnormalities in other key clinical chemistry results, at screening, to be eligible.

Study Treatment: Subjects were randomized to 1 of 5 treatment groups to receive double-blind study drug (CE-326,597 and placebo) orally for 84 ± 4 days. Subjects received their first dose of the study drug within 24 hours of randomization (randomization took place on Day 1) and were instructed to take the study drug at the same time of day with their morning meal each day. Subjects were asked to delay self-administration of the study drug on the days of their outpatient visit to the site. On the day of the outpatient visits, study drug was administered at the site, witnessed by the site staff.

In addition to treatment with study drug, all subjects were provided a sponsor-specific Disease Management Plan (DMP) by a dietician or nutritionist. The DMP consisted of physical activity, and dietary and behavioral advice based on current American Diabetes Association (ADA) recommendations, as well as an approximate 750 calories/day energy intake deficit plan. The details of the energy intake deficit plan were provided to each site as a study-specific manual prior to the initiation of dosing.

The study drug was supplied as 5-mg and 25-mg CE-326,597 tablets or matching placebo. Each dose form was packaged in a separate packaged bottle and each bottle contained a 35-fill count. Each daily dose of study drug consisted of 5 tablets – 1 tablet from each of the 5 bottles dispensed at the Day 1, Day 28 and Day 56 visits.

Efficacy Evaluations: The study evaluations included HbA1c and GlycoMark™, body weight, waist circumference, MMTT, and exploratory biomarkers.

Pharmacokinetic Evaluations and Pharmacogenomics Collection : The study was conducted with a sparse sampling strategy to minimize blood collection. Trough samples were obtained for quantification of CE-326,597 concentration in serum on Days 28 and 84. Additionally, a sample was obtained during a 3-5 hour window post dose on Day 28 and a 5-10 hour window post dose on Day 84.

Subjects were permitted to participate separately in an additional research component involving collection of blood sample for de-identified exploratory pharmacogenomics analysis. Results of these analyses, if completed, were to be reported separately.

Safety Evaluations: Safety was assessed by supine vital signs (blood pressure [BP] and pulse rate), clinical laboratory tests, and supine 12-lead electrocardiograms (ECGs) obtained at the pre-defined nominal time points. An assessment of gallbladder using transabdominal ultrasonography was undertaken at screening and Day 84. In addition, AEs, including serious adverse events (SAEs), and relevant subject-reported AEs (GI symptoms and episodes of hypoglycemia) were monitored throughout the study.

Subjects who reported GI-related AEs (upon general inquiry concerning AEs) were further questioned using the Gastrointestinal Symptoms Questionnaire (GSQ). Reports of hypoglycemic episodes were captured on the hypoglycemic AE (HAE) form.

Statistical Methods: The analysis sets included:

- Full Analysis Set (FAS) and Safety Analysis Set: All randomized subjects who received at least 1 dose of study drug (CE-326,597 or placebo).
- Proof of Concept (POC) Analysis Set: All randomized subjects who received ≥80% of the required doses of study drug and had HbA1c and body weight measurements at both baseline and Day 84.

The primary efficacy analyses (for change in HbA1c and body weight) were based on the POC Analysis Set.

Analysis of Primary Endpoints:

- HbA1c (%) – Baseline HbA1c and absolute change in HbA1c were summarized descriptively (using n, mean, median, standard deviation [SD], minimum, maximum) by dose and day of measurement. The absolute change in HbA1c from baseline to Day 84 was analyzed using analysis of covariance (ANCOVA) with treatment (categorical) and baseline HbA1c as covariate. Least squares (LS) mean difference between each dose of CE-326,597 and the placebo group, along with a 90% confidence interval (CI), was provided for comparison.

- Body Weight (kg) – Baseline weight and percent change in weight were summarized descriptively (using n, mean, median, SD, minimum, maximum) by dose and day of measurement. The percent change in body weight from baseline to Day 84 was analyzed using analysis of variance (ANOVA). Randomized treatment group was the independent variable. Group mean difference between each dose of CE-326,597 and the placebo group, along with a 90% CI, was also provided.

In addition, a longitudinal mixed effects ANOVA model using dose (categorical) and time (categorical) as predictors was fit to the change (for HbA1c) or percent change (for body weight) from baseline at postbaseline time points. Tests for linear and quadratic trends were

applied. LS means with associated 90% confidence limits were reported and provided graphically.

RESULTS

Subject Disposition and Demography: A total of 731 subjects were screened and 252 subjects were assigned to and received treatment. A total of 214 subjects completed the study with 38 subjects (8.0% – 20.0% across treatment groups) discontinuing. Data from all subjects randomized to study treatment (N = 252) were included in the safety and FAS datasets; of these, 83.3% (ie, 210/252) were included in the POC analysis set.

Subject disposition is summarized in Table S2.

Table S2. Subject Disposition

	Placebo	CE-326,597 5 mg	CE-326,597 25 mg	CE-326,597 50 mg	CE-326,597 100 mg
Number (%) of subjects					
Screened, N=731					
Assigned to study treatment, N=252					
Treated	51	50	51	50	50
Completed	41 (80.4)	46 (92.0)	45 (88.2)	42 (84.0)	40 (80.0)
Discontinued	10 (19.6)	4 (8.0)	6 (11.8)	8 (16.0)	10 (20.0)
Related to study drug	3 (5.9)	1 (2.0)	2 (3.9)	3 (6.0)	4 (8.0)
AE	3 (5.9)	1 (2.0)	2 (3.9)	3 (6.0)	4 (8.0)
Not related to study drug	7 (13.7)	3 (6.0)	4 (7.8)	5 (10.0)	6 (12.0)
AE	1 (2.0)	0	0	1 (2.0)	0
Lost to follow-up	1 (2.0)	0	3 (5.9)	1 (2.0)	3 (6.0)
Subject no longer willing to participate in study	4 (7.8)	1 (2.0)	1 (2.0)	2 (4.0)	2 (4.0)
Other	1 (2.0)	2 (4.0)	0	1 (2.0)	1 (2.0)
Analyzed for efficacy					
Full Analysis Set	51 (100.0)	50 (100.0)	51 (100.0)	50 (100.0)	50 (100.0)
POC Analysis Set	39 (76.5)	43 (86.0)	44 (86.3)	42 (84.0)	40 (80.0)
Analyzed for safety					
AEs	51 (100.0)	50 (100.0)	51 (100.0)	50 (100.0)	50 (100.0)
Laboratory data	51 (100.0)	50 (100.0)	50[a] (98.0)	49[a] (98.0)	50 (100.0)

AE = adverse event; POC = Proof of Concept.
[a] One subject in each arm was withdrawn prior to the first post-dose assessment on Day 7 and was thus not included in analyses for laboratory data.

Demography: Subjects' age ranged at screening from 29 to 65 years, their BMI ranged from 27.1 to 45.3 kg/m^2 and baseline HbA1c ranged from 6.1% to 11.7% .

Efficacy Results: Table S3 provides results from the ANCOVA of change from baseline to Day 84 in HbA1c for the POC analysis set. All dose groups receiving CE-326,597 showed reductions in HbA1c. However, the magnitude of change was similar to that of placebo for all dose groups except for the 50 mg QD dose group. The placebo-adjusted LS mean change in HbA1c from baseline to Day 84 for the 50 mg dose group was -0.41% (90% CI: -0.69%, -0.13%).

Table S3. Analysis of HbA1c (%): Baseline Raw Value and Change from Baseline at Day 84 (POC Analysis Set)

	Placebo	**CE-326,597 5 mg QD**	**CE-326,597 25 mg QD**	**CE-326,597 50 mg QD**	**CE-326,597 100 mg QD**
	N=40	N=43	N=45	N=42	N=40
Baseline, raw value Mean, % (SD)	7.64 (0.982)	8.02 (1.11)	7.75 (1.10)	7.71 (1.10)	7.96 (1.15)
Day 84, Change from baseline					
LS mean (%)	-0.54	-0.67	-0.59	-0.95	-0.71
90% LS mean CI	(-0.74, -0.34)	(-0.86, -0.47)	(-0.78, -0.41)	(-1.15, -0.76)	(-0.91, -0.51)
LS mean difference versus placebo		-0.12	-0.05	-0.41	-0.16
90% CI for difference		(-0.40, 0.16)	(-0.33, 0.22)	(-0.69, -0.13)	(-0.45, 0.12)

LS means were based on an analysis of covariance on change from baseline, with treatment and baseline HbA1c values as covariates.
CI = confidence interval; HbA1c = glycosylated hemoglobin; LS = least squares; POC = Proof of Concept; QD = once daily; SD = standard deviation.

Table S4 provides results from the ANOVA of percent change from baseline to Day 84 in body weight for the POC analysis set. All groups receiving CE-326,597 showed reductions in body weight at all studied doses. However, the magnitude of change was similar to that of placebo for all dose groups except for the 50 mg QD dose. The placebo-adjusted mean percent change in body weight from baseline to Day 84 for the 50 mg dose was -1.45% (90% CI: -2.62%, -0.29%).

Table S4. Analysis of Percent Change from Baseline in Body Weight (kg) at Day 84 POC Analysis Set

	Placebo	CE-326,597 5 mg QD	CE-326,597 25 mg QD	CE-326,597 50 mg QD	CE-326,597 100 mg QD
Baseline, Raw value (kg)	N=40	N=43	N=45	N=42	N=40
Mean (SD)	96.77 (18.90)	96.00 (21.09)	96.72 (22.34)	100.9 (15.90)	95.95 (16.76)
Day 84, Percent Change from baseline					
Mean	-2.88	-2.59	-3.25	-4.33	-3.36
90% mean CI	(-3.71, -2.05)	(-3.39, -1.79)	(-4.03, -2.47)	(-5.15, -3.52)	(-4.20, -2.53)
Mean difference versus placebo		0.29	-0.37	-1.45	-0.48
90% CI for difference		(-0.86, 1.45)	(-1.51, 0.77)	(-2.62, -0.29)	(-1.66, 0.69)

Note: CIs are based on an analysis of variance on percent change from baseline, with treatment as the independent variable.
CI = confidence interval; LS= least squares; POC = Proof of Concept; SD = standard deviation.

Pharmacokinetic Results: There was a fair degree of variability at any given dose level, with coefficient of variation approaching or exceeding 100%. With the exception of the Day 84 predose concentration, CE-326,597 exhibited fairly dose-linear increases in concentration with increasing dose.

PK results are summarized in Table S5.

Table S5. Descriptive Summary of CE-326,597 Serum Concentrations

Visit	Statistic (ng/mL)	CE-326,597			
		5 mg QD	25 mg QD	50 mg QD	100 mg QD
Predose Day 28	Mean	0.86	4.52	8.13	22.1
	Median	0.66	2.72	6.48	16.0
	SD	0.98	4.65	8.32	16.2
	CV%	114%	103%	102%	73.2%
3-5 hr Window	Mean	2.52	13.0	38.9	47.0
Post-dose	Median	1.79	11.4	21.0	39.7
Day 28	SD	2.37	8.08	51.5	26.3
	CV%	94.3%	62.0%	132%	56.0%
Predose Day 84	Mean	0.78	4.23	8.21	10.7
	Median	0.68	2.09	5.57	9.82
	SD	0.44	5.07	9.83	10.0
	CV%	56.9%	120%	120%	94.0%
5-10 hr Window	Mean	3.28	13.9	38.0	55.3
Postdose Day 84	Median	2.84	12.7	23.8	49.1
	SD	1.58	9.71	29.6	38.6
	CV%	48.1%	70.0%	77.9%	69.8%

CV = coefficient of variation; QD = once daily; SD =standard deviation.

Safety Results:

- No deaths were reported in the study. A total of 4 SAEs in 4 separate subjects were reported; each of the subjects recovered from these events. One (1) SAE was judged to be related to study drug by the investigator. This subject, while receiving CE-326,597 50 mg QD, experienced atrial fibrillation on Day 10 of dosing and was withdrawn from the study. The other 3 SAEs were deemed unrelated to study drug by the investigator and did not require permanent discontinuation from the study.

- A total of 38 subjects were discontinued from the study prematurely; of these, 15 subjects were discontinued due to AEs.

- Temporary discontinuations due to AEs were reported in 12 subjects.

- Three (3) subjects were withdrawn due to abnormalities in laboratory parameters.

A summary of treatment-emergent AEs is presented in S6.

Table S6. Summary of All Causality (Treatment-Related) Treatment-Emergent Adverse Events

		CE-326,597			
	Placebo	**5 mg QD**	**25 mg QD**	**50 mg QD**	**100 mg QD**
Number of subjects evaluable for AEs	51	50	51	50	50
Number of AEs	58 (30)	42 (25)	74 (40)	91 (50)	123 (97)
Subjects with AEs	24 (16)	28 (19)	24 (14)	26 (18)	38 (34)
Subjects with SAEs	2 (0)	1 (0)	0	1 (1)	0
Subjects with severe AEs	2 (1)	2 (0)	1 (1)	3 (2)	3 (3)
Subjects discontinued due to AEs	4 (3)	1 (1)	2 (2)	4 (3)	4 (4)
Subjects with dose reduced or temporary discontinuation due to AEs	2 (1)	3 (1)	2 (2)	1 (1)	4 (4)

AEs (serious and non-serious) were recorded from the time the subject has taken at least 1 dose of study drug through last subject visit. Any SAEs occurring thereafter were reported if a causal relationship to study drug was suspected. Except for the number of AEs, subjects are counted only once per treatment in each row.
SAEs were reported based on the investigator's assessment.
MedDRA (v11.1) coding was applied.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily;
SAE = serious adverse event.

The 7 most frequent AEs reported in this study were diarrhea, nausea, abdominal distension, abdominal pain, defecation urgency, flatulence and hypoglycemia. A detailed overview of treatment-emergent all causality AEs reported in ≥5% subjects in any 1 treatment arm is summarized in S7.

Table S7. Frequency of Treatment-Emergent All Causality Adverse Events Reported in ≥5% Subjects

	Number of Subjects (%) With AE				
		CE-326,597			
SOC and MedDRA Preferred Term	**Placebo**	**5 mg QD**	**25 mg QD**	**50 mg QD**	**100 mg QD**
Subjects evaluable for AEs	51	50	51	50	50
Gastrointestinal disorders	12 (23.5)	13 (26.0)	13 (25.5)	19 (38.0)	28 (56.0)
Abdominal distension	0	0	4 (7.8)	5 (10.0)	7 (14.0)
Abdominal pain	2 (3.9)	1 (2.0)	1 (2.0)	4 (8.0)	7 (14.0)
Constipation	3 (5.9)	2 (4.0)	2 (3.9)	2 (4.0)	2 (4.0)
Defecation urgency	1 (2.0)	2 (4.0)	2 (3.9)	3 (6.0)	6 (12.0)
Diarrhea	5 (9.8)	4 (8.0)	7 (13.7)	13 (26.0)	17 (34.0)
Dyspepsia	2 (3.9)	1 (2.0)	0	2 (4.0)	3 (6.0)
Eructation	0	0	2 (3.9)	1 (2.0)	3 (6.0)
Feces hard	1 (2.0)	2 (4.0)	1 (2.0)	3 (6.0)	5 (10.0)
Flatulence	1 (2.0)	1 (2.0)	4 (7.8)	5 (10.0)	6 (12.0)
Gastrointestinal sounds abnormal	3 (5.9)	1 (2.0)	2 (3.9)	4 (8.0)	3 (6.0)
Nausea	2 (3.9)	2 (4.0)	4 (7.8)	6 (12.0)	9 (18.0)
Vomiting	0	0	1 (2.0)	0	3 (6.0)
Infections and infestations	4 (7.8)	5 (10.0)	5 (9.8)	9 (18.0)	8 (16.0)
Upper respiratory tract infection	0	1 (2.0)	3 (5.9)	3 (6.0)	3 (6.0)
Investigations	1 (2.0)	0	1 (2.0)	0	3 (6.0)
Alanine aminotransferase increased	0	0	0	0	3 (6.0)
Metabolism and nutrition disorders	4 (7.8)	7 (14.0)	4 (7.8)	4 (8.0)	4 (8.0)
Hypoglycemia	1 (2.0)	6 (12.0)	1 (2.0)	3 (6.0)	4 (8.0)
Musculoskeletal and connective tissue disorders	6 (11.8)	5 (10.0)	6 (11.8)	6 (12.0)	5 (10.0)
Back pain	2 (3.9)	2 (4.0)	0	2 (4.0)	4 (8.0)
Pain in extremity	1 (2.0)	2 (4.0)	2 (3.9)	3 (6.0)	0
Nervous system disorders	4 (7.8)	1 (2.0)	3 (5.9)	4 (8.0)	5 (10.0)
Headache	3 (5.9)	0	1 (2.0)	3 (6.0)	2 (4.0)

Note: If the same subject in a given treatment had >1 occurrence in the same preferred term event category, only the most severe occurrence was counted. Subjects were counted only once per treatment in each row. Includes all data collected since the first dose of study drug. MedDRA (v11.1) coding was applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; QD = once daily; SOC = system organ class.

Approximately 60% to 70% of the AEs were considered mild in intensity. The number of mild AEs across the 5 treatment arms were: 72% (42/58 on placebo), 71% (30/42 on 5 mg), 57% (42/74 on 25 mg), 65% (59/91 on 50 mg), and 70% (86/123 on 100 mg). The AEs classified as moderate to severe were most often reported under the SOC of Gastrointestinal Disorders.

A summary of subjects with isolated potentially clinically significant changes in supine systolic blood pressure (SBP), diastolic blood pressure (DBP) or pulse rate is presented in Table S8.

Table S8. Vital Signs: Categorical Summary of Post Baseline Data - Clinically Significant Maximum Change from Baseline

		CE-326,597			
	Placebo	**5 mg QD**	**25 mg QD**	**50 mg QD**	**100 mg QD**
Number of Subjects Evaluable for Vital Signs	51	50	50	49	50
Systolic Blood Pressure					
<90 mmHg	0	0	0	1[a]	0
≥30 mmHg decrease from baseline	6	3	6	9[b]	6
≥30 mmHg increase from baseline	2	4	4	0	2
Diastolic Blood Pressure					
≥20 mmHg decrease from baseline	4	4	6	6	7
≥20 mmHg increase from baseline	2	1	1	3	6
Pulse Rate >120 bpm	1[c]	0	0	0	0

BPM= bpm; QD = once daily.
[a] Subject was asymptomatic at time of this isolated occurrence on Day 14 visit; no similar SBP drop was noted thereafter.
[b] One subject was withdrawn due to hypotension (SBP drop of 31 mmHg from baseline of 138 mmHg) that was deemed to be secondary to anti-hypertensive medications by investigator.
[c] An unplanned collection at time of atrial fibrillation (reported as an SAE).

No relationship between CE-326,597 exposure and ECG parameters was apparent. The frequency of QT changes was similar across treatment arms and no clinically significant changes were observed in RR, PR, and QRS intervals or heart rate. A categorical summary of postbaseline QTc, QTcB and QTcF interval changes is presented in Table S9.

Table S9. QTc, QTcB and QTcF Interval: Categorical Summary of Post-Baseline Data – Clinically Significant Maximum Absolute Values and Clinically Significant Maximum Increase From Baseline

		CE-326,597			
Parameter Criteria	**Placebo (N=51) n/N (%)**	**5 mg QD (N=50) n/N (%)**	**25 mg QD (N=51) n/N (%)**	**50 mg QD (N=50) n/N (%)**	**100 mg QD (N=50) n/N (%)**
Maximum QTc Interval					
450 - <480 msec	8 (15.7)	8 (16.0)	2 (3.9)	5 (10.0)	7 (14.0)
480 - <500 msec	1 (2.0)	1 (2.0)	1 (2.0)	0	1 (2.0)
≥500 msec	0	0	0	0	1 (2.0)
Maximum QTcB Interval					
450 - <480 msec	11 (21.6)	9 (18.0)	8 (15.7)	8 (16.0)	7 (14.0)
480 - <500 msec	2 (3.9)	1 (2.0)	1 (2.0)	0	2 (4.0)
≥500 msec	0	0	0	0	2 (4.0)
Maximum QTcF Interval					
450 - <480 msec	4 (7.8)	6 (12.0)	4 (7.8)	2 (4.0)	5 (10.0)
480 - <500 msec	0	0	0	0	1 (2.0)
≥500 msec	0	0	0	0	1 (2.0)
	Placebo (N=49)	**5 mg (N=48)**	**25 mg (N=48)**	**50 mg (N=47)**	**100 mg (N=46)**

Maximum QTc Interval Increase from Baseline					
30 msec ≤ change <60 msec	1 (2.0)	3 (6.3)	1 (2.1)	5 (10.6)	2 (4.3)
change ≥60 msec	3 (6.1)	0	0	0	2 (4.3)

Note: Baseline was defined to be a specific measurement prior to dosing on Day 1; Readings: from Day 7 to Day 84 and follow-up.
ECG = electrocardiogram; QD = once daily; QTcB = QTc interval using Bazett's correction; QTcF = QTc interval using Fridericia's correction.

Other Safety Results: Based on complete physical examinations performed at Screening and Follow-up visits (as well as early termination, where applicable), no gross difference between the 5 treatment arms in physical examination findings was evident.

Gastrointestinal Symptoms Questionnaire (GSQ): The total number of subjects who described having abdominal pain on the GSQ across all CE-326,597 dose levels at any time (Days 7, 14, 28, 56, and 84 combined) were: placebo 8/51, 5 mg 2/50, 25 mg 1/51, 50 mg 4/50, and 100 mg 12/50. None of the subjects displayed symptoms suggestive of hepato-biliary-pancreatic injury.

There appeared to be a greater proportion of subjects experiencing abdominal pain, especially on Day 7, with increasing dose (2/50 subjects in the 50 mg group, 4/50 in the 100 mg group, versus 1/50 in the 5 mg group). However, the use of medication to relieve abdominal pain was small and occurred only in the placebo and 100 mg groups.

Transabdominal Ultrasonography: Three (3) subjects (1 on CE-326,597 5 mg and 2 on CE-326,597 100 mg) on their Day 84 transabdominal ultrasound were noted to have cholelithiasis when no such evidence was present on the ultrasound obtained at screening; all 3 subjects, however, were asymptomatic at the time of image acquisition at the Day 84 visit. Additionally, all 3 subjects had unremarkable laboratory parameters including total and direct bilirubin, alanine aminotransferase alkaline phosphatase, as well as amylase and lipase. A repeat transabdominal ultrasound obtained at least 3 months following last dose of study drug revealed no presence of cholelithiasis in 2 subjects (1 subject on CE-326,597 5 mg and 1 subject on CE-326,597 100 mg) while the third subject (who received CE-326,597 100 mg) had the gallstones present with no change in size since the Day 84 ultrasound.

Hypoglycemic Adverse Events (HAE):

Thirty-three (33) HAEs were reported in 15 subjects across the 5 treatment arms studied. The number of subjects reporting HAEs were 1 (placebo), 6 (5 mg), 1 (25 mg), 3 (50 mg) and 4 (100 mg). The median number of HAEs reported was 1 to 2 per subject across dose groups; however, 1 subject randomized to CE-326,597 5 mg experienced 12 separate episodes of HAE. Of the subjects reporting HAE, 87% (ie, 13/15) were on background sulfonylurea or meglitinide analogue either alone or in combination with metformin. One (1) subject randomized to CE-326,597 100 mg was on metformin alone, and 1 subject on 100 mg CE-326,597 was not receiving any background medications for glycemic control (ie, the subject was treatment naïve).

Conclusions:

- The magnitude of change in HbA1c with a range of oral doses of CE-326,597, administered over 12 weeks, in overweight and obese adult subjects with T2DM either treatment naïve or on stable (up to 2) oral, anti-diabetic agents was similar to placebo with the exception of the 50 mg dose group. There was no dose-related trend in HbA1c response.

- The magnitude of weight loss with a range of oral doses of CE-326,597, administered over 12 weeks, was similar to placebo with the exception of the 50 mg dose group. There was no dose-related trend in weight loss.

- CE-326,597 appeared to be well-tolerated in subjects with T2DM. A dose-related increase in AE frequency, particularly related to GI symptoms, was observed with increasing dose.

- CE-326,597 exhibited fairly dose-linear increases in concentration with increasing dose.