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COMPOUND NUMBER: PF-04991532

PROTOCOL NO.: B2611003

PROTOCOL TITLE: A 12-Week, Phase 2, Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging, Parallel Group Study to Evaluate the Efficacy and Safety of Twice Daily PF-04991532 and Once Daily Sitagliptin in Adult Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Metformin

Study Centers: Forty-one (41) centers took part in the study and enrolled subjects; Canada (6 centers), Hungary (2 centers), Mexico (3 centers), Slovakia (4 centers), Taiwan (2 centers), and the United States (24 centers).

Study Initiation Date and Final Completion Date: 02 June 2011 to 27 March 2012

Phase of Development: Phase 2

Study Objectives: The objectives of the study were as below:

Primary Objective:

- To evaluate the dose-response of PF-04991532 administered twice daily over 12 weeks on glycosylated hemoglobin (HbA1c) in adults with type 2 diabetes mellitus (T2DM) on stable doses of metformin.

Secondary Objectives:

- To characterize the dose-responses of PF-04991532 administered twice daily and sitagliptin 100 mg administered once daily on fasting plasma glucose over 12 weeks in adults with T2DM on stable doses of metformin.

- To evaluate the dose-responses of PF-04991532 administered twice daily and sitagliptin 100 mg administered once daily over 12 weeks on body weight in adults with T2DM on stable doses of metformin.

- To evaluate the safety and tolerability of a range of oral doses of PF-04991532 administered twice daily and sitagliptin 100 mg administered once daily over 12 weeks in adults with T2DM on stable doses of metformin.

METHODS

Study Design: This was a randomized, double-blinded, double-dummy, placebo-controlled, 6-arm, parallel-group, study in adult subjects with T2DM on stable doses of metformin, using sitagliptin as an internal reference standard. Subjects were randomized to 1 of 4 doses (25, 75, 150, 300 mg) of PF-04991532, placebo, or sitagliptin 100 mg. The study included a total of up to 10 planned outpatient visits to the study site. Total participation in the study for each subject was approximately 17 to 23 weeks (up to 27 weeks if a longer stabilization period was needed), including the screening, washout, and Baseline periods.

Once subjects were deemed eligible based on procedures completed at Visit 1 (ie, screening), they returned to the site approximately 1 week later (ie, Visit 2) at which time subjects were switched to sponsor-provided metformin. The dose of metformin (ie, total daily dose) remained the same as that administered prior to Visit 1 or subjects were placed on a revised dose (which was a multiple of 500 mg) during the washout/re-stabilization period (Visit 2 to Visit 3) before initiating the run-in period (Visit 3). Those subjects who were also taking a second acceptable oral antidiabetic agent had the second medication discontinued for at least 6 weeks prior to Visit 3.

All subjects entered a 2 week run-in period during which time they received single-blind placebo twice daily for PF-04991532 and single-blind placebo twice daily for sitagliptin, in addition to receiving metformin. Subjects ≥90% compliant (based on pill count) during the run-in period were randomized to receive, in addition to sponsor-provided metformin, 1 of 4 doses of PF-04991532, 100 mg sitagliptin, or matching placebo for a 12-week treatment period. The timing of activities has been summarized in Table 1.

Table 1. Timetable of Study Procedures/Evaluations

Protocol Activity	Screen	Washout[a]	Run-In	Treatment Phase[b]						Follow-Up
Weeks Relative to Dosing on Day 1	**--**	**--**	**-2**	**0**	**1**	**2**	**4**	**8**	**12**	**14**
Days Relative to Dosing on Day 1	**--**	**--**	**-14**	**1**	**7±1**	**14±1**	**28±2**	**56±2**	**84±2**	**98±2**
Visit to Site	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Informed consent	X									
Contact telerandomization system	X		X	X	X	X	X	X	X	
(Update) Medical and medication history	X	X	X	X	X	X	X	X	X	X
Demographic history	X									
Physical examination	X[c]									X
Body weight	X			X	X	X	X	X	X	X
Supine 12-lead electrocardiogram	X			X			X		X	X
Sitting blood pressure and pulse rate	X			X	X	X	X	X	X	X
Assessment of baseline symptoms/adverse events		X	X	X	X	X	X	X	X	X
Counseling on dietary, exercise guidelines for T2DM, and identification/ management of hypo- & hyperglycemia		X		X						
Review/provide hypoglycemia log		X	X	X	X	X	X	X	X	X
Review glucometer results		X	X	X	X	X	X	X	X	X
Glucometer blood glucose (finger stick)		X	X							

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Visit to Site	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Discontinue background OAD medication, if applicable		X								X[d]
Administration of sponsor-provided metformin		X	→	→	→	→	→	→	→	X
Administration of blinded placebo			X							
Randomization				X						
Dispense blinded study medication				X	X	X	X	X		
Witnessed dosing at site			X	X	X	X	X	X	X	
Administration of double-blinded study medications				X	→	→	→	→	X	
Compliance check (via pill count)				X[e]	X[e]	X	X	X	X	
Clinical laboratory tests (chemistry, hematology, urinalysis, lipids)	X			X	X	X	X	X	X	X
Urine drug screen	X									
Insulin, C-peptide, and HbA1c	X			X	X	X	X	X	X	
PF-04991532 PK ± metabolite(s) sample				X	X		X		X	

Table 1. Timetable of Study Procedures/Evaluations

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Days Relative to Dosing on Day 1	**--**	**--**	**-14**	**1**	**7±1**	**14±1**	**28±2**	**56±2**	**84±2**	**98±2**
Visit to Site	**V1**	**V2**	**V3**	**V4**	**V5**	**V6**	**V7**	**V8**	**V9**	**V10**
Follicle-stimulating hormone (postmenopausal women 45 to 60 years of age)	X									
Thyroid-stimulating hormone	X									
Genomic and biomarker sample (optional)				X					X	

HbA1c = glycosylated hemoglobin; OAD = oral antidiabetic; PK = pharmacokinetic; T2DM = type 2 diabetes mellitus; V = visit.

a. Minimum = 6 weeks for those discontinuing OAD agent; could have been combined with Visit 3 for those on a stable dose of metformin at Visit 1.
b. Procedures to be completed prior to witnessed dosing on site.
c. Included height with physical examination (screening only).
d. Re-initiated OAD therapy.
e. ≥90% compliance rate required for randomization.

Number of Subjects (Planned and Analyzed): It was planned to enroll a total of 288 subjects (48 per treatment arm). Overall, 566 subjects were screened for entry to the study, of which 301 subjects were randomized to treatment and received at least 1 dose of study medication. Of these 301 subjects, 49 were in the 25 mg group, 50 were in the 75 mg group, 50 were in the 150 mg group, 52 were in the 300 mg group, 50 were in the sitagliptin group, and 50 were in the placebo group. Approximately 75 to 89% of the subjects in all 6 treatment groups completed the study.

Diagnosis and Main Criteria for Inclusion: The study included males and/or females of non-childbearing potential between 18 and 70 years of age with T2DM on stable doses of background medicines for management of diabetes, with a body mass index between 22.5 and 45.5 kg/m^2. Subjects suffering from type 1 diabetes, heart attack or stroke in the past 6 months, uncontrolled blood pressure or significant kidney disease were excluded from the study.

Study Treatment: Subjects were randomized to 1 of 4 doses (25, 75, 150, 300 mg) of PF-04991532, placebo, or sitagliptin 100 mg. Matching placebos for PF-04991532 and sitagliptin were used to maintain the study blind. In addition to the study treatment, all subjects were switched to sponsor-provided metformin.

Subjects were instructed to take the study medication orally each day at the same time of day with the morning and evening meal (ie, twice daily). Metformin was taken with meals on a schedule that was appropriate for the subject's dosing regimen (eg, once daily and twice daily). All study medication was provided in tablet form.

Efficacy Endpoints:

Primary Endpoint: Change from Baseline in HbA1c (%) at Week 12 (Day 84) as compared to placebo.

Secondary Endpoints:

- Change from Baseline in fasting plasma glucose (mg/dL) at Weeks 1, 2, 4, 8 and 12.
- Change from Baseline in HbA1c at Weeks 1, 2, 4, and 8.
- Proportion of subjects achieving HbA1c <7%, as well as the proportion achieving <6.5% at Week 12.
- Change from Baseline in body weight at Weeks 1, 2, 4, 8 and 12.
- Proportion of subjects at Week 12 with body weight gain from Baseline ≥1%.
- Proportion of subjects at Week 12 with body weight loss from Baseline ≥1%.
- Proportion of subjects at Week 12 with body weight gain from Baseline ≥2%.
- Proportion of subjects at Week 12 with body weight loss from Baseline ≥2%.

- Assessment of clinical laboratory tests, 12-lead electrocardiograms (ECGs), vital signs, adverse events (AEs), as well as serious AEs (SAEs) and including episodes of hypoglycemic adverse events (HAEs).

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead ECGs, AEs and safety laboratory tests. The timings have been given in Table 1.

Statistical Methods: The primary efficacy endpoint was the HbA1c change from Baseline at Week 12. The treatment effect on the endpoint was analyzed using the mixed-model repeated measure (MMRM) approach with treatment group, time, and treatment-by-time interaction as fixed effects, subject as random effect, Baseline, Baseline-by-time interaction, and Baseline-by-time-by-treatment interaction as the covariates. The analysis was performed on all observed cases from Weeks 1, 2, 4, 8, and 12. The primary comparison was the difference of each PF-04991532 dose against placebo at Week 12.

The treatment effect of PF-04991532 and sitagliptin 100 mg at all on-treatment visits was estimated by the least-square (LS) means as well as LS mean differences against placebo, respectively, from the model described above.

The changes from Baseline in fasting plasma glucose and body weight were analyzed using the MMRM approach with treatment group, time, and treatment-by-time interaction as fixed effects, subject as random effect, and Baseline as the covariate. The following categorical data were summarized: the proportion of subjects achieving HbA1c <6.5% and <7%, and the proportion of subjects with body weight gain/loss from Baseline ≥1% or ≥2%.

For endpoints other than HbA1c, 95% confidence intervals (CIs) were presented for the LS mean differences along with the corresponding 2-sided p-values. For HbA1c, 80% CIs were presented for the LS mean differences along with the corresponding 1-sided p-values.

Statistical inference could have been determined for safety measures of clinical concern. Safety data were presented in tabular and/or graphical format and summarized descriptively, as appropriate to the sponsor's standards.

Analysis Populations: The primary and secondary analyses were based on the full analysis set (FAS), which included all randomized subjects who received at least 1 dose of randomized study treatment. All the subjects randomized to treatment were included in the safety analysis set.

RESULTS

Subject Disposition and Demography: Overall, 566 subjects were screened for entry to the study, of which 301 subjects were randomized to treatment and received at least 1 dose of study medication. Of these 301 subjects, 49 were in the 25 mg group, 50 were in the 75 mg group, 50 were in the 150 mg group, 52 were in the 300 mg group, 50 were in the sitagliptin group, and 50 were in the placebo group. A total of 53 subjects discontinued the study. Of these subjects, 12 (24.5%) were in the 25 mg group, 11 (22.0%) were in the 75 mg group, 9 (18.0%) were in the 150 mg group, 6 (11.5%) were in the 300 mg group, 6 (12.0%) were in

the sitagliptin group, and 9 (18.0%) were in the placebo group. The most frequent reason for discontinuation was "other" reasons (13 subjects). Of these, most were due to schedule conflicts with study visits for reasons such as moving away or vacation. Three subjects in the 25 mg group, 1 subject in the 75 mg group, 3 subjects in the 150 mg group, 2 subjects in the 300 mg group, 1 subject in the sitagliptin group, and 5 subjects in the placebo group discontinued due to insufficient clinical response. The investigator-coded reason for these subjects discontinuing included "other" reasons, AEs of hyperglycemia or elevated blood glucose level, or were no longer willing to participate in the study (Table 2). All of the 301 subjects randomized to treatment were also included in the FAS. All 301 subjects were included in the safety analysis set for AEs and 300 subjects were included in the safety analysis for the laboratory data.

Table 2. Subject Disposition

	Number (%) of Subjects					
	PF-04991532				Sitagliptin	Placebo
	25 mg	75 mg	150 mg	300 mg	100 mg	
Screened = 566						
Assigned to study treatment	49	50	50	52	50	50
Treated	49	50	50	52	50	50
Completed	37 (75.5)	39 (78.0)	41 (82.0)	46 (88.5)	44 (88.0)	41 (82.0)
Discontinued	12 (24.5)	11 (22.0)	9 (18.0)	6 (11.5)	6 (12.0)	9 (18.0)
Relation to study drug not defined	8 (16.3)	10 (20.0)	4 (8.0)	2 (3.8)	5 (10.0)	5 (10.0)
Lost to follow-up	0	1 (2.0)	0	1 (1.9)	0	0
No longer willing to participate in study	3 (6.1)	4 (8.0)	0	0	2 (4.0)	2 (4.0)
Other	3 (6.1)	3 (6.0)	2 (4.0)	0	2 (4.0)	3 (6.0)
Protocol violation	2 (4.1)	2 (4.0)	2 (4.0)	1 (1.9)	1 (2.0)	0
Related to study drug	2 (4.1)	1 (2.0)	2 (4.0)	3 (5.8)	1 (2.0)	1 (2.0)
Adverse event	2 (4.1)	1 (2.0)	2 (4.0)	3 (5.8)	1 (2.0)	1 (2.0)
Not related to study drug	2 (4.1)	0	3 (6.0)	1 (1.9)	0	3 (6.0)
Adverse event	2 (4.1)	0	3 (6.0)	1 (1.9)	0	3 (6.0)

Discontinuations have been attributed to the last study treatment received.

Most subjects in this study were male (Table 3). The subjects' ages ranged from 28 to 70 years. Most subjects (≥78%) were white. The demographic characteristics were well balanced across the treatment groups.

Table 3. Subject Demographics

	PF-04991532				Sitagliptin	Placebo
	25 mg	75 mg	150 mg	300 mg	100 mg	
Gender (n)						
Male	19	29	30	22	35	34
Female	30	21	20	30	15	16
Age (n [%])						
18–44 years	1 (2.0)	7 (14.0)	3 (6.0)	3 (5.8)	6 (12.0)	6 (12.0)
45–64 years	36 (73.5)	37 (74.0)	35 (70.0)	41 (78.8)	37 (74.0)	39 (78.0)
≥65 years	12 (24.5)	6 (12.0)	12 (24.0)	8 (15.4)	7 (14.0)	5 (10.0)
Age (years)						
Mean (SD)	59.2 (6.8)	56.1 (8.6)	57.2 (8.7)	56.0 (7.7)	55.6 (9.0)	55.7 (8.8)
Range	42-70	33-70	28-70	35-70	35-69	29-70
Race (n [%])						
White	43 (87.8)	39 (78.0)	43 (86.0)	43 (82.7)	41 (82.0)	39 (78.0)
Black	3 (6.1)	3 (6.0)	1 (2.0)	4 (7.7)	5 (10.0)	3 (6.0)
Asian	2 (4.1)	5 (10.0)	3 (6.0)	5 (9.6)	3 (6.0)	4 (8.0)
Other	1 (2.0)	3 (6.0)	3 (6.0)	0	1 (2.0)	4 (8.0)
Weight (kg)						
Mean (SD)	87.9 (20.1)	86.5 (20.2)	86.0 (18.4)	92.3 (21.6)	91.4 (20.9)	90.4 (17.5)
Range	58.4-136.5	53.0-134.2	48.4-140.2	56.9-144.0	55.1-136.0	58.5-147.7
Body mass index (kg/m^2)						
Mean (SD)	32.3 (5.9)	31.1 (5.5)	31.2 (5.3)	33.4 (5.8)	31.7 (5.4)	31.5 (5.2)
Range	23.3-45.4	23.3-44.3	21.0-41.8	22.9-45.1	23.0-44.3	23.1-45.6

Body mass index was defined as weight/(height × 0.01)^2.
n = number of subjects; SD = standard deviation.

Efficacy Results:

Primary: The primary efficacy endpoint was the change from Baseline in HbA1c (%) at Week 12 (Day 84) as compared to placebo. The HbA1c LS mean change from Baseline to Week 12 for the FAS is provided in Table 4. At Week 12, PF-04991532 showed significant improvement over placebo at the 75 mg, 150 mg, and 300 mg doses, with LS mean differences from placebo of -0.28%, -0.24%, and -0.53%, respectively ($p \leq 0.0440$). Sitagliptin also showed significant benefit over placebo with an LS mean difference from placebo of -0.43% ($p=0.0013$).

Table 4. LS Mean Change From Baseline at Week 12 for HbA1c (%) - Full Model - FAS, OC

Treatment	N	LS Mean	SE	80% CI	Difference From Placebo			
					LS Mean	SE	80% CI	p-Value
PF-04991532 25 mg	37	-0.13	0.106	(-0.26, 0.01)	0.10	0.145	(-0.08, 0.29)	0.7606
PF-04991532 75 mg	39	-0.51	0.102	(-0.64, -0.38)	-0.28	0.142	(-0.46, -0.09)	0.0266
PF-04991532 150 mg	40	-0.47	0.101	(-0.60, -0.34)	-0.24	0.141	(-0.42, -0.06)	0.0440
PF-04991532 300 mg	46	-0.76	0.094	(-0.88, -0.64)	-0.53	0.137	(-0.71, -0.36)	0.0001
Sitagliptin 100 mg	44	-0.66	0.098	(-0.78, -0.53)	-0.43	0.139	(-0.60, -0.25)	0.0013
Placebo	42	-0.23	0.099	(-0.36, -0.10)	-	-	-	-

Baseline was defined as the latest evaluation performed prior to the first dose of randomized treatment.
Measurements which fell out of the protocol-specified visit windows were excluded.
The mixed-model repeated measure with model terms: treatment, time, treatment-by-time interaction as fixed effects, Baseline, Baseline-by-time interaction, Baseline-by-treatment interaction, Baseline-by-treatment-by-time interaction as the covariates, time was repeated for subject.
The covariance structure - unstructured was used.
p-value was 1-sided.
CI = confidence interval; FAS = full analysis set; HbA1c = glycosylated hemoglobin; LS = least square; N = number of subjects; OC = observed cases; SE = standard error.

Secondary:

Fasting Plasma Glucose: Table 5 presents a summary of the LS mean change from Baseline and mean difference from placebo for fasting plasma glucose in the FAS. At Weeks 1, 2, 4, 8, and 12, PF-04991532 showed significant improvement over placebo at the 300 mg dose, with LS mean differences from placebo of -15.92 mg/dL,-13.88 mg/dL, -19.57 mg/dL, -15.30 mg/dL, and -15.30 mg/dL, respectively ($p \leq 0.0159$). Sitagliptin also showed significant improvement over placebo at Weeks 1, 2, 4, 8, and 12, with LS mean differences from placebo of -21.09 mg/dL, -18.69 mg/dL, -19.08 mg/dL, -18.62 mg/dL, and -14.95 mg/dL, respectively ($p \leq 0.0126$). The improvements occurred as early as Week 1 and appeared more pronounced from Week 4 through Week 12.

Table 5. LS Mean Change From Baseline for Fasting Plasma Glucose (mg/dL) - FAS, OC

Treatment					Difference From Placebo			
	N	LS Mean	SE	95% CI	LS Mean	SE	95% CI	p-Value
Week 1								
PF-04991532 25 mg	47	-0.71	4.068	(-8.69, 7.28)	-5.21	5.700	(-16.40, 5.98)	0.3611
PF-04991532 75 mg	47	-4.95	4.048	(-12.89, 3.00)	-9.45	5.686	(-20.61, 1.71)	0.0969
PF-04991532 150 mg	46	-3.59	4.079	(-11.60, 4.41)	-8.10	5.710	(-19.30, 3.11)	0.1566
PF-04991532 300 mg	46	-11.41	4.046	(-19.35, -3.47)	-15.92	5.678	(-27.06, -4.77)	0.0052
Sitagliptin 100 mg	45	-16.59	4.093	(-24.62, -8.56)	-21.09	5.712	(-32.30, -9.88)	0.0002
Placebo	48	4.50	3.992	(-3.33, 12.34)				
Week 2								
PF-04991532 25 mg	44	0.26	4.162	(-7.91, 8.43)	0.08	5.852	(-11.41, 11.56)	0.9893
PF-04991532 75 mg	45	-3.96	4.108	(-12.03, 4.10)	-4.14	5.814	(-15.55, 7.27)	0.4767
PF-04991532 150 mg	45	-2.69	4.110	(-10.76, 5.38)	-2.87	5.816	(-14.28, 8.55)	0.6222
PF-04991532 300 mg	47	-13.71	4.015	(-21.59, -5.83)	-13.88	5.744	(-25.16, -2.61)	0.0159
Sitagliptin 100 mg	48	-18.52	4.002	(-26.37, -10.66)	-18.69	5.735	(-29.95, -7.44)	0.0012
Placebo	44	0.18	4.113	(-7.89, 8.25)				
Week 4								
PF-04991532 25 mg	42	5.87	4.260	(-2.49, 14.23)	3.86	5.895	(-7.71, 15.43)	0.5125
PF-04991532 75 mg	44	-6.46	4.150	(-14.61, 1.68)	-8.47	5.815	(-19.89, 2.94)	0.1455
PF-04991532 150 mg	45	2.95	4.119	(-5.14, 11.03)	0.94	5.794	(-10.43, 12.31)	0.8712
PF-04991532 300 mg	48	-17.56	3.998	(-25.40, -9.71)	-19.57	5.707	(-30.77, -8.36)	0.0006
Sitagliptin 100 mg	49	-17.07	3.981	(-24.88, -9.25)	-19.08	5.696	(-30.26, -7.90)	0.0008
Placebo	46	2.01	4.074	(-5.99, 10.01)				
Week 8								
PF-04991532 25 mg	40	9.86	4.364	(1.29, 18.42)	6.99	6.055	(-4.90, 18.87)	0.2488
PF-04991532 75 mg	41	-4.69	4.293	(-13.12, 3.74)	-7.56	6.004	(-19.34, 4.23)	0.2084
PF-04991532 150 mg	42	3.58	4.248	(-4.76, 11.92)	0.71	5.971	(-11.01, 12.43)	0.9053
PF-04991532 300 mg	46	-12.43	4.075	(-20.43, -4.43)	-15.30	5.853	(-26.79, -3.81)	0.0091
Sitagliptin 100 mg	45	-15.75	4.106	(-23.81, -7.69)	-18.62	5.875	(-30.15, -7.09)	0.0016
Placebo	43	2.87	4.199	(-5.37, 11.11)				
Week 12								
PF-04991532 25 mg	37	7.71	4.518	(-1.16, 16.58)	6.50	6.217	(-5.71, 18.70)	0.2963
PF-04991532 75 mg	38	-8.50	4.456	(-17.24, 0.25)	-9.71	6.170	(-21.82, 2.40)	0.1159
PF-04991532 150 mg	40	5.92	4.362	(-2.64, 14.48)	4.70	6.103	(-7.28, 16.68)	0.4413
PF-04991532 300 mg	46	-14.08	4.089	(-22.11, -6.05)	-15.30	5.918	(-26.91, -3.68)	0.0099
Sitagliptin 100 mg	44	-13.73	4.177	(-21.93, -5.54)	-14.95	5.981	(-26.69, -3.21)	0.0126
Placebo	42	1.22	4.274	(-7.17, 9.60)				

Baseline was defined as the latest evaluation performed prior to the first dose of randomized treatment.
Measurements that fell out of the protocol-specified visit windows were excluded.
The mixed-model repeated measure with model terms: treatment, time, treatment-by-time interaction as fixed effects, baseline as the covariate; time was repeated for subject.
The covariance structure - CSH was selected based on the principle of the smallest AIC/BIC from CS, AR (1), CSH, ARH (1), unstructured. If the results using AIC and BIC conflict, the simple structure was adopted.
p-value was 2-sided.
AIC = Akaike Information Criterion; AR (1) = Autoregressive (1); ARH (1) = Heterogeneous autoregressive (1); BIC = Baysian Information Criterion; CI = confidence interval; CSH = heterogeneous compound symmetry; CS = compound symmetry; FAS = full analysis set; LS = least square; N = number of subjects; OC = observed case; SE = standard error.

HbA1c: The HbA1c LS mean change from Baseline at Week 1, 2, 4 and 8 for the FAS is provided in Table 6. Table 7 presents a summary of the proportion of subjects achieving HbA1c levels of <6.5% or <7% at Week 12 for the FAS. The PF-04991532 300 mg treatment group had the highest number of responders with 17.4% (8/46) of subjects achieving an HbA1c <6.5% and 43.5% (20/46) of subjects achieving an HbA1c <7%.

Table 6. LS Mean Change From Baseline at Weeks 1, 2, 4 and 8 for HbA1c (%) - Full Model - FAS, OC

Treatment	N	LS Mean	SE	80% CI	Difference From Placebo			
					LS Mean	SE	80% CI	p-Value
Week 1								
PF-04991532 25 mg	47	-0.01	0.41	(-0.06, 0.05)	-0.05	0.058	(-0.13, 0.02)	0.1797
PF-04991532 75 mg	47	-0.07	0.41	(-0.12, -0.02)	-0.12	0.058	(-0.19, -0.04)	0.0234
PF-04991532 150 mg	46	-0.06	0.41	(-0.11, 0.00)	-0.10	0.058	(-0.18, -0.03)	0.0400
PF-04991532 300 mg	46	-0.01	0.040	(-0.06, 0.04)	-0.06	0.057	(-0.13, 0.02)	0.1568
Sitagliptin 100 mg	47	-0.13	0.041	(-0.19, -0.08)	-0.18	0.058	(-0.13, 0.02)	0.0010
Placebo	48	0.05	0.041	(-0.01, 0.10)				
Week 2								
PF-04991532 25 mg	44	-0.09	0.051	(-0.16, -0.03)	-0.10	0.070	(-0.19, -0.01)	0.0695
PF-04991532 75 mg	45	-0.10	0.049	(-0.16, -0.03)	-0.11	0.069	(-0.20, -0.02)	0.0636
PF-04991532 150 mg	45	-0.10	0.049	(-0.17, -0.04)	-0.11	0.069	(-0.20, -0.02)	0.0512
PF-04991532 300 mg	47	-0.17	0.047	(-0.23, -0.10)	-0.18	0.068	(-0.26, -0.09)	0.0051
Sitagliptin 100 mg	48	-0.21	0.048	(-0.27, -0.14)	-0.22	0.069	(-0.30, -0.13)	0.0009
Placebo	45	0.01	0.049	(-0.05, 0.07)				
Week 4								
PF-04991532 25 mg	42	-0.15	0.068	(-0.24, -0.07)	-0.07	0.094	(-0.19, 0.05)	0.2392
PF-04991532 75 mg	44	-0.26	0.065	(-0.34, -0.17)	-0.17	0.091	(-0.29, -0.05)	0.0308
PF-04991532 150 mg	45	-0.35	0.064	(-0.44, -0.27)	-0.27	0.091	(-0.38, -0.15)	0.0019
PF-04991532 300 mg	48	-0.33	0.062	(-0.41, -0.25)	-0.24	0.089	(-0.36, -0.13)	0.0034
Sitagliptin 100 mg	49	-0.41	0.063	(-0.49, -0.33)	-0.32	0.090	(-0.44, -0.21)	0.0002
Placebo	46	-0.09	0.064	(-0.17, 0.00)				
Week 8								
PF-04991532 25 mg	40	-0.11	0.092	(-0.22, 0.01)	0.10	0.126	(-0.06, 0.26)	0.7854
PF-04991532 75 mg	41	-0.38	0.088	(-0.49, -0.27)	-0.18	0.123	(-0.33, -0.02)	0.0778
PF-04991532 150 mg	42	-0.51	0.087	(-0.62, -0.40)	-0.31	0.122	(-0.46, -0.15)	0.0065
PF-04991532 300 mg	45	-0.57	0.082	(-0.68, -0.47)	-0.37	0.119	(-0.52, -0.21)	0.0011
Sitagliptin 100 mg	45	-0.57	0.085	(-0.68, -0.46)	-0.37	0.121	(-0.52, -0.21)	0.0013
Placebo	43	-0.21	0.086	(-0.32, -0.09)				

Baseline was defined as the latest evaluation performed prior to the first dose of randomized treatment.
Measurements which fell out of the protocol-specified visit windows were excluded.
The mixed-model repeated measure with model terms: treatment, time, treatment-by-time interaction as fixed effects, Baseline, Baseline-by-time interaction, Baseline-by-treatment interaction, Baseline-by-treatment-by-time interaction as the covariates, time was repeated for subject.
The covariance structure - unstructured was used.
p-value was 1-sided.
CI = confidence interval; FAS = full analysis set; HbA1c = glycosylated hemoglobin; LS = least square; N = number of subjects; OC = observed cases; SE = standard error.

Table 7. Proportion of Subjects Achieving HbA1c <6.5% or <7% at Week 12 - FAS, OC

	Number (%) of Subjects					
	PF-04991532				Sitagliptin	
	25 mg (N = 37)	75 mg (N = 39)	150 mg (N = 40)	300 mg (N = 46)	100 mg (N = 44)	Placebo (N = 42)
<6.5%	3 (8.1)	6 (15.4)	7 (17.5)	8 (17.4)	7 (15.9)	5 (11.9)
<7%	11 (29.7)	15 (38.5)	14 (35.0)	20 (43.5)	16 (36.4)	10 (23.8)

FAS = full analysis set; HbA1c = glycosylated hemoglobin; N = total number of subjects with no missing Week 12 observation in each treatment group; OC = observed cases.

Body Weight: Table 8 presents a summary of the LS mean change from Baseline and mean difference from placebo for body weight in the FAS. At Week 12, all PF-04991532 treatment groups reduced body weight by 0.03 kg to 0.82 kg. None of the PF-04991532 treatment groups showed any significant difference in body weight change from placebo. At Week 12, the LS mean for the sitagliptin group was -0.82 kg; the difference from placebo was not statistically significant (p = 0.4081).

Table 9 presents summary of proportion of subjects at Week 12 with ≥1% or ≥2% body weight gain or body weight loss.

Table 8. LS Mean Change From Baseline for Weight (kg) - FAS, OC

Treatment	N	LS Mean	SE	95% CI	Difference From Placebo			
					LS Mean	SE	95% CI	p-value
Week 1								
PF-04991532 25 mg	47	-0.19	0.195	(-0.57, 0.19)	-0.16	0.272	(-0.69, 0.38)	0.5636
PF-04991532 75 mg	47	0.15	0.194	(-0.23, 0.54)	0.19	0.271	(-0.35, 0.72)	0.4889
PF-04991532 150 mg	46	-0.18	0.194	(-0.56, 0.20)	-0.15	0.272	(-0.68, 0.39)	0.5849
PF-04991532 300 mg	47	-0.21	0.189	(-0.58, 0.16)	-0.18	0.268	(-0.70, 0.35)	0.5104
Sitagliptin 100 mg	47	-0.33	0.191	(-0.71, 0.04)	-0.30	0.269	(-0.83, 0.23)	0.2640
Placebo	48	-0.03	0.190	(-0.41, 0.34)	-	-	-	-
Week 2								
PF-04991532 25 mg	44	-0.47	0.257	(-0.98, 0.03)	-0.71	0.357	(-1.42,-0.01)	0.0464
PF-04991532 75 mg	45	0.11	0.252	(-0.39, 0.61)	-0.13	0.353	(-0.83, 0.56)	0.7107
PF-04991532 150 mg	45	-0.26	0.250	(-0.75, 0.23)	-0.50	0.352	(-1.19, 0.19)	0.1564
PF-04991532 300 mg	47	-0.06	0.240	(-0.53, 0.41)	-0.30	0.345	(-0.98, 0.38)	0.3834
Sitagliptin 100 mg	48	-0.29	0.242	(-0.76, 0.19)	-0.53	0.346	(-1.21, 0.15)	0.1279
Placebo	45	0.24	0.247	(-0.25, 0.73)	-	-	-	-
Week 4								
PF-04991532 25 mg	42	-0.55	0.244	(-1.03, -0.07)	-0.39	0.339	(-1.06, 0.28)	0.2520
PF-04991532 75 mg	44	0.21	0.240	(-0.27, 0.68)	0.37	0.336	(-0.30, 1.03)	0.2772
PF-04991532 150 mg	45	-0.29	0.239	(-0.76, 0.18)	-0.13	0.335	(-0.79, 0.53)	0.7038
PF-04991532 300 mg	48	-0.58	0.231	(-1.03, -0.13)	-0.42	0.329	(-1.07, 0.23)	0.2031
Sitagliptin 100 mg	49	-0.29	0.232	(-0.75, 0.17)	-0.13	0.330	(-0.78, 0.52)	0.6948
Placebo	46	-0.16	0.235	(-0.62, 0.30)	-	-	-	-
Week 8								
PF-04991532 25 mg	40	-0.55	0.307	(-1.15, 0.06)	-0.24	0.421	(-1.07, 0.59)	0.5691
PF-04991532 75 mg	41	0.09	0.299	(-0.50, 0.67)	0.39	0.415	(-0.42, 1.21)	0.3447
PF-04991532 150 mg	42	-0.54	0.295	(-1.12, 0.04)	-0.23	0.413	(-1.04, 0.58)	0.5769
PF-04991532 300 mg	46	-0.68	0.281	(-1.23, -0.12)	-0.37	0.402	(-1.16, 0.42)	0.3599
Sitagliptin 100 mg	45	-0.61	0.287	(-1.17, -0.04)	-0.30	0.407	(-1.10, 0.50)	0.4600
Placebo	43	-0.31	0.289	(-0.88, 0.26)	-	-	-	-
Week 12								
PF-04991532 25 mg	37	-0.82	0.368	(-1.54, -0.09)	-0.40	0.504	(-1.39, 0.59)	0.4253
PF-04991532 75 mg	39	-0.03	0.357	(-0.73, 0.68)	0.39	0.497	(-0.59, 1.37)	0.4349
PF-04991532 150 mg	41	-0.63	0.351	(-1.32, 0.07)	-0.21	0.492	(-1.18, 0.76)	0.6697
PF-04991532 300 mg	46	-0.70	0.329	(-1.35, -0.05)	-0.28	0.476	(-1.22, 0.65)	0.5501
Sitagliptin 100 mg	44	-0.82	0.340	(-1.49, -0.15)	-0.40	0.484	(-1.35, 0.55)	0.4081
Placebo	42	-0.41	0.345	(-1.09, 0.26)	-	-	-	-

Baseline was defined as the measurement performed on Day 1.
Measurements which fell out of the protocol-specified visit windows were excluded.
The mixed-model repeated measure with model terms: treatment, time, treatment-by-time interaction as fixed effects, Baseline as the covariate; time was repeated for subject.
The covariance structure – ARH (1) was selected based on the principle of the smallest AIC/BIC from CS, AR(1), CSH, ARH (1), unstructured. If the results using AIC and BIC conflict, the simple structure was adopted.
p-value was 2-sided.
AIC = Akaike Information Criterion; AR (1) = Autoregressive (1); ARH (1) = Heterogeneous autoregressive (1); BIC = Baysian Information Criterion; CI = confidence interval; CSH = heterogeneous compound symmetry; CS = compound symmetry; FAS = full analysis set; LS = least square; N = number of subjects; OC = observed case; SE = standard error.

Table 9. Proportion of Subjects at Week 12 with ≥1% or ≥2% Body Weight Gain or Body Weight Loss - FAS, OC

	Number (%) of Subjects					
	PF-04991532				Sitagliptin	
	25 mg (N = 37)	75 mg (N = 39)	150 mg (N = 41)	300 mg (N = 46)	100 mg (N = 44)	Placebo (N = 42)
Body weight gain (n %)						
≥1%	10 (27.03)	15 (38.46)	9 (21.95)	7 (15.22)	14 (31.82)	10 (23.81)
≥2%	1 (2.70)	6 (15.38)	3 (7.32)	3 (6.52)	7 (15.91)	1 (2.38)
Body weight loss (n %)						
≥1%	13 (35.14)	12 (30.77)	20 (48.78)	19 (41.30)	18 (40.91)	16 (38.10)
≥2%	10 (27.03)	7 (17.95)	11 (26.83)	14 (30.43)	13 (29.55)	10 (23.81)

FAS = full analysis set; N = total number of subjects with no missing Week 12 observation in each treatment group; n = number of subjects with the observation meeting specified criteria; OC = observed cases.

Safety Results: Overall, 30 subjects reported 66 treatment-emergent AEs (TEAEs) in the 25 mg group, 27 subjects reported 51 TEAEs in the 75 mg group, 26 subjects reported 44 TEAEs in the 150 mg group, 27 subjects reported 51 TEAEs in the 300 mg group, 27 subjects reported 45 TEAEs in the sitagliptin group, and 25 subjects reported 50 TEAEs in the placebo group. No subject reported a treatment-emergent SAE. Fourteen subjects discontinued the study due to TEAEs. Two subjects in the 25 mg group, 1 subject in the 150 mg group, and 1 subject in the 300 mg group experienced a severe TEAE. One subject in the 25 mg group and 1 subject in the 75 mg group experienced a TEAE that led to temporary discontinuation of study medication.

Non-Serious Adverse Events: Among all 6 treatment groups, AEs were most commonly reported in the gastrointestinal disorders and infections and infestations system organ classes. The most common AEs were urinary tract infection, hyperglycemia and headache. No subjects in the 300 mg group reported urinary tract infection; no subjects in the 75 mg group reported hyperglycemia, and no subjects in the placebo group reported headache. Summaries of non-serious treatment-emergent AEs for events having frequency rate ≥5% are presented in Table 10 (all causality AEs) and Table 11 (treatment-related AEs).

Table 10. Summary of Non-Serious Treatment-Emergent Adverse Events (All Causality) For Events Having Frequency Rate ≥5%

Number (%) of Subjects With Adverse Events by: System Organ Class MedDRA (v15.0) Preferred Term	PF-04991532 25 mg (N = 49)	PF-04991532 75 mg (N = 50)	PF-04991532 150 mg (N = 50)	PF-04991532 300 mg (N = 52)	Sitagliptin 100 mg (N = 50)	Placebo (N = 50)
	n (%)					
Any AE	16 (32.7)	14 (28.0)	11 (22.0)	15 (28.8)	11 (22.0)	14 (28.0)
Gastrointestinal disorders	0	3 (6.0)	1 (2.0)	2 (3.8)	0	2 (4.0)
Diarrhoea	0	3 (6.0)	1 (2.0)	2 (3.8)	0	2 (4.0)
Infections and infestations	5 (10.2)	7 (14.0)	7 (14.0)	6 (11.5)	7 (14.0)	9 (18.0)
Nasopharyngitis	1 (2.0)	0	1 (2.0)	1 (1.9)	4 (8.0)	0
Pharyngitis	2 (4.1)	2 (4.0)	1 (2.0)	4 (7.7)	0	1 (2.0)
Upper respiratory tract infection	1 (2.0)	3 (6.0)	2 (4.0)	2 (3.8)	1 (2.0)	3 (6.0)
Urinary tract infection	1 (2.0)	2 (4.0)	3 (6.0)	0	2 (4.0)	5 (10.0)
Metabolism and nutrition disorders	6 (12.2)	0	4 (8.0)	2 (3.8)	3 (6.0)	3 (6.0)
Hyperglycaemia	5 (10.2)	0	3 (6.0)	1 (1.9)	1 (2.0)	3 (6.0)
Hypoglycaemia	1 (2.0)	0	1 (2.0)	1 (1.9)	3 (6.0)	0
Nervous system disorders	6 (12.2)	4 (8.0)	1 (2.0)	4 (7.7)	1 (2.0)	0
Dizziness	3 (6.1)	0	0	1 (1.9)	0	0
Headache	4 (8.2)	4 (8.0)	1 (2.0)	3 (5.8)	1 (2.0)	0
Vascular disorders	1 (2.0)	2 (4.0)	0	3 (5.8)	0	1 (2.0)
Hypertension	1 (2.0)	2 (4.0)	0	3 (5.8)	0	1 (2.0)

Subjects were only counted once per treatment for each row.
Includes data up to 9999 days after last dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects per treatment group; n = number of subjects with observation.

Table 11. Summary of Non-Serious Treatment-Emergent Adverse Events (Treatment Related) For Events Having Frequency Rate ≥5%

Number (%) of Subjects With Adverse Events by: MedDRA Preferred Term	PF-04991532				Sitagliptin	Placebo
	25 mg (N = 49)	75 mg (N = 50)	150 mg (N = 50)	300 mg (N = 52)	100 mg (N = 50)	(N = 50)
Diarrhoea	0	3 (6.0)	0	0	0	0
Dizziness	3 (6.1)	0	0	0	0	0
Headache	2 (4.1)	3 (6.0)	0	2 (3.8)	1 (2.0)	0

Includes all data collected since the first dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities; N = number of subjects per treatment group; n = number of subjects with observation.

SAEs: One subject reported a SAE (dyspnea) that occurred during the screening period (before the subject was randomized to treatment) and another SAE (pneumonia) was not considered to be treatment-emergent.

Other Significant Adverse Event (HAEs): Overall, 1 subject in the 25-mg group, 1 subject in the 300-mg group, and 4 subjects in the sitagliptin group had any hypoglycemic event. No subject had a severe hypoglycemic event. Table 12 presents a summary of the analysis of total hypoglycemic events.

Table 12 . Analysis of Protocol-Defined Total Hypoglycemic Event Rates

	PF-04991532				Sitagliptin	Placebo
	25 mg	75 mg	150 mg	300 mg	100 mg	
Total number of subjects	49	50	50	52	50	50
Number (%) of subjects with any event	1 (2.0)	0	0	1 (1.9)	4 (8.0)	0
Total number of events	2	0	0	2	6	0
Total subject-months	115.0	120.8	124.5	133.3	130.7	125.0
Event rate	0.0174	0	0	0.0150	0.0459	0

For each subject, subject-month was calculated as the elapsed number of months from the first day of treatment to the last day of treatment plus 1 day.
Event rate = total number of events/total subject-months.

Deaths: No subject died during the study.

Permanent Discontinuations Due to Adverse Events: Five subjects discontinued the study due to non-treatment-emergent AEs. Of these subjects, 2 were in the 150 mg group, and 1 subject each was in the 300 mg group, sitagliptin group, and placebo group. Fourteen subjects discontinued the study due to TEAEs. Of these subjects, 4 were in the 25 mg group, 1 was in the 75 mg group, 3 each were in the 150 mg group, 300 mg group, and placebo group.

Clinical Laboratory Evaluations: There was a higher frequency of subjects with alanine aminotransferase (ALT) values ≥2 × ULN in the 75 mg group and 150 mg group. No subjects had >3 × ULN elevations in ALT or aspartate transaminase. Serum creatinine

values above the upper limit of the reference range were similar across the 6 treatment groups. No other values reached levels of potential clinical concern. Table 13 presents the incidence of laboratory tests results that fell into specific ranges of interest. Overall, the laboratory test abnormalities were small.

There was a dose-related trend for increases in triglyceride values in the PF-04991532 treatment groups. At Week 12, the 150 mg and 300 mg groups showed triglyceride elevations from Baseline of 23% and 19%, respectively. A signal was present as early as Week 1, but there was no clear increase with time.

Table 13. Incidence of Laboratory Test Results That Fell Into Specific Ranges of Interest

	Number (%) of Subjects					
	PF-04991532				Sitagliptin	Placebo
	25 mg	75 mg	150 mg	300 mg	100 mg	
Fasting Plasma Glucose (≤49 mg/dL)	0	0	0	0	0	0
Fasting Plasma Glucose (≤70 mg/dL)	0	0	0	0	0	0
Fasting Plasma Glucose (≥140 mg/dL)	44 (90.0)	40 (82.0)	42 (84.0)	42 (81.0)	41 (82.0)	40 (80.0)
Fasting Plasma Glucose (≥270 mg/dL)	4 (8.0)	3 (6.0)	5 (10.0)	4 (8.0)	0	5 (10.0)
ALT ≥2 × ULN	1 (2.0)	6 (12.0)	6 (12.0)	2 (4.0)	0	0
ALT >3 × ULN	0	0	0	0	0	0
AST ≥2 × ULN	0	1 (2.0)	0	3 (6.0)	0	0
AST >3 × ULN	0	0	0	0	0	0
Total Bilirubin >1.5 × ULN	1 (2.0)	0	1 (2.0)	0	1 (2.0)	1 (2.0)
Serum Creatinine >ULN	2 (4.0)	2 (4.0)	4 (8.0)	0	4 (8.0)	3 (6.0)
Serum Creatinine >1.3 × ULN	1 (2.0)	0	0	0	0	0
Triglycerides ≥400 mg/dL	5 (10.0)	5 (10.0)	9 (18.0)	8 (15.0)	5 (10.0)	6 (12.0)
Triglycerides >650 mg/dL	1 (2.0)	0	3 (6.0)	2 (4.0)	2 (4.0)	0
Triglycerides ≥800 mg/dL	0	0	2 (4.0)	2 (4.0)	1 (2.0)	0

AST = aspartate aminotransferase; ALT = alanine aminotransferase; ULN = upper limit of normal.

Vital Signs: Overall, the mean changes in vital signs were small and not clinically meaningful. The incidences of increases or decreases in systolic and diastolic blood pressure of ≥5 mm Hg, ≥10 mm Hg, or ≥20 mm Hg were generally similar among the 6 treatment groups.

ECG Data: Overall, the mean changes in ECG parameters were small and not clinically meaningful.

CONCLUSIONS:

- Twice-daily doses of PF-04991532 75 mg, 150 mg, and 300 mg demonstrated dose-related reductions in HbA1c at Week 12 relative to placebo. There was no reduction in HbA1c following daily administration of PF-04991532 25 mg.
- Relative to placebo or sitagliptin, a higher percentage of subjects in the 300 mg group reached the HbA1c treatment target goals of <7% and <6.5%.
- The PF-04991532 300 mg dose had significant effects on fasting plasma glucose post-dose over 12 weeks relative to placebo.

- All doses of PF-04991532 demonstrated no significant change in body weight (increase or decrease) relative to placebo at Week 12.

- PF-04991532 doses of 25 mg to 300 mg, as well as sitagliptin 100 mg, were safe and well tolerated in subjects with T2DM over a period of 12 weeks.