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COMPOUND NUMBER: PF-04991532

PROTOCOL NO.: B2611002

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

Study Centers: A total of 41 centers took part in the study and randomized subjects; 25 in the United States (US), 6 in Canada, 3 each in the Republic of Korea and Mexico, 2 in Taiwan, and 1 each in Hungary and Slovakia.

Study Initiation Date and Final Completion Date: 02 June 2011 to 15 March 2012

Phase of Development: Phase 2

Study Objectives:

Primary Objective:

- To evaluate the dose-response of PF-04991532 administered once daily (QD) 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 QD and sitagliptin 100 mg administered QD 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 QD and sitagliptin 100 mg administered QD 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 QD and sitagliptin 100 mg administered QD, 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, 5-arm, parallel-group study in adult subjects with T2DM on stable doses of metformin, using sitagliptin as an internal reference standard.

Once subjects were deemed eligible, they 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 before initiating the run-in period. Those subjects who were also taking a second acceptable oral antidiabetic (OAD) agent had the second medication discontinued for at least 6 weeks prior to the run-in period.

All subjects entered a 2-week run-in period during which time they received single-blind placebo QD for PF-04991532 and single-blind placebo QD 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 3 doses of PF-04991532 (150 mg, 450 mg or 750 mg), 100 mg sitagliptin, or matching placebo for a 12-week treatment period.

The schedule of activities for the study is presented in Table 1.

Table 1. Schedule of Activities

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							
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		
Witness 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	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	
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-initiate OAD therapy.
e. ≥90% compliance rate required for randomization.

Number of Subjects (Planned and Analyzed): It was planned to enroll a total of 240 subjects (48 per treatment arm). A total of 266 subjects were randomized to treatment and received at least 1 dose of study medication. Of these 266 subjects, 52 were in the 150 mg group, 54 were in the 450 mg group, 53 were in the 750 mg group, 54 were in the sitagliptin group, and 53 were in the placebo group.

Of the 266 subjects; 183 subjects were randomized in the US, 32 each in Canada and Mexico, 9 in Taiwan, 5 in the Republic of Korea, 4 in Hungary, and 1 in Slovakia.

Diagnosis and Main Criteria for Inclusion: Subjects between the ages of 18 and 70 years with a body mass index between 22.5 and 45.5 kg/m^2 and on a stable dose of metformin either alone or in combination with an acceptable OAD agent (other than metformin) for their T2DM were eligible for the study. Subjects with type 1 diabetes, heart attack or stroke in the past 6 months, uncontrolled blood pressure (BP), or significant kidney disease were excluded from the study.

Study Treatment: Subjects were randomized to 1 of 3 doses (150, 450, 750 mg) of PF-04991532, placebo, or sitagliptin 100 mg. 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 meal. Metformin was taken with meals on a schedule that was appropriate for the subject's dosing regimen (eg, QD, twice daily). All study medications were provided in tablet form.

Efficacy and Safety Endpoints:

Efficacy Endpoints:

Primary Endpoint: The 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%.

Safety Endpoints: 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 AEs (HAEs).

Safety Evaluation: Clinical monitoring, vital signs (heart rate, BP), 12-lead ECGs, assessment of AEs, and safety laboratory tests were performed at specified times during the study (Table 1).

Statistical Methods:

Full Analysis Set (FAS): This was the most inclusive subset of randomized subjects in a trial and was therefore compatible with intention-to-treat analyses. This set included all randomized subjects who received at least 1 dose of randomized study treatment.

Per Protocol Analysis Set (PPAS): The PPAS was a subset of the FAS excluding the following subjects:

- Subjects with compliance <80%.
- Subjects who withdrew during the randomized treatment period of the trial (post randomization and before Day 84).
- Subjects with protocol deviation(s) deemed as compromising efficacy assessment (the list of subjects was finalized prior to database unblinding).

Safety Analysis Set: The safety analysis set was all subjects who received at least 1 dose of study treatment.

The primary and secondary analyses were based on the FAS. The treatment effect on the primary 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, and baseline-by-time 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 change 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.

Safety data were evaluated using descriptive statistics.

RESULTS:

Subject Disposition and Demography: Overall, 508 subjects were screened for entry into the study, of which 266 subjects were randomized to treatment and received at least 1 dose of study medication.

Approximately 85% of the subjects in all 5 treatment groups completed the study. Of the 41 subjects who discontinued the study, 7 (13.5%) were in the 150 mg group, 9 (16.7%) were in the 450 mg group, 8 (15.1%) were in the 750 mg group, 7 (13.0%) were in the sitagliptin group, and 10 (18.9%) were in the placebo group. Subject disposition and subjects analyzed are summarized in Table 2.

Table 2. Subject Disposition and Subjects Analyzed

	Number (%) of Subjects				
	PF-04991532			Sitagliptin	Placebo
	150 mg	450 mg	750 mg	100 mg	
Screened = 508					
Assigned to study treatment	52	54	53	54	53
Treated	52	54	53	54	53
Completed	45 (86.5)	45 (83.3)	45 (84.9)	47 (87.0)	43 (81.1)
Discontinued	7 (13.5)	9 (16.7)	8 (15.1)	7 (13.0)	10 (18.9)
Relation to study drug not defined	7 (13.5)	6 (11.1)	6 (11.3)	6 (11.1)	7 (13.2)
Did not meet entrance criteria	0	1 (1.9)	0	0	0
Lost to follow-up	2 (3.8)	1 (1.9)	2 (3.8)	2 (3.7)	2 (3.8)
No longer willing to participate in study	2 (3.8)	0	2 (3.8)	1 (1.9)	1 (1.9)
Other	3 (5.8)	3 (5.6)	2 (3.8)	3 (5.6)	4 (7.5)
Protocol violation	0	1 (1.9)	0	0	0
Related to study drug	0	2 (3.7)	1 (1.9)	1 (1.9)	1 (1.9)
Adverse event	0	2 (3.7)	1 (1.9)	1 (1.9)	1 (1.9)
Not related to study drug	0	1 (1.9)	1 (1.9)	0	2 (3.8)
Adverse event	0	1 (1.9)	1 (1.9)	0	2 (3.8)
Analyzed for efficacy					
Full analysis set[a]	52 (100.0)	53 (98.1)	52 (98.1)	54 (100.0)	53 (100.0)
Per-protocol[b]	45 (86.5)	44 (81.5)	45 (84.9)	47 (87.0)	43 (81.1)
Analyzed for safety					
Adverse events	52 (100.0)	54 (100.0)	53 (100.0)	54 (100.0)	53 (100.0)
Laboratory data	52 (100.0)	54 (100.0)	53 (100.0)	54 (100.0)	53 (100.0)

Discontinuations were attributed to the last study treatment received.

a. A total of 264 subjects were included in the full analysis set. Two subjects (1 each in the 450 mg and 750 mg groups) were not included in the full analysis set.

b. A total of 224 subjects were included in the per-protocol analysis set.

Most subjects in this study were male. The subjects' age ranged from 29 to 70 years. Most subjects (≥74%) were White. The demographic characteristics were well balanced across the treatment groups. A summary of demographic characteristics is presented in Table 3.

Table 3. Subject Demographics

	PF-04991532			Sitagliptin	Placebo
	150 mg	450 mg	750 mg	100 mg	
Gender (n)					
Male	36	30	36	31	39
Female	16	24	17	23	14
Age (n [%])					
18–44 years	7 (13.5)	8 (14.8)	5 (9.4)	5 (9.3)	5 (9.4)
45–64 years	36 (69.2)	38 (70.4)	44 (83.0)	38 (70.4)	39 (73.6)
≥65 years	9 (17.3)	8 (14.8)	4 (7.5)	11 (20.4)	9 (17.0)
Age (years)					
Mean ± SD	55.3 (9.9)	55.1 (9.3)	55.5 (7.3)	57.8 (8.3)	55.6 (8.5)
Range	30-69	29-68	37-69	36-70	35-70
Race (n [%])					
White	45 (86.5)	40 (74.1)	43 (81.1)	41 (75.9)	47 (88.7)
Black	4 (7.7)	9 (16.7)	5 (9.4)	8 (14.8)	3 (5.7)
Asian	3 (5.8)	8 (9.3)	5 (9.4)	5 (9.3)	3 (5.7)
Weight (kg)					
Mean ± SD	93.4 (20.2)	89.7 (22.5)	86.5 (17.8)	87.9 (20.1)	88.5 (19.6)
Range	49.6-143.3	53.0-153.0	49.0-125.6	55.4-136.3	58.4-133.4
Body mass index (kg/m^2)					
Mean ± SD	32.6 (4.7)	31.7 (5.6)	30.5 (4.9)	31.7 (5.4)	31.3 (5.6)
Range	23.6-44.8	22.7-45.2	22.7-42.1	23.0-44.8	22.6-43.8

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

Efficacy Results:

Change From Baseline in HbA1c (%) at Week 12: At Week 12, PF-04991532 showed significant improvement over placebo at both the 450 mg and 750 mg doses, with LS mean differences from placebo of -0.49% and -0.58%, respectively ($p \leq 0.0017$). Sitagliptin also showed significant benefit over placebo with an LS mean difference from placebo of -0.71% ($p < 0.0001$). The HbA1c LS mean change from baseline to Week 12 for the FAS is provided in Table 4.

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

					Difference From Placebo			
Treatment	N	LS Mean	SE	80% CI	LS Mean	SE	80% CI	p-Value
PF-04991532 150 mg	44	0.00	0.116	(-0.15, 0.15)	0.08	0.164	(-0.13, 0.29)	0.6803
PF-04991532 450 mg	44	-0.57	0.118	(-0.72, -0.42)	-0.49	0.166	(-0.71, -0.28)	0.0017
PF-04991532 750 mg	43	-0.66	0.119	(-0.81, -0.51)	-0.58	0.168	(-0.80, -0.36)	0.0003
Sitagliptin 100 mg	48	-0.79	0.111	(-0.93, -0.64)	-0.71	0.162	(-0.91, -0.50)	<0.0001
Placebo	43	-0.08	0.118	(-0.23, 0.07)				

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 and baseline-by-time interaction as the covariates; time was repeated for subject.
The covariance structure - unstructured was selected.
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.

Change From Baseline in Fasting Plasma Glucose (mg/dL) at Weeks 1, 2, 4, 8 and 12: None of the 3 PF-04991532 treatment groups demonstrated a clear improvement in fasting plasma glucose over placebo for any dose or visit, although there was a trend of decreased fasting plasma glucose at Weeks 4 and 8 for the PF-04991532 450 mg and 750 mg dose groups. The sitagliptin group showed a significant (p=0.0003) benefit over placebo of approximately 25 mg/dL. The improvement occurred as early as Week 1 and appeared more pronounced from Week 4 through Week 12. Table 5 presents a summary of the LS mean change from baseline and mean difference from placebo for fasting plasma glucose in the FAS.

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

					Difference From Placebo			
Treatment	**N**	**LS Mean**	**SE**	**95% CI**	**LS Mean**	**SE**	**95% CI**	**p-Value**
Week 1								
PF-04991532 150 mg	50	4.23	3.760	(-3.17, 11.64)	3.78	5.292	(-6.64, 14.20)	0.4757
PF-04991532 450 mg	51	1.77	3.738	(-5.59, 9.14)	1.32	5.296	(-9.11, 11.75)	0.8031
PF-04991532 750 mg	49	-2.77	3.802	(-10.25, 4.72)	-3.22	5.364	(-13.78, 7.34)	0.5490
Sitagliptin 100 mg	49	-14.61	3.768	(-22.03, -7.19)	-15.07	5.340	(-25.58, -4.55)	0.0051
Placebo	51	0.45	3.758	(-6.95, 7.85)				
Week 2								
PF-04991532 150 mg	50	-2.30	3.517	(-9.22, 4.63)	-2.43	5.020	(-12.31, 7.46)	0.6291
PF-04991532 450 mg	51	4.00	3.471	(-2.83, 10.83)	3.87	5.001	(-5.98, 13.72)	0.4396
PF-04991532 750 mg	51	-6.43	3.492	(-13.30, 0.45)	-6.56	5.030	(-16.46, 3.34)	0.1934
Sitagliptin 100 mg	50	-17.19	3.504	(-24.08, -10.29)	-17.32	5.039	(-27.24, -7.40)	0.0007
Placebo	47	0.13	3.605	(-6.97, 7.23)				
Week 4								
PF-04991532 150 mg	49	2.86	3.626	(-4.28, 9.99)	3.13	5.201	(-7.11, 13.37)	0.5479
PF-04991532 450 mg	49	-4.41	3.620	(-11.54, 2.72)	-4.14	5.209	(-14.39, 6.12)	0.4276
PF-04991532 750 mg	49	-7.66	3.635	(-14.81, -0.50)	-7.38	5.235	(-17.69, 2.92)	0.1596
Sitagliptin 100 mg	50	-23.10	3.582	(-30.15, -16.05)	-22.83	5.198	(-33.06, -12.60)	<0.0001
Placebo	45	-0.27	3.748	(-7.65, 7.10)				
Week 8								
PF-04991532 150 mg	46	6.25	4.135	(-1.90, 14.39)	-1.10	5.855	(-12.63, 10.43)	0.8509
PF-04991532 450 mg	44	-1.18	4.204	(-9.46, 7.10)	-8.53	5.913	(-20.17, 3.12)	0.1505
PF-04991532 750 mg	44	0.73	4.217	(-7.58, 9.04)	-6.62	5.940	(-18.31, 5.08)	0.2662
Sitagliptin 100 mg	47	-14.17	4.048	(-22.14, -6.20)	-21.52	5.818	(-32.97, -10.07)	0.0003
Placebo	45	7.35	4.163	(-0.85, 15.54)				
Week 12								
PF-04991532 150 mg	45	4.69	4.878	(-4.92, 14.31)	-2.01	6.940	(-15.68, 11.66)	0.7724
PF-04991532 450 mg	44	6.00	4.931	(-3.72, 15.72)	-0.70	6.986	(-14.47, 13.07)	0.9202
PF-04991532 750 mg	44	5.09	4.925	(-4.61, 14.80)	-1.61	6.998	(-15.40, 12.18)	0.8183
Sitagliptin 100 mg	48	-18.26	4.672	(-27.46, -9.06)	-24.96	6.821	(-38.40, -11.53)	0.0003
Placebo	43	6.70	4.954	(-3.05, 16.46)				

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

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 conflicted, 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; CS = compound symmetry; CSH = heterogeneous compound symmetry; FAS = full analysis set; LS = least square; N = number of subjects; OC = observed cases; SE = standard error.

Change From Baseline in HbA1c at Weeks 1, 2, 4, and 8: The results for change from baseline in HbA1c at Weeks 1, 2, 4 and 8 are presented by treatment groups in Table 6. The onset of the response was observed as early as Weeks 2 and 4, becoming more pronounced at Weeks 8 and 12.

Table 6. Summary of Statistical Analysis (MMRM) - Change from Baseline in HbA1c (%) - Full Model - FAS, OC

						Difference From Placebo			
Visit	Treatment	N	LS Mean	SE	80% CI	LS Mean	SE	80% CI	p-Value
Week 1	PF-04991532 150 mg	50	-0.05	0.034	(-0.09, 0.00)	-0.04	0.048	(-0.10, 0.03)	0.2327
	PF-04991532 450 mg	51	-0.03	0.034	(-0.07, 0.01)	-0.02	0.048	(-0.08, 0.04)	0.358
	PF-04991532 750 mg	49	-0.15	0.035	(-0.19, -0.10)	-0.13	0.049	(-0.20, -0.07)	0.0036
	Sitagliptin 100 mg	49	-0.07	0.034	(-0.11, -0.02)	-0.06	0.049	(-0.12, 0.01)	0.1251
	Placebo	48	-0.01	0.035	(-0.06, 0.03)				
Week 2	PF-04991532 150 mg	50	-0.05	0.046	(-0.11, 0.01)	-0.03	0.066	(-0.11, 0.06)	0.3466
	PF-04991532 450 mg	52	-0.14	0.046	(-0.20, -0.08)	-0.11	0.066	(-0.20, -0.03)	0.0439
	PF-04991532 750 mg	49	-0.2	0.047	(-0.26, -0.14)	-0.18	0.067	(-0.27, -0.09)	0.004
	Sitagliptin 100 mg	49	-0.23	0.045	(-0.29, -0.17)	-0.2	0.065	(-0.29, -0.12)	0.0009
	Placebo	47	-0.02	0.047	(-0.08, 0.04)				
Week 4	PF-04991532 150 mg	48	-0.18	0.068	(-0.26, -0.09)	-0.1	0.096	(-0.23, 0.02)	0.1405
	PF-04991532 450 mg	49	-0.31	0.068	(-0.40, -0.23)	-0.24	0.097	(-0.36, -0.12)	0.0067
	PF-04991532 750 mg	48	-0.44	0.07	(-0.53, -0.35)	-0.37	0.098	(-0.50, -0.24)	0.0001
	Sitagliptin 100 mg	50	-0.42	0.064	(-0.50, -0.33)	-0.34	0.094	(-0.46, -0.22)	0.0002
	Placebo	46	-0.07	0.068	(-0.16, 0.01)				
Week 8	PF-04991532 150 mg	45	-0.11	0.096	(-0.23, 0.01)	0	0.135	(-0.18, 0.17)	0.4887
	PF-04991532 450 mg	44	-0.5	0.097	(-0.63, -0.38)	-0.4	0.137	(-0.57, -0.22)	0.002
	PF-04991532 750 mg	45	-0.69	0.098	(-0.82, -0.56)	-0.58	0.138	(-0.76, -0.41)	<0.0001
	Sitagliptin 100 mg	47	-0.7	0.09	(-0.81, -0.58)	-0.59	0.133	(-0.76, -0.42)	<0.0001
	Placebo	45	-0.11	0.096	(-0.23, 0.02)				
Week 12	PF-04991532 150 mg	44	0	0.116	(-0.15, 0.15)	0.08	0.164	(-0.13, 0.29)	0.6803
	PF-04991532 450 mg	44	-0.57	0.118	(-0.72, -0.42)	-0.49	0.166	(-0.71, -0.28)	0.0017
	PF-04991532 750 mg	43	-0.66	0.119	(-0.81, -0.51)	-0.58	0.168	(-0.80, -0.36)	0.0003
	Sitagliptin 100 mg	48	-0.79	0.111	(-0.93, -0.64)	-0.71	0.162	(-0.91, -0.50)	<0.0001
	Placebo	43	-0.08	0.118	(-0.23, 0.07)				

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 had been excluded.
MMRM with model terms: treatment, time, treatment-by-time interaction as fixed effects, baseline, baseline-by-time interaction as the covariates; time was repeated for subject.
The covariance structure - UN was used.
p-Value was 1-sided.
CI = confidence interval; FAS = full analysis set; HbA1c = glycosylated hemoglobin; LS = least square;
MMRM = mixed-model repeated measure; N = total number of subjects with no missing Week 12 observation in each treatment group; OC = observed cases; SE = standard error; UN = unstructured.

Proportion of Subjects Achieving HbA1c <6.5%, and HbA1c <7% at Week 12: The PF-04991532 750 mg treatment group had the highest number of responders with 23.3% (10/43) of subjects achieving an HbA1c <6.5% and 60.5% (26/43) of subjects achieving an HbA1c <7%. Table 7 presents a summary of the proportion subjects achieving HbA1c levels of <6.5% or <7% at Week 12 for the FAS.

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

	Number (%) of Subjects				
	PF-04991532			Sitagliptin	Placebo
	150 mg (N=44)	450 mg (N=44)	750 mg (N=43)	100 mg (N=48)	(N=43)
HbA1c <6.5%, n (%)	2 (4.5)	4 (9.1)	10 (23.3)	7 (14.6)	5 (11.6)
HbA1c <7%, n (%)	6 (13.6)	16 (36.4)	26 (60.5)	19 (39.6)	7 (16.3)

FAS = full analysis set; HbA1c = glycosylated hemoglobin; 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.

Change From Baseline in Body Weight at Weeks 1, 2, 4, 8 and 12: At Week 12, all PF-04991532 treatment groups reduced body weight by 0.82 kg to 0.93 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 -0.27 kg; the difference from placebo was not statistically significant (p=0.0962). Table 8 presents a summary of the LS mean change from baseline and mean difference from placebo for body weight in the FAS.

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

					Difference From Placebo			
Treatment	**N**	**LS Mean**	**SE**	**95% CI**	**LS Mean**	**SE**	**95% CI**	**p-Value**
Week 1								
PF-04991532 150 mg	50	-0.06	0.160	(-0.37, 0.26)	0.28	0.225	(-0.16, 0.73)	0.2067
PF-04991532 450 mg	51	-0.30	0.159	(-0.62, 0.01)	0.04	0.224	(-0.40, 0.48)	0.8602
PF-04991532 750 mg	49	-0.37	0.161	(-0.68, -0.05)	-0.02	0.225	(-0.47, 0.42)	0.9200
Sitagliptin 100 mg	51	0.12	0.158	(-0.19, 0.43)	0.46	0.223	(0.02, 0.90)	0.0399
Placebo	51	-0.34	0.158	(-0.65, -0.03)				
Week 2								
PF-04991532 150 mg	50	-0.09	0.171	(-0.42, 0.25)	0.29	0.242	(-0.18, 0.77)	0.2266
PF-04991532 450 mg	52	-0.34	0.169	(-0.67, 0.00)	0.05	0.241	(-0.43, 0.52)	0.8493
PF-04991532 750 mg	51	-0.40	0.171	(-0.73, -0.06)	-0.01	0.242	(-0.49, 0.46)	0.9511
Sitagliptin 100 mg	50	-0.02	0.169	(-0.36, 0.31)	0.36	0.241	(-0.11, 0.83)	0.1369
Placebo	48	-0.38	0.172	(-0.72, -0.04)				
Week 4								
PF-04991532 150 mg	49	-0.15	0.191	(-0.53, 0.22)	0.39	0.272	(-0.15, 0.92)	0.1562
PF-04991532 450 mg	49	-0.73	0.190	(-1.10, -0.35)	-0.19	0.272	(-0.72, 0.35)	0.4913
PF-04991532 750 mg	49	-0.36	0.191	(-0.74, 0.01)	0.18	0.272	(-0.36, 0.71)	0.5130
Sitagliptin 100 mg	50	0.05	0.187	(-0.32, 0.42)	0.59	0.269	(0.06, 1.12)	0.0298
Placebo	46	-0.54	0.194	(-0.92, -0.16)				
Week 8								
PF-04991532 150 mg	46	-0.24	0.255	(-0.74, 0.26)	0.36	0.363	(-0.35, 1.08)	0.3196
PF-04991532 450 mg	44	-0.65	0.261	(-1.17, -0.14)	-0.05	0.367	(-0.77, 0.67)	0.8884
PF-04991532 750 mg	45	-0.48	0.258	(-0.98, 0.03)	0.12	0.365	(-0.59, 0.84)	0.7325
Sitagliptin 100 mg	48	-0.26	0.246	(-0.74, 0.22)	0.34	0.357	(-0.36, 1.04)	0.3395
Placebo	45	-0.60	0.258	(-1.11, -0.09)				
Week 12								
PF-04991532 150 mg	45	-0.82	0.287	(-1.38, -0.25)	0.13	0.410	(-0.68, 0.94)	0.7514
PF-04991532 450 mg	44	-0.82	0.292	(-1.39, -0.24)	0.13	0.413	(-0.68, 0.94)	0.7529
PF-04991532 750 mg	45	-0.93	0.289	(-1.50, -0.36)	0.02	0.411	(-0.79, 0.83)	0.9638
Sitagliptin 100 mg	48	-0.27	0.279	(-0.82, 0.28)	0.67	0.404	(-0.12, 1.47)	0.0962
Placebo	43	-0.95	0.293	(-1.52, -0.37)				

Baseline was defined as the measurement performed on Day 1.
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 - 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; CS = compound symmetry; CSH = heterogeneous compound symmetry; FAS = full analysis set; LS = least square; N = number of subjects; OC = observed cases; SE = standard error.

Proportion of Subjects at Week 12 with ≥1% or ≥2% Body Weight Gain or Body Weight Loss: Table 9 presents summary of the proportion of subjects at Week 12 with ≥1% or ≥2% body weight gain or body weight loss.

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

	PF-04991532 150 mg (N=45)	PF-04991532 450 mg (N=44)	PF-04991532 750 mg (N=45)	Sitagliptin 100 mg (N=48)	Placebo (N=43)
Subjects with Week 12					
Body weight gain					
≥1 % n (%)	8 (17.78)	8 (18.18)	7 (15.56)	14 (29.17)	10 (23.26)
≥2 % n (%)	3 (6.67)	5 (11.36)	5 (11.11)	7 (14.58)	3 (6.98)
Body weight loss					
≥1 % n (%)	25 (55.56)	21 (47.73)	21 (46.67)	14 (29.17)	18 (41.86)
≥2 % n (%)	12 (26.67)	15 (34.09)	14 (31.11)	9 (18.75)	15 (34.88)

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, there was an increasing number of AEs with increasing PF-04991532 doses. There was a greater incidence of diarrhea in the 750 mg group and nausea in the 450 mg and 750 mg groups. There was also a higher frequency of headaches reported in the 750 mg group. All other AEs reported in the PF-04991532 groups appeared to occur with the same approximate frequency as in the placebo and sitagliptin groups. A higher incidence of insomnia was noted in the sitagliptin group. Table 10 presents a summary of all-causality and treatment-related AEs.

Table 10. Treatment-Emergent Adverse Events (All-Causality and Treatment-Related)

	Number (%) of Subjects									
	PF-04991532 150 mg		PF-04991532 450 mg		PF-04991532 750 mg		Sitagliptin 100 mg		Placebo	
	All-Cause	TR	All-Cause	TR	All-Cause	TR	All-Cause	TR	All-Cause	TR
Subjects evaluable for AEs	52	52	54	54	53	53	54	54	53	53
Number of AEs	38	4	52	14	60	12	41	9	40	5
Subjects with AEs (%)	26 (50.0)	3 (5.8)	24 (44.4)	6 (11.1)	30 (56.6)	10 (18.9)	21 (38.9)	7 (13.0)	23 (43.4)	5 (9.4)
Subjects with SAEs	0	0	0	0	0	0	0	0	0	0
Subjects with severe AEs	0	0	0	0	0	0	1 (1.9)	0	0	0
Subjects discontinued due to AEs (%)	0	0	1 (1.9)[a]	1 (1.9)[b]	3 (5.7)[c]	2 (3.8)[c]	1 (1.9)	1 (1.9)	3 (5.7)	1 (1.9)
Subjects with temporary discontinuation due to AEs	0	0	0	0	0	0	0	0	0	0

Includes all data collected since the first dose of study drug.
Except for the number of adverse events subjects are counted only once per treatment in each row.
SAEs - according to the Investigator's assessment.
MedDRA (version 15.0) coding dictionary applied.
AEs = adverse events; All-Cause = all-causality; MedDRA = Medical Dictionary for Regulatory Activities; SAEs = serious adverse events; TR = treatment-related.

a. Two additional subjects had AEs that began during the screening period that led to discontinuation.
b. One additional subject had an AE that began during the screening period that led to discontinuation.
c. One of these subjects had an AE (treatment-related) that led to discontinuation, but was listed as completing the study.

Table 11 presents treatment-emergent AEs (TEAEs) reported in ≥3% of subjects in any treatment group during the study.

Table 11. Number (%) of Subjects in Treatment Groups Reporting Treatment-Emergent Adverse Events (Incidence ≥3% of Subjects in any Treatment Group)

System Organ Class MedDRA (v15.0) Preferred Term	PF-04991532 150 mg N=52 n (%)	PF-04991532 450 mg N=54 n (%)	PF-04991532 750 mg N=53 n (%)	Sitagliptin 100 mg N=54 n (%)	Placebo N=53 n (%)
Number of subjects with adverse events	26 (50.0)	24 (44.4)	30 (56.6)	21 (38.9)	23 (43.4)
Gastrointestinal disorders	6 (11.5)	4 (7.4)	14 (26.4)	6 (11.1)	2 (3.8)
Diarrhoea	1 (1.9)	1 (1.9)	7 (13.2)	2 (3.7)	0
Dyspepsia	2 (3.8)	0	1 (1.9)	1 (1.9)	0
Nausea	2 (3.8)	4 (7.4)	4 (7.5)	2 (3.7)	0
Toothache	1 (1.9)	0	2 (3.8)	0	0
Vomiting	1 (1.9)	2 (3.7)	1 (1.9)	0	1 (1.9)
Infections and infestations	9 (17.3)	8 (14.8)	9 (17.0)	5 (9.3)	13 (24.5)
Influenza	2 (3.8)	1 (1.9)	0	0	1 (1.9)
Nasopharyngitis	2 (3.8)	2 (3.7)	3 (5.7)	0	2 (3.8)
Pharyngitis	0	0	2 (3.8)	1 (1.9)	0
Sinusitis	1 (1.9)	0	1 (1.9)	2 (3.7)	2 (3.8)
Upper respiratory tract infection	0	5 (9.3)	1 (1.9)	1 (1.9)	2 (3.8)
Urinary tract infection	2 (3.8)	0	1 (1.9)	1 (1.9)	2 (3.8)
Injury, poisoning and procedural complications	0	3 (5.6)	1 (1.9)	3 (5.6)	2 (3.8)
Contusion	0	2 (3.7)	0	0	0
Investigations	1 (1.9)	2 (3.7)	2 (3.8)	1 (1.9)	3 (5.7)
Blood glucose increased	0	0	0	0	2 (3.8)
Metabolism and nutrition disorders	7 (13.5)	6 (11.1)	7 (13.2)	2 (3.7)	4 (7.5)
Dyslipidaemia	2 (3.8)	2 (3.7)	1 (1.9)	0	0
Hyperglycaemia	3 (5.8)	1 (1.9)	3 (5.7)	0	2 (3.8)
Hypoglycaemia	1 (1.9)	2 (3.7)	0	2 (3.7)	1 (1.9)
Musculoskeletal and connective tissue disorders	0	1 (1.9)	3 (5.7)	5 (9.3)	3 (5.7)
Pain in extremity	0	0	0	2 (3.7)	1 (1.9)
Nervous system disorders	3 (5.8)	3 (5.6)	3 (5.7)	2 (3.7)	2 (3.8)
Headache	1 (1.9)	1 (1.9)	3 (5.7)	1 (1.9)	1 (1.9)
Psychiatric disorders	1 (1.9)	0	0	3 (5.6)	1 (1.9)
Insomnia	0	0	0	3 (5.6)	0
Respiratory, thoracic and mediastinal disorders	0	2 (3.7)	2 (3.8)	2 (3.7)	4 (7.5)
Oropharyngeal pain	0	1 (1.9)	1 (1.9)	1 (1.9)	2 (3.8)
Vascular disorders	0	3 (5.6)	0	0	1 (1.9)
Hypertension	0	3 (5.6)	0	0	1 (1.9)

Subjects were only counted once per treatment for each row.
Includes all data collected since the first dose of study drug.
MedDRA (version 15.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities (version 15.0); N = number of subjects in each treatment group; n = number of subjects with adverse events.

Table 12 presents treatment-related TEAEs reported during the study.

Table 12. Treatment Emergent Treatment-Related Adverse Events Reported in Subjects During the Study

System Organ Class MedDRA (v15.0) Preferred Term	PF-04991532 150 mg (N=52) n (%)	PF-04991532 450 mg (N=54) n (%)	PF-04991532 750 mg (N=53) n (%)	Sitagliptine 100 mg (N=54) n (%)	Placebo (N=53) n (%)
Cardiac disorders	1 (1.9)	0	0	1 (1.9)	0
Sinus tachycardia	0	0	0	1 (1.9)	0
Ventricular extrasystoles	1 (1.9)	0	0	0	0
Eye disorders	0	1 (1.9)	0	0	0
Vision blurred	0	1 (1.9)	0	0	0
Gastrointestinal disorders	0	4 (7.4)	6 (11.3)	3 (5.6)	0
Diarrhoea	0	0	5 (9.4)	1 (1.9)	0
Gastritis	0	1 (1.9)	0	0	0
Gastrooesophageal reflux disease	0	0	0	1 (1.9)	0
Irritable bowel syndrome	0	1 (1.9)	0	0	0
Nausea	0	4 (7.4)	1 (1.9)	2 (3.7)	0
Vomiting	0	1 (1.9)	0	0	0
General disorders and administration site conditions	0	1 (1.9)	1 (1.9)	1 (1.9)	0
Fatigue	0	0	0	1 (1.9)	0
Malaise	0	1 (1.9)	0	0	0
Thirst	0	0	1 (1.9)	0	0
Investigations	1 (1.9)	1 (1.9)	0	0	1 (1.9)
Alanine aminotransferase increased	1 (1.9)	1 (1.9)	0	0	0
Aspartate aminotransferase increased	1 (1.9)	0	0	0	0
Blood glucose increased	0	0	0	0	1 (1.9)
Metabolism and nutrition disorders	1 (1.9)	1 (1.9)	2 (3.8)	1 (1.9)	1 (1.9)
Hyperglycaemia	0	0	1 (1.9)	0	1 (1.9)
Hypertriglyceridaemia	1 (1.9)	0	1 (1.9)	0	0
Hypoglycaemia	0	1 (1.9)	0	1 (1.9)	0
Nervous system disorders	0	1 (1.9)	2 (3.8)	1 (1.9)	1 (1.9)
Dizziness	0	1 (1.9)	0	0	0
Headache	0	0	2 (3.8)	1 (1.9)	1 (1.9)
Neuropathy peripheral	0	1 (1.9)	0	0	0
Renal and urinary disorders	0	1 (1.9)	0	0	1 (1.9)
Pollakiuria	0	0	0	0	1 (1.9)
Renal failure	0	1 (1.9)	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (1.9)
Nasal congestion	0	0	0	0	1 (1.9)
Skin and subcutaneous tissue disorders	0	0	1 (1.9)	1 (1.9)	0
Pruritus	0	0	1 (1.9)	0	0
Rash	0	0	0	1 (1.9)	0

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken.
Subjects were counted only once per treatment in each row.
Includes all data collected since the first dose of study drug.
Adverse events were classified using Medical Dictionary for Regulatory Activities (MedDRA version 15.0).
N = number of subjects in each treatment group; n = number of subjects with adverse events.

Serious Adverse Events: No SAE was reported during the study. One subject reported an SAE that occurred prior to randomization to treatment.

Permanent Discontinuation From the Study due to Adverse Events: Two subjects (both in the 450 mg group) discontinued the study due to AEs that began during the screening period. One subject reported severe hyperglycemia on Day -4 and was withdrawn from the study on Day 7 of the study. The hyperglycemia was considered to have resolved on Day 22. The

Investigator considered the hyperglycemia to be related to an insufficient response to the study drug. Another subject who reported moderate pneumonia on Day 52 of the study was withdrawn on Day 58 due to the event which was considered to be ongoing. The Investigator considered the pneumonia not to be related to study drug. The subject had previously reported moderate pneumonia from Day -25 to Day -4 before being randomized into the study.

Seven subjects discontinued the study due to TEAEs. Of these subjects, 1 was in the 450 mg group, 2 were in the 750 mg group, 1 was in the sitagliptin group, and 3 were in the placebo group. In addition, 1 subject in the 750 mg group discontinued due to a TEAE, but was listed as completing the study.

The subject in the 450 mg group reported mild nausea on Day 3 of the study which resolved on Day 54. The subject was withdrawn due to the event on Day 52 of the study. The Investigator considered the nausea to be related to study drug.

Of the 2 subjects in the 750 mg group, 1 subject reported mild hyperglycemia on Day 13 of the study which resolved on Day 32. The subject was withdrawn due to the event on Day 29 of the study. The event was considered to be not related to the study drug. Another subject in the 750 mg group reported mild headache on Day 1 of the study which resolved on Day 3. The subject was withdrawn due to the event on Day 3 of the study. The Investigator considered the headache to be related to study drug.

The subject in the sitagliptin group reported a mild rash on Day 22 of the study. The subject was withdrawn due to the event on Day 28 of the study. The event was considered to be resolved on Day 73. The Investigator considered the rash to be related to study drug.

Of the 3 subjects in the placebo group, 1 subject reported moderate hyperglycemia on Day 14 of the study. The subject was withdrawn due to the event on Day 16 of the study. The event was considered to be resolved on Day 35. The Investigator considered the hyperglycemia to be not related to study drug. One subject reported mild blood glucose increased on Day 25 of the study. The subject was withdrawn due to the event on Day 24 of the study. The event was considered to be ongoing. The Investigator considered the blood glucose increased to be not related to study drug. Another subject reported moderate blood glucose increased on Day 8 of the study. The subject was withdrawn due to the event on Day 12 of the study. The event was considered to be resolved on Day 14. The Investigator considered the blood glucose increased to be related to study drug.

Death: No death was reported during the study.

Laboratory Abnormalities: A total of 9 subjects reported hyperglycemia, 3 in the 150 mg group, 1 in the 450 mg group, 3 in the 750 mg group, and 2 in the placebo group. No subjects in the sitagliptin group reported hyperglycemia.

There was a trend for increases in triglyceride values in the PF-04991532 450 mg and 750 mg dose groups. At Week 12, the 450 mg and 750 mg groups showed triglyceride elevations from baseline of 12% and 16%, respectively. A signal was present as early as Week 1, but there was no clear increase with time.

There was a higher frequency of subjects with alanine aminotransferase (ALT) values ≥2 × upper limit of normal (ULN) in the 750 mg group. There were 2 (3.7%) subjects in the sitagliptin group that had >3 × ULN elevations in ALT, whereas no subjects in the PF-04991532 groups had similar liver enzyme elevations. There were a greater number of subjects in the PF-04991532 groups that had serum creatinine values above the upper limit of the reference range; however none of these values reached levels of potential clinical concern.

Vital Signs and Electrocardiogram Results: Compared to the placebo and sitagliptin groups, there were no clinically significant differences in postbaseline changes for values of potential clinical concern for vital signs or ECGs in the PF-04991532 groups. No subjects had QT interval corrected for heart rate using Fridericia's formula (QTcF) values >500 msec.

Hypoglycemic Adverse Events: Table 13 presents a summary of the analysis of protocol-defined total hypoglycemic event rates. Overall, 1 subject in the 150 mg group, 2 subjects in the 450 mg group, 1 subject in the sitagliptin group, and 1 subject in the placebo group had a hypoglycemic event. No subject had a severe hypoglycemic event.

Table 13. Analysis of Protocol-Defined Total Hypoglycemic Event Rates

	PF-04991532 150 mg	PF-04991532 450 mg	PF-04991532 750 mg	Sitagliptin 100 mg	Placebo
Total number of subjects	52	54	53	54	53
Number (%) of subjects with any event	1 (1.9)	2 (3.7)	0 (0.0)	1 (1.9)	1 (1.9)
Total number of events	1	2	0	1	1
Total subject-months	135.0	134.5	135.4	138.7	129.1
Hypoglycemic events/subject-months	0.0074	0.0149	0	0.0072	0.0077

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.

CONCLUSIONS:

- Once-daily doses of PF-04991532 450 mg and 750 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 150 mg.
- Relative to placebo or sitagliptin, a greater percentage of subjects in the 750 mg group reached the HbA1c treatment target goals of <7% and <6.5%.
- All 3 doses of PF-04991532 evaluated in the study had minimal effects on fasting plasma glucose postdose over 12 weeks relative to placebo.
- None of the PF-04991532 treatment groups demonstrated a significant difference in body weight change compared to placebo.
- PF-04991532 doses of 150 mg, 450 mg, and 750 mg, as well as sitagliptin 100 mg, were safe and well tolerated over a period of 12 weeks in subjects with T2DM on a stable dose of metformin. There was a low incidence of hypoglycemia in PF-04991532 groups.