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COMPOUND NUMBER: PF-04937319

PROTOCOL NO.: B1621007

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blinded, Placebo-Controlled, Dose-Ranging, Parallel Group Study to Evaluate Safety and Efficacy of PF-04937319 and Sitagliptin on Glycemic Control in Adult Patients With Type 2 Diabetes Mellitus Inadequately Controlled on Metformin.

Study Centers: A total of 56 centers randomized subjects in the study: 16 in the United States (data from 1 additional site excluded from Pfizer database due to GCP violations), 9 in Hungary, 8 each in Slovakia and South Africa, 4 each in India and Taiwan, 3 each in the Philippines and Romania.

Study Initiation Date, Primary Completion Date and Final Completion Dates:
21 November 2011, 17 January 2013 and 24 January 2013

Phase of Development: Phase 2a

Study Objectives:

Primary Objective:

- To evaluate the dose-response of PF-04937319, administered once daily (QD) over 12-weeks in adults with Type 2 Diabetes Mellitus (T2DM) on stable doses of metformin, on glycemic control.

Secondary Objective:

- To characterize the effect on additional parameters of glycemic control with a range of oral doses of PF-04937319 administered QD over 12-weeks in adults with T2DM on stable doses of metformin.

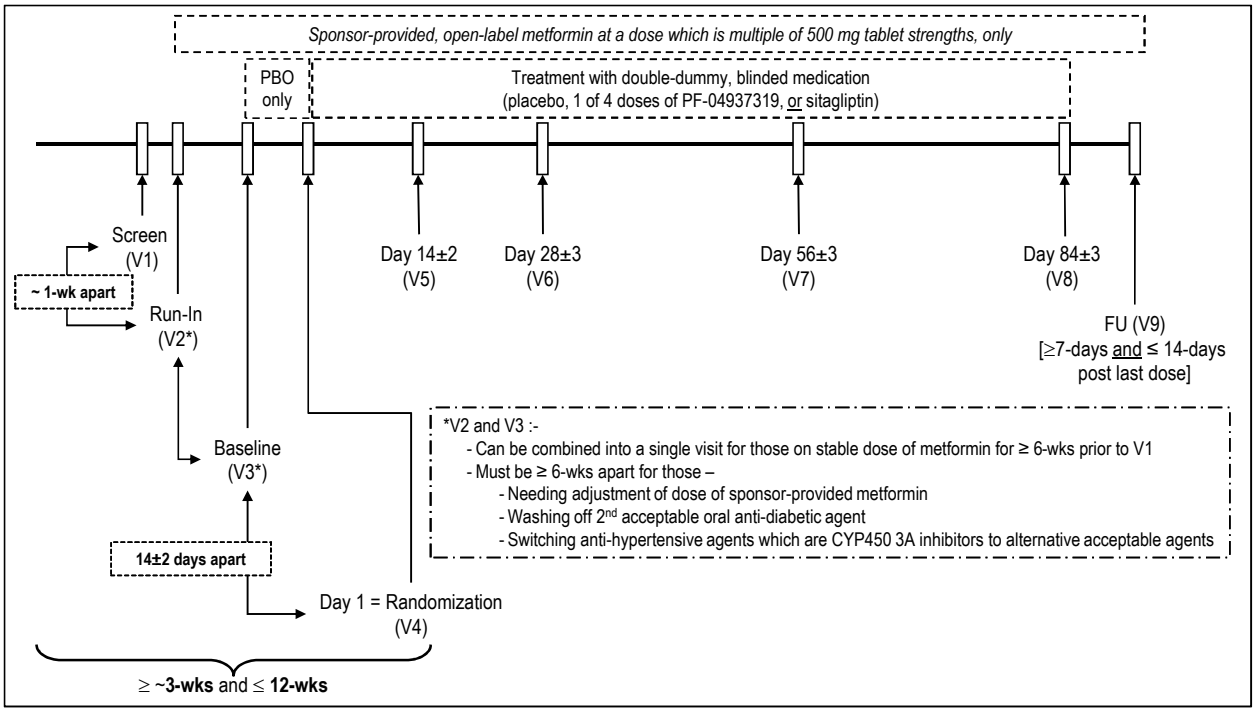
- To evaluate safety and tolerability of a range of oral doses of PF-04937319 administered QD over 12-weeks in adults with T2DM on stable doses of metformin.

- To characterize efficacy and safety/tolerability of a 100 mg QD dose of sitagliptin administered over 12-weeks in adults with T2DM on stable doses of metformin.

METHODS

Study Design: This was a randomized, double-blind, double-dummy, placebo-and active-controlled, 6-arm (placebo, 4 active doses of PF-04937319, and 1 dose of sitagliptin), parallel group study. Subjects completed the Screening procedures to determine eligibility, followed by a run-in phase when background medical treatments were stabilized, and Baseline-related visits occurred. Thereafter, subjects were randomized to receive 1 of 6 blinded treatment regimens for a duration of 84±3 days. The study included a total of up to 9 outpatient visits (including Screening, run-in, and Baseline) to the site (ie, Visit(V)1 to V9). Total participation in the study for each subject, including Screening, run-in, and Baseline, ranged from 16 weeks (minimum) to 26 weeks (maximum). Overall study design is offered in Figure 1.

Figure 1. Study Design



FU=Follow-up, V=Visit, wks=Weeks.

Number of Subjects (Planned and Analyzed): The plan was to randomize at least 300 subjects in order to ensure that at least 240 (40 per arm) complete the study. A total of 615 subjects were consented. Of these, 376 subjects (61.1%) transitioned to the Run-in period and were started on sponsor-provided metformin. A total of 335 subjects (62 subjects in Hungary, 36 subjects in India, 15 subjects in Philippines, 12 subjects in Romania, 47 subjects in Slovakia, 23 subjects in South Africa, 29 subjects in Taiwan, 111 subjects in United States [however 1 site randomized 10 subjects which were excluded from Pfizer database due to GCP violations]) who completed metformin run-in period, were randomized to 1 of the 6 treatment groups (ie, placebo, PF-04937319 at 3 mg, 20 mg, 50 mg, or 100 mg QD, or sitagliptin).

Diagnosis and Main Criteria for Inclusion: Male or female subjects with T2DM between the ages of 18 (or 21 based on country-specific age of consent) to 55 years of age, inclusive at Screening, on a stable dose of metformin either alone or in combination with another oral anti-diabetic (OAD) agent (excluding pioglitazone and rosiglitazone) for their T2DM for at least 6 weeks prior to V1 (subjects on an OAD agent other than metformin were expected to be willing to discontinue this medication starting at V2 and for duration of the study), with glycosylated hemoglobin (HbA_{1C}) of 7.0% to 11.0% (subjects on metformin monotherapy) or 6.5% to 9.5% (subjects on metformin + acceptable OAD), with fasting plasma glucose (FPG) levels <270 mg/dL, and body mass index (BMI) ≥18.5 kg/m^2 and ≤45.4 kg/m^2, at Screening.

Study Treatment: Run-in Period: During the run-in period, background medical treatments were stabilized, and Baseline-related visits occurred. Subjects received open-label metformin during the run-in period and upto the follow-up visit. Metformin was provided by the sponsor as 500 mg immediate release tablets.

Baseline Period: At V3, all subjects entered a 2-week Baseline period where subjects received metformin, as well as single-blind placebo.

Treatment Phase: At V4, subjects were randomized to 1 of 6 blinded treatment regimens (placebo, sitagliptin, or PF-04937319 3 mg, 20 mg, 50 mg, or 100 mg QD) to be taken for 84±3 days. PF-04937319/placebo and sitagliptin/placebo were provided as tablets. Each dose of PF-04937319/placebo consisted of 2 tablets while a dose of sitagliptin/placebo consisted of 1 beige tablet with overprinting.

Efficacy Endpoints:

Efficacy Evaluations:

Primary Efficacy Endpoint:

- Change from Baseline in HbA_{1C} at Week 12.

Secondary Efficacy Endpoints:

- Change from Baseline in HbA_{1C} at Weeks 4 and 8;
- Change from Baseline in FPG (mg/dL) at Weeks 2, 4, 8, and 12;
- Proportions of subjects achieving HbA_{1C} <7%, and <6.5% at Week 12.

Secondary Safety Endpoints:

Assessment of 12-lead ECGs, vital signs, AEs (as well as SAEs) including HAE, body weight, and laboratory tests (including lipid profile).

Safety Evaluations: Adverse events (AEs), serious adverse events (SAEs), clinical laboratory tests, physical examinations, electrocardiograms (ECGs), body weight and vital signs (blood pressure and pulse rate) of the subjects were evaluated for safety.

Statistical Methods:

Analysis Sets: Primary and secondary efficacy analyses were performed on full analysis set (FAS) included all randomized subjects who received at least 1 dose of randomized study treatment. Sensitivity analysis was performed on per protocol analysis set (PPAS). PPAS was a subset of the FAS excluding the following subjects: Subjects with <80% compliance; who withdrew during the randomized treatment period of the trial (post randomization and before Day 84); with protocol deviation(s) deemed as compromising efficacy assessment (the list of subjects were finalized prior to database unblinding). Safety analysis was performed on FAS and as such included all subjects who received at least 1 dose of randomized study treatment.

Efficacy Analysis: The primary endpoint values from subjects in the FAS was analyzed in a mixed model repeated measure (MMRM) framework with treatment, time, and treatment-by-time interaction as fixed effects, Baseline as covariates and subject as a random effect. Model-based least square mean (LSM) estimates of the primary response with 2-sided, 80% CIs were obtained for each treatment group. Placebo-adjusted LSM estimates with 80% confidence intervals and corresponding 1-sided p-values were also computed and tabulated. No adjustment for multiplicity was made. Depending on the observed data at the end of the study, dose-response modeling of the primary endpoint may have been explored with dose as a continuous variable to characterize and evaluate the dose-response relationship. Descriptive summaries of the observed values and change from Baseline in HbA_{1C} in each treatment group at each time point was produced.

With the exception of endpoints that were not measured repeatedly, continuous secondary were analyzed in the same manner as the primary endpoint (ie, in an MMRM framework). Analysis of covariance (ANCOVA) models with treatment × covariate interactions were performed on the primary and secondary endpoints at Week 12 data as a sensitivity analysis for the validity of the treatment main effects assumption. For comparison against placebo, 2-sided 80% CIs was produced for statistical analyses of these endpoints.

Baseline HbA_{1C}, body weight, gender, prior use of diabetes treatment and duration of the primary disease (T2DM) were used as covariates. The impact of the covariates was examined to identify potential parameters that could have influenced the efficacy endpoints. An ANCOVA model was used for each covariate, which included the treatment, covariate, and the treatment-by-covariate interaction as independent variables, and Baseline value as an additional covariate. The p-values for the treatment-by-covariate interaction were displayed.

Safety Analysis: Safety parameters were summarized descriptively as appropriate for Pfizer data standards. Statistical inference was determined for safety measures of clinical concern.

RESULTS

Subject Disposition and Demography: A total of 615 subjects were consented. Of these, 376 subjects (61.1%) transitioned to the Run-in period and were started on sponsor-provided metformin. A total of 335 subjects were randomized (54% of subjects consented and 89.1% of subjects started on sponsor-provided metformin). Of the 335 subjects randomized, 32 (9.6%) were prematurely withdrawn prior to completion of the study-prescribed follow-up visit.

All 376 subjects who received sponsor-provided metformin during the run-in period and the 335 subjects randomized to 1 of the 6 treatment groups were included in the safety analysis set. The 335 randomized subjects were included in the FAS. Of the 335 randomized subjects, 301 (89.85%) were included in the PPAS, which required subjects to have at least 80% compliance with blinded therapy, and who completed the randomized treatment period of the study. A summary of subject evaluation groups is provided in Table 1.

Table 1. Subject Evaluation Groups

Number (%) of Subjects	Metformin Run-In	Placebo	PF-04937319				Sitagliptin 100 mg
			3 mg	20 mg	50 mg	100 mg	
Screened				615			
Assigned to study treatment	376	57	57	54	56	56	55
Treated	376	57	57	54	56	56	55
Completed	335 (89.1)	48 (84.2)	53 (93.0)	46 (85.2)	52 (92.9)	51 (91.1)	53 (96.4)
Discontinued	41 (10.9)	9 (15.8)	4 (7.0)	8 (14.8)	4 (7.1)	5 (8.9)	2 (3.6)
Subject died	0	0	0	1 (1.9)	0	0	0
Relation to study drug not defined	41 (10.9)	7 (12.3)	4 (7.0)	3 (5.6)	3 (5.4)	4 (7.1)	2 (3.6)
Does not meet entrance criteria	16 (4.3)	0	0	0	0	0	0
Lost to follow-up	7 (1.9)	3 (5.3)	2 (3.5)	3 (5.6)	1 (1.8)	2 (3.6)	1 (1.8)
No longer willing to participate in study	11 (2.9)	2 (3.5)	2 (3.5)	0	2 (3.6)	2 (3.6)	0
Other	3 (0.8)	1 (1.8)	0	0	0	0	0
Protocol violation	4 (1.1)	1 (1.8)	0	0	0	0	1 (1.8)
Related to Study Drug	0	2 (3.5)	0	3 (5.6)	1 (1.8)	1 (1.8)	0
Insufficient clinical response	0	2 (3.5)	0	2 (3.7)	1 (1.8)	1 (1.8)	0
Medication error without associated adverse event	0	0	0	1 (1.9)	0	0	0
Not Related to Study Drug	0	0	0	1 (1.9)	0	0	0
Adverse event	0	0	0	1 (1.9)	0	0	0
Analyzed for Efficacy							
FAS	0	57 (100.0)	57 (100.0)	54 (100.0)	56 (100.0)	56 (100.0)	55 (100.0)
PPAS	0	47 (82.5)	53 (93.0)	47 (87.0)	51 (91.1)	51 (91.1)	52 (94.5)
Analyzed for Safety							
Adverse events	376 (100.0)	57 (100.0)	57 (100.0)	54 (100.0)	56 (100.0)	56 (100.0)	55 (100.0)
Laboratory data	0	56 (98.2)[a]	57 (100.0)	53 (98.1)[a]	56 (100.0)	55 (98.2)[a]	55 (100.0)

Discontinuations had been attributed to the last sponsor-provided Metformin or study treatment received.
FAS=Full analysis set; PPAS=Per-protocol analysis set.
a. 1 subject excluded due to lack of post randomization assessment of laboratory tests.

In this study, the age of the population randomized ranged from 20 to 55 years with a mean age of 47.5 years and 43% (143/335) of the subjects were female. For the pool of subjects randomized, the average duration of T2DM was 2.6 years with 36% having a duration less than 1 year and Baseline glycemic parameters were 8.1% (HbA_{1C}), 163 mg/dL (FPG), and 10.5 µIU/mL (fasting insulin) with fasting serum triglycerides of 185 mg/dL. Across the treatment arms, the population was similar for gender, age, BMI, race, duration of T2DM as well as Baseline HbA_{1C}, FPG, fasting Insulin, fasting C-peptide, and fasting serum triglycerides. A summary of subject demographic characteristics is provided Table 2.

Table 2. Demographic and Baseline Characteristics

Numer (%) of Subjects Experiencing	Placebo (N=57)	PF-04937319				Sitagliptin 100 mg (N=55)
		3 mg (N=57)	20 mg (N=54)	50 mg (N=56)	100 mg (N=56)	
Age (years), n (%)						
18-44	15 (26.3)	17 (29.8)	14 (25.9)	15 (26.8)	15 (26.8)	17 (30.9)
45-64	42 (73.7)	40 (70.2)	40 (74.1)	41 (73.2)	41 (73.2)	38 (69.1)
Mean (SD)	47.6 (6.3)	48.2 (5.3)	47.9 (5.9)	46.8 (7.3)	47.5 (6.3)	47.1 (5.8)
SEM	0.8	0.7	0.8	1.0	0.8	0.8
Range	33-55	33-55	22-55	20-55	32-55	31-55
Gender, n (%)						
Male	36 (63.2)	28 (49.1)	32 (59.3)	33 (58.9)	30 (53.6)	33 (60.0)
Female	21 (36.8)	29 (50.9)	22 (40.7)	23 (41.1)	26 (46.4)	22 (40.0)
Race, n (%)						
White	38 (66.7)	37 (64.9)	33 (61.1)	37 (66.1)	38 (67.9)	38 (69.1)
Black	2 (3.5)	4 (7.0)	5 (9.3)	4 (7.1)	5 (8.9)	3 (5.5)
Asian	17 (29.8)	16 (28.1)	15 (27.8)	15 (26.8)	12 (21.4)	14 (25.5)
Other	0	0	1 (1.9)	0	1 (1.8)	0
Body mass index (kg/m^2)						
Mean (SEM)	31.1 (0.7)	31.7 (0.8)	31.2 (0.7)	31.8 (0.8)	32.5 (0.8)	31.6 (0.8)
Range	20.1-43.4	19.3-44.7	19.1-44.6	21.9-44.8	21.7-45.1	19.2-44.9
Duration since first diagnosis of T2DM (years)[a]						
Mean (SEM)	2.5 (0.19)	2.8 (0.20)	2.6 (0.21)	2.9 (0.17)	2.4 (0.20)	2.6 (0.21)
Duration of T2DM by category (years)[a], n (%)						
≤1	20 (35.09)	19 (33.33)	18 (33.33)	16 (28.57)	25 (44.64)	21 (38.18)
>1 and ≤5	37 (64.91)	38 (66.67)	36 (66.67)	40 (71.43)	31 (55.36)	34 (61.82)
Disease characteristics (mean [SEM])						
HbA1C (%)	8.11 (0.15)	8.03 (0.14)	7.93 (0.15)	8.16 (0.13)	8.30 (0.14)	7.95 (0.14)
Fasting plasma glucose (mg/dL)	168.1 (5.65)	161.8 (5.67)	158.4 (6.45)	166.1 (5.69)	165.0 (5.45)	160.7 (4.84)
Fasting insulin (μIU/mL)	9.9 (0.78)	10.9 (1.18)	10.2 (0.84)	10.3 (0.77)	10.5 (0.85)	11.2 (1.84)
Fasting C-peptide (ng/mL)	2.175 (0.13)	2.180 (0.14)	2.087 (0.13)	2.248 (0.11)	2.281 (0.14)	2.216 (0.18)
Fasting triglycerides (mg/dL)	194.2 (17.88)	192.4 (13.40)	171.9 (14.69)	195.4 (14.58)	173.5 (12.28)	183.0 (13.78)

Body mass index was defined as weight in kilogram/(height in centimeter × 0.01)^2
HbA_{1C} =Glycosylated hemoglobin; n=Number of subjects with observation; N=Total number of subjects in respective group; SEM=Standard error of the mean; T2DM=Type 2 diabetes mellitus.
a. Duration since first diagnosis in years relative to time of consent in study.

Efficacy Results:

Primary Efficacy Results: At Week 12, all treatment arms, including placebo resulted in statistically significant decrease in HbA_{1C} relative to Baseline and when adjusted for placebo effect, PF-04937319 and sitagliptin at 100 mg dose showed statistically significant lowering in HbA_{1C} (Table 3).

Table 3. Summary of Statistical Analysis (MMRM) - Change in HbA_{1C} (%) at Week 12 - FAS, OC

Treatment	N	n	Difference From Baseline			Difference From Placebo			
			LSM	80% CI		LSM	80% CI		p-Value
				Lower	Upper		Lower	Upper	
Placebo	57	46	-0.37	-0.53	-0.21	NA	NA	NA	NA
PF-04937319 3 mg	57	52	-0.36	-0.51	-0.21	0.01	-0.21	0.23	0.52
PF-04937319 20 mg	54	45	-0.54	-0.71	-0.38	-0.17	-0.40	0.05	0.16
PF-04937319 50 mg	56	52	-0.54	-0.69	-0.39	-0.17	-0.39	0.05	0.16
PF-04937319 100 mg	56	50	-0.82	-0.98	-0.66	-0.45	-0.68	-0.23	≤0.05
Sitagliptin 100 mg	55	53	-0.80	-0.95	-0.64	-0.43	-0.65	-0.21	≤0.05

MMRM with model terms: treatment, time, treatment-by-time interaction as fixed effects, Baseline as the covariate, time was repeated for subject.
CI=Confidence interval; HbA_{1C}=Glycosylated hemoglobin; FAS=Full analysis set; LSM=Least square mean; NA=Not applicable; OC=Observed case; MMRM=Mixed model repeated measure; n=Number of evaluable subjects; N=Number of subjects randomized; T2DM=Type 2 diabetes mellitus.

Secondary Efficacy Results:

Change from Baseline in HbA_{1C} at Weeks 4, and 8: Beginning as early as Week 4 and continuing to Weeks 8 and 12, there was a statistically significant improvement (decrease) in HbA_{1C} observed with the highest dose of PF-04937319 and sitagliptin relative to placebo. Over the entire 12-week dosing period, the effect with the lowest dose of PF-04937319 tested (ie, 3 mg QD) did not separate from placebo; furthermore, while the mean effect with the 20 mg and 50 mg doses of PF-04937319 separated from placebo, the magnitude of effect was not statistically significant. Summary of statistical analysis (MMRM) - change from Baseline in HbA_{1C} (%) at Weeks 4 and 8 is presented in Table 4.

Table 4. Summary of Statistical Analysis (MMRM) - Change From Baseline in HbA_{1C} (%) at Weeks 4, and 8 - FAS, OC

Treatment	N	n	Difference From Baseline			Difference From Placebo			
			LSM	80% CI		LSM	80% CI		p-Value
				Lower	Upper		Lower	Upper	
Week 4									
Placebo	57	50	-0.20	-0.29	-0.11	NA	NA	NA	NA
PF-04937319 3 mg	57	55	-0.24	-0.33	-0.16	-0.04	-0.16	0.09	0.3434
PF-04937319 20 mg	54	48	-0.34	-0.43	-0.25	-0.14	-0.27	-0.01	0.0892
PF-04937319 50 mg	56	55	-0.34	-0.43	-0.25	-0.14	-0.26	-0.01	0.0826
PF-04937319 100 mg	56	53	-0.48	-0.56	-0.39	-0.27	-0.40	-0.15	0.0031
Sitagliptin 100 mg	55	53	-0.53	-0.62	-0.44	-0.33	-0.45	-0.20	0.0005
Week 8									
Placebo	57	48	-0.34	-0.47	-0.20	NA	NA	NA	NA
PF-04937319 3 mg	57	53	-0.33	-0.46	-0.20	0.00	-0.18	0.19	0.5133
PF-04937319 20 mg	54	45	-0.47	-0.61	-0.33	-0.13	-0.33	0.06	0.1873
PF-04937319 50 mg	56	52	-0.45	-0.58	-0.32	-0.12	-0.30	0.07	0.2120
PF-04937319 100 mg	56	50	-0.87	-1.01	-0.74	-0.54	-0.73	-0.35	0.0001
Sitagliptin 100 mg	55	51	-0.76	-0.89	-0.63	-0.42	-0.61	-0.23	0.0021

Baseline was defined as the measurement performed on Day 1 predose.
Measurements which fall out of the protocol-specified visit windows had been excluded.
MMRM with model terms: treatment, time, treatment-by-time interaction as fixed effects, baseline as the covariate, time was repeated for subject.
CI=Confidence interval; FAS=Full analysis set; HbA1c=glycosylated hemoglobin; LSM=Least square mean; OC=Observed case; MMRM=Mixed model repeated measure; n=Number of evaluable subjects; N=Number of subjects randomized; NA=Not applicable.

Change From Baseline in FPG (mg/dL) Over Time: By Week 2, FPG showed evidence of plateauing across all treatment arms evaluated; thereafter, FPG remained stable except with the highest dose of PF-04937319 (Table 5). At the PF-04937319 dose of 100 mg, mean FPG showed a steady climb reaching statistically significant increase relative to placebo at Week 12 with an additional increase noted at the follow-up visit ie, at least 7 to 14-days following last dose of study drug. Sitagliptin at Week 2 and Week 12 was noted to result in statistically significant reductions in FPG relative to placebo with its plateau occurring at Week 4.

Table 5. Summary of Statistical Analysis (MMRM) - Change in Fasting Plasma Glucose (mg/dL) at Weeks 2, 4, 8 and 12 - FAS, OC

Treatment	N	n	Difference From Baseline			Difference From Placebo			
			LSM	80% CI		LSM	80% CI		p-Value
				Lower	Upper		Lower	Upper	
Week 2									
Placebo	57	54	-2.49	-6.89	1.92	NA	NA	NA	NA
PF-04937319 3 mg	57	56	0.38	-3.97	4.73	2.87	-3.32	9.07	0.72
PF-04937319 20 mg	54	50	-4.26	-8.83	0.32	-1.77	-8.13	4.59	0.36
PF-04937319 50 mg	56	56	-5.73	-10.08	-1.37	-3.24	-9.42	2.95	0.25
PF-04937319 100 mg	56	54	-9.77	-14.18	-5.35	-7.28	-13.51	-1.05	0.07
Sitagliptin 100 mg	55	55	-13.71	-18.10	-9.32	-11.22	-17.44	-5.00	≤0.05
Week 4									
Placebo	57	52	0.55	-4.17	5.28	NA	NA	NA	NA
PF-04937319 3 mg	57	56	-0.58	-5.19	4.02	-1.13	(-7.73,	5.47)	0.4127
PF-04937319 20 mg	54	51	-1.33	-6.15	3.49	-1.88	(-8.64,	4.87)	0.3604
PF-04937319 50 mg	56	55	-6.8	-11.44	-2.17	-7.35	(-13.96	-0.74)	0.077
PF-04937319 100 mg	56	54	-8.24	-12.91	-3.56	-8.79	(-15.43	-2.15)	0.0451
Sitagliptin 100 mg	55	53	-19.35	-24.05	-14.65	-19.9	(-26.57	-13.23)	0.0001
Week 8									
Placebo	57	50	-0.87	-6.04	4.30	NA	NA	NA	NA
PF-04937319 3 mg	57	54	0.23	-4.76	5.23	1.11	-6.08	8.30	0.5783
PF-04937319 20 mg	54	47	-2.94	-8.27	2.38	-2.07	-9.50	5.36	0.3604
PF-04937319 50 mg	56	52	-13	-18.07	-7.92	-12.12	-19.36	-4.88	0.0161
PF-04937319 100 mg	56	51	-5.28	-10.40	-0.16	-4.41	-11.68	2.87	0.2185
Sitagliptin 100 mg	55	52	-16.29	-21.38	-11.20	-15.41	-22.67	-8.16	0.0034
Week 12									
Placebo	57	48	-4.22	-10.14	1.70	NA	NA	NA	NA
PF-04937319 3 mg	57	53	-3.05	-8.73	2.63	1.17	-7.03	9.37	0.57
PF-04937319 20 mg	54	47	-4.29	-10.30	1.73	-0.06	-8.51	8.38	0.50
PF-04937319 50 mg	56	52	-8.32	-14.05	-2.59	-4.1	-12.33	4.14	0.26
PF-04937319 100 mg	56	51	4.84	-0.94	10.62	9.06	0.79	17.34	0.92
Sitagliptin 100 mg	55	53	-12.98	-18.68	-7.29	-8.76	-16.98	-0.54	0.09

MMRM with model terms: treatment, time, treatment-by-time interaction as fixed effects, baseline as the covariate, time was repeated for subject.
CI=Confidence interval; FAS=Full analysis set; LSM=Least square mean; MMRM=Mixed model repeated measure; n=Number of evaluable subjects; N=Number of subjects randomized; OC=Observed case; T2DM=Type 2 diabetes mellitus.

Proportions of Subjects Achieving HbA_{1C} <7%, and <6.5% at Week 12: At Week 12, the proportion of subjects achieving HbA_{1C} <7% or <6.5% was higher in the PF-04937319 20 mg, 50 mg, 100 mg and sitagliptin 100 mg arms as compared to the placebo group. At the 3 mg dose of PF-04937319, the proportion of subjects meeting these categorical thresholds was similar to placebo (Table 6).

Table 6. Proportion of Subjects With HbA_{1C} <7% and <6.5% at Baseline and Week 12 - FAS, OC

	Placebo	PF-04937319				Sitagliptin 100 mg
		3 mg	20 mg	50 mg	100 mg	
Subjects Randomized	57	57	54	56	56	55
Baseline HbA_{1C}						
N	55	56	52	56	55	55
<6.5% n (%)	2 (3.6)	3 (5.4)	2 (3.8)	0 (0.0)	1 (1.8)	2 (3.6)
<7% n (%)	7 (12.7)	7 (12.5)	8 (15.4)	3 (5.4)	6 (10.9)	6 (10.9)
Week 12 HbA_{1C}						
N	48	53	47	52	51	53
<6.5% n (%)	6 (12.5)	5 (9.4)	9 (19.1)	8 (15.4)	9 (17.6)	17 (32.1)
<7% n (%)	11 (22.9)	14 (26.4)	20 (42.6)	16 (30.8)	20 (39.2)	30 (56.6)

FAS=Full analysis set; HbA_{1C} =Glycosylated hemoglobin; n=Number of subjects with the observation meeting specified criteria; N=Total number of subjects with no missing observation in each treatment group, at each visit; OC=Observed case.

Safety Results:

An overview of all-causality and treatment-related TEAEs, by treatment group, is provided in Table 7.

Table 7. Overview of All-Causality (Treatment-Related) Treatment-Emergent Adverse Events

	Metformin Run-In	Placebo	PF-04937319				Sitagliptin 100 mg
			3 mg	20 mg	50 mg	100 mg	
Subjects evaluable for AEs	376	57	57	54	56	56	55
Number of AEs	57 (6)	27 (5)	30 (3)	28 (3)	23 (1)	36 (5)	21 (4)
Subjects with AEs	37 (5)	19 (3)	19 (2)	19 (3)	16 (1)	24 (3)	18 (4)
Subjects with SAEs	0	1 (0)	0	1 (0)	0	1 (0)	0
Subjects with severe AEs	1 (0)	1 (0)	1 (0)	2 (0)	0	1 (0)	0
Subjects discontinued due to AEs	0	0	0	1 (0)	0	0	0
Subjects with dose reduced or temporary discontinuation due to AEs	0	2 (0)	0	0	0	1 (0)	0

Included all data collected since the first dose of sponsor-provided metformin.
Except for the number of AEs, subjects were counted only once per treatment in each row.
SAEs - according to the investigator's assessment.
MedDRA (Version 16.0) coding dictionary applied.
AE=Adverse event; MedDRA=Medical Dictionary for Regulatory Activities; SAE=Serious adverse event.

Table 8 summarizes the treatment-emergent all causality and treatment-related AEs reported in this study, by System Organ Class and Preferred Term, including the metformin run-in period, but limited to AEs reported in ≥3 subjects across the randomized regimens studied.

Overall, there did not appear to be a dose-response relationship in the frequency and/or severity of AEs. The most commonly reported treatment-emergent AEs were upper respiratory tract infection (9 subjects), and urinary tract infection (8 subjects).

Table 8. All-Causality Treatment-Emergent Adverse Events Occurring in ≥3 Subjects Across the Treatment Regimens

System Organ Class Preferred Term	Metformin Run-In (N=376)	Placebo (N=57)	PF-04937319				Sitagliptin 100 mg (N=55)
			3 mg (N=57)	20 mg (N=54)	50 mg (N-56)	100 mg (N=56)	
Number (%) of subjects with adverse events	12 (3.2)	8 (14.0)	7 (12.3)	11 (20.4)	10 (17.9)	9 (16.1)	7 (12.7)
Cardiac disorders	1 (0.3)	0	0	3 (5.6)	0	0	0
Bundle branch block right	1 (0.3)	0	0	3 (5.6)	0	0	0
Gastrointestinal disorders	0	0	2 (3.5)	0	1 (1.8)	1 (1.8)	0
Toothache	0	0	2 (3.5)	0	1 (1.8)	1 (1.8)	0
Infections and infestations	3 (0.8)	3 (5.3)	1 (1.8)	3 (5.6)	6 (10.7)	3 (5.4)	2 (3.6)
Influenza	1 (0.3)	0	0	2 (3.7)	0	2 (3.6)	0
Upper respiratory tract infection	0	2 (3.5)	1 (1.8)	1 (1.9)	4 (7.1)	0	1 (1.8)
Urinary tract infection	2 (0.5)	1 (1.8)	1 (1.8)	0	2 (3.6)	1 (1.8)	1 (1.8)
Investigations	0	2 (3.5)	1 (1.8)	0	0	1 (1.8)	1 (1.8)
Haemoglobin decreased	0	2 (3.5)	1 (1.8)	0	0	1 (1.8)	1 (1.8)
Metabolism and nutrition disorders	2 (0.5)	0	0	3 (5.6)	1 (1.8)	2 (3.6)	1 (1.8)
Hyperglycaemia	2 (0.5)	0	0	2 (3.7)	1 (1.8)	0	0
Hypoglycaemia	0	0	0	1 (1.9)	0	2 (3.6)	1 (1.8)
Musculoskeletal and connective tissue disorders	1 (0.3)	0	2 (3.5)	0	0	0	0
Arthralgia	1 (0.3)	0	2 (3.5)	0	0	0	0
Nervous system disorders	3 (0.8)	0	0	2 (3.7)	0	0	2 (3.6)
Dizziness	3 (0.8)	0	0	2 (3.7)	0	0	0
Headache	2 (0.5)	0	0	0	0	0	2 (3.6)
Renal and urinary disorders	1 (0.3)	0	0	0	2 (3.6)	2 (3.6)	1 (1.8)
Nephropathy	1 (0.3)	0	0	0	2 (3.6)	2 (3.6)	1 (1.8)
Respiratory, thoracic and mediastinal disorders	1 (0.3)	2 (3.5)	1 (1.8)	0	0	0	0
Oropharyngeal pain	1 (0.3)	2 (3.5)	1 (1.8)	0	0	0	0
Vascular disorders	0	1 (1.8)	2 (3.5)	0	1 (1.8)	0	0
Hypertension	0	1 (1.8)	2 (3.5)	0	1 (1.8)	0	0

Subjects were counted only once per treatment in each row.
Included all data collected since the first dose of sponsor-provided Metformin.
MedDRA (Version 16.0) coding dictionary applied.
AE=Adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of subjects evaluable; n=Number of subjects with AE.

Table 9. All Treatment Related Treatment-Emergent Adverse Events Occurring in Subjects Across the Treatment Regimens

System Organ Class Preferred Term	Metformin Run-In (N=376)	Placebo (N=57)	PF-04937319				Sitagliptin 100 mg (N=55)
			3 mg (N=57)	20 mg (N=54)	50 mg (N-56)	100 mg (N=56)	
Blood and lymphatic system disorders	0	0	0	0	0	1 (1.8)	0
Anaemia	0	0	0	0	0	1 (1.8)	0
Gastrointestinal disorders	0	0	1 (1.8)	0	0	0	0
Abdominal pain upper	0	0	1 (1.8)	0	0	0	0
General disorders and administration site conditions	1 (0.3)	1 (1.8)	0	1 (1.9)	0	0	0
Malaise	1 (0.3)	0	0	1 (1.9)	0	0	0
Pain	0	1 (1.8)	0	0	0	0	0
Pyrexia	0	1 (1.8)	0	0	0	0	0
Infections and infestations	1 (0.3)	0	0	0	0	0	0
Urinary tract infection	1 (0.3)	0	0	0	0	0	0
Investigations	0	2 (3.5)	1 (1.8)	0	0	3 (5.4)	1 (1.8)
Blood triglycerides increased	0	1 (1.8)	0	0	0	1 (1.8)	0
Haemoglobin decreased	0	2 (3.5)	1 (1.8)	0	0	1 (1.8)	1 (1.8)
Platelet count increased	0	0	0	0	0	1 (1.8)	0
Metabolism and nutrition disorders	2 (0.5)	0	1 (1.8)	2 (3.7)	0	1 (1.8)	0
Decreased appetite	1 (0.3)	0	1 (1.8)	0	0	0	0
Hyperglycaemia	1 (0.3)	0	0	0	0	0	0
Hypoglycaemia	0	0	0	1 (1.9)	0	1 (1.8)	0
Hyponatraemia	0	0	0	1 (1.9)	0	0	0
Nervous system disorders	1 (0.3)	0	0	0	0	0	0
Dizziness	1 (0.3)	0	0	0	0	0	0
Headache	1 (0.3)	0	0	0	0	0	0
Renal and urinary disorders	0	0	0	0	1 (1.8)	0	1 (1.8)
Nephropathy	0	0	0	0	0	0	1 (1.8)
Proteinuria	0	0	0	0	1 (1.8)	0	0
Reproductive system and breast disorders	0	0	0	0	0	0	1 (1.8)
Erectile dysfunction	0	0	0	0	0	0	1 (1.8)
Skin and subcutaneous tissue disorders	0	0	0	0	0	0	1 (1.8)
Hyperhidrosis	0	0	0	0	0	0	1 (1.8)

Subjects were counted only once per treatment in each row.
Included all data collected since the first dose of sponsor-provided Metformin.
MedDRA (Version 16.0) coding dictionary applied.
AE=Adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of subjects evaluable; n=Number of subjects with AE.

A total of 3 subjects reported SAEs as summarized in Table 10; 1 subject each on Placebo (anal abscess), PF-04937319 20 mg (myocardial infarction leading to death), and PF 04937319 100 mg (meningitis viral), and none of these SAE were considered related to the study drug by the investigator.

Table 10. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Metformin Run-In (N=376)	Placebo (N=57)	PF-04937319				Sitagliptin 100 mg (N=55)
			3 mg (N=57)	20 mg (N=54)	50 mg (N-56)	100 mg (N=56)	
Number of subjects with adverse events, n (%)	0	1 (1.8)	0	1 (1.9)	0	1 (1.8)	0
Cardiac disorders	0	0	0	1 (1.9)	0	0	0
Myocardial infarction	0	0	0	1 (1.9)	0	0	0
Infections and infestations	0	1 (1.8)	0	0	0	1 (1.8)	0
Anal abscess	0	1 (1.8)	0	0	0	0	0
Meningitis viral	0	0	0	0	0	1 (1.8)	0

Subjects were counted only once per treatment in each row.
Included all data collected since the first dose of sponsor-provided Metformin.
MedDRA (Version 16.0) coding dictionary applied.
AE=Adverse event; MedDRA=Medical Dictionary for Regulatory Activities; N=Total number of subjects evaluable; n=Number of subjects with AE.

A listing of permanent discontinuations due to AEs is provided in Table 11, and a listing of the permanent discontinuations due to insufficient clinical response is provided in Table 12. Dose reductions or temporary discontinuations due to adverse events is presented Table 13.

Table 11. Permanent Discontinuations Due to Adverse Events

Serial No.	Treatment at Onset	Sex/ Age at onset (years)/ Race	MedDRA Preferred Term	Event Start/ Stop Day[a]	Severity / Outcome	Causality
1	PF-04937319 20 mg	Female / 45 / Black	Hyperglycaemia	1 / 51	Mild / resolved	Background Metformin dose
2	PF-04937319 20 mg	Male / 51 / White	Myocardial Infarction	89 / 92	Severe / fatal (SAE, death)	Disease under study

Age was at Screening.
MedDRA (Version 16.0) coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities.
a. Day relative to first day of randomized treatment period (ie, Day 1, Visit 4).

Table 12. Permanent Discontinuations Due to Insufficient Clinical Response

Serial No.	Treatment	Sex/ Age at Onset (Years) / Race	Duration of Dosing With Blinded Treatment Before Decision to Withdraw (Days)
1	Placebo	Male / 54 / Asian	26
2	Placebo	Male / 35 / White	67
3	PF-04937319 20 mg	Male / 51 / White	24
4	PF-04937319 20 mg	Male / 53 / White	45
5	PF-04937319 50 mg	Female / 35 / White	44
6	PF-04937319 100 mg	Female / 50 / White	22

Table 13. Dose Reductions or Temporary Discontinuations Due to Adverse Events

Serial No.	Treatment at Onset	Sex/Age at onset (years)/Race	MedDRA Preferred Term	Event Start/Stop Day[a]	Severity/ Outcome	Action/Causality
1	Placebo	Male/45/White	Anal abscess[b]	13/18	Severe/ resolved	Stopped temporarily/Other illness-concomitant infection
2	Placebo	Female/47/Asian	Abdominal pain upper	23/25	Mild/ resolved	Stopped temporarily/Other-food intake of seaweed
3	PF-049373 19 100 mg	Female/45/White	Meningitis viral[b]	59/61	Severe/ resolved	Stopped temporarily/Other illness-viral infection

Age was at Screening.
MedDRA (Version 16.0) coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities.
a. Day relative to first day of randomized treatment period (ie, Day 1, Visit 4).
b. Reported as SAEs

One subject died who was hospitalized 5-days following last dose of study drug with symptoms of dizziness and lower bilateral extremity pain. After 4 days, the subject died due to myocardial infarction.

CONCLUSIONS:

- PF-04937319 at a dose of 100 mg QD demonstrated clinically relevant effect on HbA_{1C} though this dose caused no statistically significant reduction in FPG at Week 12 in this study; in contrast sitagliptin showed comparable reduction in HbA_{1C} with clinically meaningful decrease in FPG.

- PF-04937319 doses evaluated in this trial along with sitagliptin were safe and well-tolerated – including lack of adverse effects on fasting lipid profile, body weight, BP and 12-lead ECG parameters – in subjects with 'early' T2DM for a period of 12-weeks.