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COMPOUND NUMBER: PF-04937319

PROTOCOL NO.: B1621002

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

Study Centers: A total of 51 centers randomized subjects in this study: Bulgaria (6 centers), Canada (9 centers), Hungary (4 centers), India (3 centers), Slovakia (5 centers), Taiwan (3 centers) and United States (21 centers).

Study Initiation Date, Primary completion Date and Final Completion Dates:
21 February 2012, 17 January 2013 and 28 January 2013

Phase of Development: Phase 2a

Study Objectives:

Primary Objective:

- To evaluate the dose response for the effect on glycemic control with a range of doses of PF-04937319 administered once daily (QD) over 12 weeks in adults with Type 2 diabetes mellitus (T2DM) on stable doses of metformin.

Secondary Objectives:

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

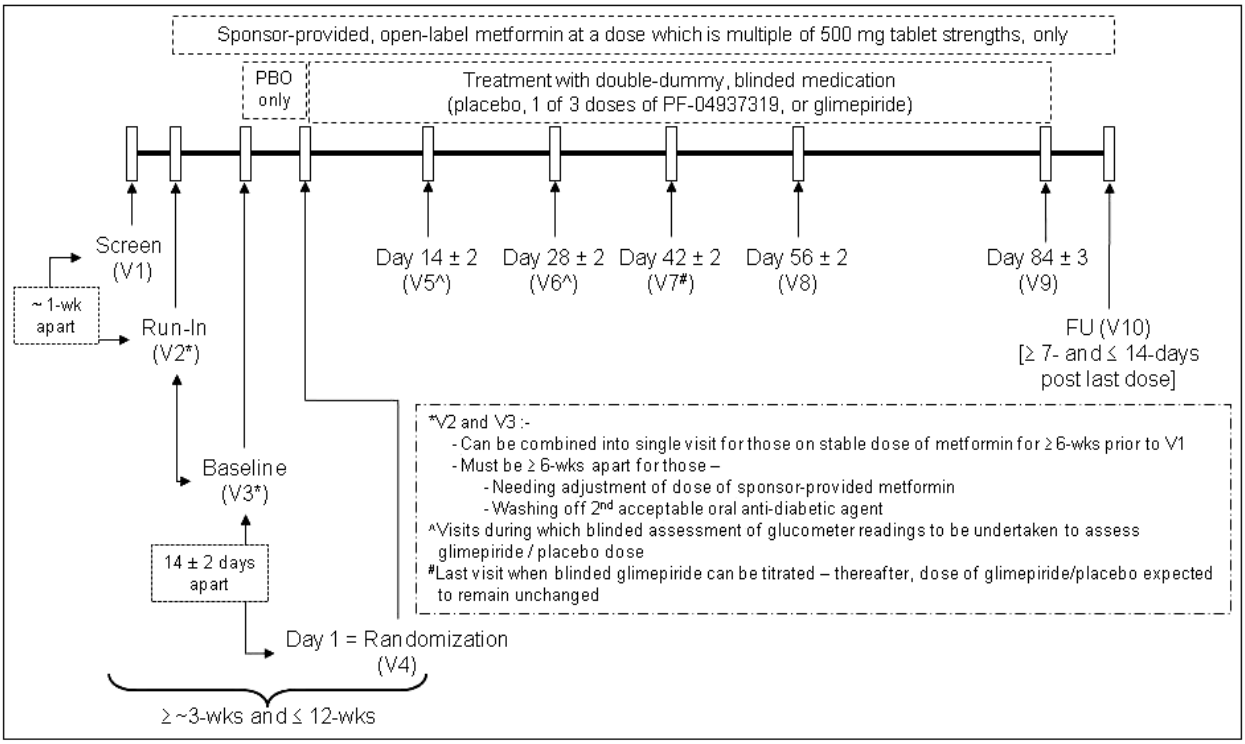
- To characterize the safety and efficacy of glimepiride (titrated) to a maximum of 6 mg/day (or highest approved dose in individual countries if <6 mg) administered over 12 weeks in adults with T2DM on stable doses of metformin.

- To evaluate the dose response for effect on additional parameters of glycemic control with a range of doses of PF-04937319 administered QD 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, 5-arm (placebo, 3 active doses of PF-04937319, and glimepiride), parallel-group study. Screening procedures were completed at Visit (V) 1 to determine subject 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 5 blinded treatment regimens for a duration of 84±3 days. The study included a total of 10 outpatient visits (including Screening, run-in, and Baseline) to the site (V1 to V10). Total participation in the study for each subject, including screening, run-in, and baseline, ranged from 16 weeks (minimum) to 27 weeks (maximum). Overall study design is presented in Figure 1.

Figure 1. Study Design



FU=Follow-up; PBO=Placebo; V=Visit; WK=Week.

Number of Subjects (Planned and Analyzed): The study planned to randomize at least 300 subjects to ensure that at least 250 (50 per arm) complete the study. A total of 628 subjects were consented. Of these, 361 subjects (57.5%) transitioned to the Run-in period and were started on sponsor-provided metformin. A total of 305 subjects (33 subjects in Bulgaria, 61 subjects in Canada, 14 subjects in Hungary, 22 subjects in India, 24 subjects Slovakia, 15 subjects Taiwan and 135 subjects in United States) who completed metformin run-in period, were randomized to 1 of the 5 treatment groups (ie, placebo, PF-04937319 at 10 mg, 50 mg, or 100 mg QD, or titrated glimepiride).

Diagnosis and Main Criteria for Inclusion: Male or female subjects with T2DM between the ages of 18 (or the minimum country specific age of consent if >18) and 70 years, inclusive at screening, on a stable dose of metformin either alone or in combination with another oral anti-diabetic agent (excluding pioglitazone and rosiglitazone) for their T2DM for at least 6 weeks prior to V1 (subjects on an oral anti-diabetic 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 oral anti-diabetic drug), 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 up to the follow-up visit in the study. Metformin was provided by the sponsor as 500 mg immediate-release tablets requiring dose to be a multiple of 500 mg.

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 5 blinded treatment regimens (placebo, titrated glimepiride, or PF-04937319 10 mg, 50 mg, or 100 mg QD) to be taken for 84±3 days. PF-04937319/placebo was administered as tablets (2 per dose) and glimepiride/placebo was offered as 2 mg capsules – with dose starting of 1 capsule/day, increased to 2 capsules/day at Week 2 and maximum of 3 capsules/day at Week 6.

Efficacy and Safety Endpoints:

Efficacy Endpoints:

Primary Efficacy Endpoint:

- Change from Baseline in HbA_{1C} at Week 12.
- Change from Baseline in HbA_{1C} at Weeks 4, 6 and 8

Secondary Efficacy Endpoints:

- Change from Baseline in FPG (mg/dL) at Weeks 2, 4, 6, 8, and 12;
- Proportions of subjects achieving HbA_{1C} <7%, and <6.5% at Week 12.

Safety Endpoints:

Secondary Safety Endpoints: Safety and tolerability assessment included: 12-lead ECGs, vital signs, adverse events (AEs) including hypoglycemic episodes (HAE), SAEs, body weight, and laboratory tests (including lipid profile). HAE endpoints included the following:

- Proportion of subjects with at least one HAE episode over treatment period;
- Number of HAE episodes in each subject;
- Time to each recurrent HAE episode in each subject.

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 un-blinding). Safety analysis was performed on safety analysis set 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% confidence interval (CIs) were obtained for each treatment group. Placebo-adjusted LSM estimates with 80% CIs and corresponding 1-sided p-values were also computed and tabulated. No adjustment for multiplicity was made.

All the secondary endpoints were analyzed on the FAS. These analyses were based on observed cases. With the exception of endpoints that were not measured repeatedly, continuous secondary/tertiary endpoints 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.

Categorical secondary endpoints were summarized by number and percentage in each treatment group.

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 628 subjects were consented. Of these, 361 subjects (57.5%) transitioned to the Run-in period and were started on sponsor-provided metformin. A total of 304 subjects were randomized (48.4% of subjects' consented and 84.2% of subjects' started on sponsor-provided metformin). Of the 304 subjects randomized, 30 (9.9%) were prematurely withdrawn prior to completion of the study-prescribed follow-up visit.

All 361 subjects who received sponsor-provided metformin during the run-in period and the 304 subjects randomized to 1 of the 5 treatment groups were included in the safety analysis set. The 304 randomized subjects were included in the FAS. Of the 304 randomized subjects, 272 (89.5%) were included in the PPAS, which required subjects to have at least 80% compliance with blinded therapy, completed the randomized treatment period of the study.

In this study, the age of the population randomized ranged from 20 to 70 years with a mean age of 55.5 years and 131/304 (43%) of the subjects were female. For the pool of randomized subjects, the average duration of T2DM was 6.9 years with 13.5% having the disease for <1 year and 37.5% having it for 1 to 5 years with the remaining 149/304 (49%) having the disease for >5 years. The average baseline glycemic parameters across the 304 randomized subjects were 8.0% (HbA_{1C}), 166 mg/dL (FPG), and 10.98 µIU/mL (fasting plasma insulin) with fasting serum triglycerides of 183 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 plasma insulin, fasting serum C-peptide, and fasting serum triglycerides. A summary of subject evaluation groups is provided in Table 1.

Table 1. Subject Evaluation Groups

Number (%) of Subjects Analyzed for	Metformin Run-In	Placebo	PF-04937319			Titrated Glimepiride
			10 mg	50 mg	100 mg	
Screened				628		
Assigned to Study Treatment	361	61	60	61	61	61
Treated	361	61	60	61	61	61
Completed	304 (84.2)	57 (93.4)	54 (90.0)	54 (88.5)	55 (90.2)	54 (88.5)
Discontinued	57 (15.8)	4 (6.6)	6 (10.0)	7 (11.5)	6 (9.8)	7 (11.5)
Subject died	1 (0.3)	0	0	0	0	0
Relation to study drug not defined	51 (14.1)	3 (4.9)	3 (5.0)	3 (4.9)	4 (6.6)	3 (4.9)
Does not meet entrance criteria	34 (9.4)	0	0	0	0	0
Lost to follow-up	1 (0.3)	0	1 (1.7)	1 (1.6)		
No longer willing to participate in study	12 (3.3)	3 (4.9)	2 (3.3)	2 (3.3)	2 (3.3)	3 (4.9)
Other	4 (1.1)	0	0	0	1 (1.6)	0
Protocol violation	0	0	0	0	1 (1.6)	0
Related to study drug	1 (0.3)	1 (1.6)	3 (5.0)	4 (6.6)	2 (3.3)	3 (4.9)
Adverse event	1 (0.3)	0	0	0	0	1 (1.6)
Insufficient clinical response	0	1 (1.6)	1 (1.7)	3 (4.9)	2 (3.3)	0
Medication error without associated adverse event	0	0	2 (3.3)	1 (1.6)	0	2 (3.3)
Not related to study drug	4 (1.1)	0	0	0	0	1 (1.6)
Adverse event	4 (1.1)	0	0	0	0	1 (1.6)
Efficacy						
FAS	0	61 (100.0)	60 (100.0)	61 (100.0)	61 (100.0)	61 (100.0)
PPAS	0	56 (91.8)	54 (90.0)	52 (85.2)	55 (90.2)	55 (90.2)
Safety						
Adverse event	361 (100.0)	61 (100.0)	60 (100.0)	61 (100.0)	61 (100.0)	61 (100.0)
Laboratory data	0	60 (98.4)[a]	60 (100.0)	60 (98.4)[a]	61 (100.0)	61 (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. One subject in each treatment group excluded due to lack of post randomization assessment of laboratory tests.

Efficacy Results:

Primary Efficacy Results: At Week 12, all treatment groups, including placebo resulted in statistically significant decrease in HbA_{1C} relative to baseline and when adjusted for placebo effect, PF-04937319 at the 50 and 100 mg doses and titrated glimepiride showed statistically significant lowering in HbA_{1C} (Table 2).

Table 2. 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		Difference	80% CI		p-value
				Lower	Upper		Lower	Upper	
Placebo	61	56	-0.14	-0.27	-0.01				
PF-04937319 10 mg	60	53	-0.16	-0.30	-0.03	-0.02	-0.21	0.17	0.45
PF-04937319 50 mg	61	53	-0.44	-0.57	-0.31	-0.30	-0.48	-0.11	≤0.05
PF-04937319 100 mg	61	54	-0.61	-0.74	-0.48	-0.47	-0.65	-0.28	≤0.05
Titrated glimepiride	61	54	-0.97	-1.11	-0.84	-0.83	-1.02	-0.65	≤0.05

MMRM with model terms: treatment, duration of T2DM, 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 squares mean; OC=Observed case; MMRM=Mixed model repeated measure; n=Number of evaluable subjects; N=Number of randomized subjects; T2DM=Type 2 diabetes mellitus.

Change from Baseline in HbA_{1C} at Weeks 4, 6 and 8: Beginning as early as Week 4 and continuing to Weeks 6, 8 and 12, there was a statistically significant improvement (decrease) in HbA_{1C} observed with the 2 highest doses of PF-04937319 and titrated glimepiride relative to placebo. Over the entire 12 weeks dosing period, the effect with the lowest dose of PF-04937319 tested (ie, 10 mg QD) did not separate from placebo.

Table 3. Summary of Statistical Analysis (MMRM) - Change in HbA_{1C} (%) at Week 4, 6 and 8 - FAS, OC

Treatment	N	n	Difference From Baseline			Difference From Placebo			
			LSM	80% CI		Difference	80% CI		p-Value
				Lower	Upper		Lower	Upper	
Week 4									
Placebo	61	58	-0.09	-0.17	-0.01				
PF-04937319 10 mg	60	57	-0.06	-0.14	0.02	0.02	-0.09	0.14	0.6112
PF-04937319 50 mg	61	55	-0.23	-0.31	-0.15	-0.14	-0.25	-0.03	0.055
PF-04937319 100 mg	61	58	-0.32	-0.40	-0.25	-0.24	-0.35	-0.13	0.0032
Titrated glimepiride	61	60	-0.53	-0.60	-0.45	-0.44	-0.55	-0.33	<0.0001
Week 6									
Placebo	61	57	-0.16	-0.25	-0.07				
PF-04937319 10 mg	60	55	-0.13	-0.22	-0.04	0.03	-0.10	0.16	0.6146
PF-04937319 50 mg	61	55	-0.22	-0.32	-0.13	-0.07	-0.19	0.06	0.2606
PF-04937319 100 mg	61	58	-0.48	-0.57	-0.39	-0.32	-0.45	-0.20	0.0006
Titrated glimepiride	61	55	-0.73	-0.82	-0.64	-0.57	-0.70	-0.44	<0.0001
Week 8									
Placebo	61	58	-0.21	-0.31	-0.10				
PF-04937319 10 mg	60	55	-0.16	-0.27	-0.05	0.05	-0.10	0.20	0.6618
PF-04937319 50 mg	61	53	-0.37	-0.48	-0.26	-0.16	-0.31	-0.01	0.0878
PF-04937319 100 mg	61	57	-0.54	-0.65	-0.44	-0.34	-0.49	-0.19	0.0022
Titrated glimepiride	61	55	-0.86	-0.97	-0.76	-0.66	-0.81	-0.51	<0.0001

MMRM with model terms: treatment, duration of T2DM, 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 squares mean; OC=Observed case; MMRM=Mixed model repeated measure; n=Number of evaluable subjects; N=Number of randomized subjects; T2DM=Type 2 diabetes mellitus.

Secondary Efficacy Results:

Change from Baseline in Fasting Plasma Glucose (mg/dL) Over Time: By Week 2, FPG showed evidence of plateauing across all treatment groups evaluated; thereafter, FPG remained stable (Table 4). By Week 12, the 2 highest doses of PF-04937319 evaluated and titrated glimepiride resulted in statistically significant decreases in FPG relative to placebo.

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

Treatment	N	n	Difference From Baseline			Difference From Placebo			
			LSM	80% CI		Difference	80% CI		p-Value
				Lower	Upper		Lower	Upper	
Week 2									
Placebo	61	60	1.93	-2.79	6.64				
PF-04937319 10 mg	60	59	-0.17	-4.92	4.59	-2.09	-8.80	4.62	0.34
PF-04937319 50 mg	61	60	-4.20	-8.93	0.54	-6.12	-12.81	0.57	0.12
PF-04937319 100 mg	61	61	-11.81	-16.48	-7.14	-13.74	-20.37	-7.10	≤0.05
Titrated glimepiride	61	59	-19.42	-24.13	-14.70	-21.34	-28.01	-14.67	≤0.05
Week 4									
Placebo	61	59	-1.52	-6.20	3.17				
PF-04937319 10 mg	60	58	-6.65	-11.38	-1.92	-5.14	-11.80	1.53	0.16
PF-04937319 50 mg	61	56	-5.96	-10.75	-1.17	-4.45	-11.15	2.26	0.20
PF-04937319 100 mg	61	59	-13.14	-17.79	-8.48	-11.62	-18.22	-5.02	0.01
Titrated glimepiride	61	60	-26.30	-30.94	-21.67	-24.79	-31.37	-18.20	≤0.05
Week 6									
Placebo	61		-3.58	-8.68	1.53				
PF-04937319 10 mg	60		-5.54	-10.73	-0.36	-1.97	-9.26	5.32	0.36
PF-04937319 50 mg	61		-5.50	-10.70	-0.31	-1.93`	-9.22	5.36	0.37
PF-04937319 100 mg	61		-11.08	-16.14	-6.01	-7.50	-14.69	-0.31	0.09
Titrated glimepiride	61		-23.26	-28.37	-18.15	-19.69	-26.91	-12.46	≤0.05
Week 8									
Placebo	61		-0.44	-5.41	4.53				
PF-04937319 10 mg	60		-5.62	-10.69	-0.56	-5.18	-12.29	1.93	0.17
PF-04937319 50 mg	61		-10.97	-16.11	-5.84	-10.54	-17.69	-3.38	0.03
PF-04937319 100 mg	61		-12.88	-17.85	-7.91	-12.44	-19.47	-5.41	0.01
Titrated glimepiride	61		-27.44	-32.42	-22.45	-27.00	-34.04	-19.96	≤0.05
Week 12									
Placebo	61	57	3.24	-2.40	8.87				
PF-04937319 10 mg	60	54	-4.79	-10.56	0.97	-8.03	-16.10	0.04	0.10
PF-04937319 50 mg	61	54	-7.75	-13.54	-1.97	-10.99	-19.07	-2.91	≤0.05
PF-04937319 100 mg	61	55	-11.64	-17.33	-5.94	-14.87	-22.88	-6.86	≤0.05
Titrated glimepiride	61	55	-22.69	-28.38	-17.00	-25.93	-33.93	-17.92	≤0.05

MMRM with model terms: treatment, duration of T2DM, 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 squares mean; OC=Observed case; MMRM=Mixed model repeated measure; n=Number of evaluable subjects; N=Number of randomized subjects; T2DM=Type 2 diabetes mellitus.

Proportions of Subjects Achieving HbA_{1C} <7%, and <6.5% at Week 12: The proportion of subjects achieving HbA_{1C} <6.5% was higher in all the PF-04937319 and titrated glimepiride treatment groups compared to the placebo group. In comparison, the proportion of subjects achieving HbA_{1C} <7% was higher in the 100 mg PF-04937319 and the titrated glimepiride treatment groups compared to the placebo group (Table 5).

Table 5. Proportion of Subjects With HbA_{1C} <7% and <6.5% at Baseline and Week 12 - FAS, OC

	Placebo	PF-04937319			Titrated Glimepiride
		10 mg	50 mg	100 mg	
Number of randomized subjects	61	60	61	61	61
Baseline HbA_{1C}					
N	60	59	59	60	60
<6.5% n (%)	2 (3.3)	1 (1.7)	1 (1.7)	2 (3.3)	0 (0.0)
<7% n (%)	9 (15.0)	6 (10.2)	6 (10.2)	10 (16.7)	3 (5.0)
Week 12 HbA_{1C}					
N	57	54	54	55	55
<6.5% n (%)	4 (7.0)	7 (13.0)	10 (18.5)	15 (27.3)	10 (18.2)
<7% n (%)	15 (26.3)	17 (31.5)	15 (27.8)	29 (52.7)	25 (45.5)

HbA_{1C}=Glycosylated hemoglobin; FAS=Full analysis set; OC=Observed case; 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.

Safety Results:

An overview of all-causality and treatment-related TEAEs, by treatment group, is provided in Table 6.

Table 6. Overview of All-Causality (Treatment-Related) Treatment-Emergent Adverse Events

Number of Subjects	Metformin Run-In	Placebo	PF-04937319			Titrated Glimepiride
			10 mg	50 mg	100 mg	
Subjects evaluable for AEs	361	61	60	61	61	61
Number of AEs	91 (7)	60 (18)	71 (15)	59 (7)	63 (5)	66 (20)
Subjects with AEs	67 (5)	26 (11)	28 (8)	31 (4)	29 (5)	36 (15)
Subjects with SAEs	4 (0)	0	1 (0)	2 (0)	1 (0)	1 (0)
Subjects with severe AEs	5 (0)	0	1 (0)	1 (0)	0	2 (1)
Subjects discontinued due to AEs	5 (1)	0	0	0	0	2 (1)
Subjects with dose reduced or temporary discontinuation due to AEs	0	0	2 (1)	2 (0)	1 (1)	2 (2)

Included all data collected since the first dose of sponsor-provided metformin.
Except for the number of adverse events, subjects were counted only once per treatment in each row.
Serious adverse events - 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 7 summarizes the all causality treatment-emergent AEs reported in this study, by System Organ Class (SOC) and Preferred Term (PT), 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 hypoglycemia and diarrhea.

Table 7. All-Causality Treatment-Emergent Adverse Events Occurring in ≥3 Subjects Across the Treatment Regimens

System Organ Class Preferred Term	Metformin Run-In (N=361) n (%)	Placebo (N=61) n (%)	PF-04937319 10 mg (N=60) n (%)	PF-04937319 50 mg (N=61) n (%)	PF-04937319 100 mg (N=61) n (%)	Titrated Glimepiride (N=61) n (%)
Blood and lymphatic system disorders	0	0	0	2 (3.3)	0	0
Anaemia	0	0	0	2 (3.3)	0	0
Gastrointestinal disorders	7 (1.9)	4 (6.6)	5 (8.3)	4 (6.6)	4 (6.6)	5 (8.2)
Diarrhoea	6 (1.7)	2 (3.3)	4 (6.7)	2 (3.3)	2 (3.3)	4 (6.6)
Hyperchlorhydria	0	2 (3.3)	0	1 (1.6)	0	0
Nausea	2 (0.6)	2 (3.3)	2 (3.3)	0	1 (1.6)	1 (1.6)
Toothache	0	0	2 (3.3)	0	0	0
Vomiting	0	1 (1.6)	0	1 (1.6)	2 (3.3)	0
Infections and infestations	10 (2.8)	4 (6.6)	7 (11.7)	5 (8.2)	6 (9.8)	4 (6.6)
Folliculitis	1 (0.3)	0	0	0	2 (3.3)	0
Influenza	1 (0.3)	0	0	2 (3.3)	1 (1.6)	0
Nasopharyngitis	3 (0.8)	2 (3.3)	3 (5.0)	2 (3.3)	1 (1.6)	0
Upper respiratory tract infection	4 (1.1)	1 (1.6)	3 (5.0)	0	2 (3.3)	3 (4.9)
Urinary tract infection	1 (0.3)	1 (1.6)	1 (1.7)	2 (3.3)	1 (1.6)	1 (1.6)
Injury, poisoning and procedural complications	0	0	2 (3.3)	0	0	0
Laceration	0	0	2 (3.3)	0	0	0
Metabolism and nutrition disorders	4 (1.1)	3 (4.9)	2 (3.3)	6 (9.8)	5 (8.2)	21 (34.4)
Hypoglycaemia	3 (0.8)	3 (4.9)	2 (3.3)	3 (4.9)	5 (8.2)	21 (34.4)
Hypolipidaemia	1 (0.3)	0	1 (1.7)	3 (4.9)	0	0
Musculoskeletal and connective tissue disorders	3 (0.8)	2 (3.3)	0	1 (1.6)	3 (4.9)	3 (4.9)
Musculoskeletal pain	1 (0.3)	0	0	1 (1.6)	1 (1.6)	3 (4.9)
Myalgia	1 (0.3)	0	0	0	2 (3.3)	0
Pain in jaw	1 (0.3)	2 (3.3)	0	0	0	0
Nervous system disorders	5 (1.4)	2 (3.3)	2 (3.3)	3 (4.9)	2 (3.3)	1 (1.6)
Dizziness	2 (0.6)	1 (1.6)	2 (3.3)	1 (1.6)	0	1 (1.6)
Headache	3 (0.8)	2 (3.3)	1 (1.7)	2 (3.3)	2 (3.3)	0
Psychiatric disorders	0	0	0	2 (3.3)	0	0
Anxiety	0	0	0	2 (3.3)	0	0
Respiratory, thoracic and mediastinal disorders	2 (0.6)	0	1 (1.7)	1 (1.6)	2 (3.3)	2 (3.3)
Cough	1 (0.3)	0	0	0	2 (3.3)	0
Oropharyngeal pain	1 (0.3)	0	1 (1.7)	1 (1.6)	0	2 (3.3)
Skin and subcutaneous tissue disorders	1 (0.3)	0	0	1 (1.6)	2 (3.3)	0
Pruritus	1 (0.3)	0	0	1 (1.6)	2 (3.3)	0
Vascular disorders	0	1 (1.6)	2 (3.3)	0	2 (3.3)	0
Hypertension	0	1 (1.6)	2 (3.3)	0	2 (3.3)	0

Table 7. All-Causality Treatment-Emergent Adverse Events Occurring in ≥3 Subjects Across the Treatment Regimens

System Organ Class Preferred Term	Metformin Run-In (N=361) n (%)	Placebo (N=61) n (%)	PF-04937319 10 mg (N=60) n (%)	PF-04937319 50 mg (N=61) n (%)	PF-04937319 100 mg (N=61) n (%)	Titrated Glimepiride (N=61) n (%)

Subjects were counted only once per treatment in each row.
Includes 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=Number of subjects with AE; N=Total number of subjects evaluable for AEs.

Treatment related adverse events in ≥3 subjects by SOC are presented in Table 8.

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

System Organ Class Preferred Term	Metformin Run-In (N=361)	Placebo (N=61)	PF-04937319 10 mg (N=60)	PF-04937319 50 mg (N=61)	PF-04937319 100 mg (N=61)	Titrated Glimepiride (N=61)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Gastrointestinal disorders	3 (0.8)	3 (4.9)	2 (3.3)	0	1 (1.6)	5 (8.2)
Abdominal discomfort	0	0	0	0	0	1 (1.6)
Abdominal pain upper	0	0	0	0	0	1 (1.6)
Bowel movement irregularity	0	0	0	0	0	1 (1.6)
Diarrhoea	1 (0.3)	2 (3.3)	1 (1.7)	0	0	2 (3.3)
Dry mouth	1 (0.3)	0	0	0	0	1 (1.6)
Flatulence	1 (0.3)	0	1 (1.7)	0	0	0
Frequent bowel movements	0	0	0	0	1 (1.6)	0
Nausea	0	1 (1.6)	0	0	0	1 (1.6)
Investigations	0	3 (4.9)	1 (1.7)	1 (1.6)	0	0
Alanine aminotransferase increased	0	1 (1.6)	0	0	0	0
Aspartate aminotransferase increased	0	1 (1.6)	0	0	0	0
Blood bilirubin increased	0	0	1 (1.7)	1 (1.6)	0	0
Electrocardiogram QT prolonged	0	1 (1.6)	0	0	0	0
Hepatic enzyme increased	0	1 (1.6)	0	0	0	0
Metabolism and nutrition disorders	1 (0.3)	2 (3.3)	3 (5.0)	4 (6.6)	3 (4.9)	11 (18.0)
Hypochloraemia	0	1 (1.6)	1 (1.7)	0	0	0
Hypoglycaemia	0	1 (1.6)	2 (3.3)	1 (1.6)	3 (4.9)	11 (18.0)
Hypolipidaemia	1 (0.3)	0	1 (1.7)	3 (4.9)	0	0
Hyponatraemia	0	1 (1.6)	1 (1.7)	0	0	0

Subjects were counted only once per treatment in each row.
Includes all data collected since the first dose of sponsor-provided Metformin.
MedDRA (Version 16.0) coding dictionary applied.
AEs and SAEs are not separated.
AE=Adverse event; MedDRA=Medical Dictionary for Regulatory Activities; n=Number of subjects with AE; N=Total number of subjects evaluable for AEs.

A total of 9 subjects experienced an SAE during the study (Table 9) none of which were considered treatment-related by the investigator.

Table 9. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities)

System Organ Class Preferred Term	Metformin Run-In (N=361)	Placebo (N=61)	PF-04937319			Titrated Glimeperide (N=61)
			10 mg (N=60)	50 mg (N=61)	100 mg (N=61)	
Number of subjects with serious adverse events, n (%)	4 (1.1)	0	1 (1.7)	2 (3.3)	1 (1.6)	1 (1.6)
Cardiac disorders	0	0	1 (1.7)	0	0	1 (1.6)
Aortic valve incompetence	0	0	1 (1.7)	0	0	0
Cardiac failure congestive	0	0	0	0	0	1 (1.6)
General disorders and administration site conditions	1 (0.3)	0	0	0	0	0
Death	1 (0.3)	0	0	0	0	0
Infections and infestations	1 (0.3)	0	1 (1.7)	0	0	0
Cellulitis	0	0	1 (1.7)	0	0	0
Pneumonia	1 (0.3)	0	0	0	0	0
Sepsis syndrome	0	0	1 (1.7)	0	0	0
Injury, poisoning and procedural complications	0	0	0	1 (1.6)	0	0
Ankle fracture	0	0	0	1 (1.6)	0	0
Metabolism and nutrition disorders	1 (0.3)	0	0	0	0	0
Dehydration	1 (0.3)	0	0	0	0	0
Hyperglycaemia	1 (0.3)	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (0.3)	0	0	0	0	0
Pain in extremity	1 (0.3)	0	0	0	0	0
Nervous system disorders	1 (0.3)	0	0	0	0	0
Presyncope	1 (0.3)	0	0	0	0	0
Psychiatric disorders	1 (0.3)	0	0	0	0	0
Alcohol abuse	1 (0.3)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	0	0	0	1 (1.6)	0
Chronic obstructive pulmonary disease	0	0	0	0	1 (1.6)	0
Vascular disorders	0	0	1 (1.7)	1 (1.6)	0	0
Aortic aneurysm	0	0	1 (1.7)	0	0	0
Deep vein thrombosis	0	0	0	1 (1.6)	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.

A listing of permanent discontinuations due to AEs is provided in Table 10, and a listing of the permanent discontinuations due to insufficient clinical response is provided in Table 11.

Table 10. Permanent Discontinuations Due to Adverse Events

Serial Number	Treatment at Onset	Sex/ Age at Onset (Years)/ Race	MedDRA Preferred Term	Event Start/ Stop Day[a]	Severity/ Outcome	Causality
1	Metformin run-in	Female/63/ Black	Nephrolithiasis	1/184	Mild/ resolved	Other
2	Metformin run-in	Male/59/ Black	Blood glucose increased[b]	4/8	Mild/ resolved	Study drug
3	Metformin run-in	Female/69/ White	Abscess intestinal	27/65	Severe/ resolved	Other
4	Metformin run-in	Male/47/ Black	Pneumonia	53/60	Severe/ resolved	Other
5	Metformin run-in	Male/48/ White	Diarrhoea	7/>10	Moderate/ unknown	Study drug
6	Titrated glimepiride	Male/60/ White	Cardiac failure congestive	29/33[c]	Severe/ resolved	Other
7	Titrated glimepiride	Male/53/ White	Hypoglycaemia	48/48[c]	Moderate/ unknown	Study drug

MedDRA (Version 16.0) coding dictionary applied.
MedDRA=Medical Dictionary for Regulatory Activities.
a. Day relative to first day of treatment with sponsor-provided metformin.
b. Not deemed 'insufficient clinical response' since withdrawal was pre randomization.
c. Day relative to first dose of randomized treatment (ie, Visit 4, Day 1).

Table 11. Permanent Discontinuations due to Insufficient Clinical Response

Serial Number	Treatment	Sex/ Age at Onset (Years)/ Race	Duration of Dosing With Blinded Treatment Before Decision to Withdraw (Days)
1	Placebo	Male/ 43/ White	58
2	PF-04937319 10 mg	Male/ 65/ White	15
3	PF-04937319 50 mg	Male/ 52/ Asian	19
4	PF-04937319 50 mg	Female/ 59/ White	56
5	PF-04937319 50 mg	Female/ 63/ White	28
6	PF-04937319 100 mg	Female/ 54/ White	73
7	PF-04937319 100 mg	Male/ 54/ Asian	51

CONCLUSIONS:

- PF-04937319 at doses of 50 and 100 mg QD demonstrated clinically relevant effect on HbA_{1C} and FPG at Week 12 in this study; this effect was lower than that observed with titrated glimepiride.

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