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COMPOUND NUMBER: PF-00232798

PROTOCOL NO.: A7691009

PROTOCOL TITLE: A Randomised, Double-Blind, Placebo-Controlled, Multicentre Study in Asymptomatic HIV-Infected Patients to Investigate the Pharmacodynamics, Pharmacokinetics, Safety and Toleration of PF-00232798

Study Centers: Two (2) centers in Germany took part in the study and enrolled subjects.

Study Initiation and Final Completion Dates: 27 June 2007 to 15 September 2008

Phase of Development: Phase 2

Study Objectives:

- To investigate the effects of PF-00232798, 10-day monotherapy, on viral load response in asymptomatic human immunodeficiency virus (HIV)-infected subjects and to assess its dose-response relationship.
- To assess the pharmacokinetics (PK), safety and tolerability of PF-00232798 in HIV-infected subjects.

METHODS

Study Design: This was a randomized, double-blind, parallel group study, to investigate the viral load response effects, dose-response relationship, PK/pharmacodynamics (PD), safety and tolerability of PF-00232798, 10-day monotherapy, in asymptomatic HIV-infected subjects.

The study consisted of 2 stages; Stage 1 was double-blind (subject- and Investigator-blind) with a placebo control, while Stage 2 was double-blind but Sponsor-open.

- Stage 1 subjects were randomized to 1 of 4 treatment regimes (n = number of subjects planned):
  - Placebo (n = 2)
  - 5 mg once daily (QD) PF-00232798 (Fasted; n = 6)
  - 20 mg QD PF-00232798 (Fasted; n = 6)

- 150 mg QD PF-00232798 (Fasted; n = 6)

- Stage 2 subjects were randomized to 1 of 3 treatment regimes:
  - 40 mg QD PF-00232798 (Fasted; n = 8)
  - 300 mg QD PF-00232798 (Fasted; n = 8)
  - 400 mg QD PF-00232798 (Fasted; n = 8)

After the screening period (21 to 45 days prior to randomization), subjects were randomized to a treatment regimen and returned for 17 visits. On Days 1 to 9, subjects were admitted to the clinic in the morning (or evening prior to Day 1) and were discharged after 4 hours following dosing and sampling. On Day 10 subjects were admitted to the clinic in the morning (or in the evening of Day 9) and were discharged 12 hours following dosing, returning for sampling on the mornings of Days 11 to 13, 15, 19, 22 and 25 (follow-up visit).

Evaluations included blood for PF-00232798 PK analysis, HIV viral load isolation and tropism, hepatitis C virus (HCV) ribonucleic acid (RNA) and electrocardiogram (ECG), blood pressure (BP) and pulse rate measurements. The study schedule is presented in Table 1.

Table 1. Study Schedule

Protocol Activity	Screen	Randomization	Day 1	Day 2	Day 3	Day 4-6	Day 7	Day 8-9	Day 10	Day 11	Day 12	Day 13	Day 15	Day 19	Day 22	Follow -up
Informed consent	X															
Medical history	X		X[a,b]													
Physical examination	X		X[b]							X						X
Safety laboratory	X	X	X[b]		X[b]		X[b]			X			X			X
Urine drug test	X	X	X[b]						X							
Breath alcohol test			X[b]						X							
CD4 count	X															
Viral serology[c]	X															
Viral tropism sample	X		X[b]							X						X
HCV viral load[d]			X[b]							X						X
Pharmacogenomic sample			X[b]													
Viral isolation			X[b]							X						X
HIV viral load measurement	X	X	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X	X	X	X	X	X	X
Supine and standing BP and pulse rate	X		X[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[e]	X						X
ECG	X		X[e]	X[b]	X[b]	X[b]	X[b]	X[b]	X[e]	X						X
Study drug administration			X	X	X[b]	X[b]	X[b]	X[b]	X							
PF-00232798 PK blood sampling			X[b]	X[b]	X[b]	X[b]	X[b]	X[b]	X[f]		X[g]	X[g]	X[g]			
AE monitoring	X															
Concomitant medication	X															

AE = adverse event; BP = blood pressure; CD4 = cluster of differentiation 4; ECG = electrocardiogram; HCV = hepatitis C virus; HIV = human immunodeficiency virus; PK = pharmacokinetic; RNA = ribonucleic acid.

a. Reviewed changes since screening.
b. Predose only.
c. HIV, Hepatitis B virus and HCV serology.
d. HCV RNA only if screening HCV was positive.
e. -1.5, -1.0, -0.5 hour predose; 1, 2, 3 and 4 hours postdose.
f. Predose 1, 2, 3, 4, 6, 8, 12 and 24 hours postdose.
g. Day 12, 13 and 15 PK samples collected in the morning.

Number of Subjects (Planned and Analyzed): Twenty subjects were planned and analyzed in Stage 1; 24 subjects were planned and 23 analyzed in Stage 2.

Diagnosis and Main Criteria for Inclusion: Asymptomatic HIV-1 male subjects aged between 18 and 55 years with human chemokine receptor 5 (CCR5) tropic virus as determined by the Monogram Phenosense Entry assay. Exclusion criteria included subjects who had received any experimental drug within the past 4 months (prior to the first dosing day of the study) or who had previously received another CCR5 antagonist, or evidence of decompensated liver disease.

Study Treatment: Study drug was administered QD as an oral solution (≤240 mL) for 10 days starting at Day 1. Stage 1 subjects were randomized to 1 of 4 treatment regimes (placebo, 5 mg QD, 20 mg QD or 150 mg QD PF-00232798). Stage 2 subjects were randomized to 1 of 3 treatment regimes (40 mg QD, 300 mg QD or 400 mg QD PF-00232798). Subjects were required to fast for 8 hours prior to their dose of study drug; taken between 07:00 and 10:00.

Pharmacodynamic, Pharmacokinetic and Safety Endpoints:

Primary Endpoint: Viral load.

Secondary Endpoints:

- PF-00232798 steady state PK: Day 10 maximum plasma concentration (C_{max}), time for C_{max} (T_{max}), and area under the plasma concentration-time profile from time 0 to the time = 24 hours postdose (AUC_{24});
- PF-00232798 safety and toleration.

No efficacy evaluations were performed during this study.

Safety Evaluations: Adverse events (AEs), safety laboratory assessments and vital signs were recorded during the study.

Statistical Methods:

Analysis Sets:

Pharmacokinetic Analysis Set:

- Concentration Analysis Set: The PK concentration population was defined as all subjects randomized and treated who had at least 1 postdose concentration in the study.
- Parameter Analysis Set: The PK parameter analysis population was defined as all subjects randomized and treated who had at least 1 of the PK parameters of interest in the study.

Pharmacodynamic Analysis Set:

- Analysis Set: The PD population was defined as all subjects who were randomized and treated, and who had at least 1 postdose HIV viral load measurement in the study.

- Modeling Analysis Set: The PD modeling analysis population was defined as all subjects who were randomized and treated, and who had HIV viral load assessments available for Baseline and Day 11.

Safety Analysis Set: All subjects who received at least 1 dose of study medication were included in the safety analyses and listings.

The primary endpoint was the change in HIV viral load from Baseline to Day 11, performed on those subjects who were randomized, treated and had HIV viral load values both predose and Day 11. Prior to analysis, the HIV viral load data was $\log_{10}$ transformed, and the change from Baseline to Day 11 was calculated. Baseline $\log_{10}$ HIV viral load values were calculated as the arithmetic mean of the 3 predose values (screening, randomization and pre-first dose). The primary analysis method was maximum effect attributable to the drug (E_{max}) dose response model. No formal statistical analysis of safety or PK data was planned. PK/PD modeling analysis was planned and reported separately.

RESULTS

Subject Disposition and Demography: Subject disposition is summarized in Table 2. The study was completed in 2 stages; Stage 1: PF-00232798 5, 20, 150 mg and placebo; Stage 2: PF-00232798 40, 300 and 400 mg. Overall, 43 subjects were assigned and treated with study drug, and 42 subjects completed the study. One subject discontinued from the study due to an AE.

Table 2. Subject Disposition

	PF-00232798 (mg)						Placebo
	5	20	40	150	300	400	
Number of subjects							
Assigned to study treatment	6	6	8	6	8	7	2
Treated	6	6	8	6	8	7	2
Completed	6	5	8	6	8	7	2
Discontinued	0	1	0	0	0	0	0
Adverse event		1					
Analyzed for PK							
Concentration	6	6	8	6	8	7	0
Parameter	6	5	8	6	8	7	0
Analyzed for safety							
Adverse events	6	6	8	6	8	7	2
Laboratory data	6	6	8	6	8	7	2

PK = pharmacokinetics.

All subjects were male with an age range 22-53 years; age ranges within each dose group were similar. Demographic characteristics are summarized in Table 3.

Table 3. Demographic Characteristics

	PF-00232798 (mg)						Placebo
	5	20	40	150	300	400	
Number of subjects	6	6	8	6	8	7	2
Age (years)							
Mean (SD)	31.5 (8.9)	39.8 (8.5)	36.5 (5.4)	36.2 (9.1)	36.1 (9.6)	32.9 (5.0)	29.0 (5.7)
Range	22-46	27-49	26-45	23-49	24-53	26-41	25-33
Race							
White	6	5	8	6	8	6	2
Other	0	1	0	0	0	1	0
Body mass index (kg/m^2)							
Mean (SD)	22.9 (2.1)	22.3 (2.5)	22.3 (3.1)	22.4 (1.2)	24.9 (1.8)	23.8 (3.0)	25.2 (5.2)
Range	20.9-26.4	18.3-25.9	18.7-28.3	21.0-24.2	22.4-28.5	19.7-28.9	21.6-28.9

SD = standard deviation.

Pharmacodynamic and Pharmacokinetic Results:

Pharmacodynamic Results:

Dose-Response Model: The primary endpoint was the change in viral load from Baseline to Day 11 in $\log_{10}$ scale. The pharmacodynamic modeling dataset was defined as all subjects having both valid Baseline and Day 11 viral load measurements. Descriptive statistics for the changes in $\log_{10}$ viral load from Baseline to Day 11 (or nadir) are shown in Table 4 and Table 5. The primary statistical analysis consisted of a 4-parameter E_{max} model fit to the dose response data. Bayesian methodology was used with information from QD regimens in 2 maraviroc studies as prior information in the model. The parameter estimates (median and credible interval) for E_{max}, median effective dose ($ED50_{maraviroc}$) and relative potency ($ED50_{PF232}$ = $ED50_{maraviroc}$/ relative potency) were 1.71 (1.51, 1.94), 32.49 (15.15, 71.63) and 3.07 (1.19, 7.97), respectively.

Viral Load Change From Baseline: Log_{10} HIV viral load changes from Baseline to Day 11 are summarized in Table 4. Median change from Baseline to Day 11 in $\log_{10}$ viral load increased with increasing PF-00232798 dose up to 400 mg PF-00232798 (Table 4). A similar dose-dependent response was observed for change from Baseline to nadir (Table 5). Subject's cluster of differentiation 4 (CD4) count at Screening appeared to have no effect on their subsequent viral load mean change from Baseline.

Table 4. Descriptive Statistics for Log_{10} Viral Load Changes From Baseline to Day 11 for all Dose Groups (PD Population)

Dose Group (QD)	N	Arithmetic Mean Change From Baseline in Viral Load (SD) (copies/mL)	Median	Min, Max
Placebo	2	-0.14 (0.01)	-0.13	-0.14, -0.13
5 mg PF-00232798	6	-0.25 (0.33)	-0.19	-0.79, 0.12
20 mg PF-00232798	5	-0.69 (0.43)	-0.82	-1.13, -0.06
40 mg PF-00232798	8	-0.92 (0.43)	-1.02	-1.53, -0.27
150 mg PF-00232798	6	-1.33 (0.39)	-1.25	-1.94, -0.89
300 mg PF-00232798	8	-1.55 (0.30)	-1.46	-2.09, -1.21
400 mg PF-00232798	7	-1.49 (0.51)	-1.61	-1.92, -0.43

Max = maximum; Min = minimum; N= number of evaluable subjects; PD = pharmacodynamic; QD = once daily; SD = standard deviation.

Table 5. Descriptive Statistics for Log_{10} Viral Load Changes From Baseline to Nadir for all Dose Groups (PD Population)

Dose Group (QD)	N	Arithmetic Mean Change From Baseline (SD) (copies/mL)	Median	Min, Max
Placebo	2	-0.17 (0.06)	-0.17	-0.21, -0.13
5 mg PF-00232798	6	-0.42 (0.27)	-0.33	-0.79, -0.11
20 mg PF-00232798	5	-0.89 (0.45)	-0.94	-1.46, -0.36
40 mg PF-00232798	8	-1.27 (0.47)	-1.36	-1.81, -0.41
150 mg PF-00232798	6	-1.43 (0.37)	-1.49	-1.94, -0.99
300 mg PF-00232798	8	-1.79 (0.37)	-1.77	-2.36, -1.35
400 mg PF-00232798	7	-1.67 (0.46)	-1.80	-1.97, -0.67

Max = maximum; Min = minimum; N = number of evaluable subjects; PD = pharmacodynamic; QD = once daily; SD = standard deviation.

Time to Rebound of Viral Load: The time to rebound of HIV viral load is summarized in Table 6. There was a quicker viral load rebound with lower doses with slow rise in viral load with higher doses.

Table 6. Summary of Time to Rebound of HIV Viral Load (PD Population)

Dose Group (QD)		Number of Subjects						
		Time to Rebound (Days)						
	N	2	3	5	9	12	15	None
Placebo	2	1	0	0	0	0	0	1
5 mg PF-00232798	6	1	1	3	0	0	0	1
20 mg PF-00232798	5	0	0	0	1	2	1	1
40 mg PF-00232798	8	0	0	0	2	0	0	6
150 mg PF-00232798	6	0	0	0	1	0	1	4
300 mg PF-00232798	8	0	0	0	1	0	1	6
400 mg PF-00232798	7	0	0	0	0	1	0	6

The time to rebound of viral load was calculated as the time from the last dose to the time of the first occasion at which the viral load was greater than the baseline value.
HIV = human immunodeficiency virus; N =number of evaluable subjects; PD = pharmacodynamic; QD = once daily.

Pharmacokinetic Results: Consistent with the median PF-00232798 profiles, steady-state (Day 10) exposure to PF-00232798 increased with increasing doses (Table 7). Increases in steady-state exposure were non-linear to increases in dose following administration of doses ranging from 5 to 400 mg as an 80-fold increase in dose led to a 155-fold increase in

exposure; however, increases in exposure following administration of 150 mg or greater were approximately proportional with a 2.7-fold increase in dose, which led to a 2.4-fold increase in exposure.

PF-00232798 absorption was rapid on Day 10, with median T_{max} values ranging from 1-6 hours postdose across all doses (Table 7). Following attainment of C_{max}, plasma concentrations exhibited a multi-phasic decline over time. Inter-subject variability, as measured by %CV, was moderate to high for AUC_{24} (41%-64%) and C_{max} (31%-100%) with the exception of the 300 mg dose group, where variability was low (19% for AUC_{24} and 8% for C_{max}). In general, steady-state appeared to have been achieved by study Day 5 for all doses studied.

Median plasma concentrations at steady state were sustained for at least 24 hours above the protein-binding adjusted in vitro concentration of drug needed to reduce HIV replication in cell culture by 90% (IC_{90}) (21.2 ng/mL) for doses ≥40 mg. For the 2 highest dose levels (300 and 400 mg), these levels were sustained for at least 120 hours. Median plasma concentrations at steady state were sustained for at least 24 hours above 10 times the protein-binding adjusted in vitro IC_{90} (ie, 212 ng/mL) for doses ≥300 mg.

Table 7. Summary of PF-00232798 Plasma Pharmacokinetic Parameters on Day 10

Parameter (Units)[a]	PF-00232798 Dose					
	5 mg	20 mg	40 mg	150 mg	300 mg	400 mg
N	6	5	8	6	8	7
AUC_{24} (ng•hr/mL)	265.3 (59)	1157.4 (64)	2945.1 (47)	17319.1 (41)	28347.9 (19)	41027.3 (45)
C_{max} (ng/mL)	25.21 (49)	185.6 (100)	379.3 (54)	2676 (31)	3793 (8)	4803 (40)
T_{max} (hr)	3.00 (1.00–6.00)	1.03 (1.00–3.00)	4.00 (1.00–4.00)	3.04 (2.00–4.00)	2.00 (2.00–4.00)	2.00 (1.00–3.00)
C_{24} (ng/mL)	4.321 (71)	18.80 (53)	46.48 (60)	187.8 (63)	343.3 (37)	519.5 (45)

AUC_{24} = area under the plasma concentration-time profile from time 0 to the time =24 hours postdose; C_{max} = maximum plasma concentration; C_{24} = concentration at Time =24 hours postdose; N = number of evaluable subjects; T_{max} = time for C_{max}.

a. Geometric mean (%CV) for AUC_{24}, C_{max}, and C_{24}; median (range) for T_{max}.

Safety Results:

Adverse Events: All causality and treatment-related treatment-emergent AEs are summarized in Table 8. Overall, 32 subjects (74.4%) experienced at least 1 AE during the study. The number of AEs did not increase with increasing PF-00232798 dose; the highest number of AEs (15) occurred in the PF-00232798 40 mg dose group. The highest number of treatment-related AEs (11) occurred in the PF-00232798 40 and 300 mg dose groups.

Table 8. Treatment-Emergent All-Causality (Treatment-Related) Adverse Events

	PF-00232798						Placebo
	5 mg (N=6)	20 mg (N=6)	40 mg (N=8)	150 mg (N=6)	300 mg (N=8)	400 mg (N=7)	(N=2)
Subjects evaluable for AEs	6	6	8	6	8	7	2
Number of AEs	3 (2)	12 (5)	15 (11)	9 (4)	11 (11)	9 (7)	6 (3)
Number of mild AEs	2 (2)	8 (5)	12 (11)	8 (4)	10 (10)	6 (5)	3 (2)
Number of moderate AEs	1 (0)	4 (0)	3 (0)	1 (0)	1 (1)	3 (2)	3 (1)
Number of severe AEs	0	0	0	0	0	0	0
Number of subjects with AEs	2 (2)	6 (4)	7 (6)	5 (4)	6 (6)	4 (3)	2 (2)
Number of subjects with SAEs	0	1 (0)	0	0	0	1 (0)	0
Number of subjects discontinuing due to AEs	0	1 (0)	0	0	0	0	0

AEs and SAEs are not separated out.
Treatment-related events in parentheses.
AE = adverse event; N = total number of subjects; SAE = serious adverse event.

The incidence of all-causality non serious AEs by system organ class (SOC) and preferred term are summarized in Table 9. AEs classified as nervous system disorders were the most frequently reported across all dose groups. AEs classified as gastrointestinal disorders were the most frequently reported for the 400 mg PF-00232798 dose group and general disorders and administration site conditions for the 300 mg PF-002232798 dose group.

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

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v11.0) Preferred Term	PF-00232798						Placebo
	5 mg n (%)	20 mg n (%)	40 mg n (%)	150 mg n (%)	300 mg n (%)	400 mg n (%)	n (%)
Number % of subjects							
Evaluable for adverse events	6	6	8	6	8	7	2
With adverse events	2 (33.3)	6 (100.0)	7 (87.5)	5 (83.3)	6 (75.0)	3 (42.9)	2 (100.0)
Ear and labyrinth disorders	0	0	1 (12.5)	0	0	0	0
Vertigo	0	0	1 (12.5)	0	0	0	0
Eye disorders	0	0	0	0	0	0	1 (50.0)
Panophthalmitis	0	0	0	0	0	0	1 (50.0)
Gastrointestinal disorders	1 (16.7)	3 (50.0)	2 (25.0)	2 (33.3)	1 (12.5)	3 (42.9)	0
Abdominal pain upper	0	0	0	2 (33.3)	0	0	0
Constipation	1 (16.7)	1 (16.7)	0	0	0	0	0
Diarrhoea	0	1 (16.7)	1 (12.5)	0	0	1 (14.3)	0
Dry mouth	0	1 (16.7)	0	0	0	0	0
Flatulence	0	0	0	0	1 (12.5)	1 (14.3)	0
Gastric disorder	0	0	1 (12.5)	0	0	0	0
Nausea	0	0	1 (12.5)	0	0	0	0
Vomiting	0	0	0	0	0	1 (14.3)	0
General disorders and administration site conditions	0	2 (33.3)	3 (37.5)	0	5 (62.5)	2 (28.6)	0
Chest pain	0	1 (16.7)	0	0	0	0	0
Fatigue	0	1 (16.7)	2 (25.0)	0	4 (50.0)	0	0
Hunger	0	0	1 (12.5)	0	2 (25.0)	2 (28.6)	0
Infections and infestations	1 (16.7)	2 (33.3)	1 (12.5)	2 (33.3)	0	0	2 (100.0)
Fungal skin infection	0	0	1 (12.5)	0	0	0	0
Hordeolum	0	0	0	1 (16.7)	0	0	0
Lymphangitis	0	1 (16.7)	0	0	0	0	0
Nasopharyngitis	0	1 (16.7)	0	2 (33.3)	0	0	1 (50.0)
Tinea pedis	0	0	0	0	0	0	1 (50.0)
Urinary tract infection	1 (16.7)	0	0	0	0	0	0
Investigations	0	0	0	0	1 (12.5)	0	0
Transaminases abnormal	0	0	0	0	1 (12.5)	0	0
Metabolism and nutrition disorders	0	0	0	0	1 (12.5)	0	0
Anorexia	0	0	0	0	1 (12.5)	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (12.5)	0	0	0	0
Flank pain	0	0	1 (12.5)	0	0	0	0
Nervous system disorders	1 (16.7)	3 (50.0)	4 (50.0)	3 (50.0)	0	2 (28.6)	2 (100.0)
Dizziness	0	2 (33.3)	0	0	0	0	0
Headache	0	1 (16.7)	3 (37.5)	2 (33.3)	0	2 (28.6)	1 (50.0)
Hypersomnia	1 (16.7)	0	0	1 (16.7)	0	0	1 (50.0)
Migraine	0	0	1 (12.5)	0	0	1 (14.3)	1 (50.0)
Psychiatric disorders	0	0	0	0	1 (12.5)	0	0
Sleep disorder	0	0	0	0	1 (12.5)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (16.7)	1 (12.5)	0	0	0	0
Dyspnoea	0	0	1 (12.5)	0	0	0	0
Nasal congestion	0	1 (16.7)	0	0	0	0	0
Skin and subcutaneous tissue disorders	0	0	1 (12.5)	1 (16.7)	0	0	0
Rash	0	0	1 (12.5)	1 (16.7)	0	0	0
Vascular disorders	0	0	0	0	1 (12.5)	0	0
Hot flush	0	0	0	0	1 (12.5)	0	0

Subjects are only counted once per treatment for each row.
Includes data up to 10 days after last dose of study drug.
MedDRA (v11.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

The incidence of treatment-related AEs by preferred term is summarized in Table 10.

Table 10. Incidence of Treatment-Emergent Adverse Events (Treatment Related)

Number of Subjects with Adverse Events by: System Organ Class and MedDRA (v11.0) Preferred Term	PF-00232798						Placebo
	5 mg (n=6)	20 mg (n=6)	40 mg (n=8)	150 mg (n=6)	300 mg (n=8)	400 mg (n=7)	(n=2)
Ear and labyrinth disorders	0	0	1	0	0	0	0
Vertigo	0	0	1	0	0	0	0
Gastrointestinal disorders	1	2	2	1	1	2	0
Abdominal pain upper	0	0	0	1	0	0	0
Constipation	1	1	0	0	0	0	0
Diarrhoea	0	0	1	0	0	0	0
Dry mouth	0	1	0	0	0	0	0
Flatulence	0	0	0	0	1	1	0
Gastric disorder	0	0	1	0	0	0	0
Nausea	0	0	1	0	0	0	0
Vomiting	0	0	0	0	0	1	0
General disorders and administration site conditions	0	1	3	0	5	2	0
Fatigue	0	1	2	0	4	0	0
Hunger	0	0	1	0	2	2	0
Investigations	0	0	0	0	1	0	0
Transaminases abnormal	0	0	0	0	1	0	0
Metabolism and nutrition disorders	0	0	0	0	1	0	0
Anorexia	0	0	0	0	1	0	0
Musculoskeletal and connective tissue disorders	0	0	1	0	0	0	0
Flank pain	0	0	1	0	0	0	0
Nervous system disorders	1	2	3	3	0	2	2
Dizziness	0	1	0	0	0	0	0
Headache	0	1	3	2	0	2	1
Hypersomnia	1	0	0	1	0	0	1
Migraine	0	0	0	0	0	1	1
Psychiatric disorders	0	0	0	0	1	0	0
Sleep disorder	0	0	0	0	1	0	0
Vascular disorders	0	0	0	0	1	0	0
Hot flush	0	0	0	0	1	0	0

Adverse events and serious adverse events are not separated out.
Subjects are only counted once per treatment for each row.
Includes data up to 10 days after last dose of study drug.
MedDRA (v11.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Serious Adverse Events: Two SAEs were reported during the study. Neither SAE was considered related to study treatment. The treatment-emergent SAEs are summarized in Table 11.

Table 11. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All-Causalities)

Number (%) of Subjects With Adverse Events by: System Organ Class and MedDRA (v11.0) Preferred Term	PF-00232798						Placebo
	5 mg n (%)	20 mg n (%)	40 mg n (%)	150 mg n (%)	300 mg n (%)	400 mg n (%)	n (%)
Number % of subjects							
Evaluable for adverse events	6	6	8	6	8	7	2
With adverse events	0	1 (16.7)	0	0	0	1 (14.3)	0
Gastrointestinal disorders	0	0	0	0	0	1 (14.3)	0
Anal haemorrhage	0	0	0	0	0	1 (14.3)	0
Vascular disorders	0	1 (16.7)	0	0	0	0	0
Angiopathy	0	1 (16.7)	0	0	0	0	0

Subjects are only counted once per treatment for each row.
Includes data up to 10 days after last dose of study drug.
MedDRA (v11.0) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects.

Permanent Discontinuations due to Adverse Events: One subject permanently discontinued from the study due to 3 concurrent AEs (chest pain, dizziness and angiopathy), as summarized in Table 12.

Table 12. Discontinuations due to Adverse Events

Serial No. (Sex/Age [Years])	Preferred Term	Treatment at Onset	Severity	Outcome	Related	SAE
1 (Male/33)	Chest pain	PF-00232798 20 mg	Moderate	Resolved	No	No
	Dizziness		Moderate	Resolved	No	No
	Angiopathy		Moderate	Ongoing	No	Yes

SAE = serious adverse event.

Dose Reductions or Temporary Discontinuations due to Adverse Events: There were no dose reductions or temporary discontinuations due to AEs during the study.

Deaths: There were no deaths reported during this study.

Laboratory Evaluations: One subject experienced an AE of abnormal transaminases on Day 1 prior to dosing and again on Day 3 while receiving 300 mg PF-00232798. The AE postdose was considered moderate in intensity and related to study drug by the Investigator. Test results had returned to normal by Day 11.

No subjects had supine or standing BP value of <90 mmHg or a supine or standing diastolic BP value of <50 mmHg. One subject had at least 1 supine pulse rate value of >120 bpm and at least 1 standing pulse rate value of >140 bpm while receiving 150 mg PF-00232798.

The maximum Fridericia corrected QT interval (QTcF) interval recorded was <450 msec for all dose groups. No subject had a PR interval or QRS complex change of ≥25%/50% or a maximum PR interval increase of ≥300 msec.

CONCLUSIONS:

- Median change from Baseline to Day 11 in $\log_{10}$ viral load increased with increasing doses of PF-00232798 up to 400 mg.

- From the dose-response model, the E_{max} parameter for log viral load decrease from Baseline to Day 11 was over 1.70. For higher doses, 300 and 400 mg QD, the mean log viral load decrease from the model was 1.53 and 1.57, and the majority of subjects at these doses would be predicted to achieve 1.5 log viral load decrease.

- PF-00232798 was safe and well tolerated when administered once daily for 10 days at dose levels up to 400 mg in asymptomatic HIV-infected subjects.

- Increases in steady-state exposure were non-linear to increases in dose following administration of doses ranging from 5 to 400 mg as an 80-fold increase in dose led to a 155-fold increase in exposure; however, increases in exposure following administration of 150 mg or greater were approximately proportional with a 2.7-fold increase in dose, which led to a 2.4-fold increase in exposure.