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COMPOUND NUMBER: PF-00489791

PROTOCOL NO.: A7331010

PROTOCOL TITLE: A Phase 2A Randomized Double-Blinded, Placebo and Active Controlled Two Cohort Two Doses Cross-Over Multi-Center Clinical Study to Assess Efficacy of a Once Daily Administration of a Phosphodiesterase 5 Inhibitor (PF-00489791) for the Treatment of Vasospasm in Primary and Secondary Raynaud's Phenomenon

Study Centers: In total, 49 centers took part in the study and randomized subjects: Canada (4), Columbia (4), Czech Republic (3), Germany (1), Hungary (3), Republic of Korea (3), Mexico (3), Poland (2), Spain (3), Sweden (3), and the United States (20).

Study Initiation and Completion Dates: 04 August 2010 to 31 May 2011

Phase of Development: Phase 2a

Study Objectives:

Primary Objective: To evaluate the efficacy of different doses of PF-00489791 on the Raynaud's condition score (RCS) in primary Raynaud's phenomenon (PRP) and secondary Raynaud's phenomenon (SRP) subjects.

Secondary Objectives:

- To evaluate the efficacy of different doses of PF-00489791 on the frequency of Raynaud's phenomenon (RP) attacks in PRP and SRP subjects;
- To evaluate the efficacy of different doses of PF-00489791 on the total duration of RP attacks in PRP and SRP subjects;
- To evaluate the efficacy of different doses of PF-00489791 on the Raynaud's pain score in PRP and SRP subjects;
- To evaluate the efficacy of different doses of PF-00489791 on the ulcer counts and scores in SRP subjects.

METHODS

Study Design: This was a randomized, double-blind, placebo-controlled, crossover, multicenter study in subjects with PRP and SRP using 2 doses of PF-00489791 (ie, 4 mg and 20 mg). PRP and SRP subjects were stratified and enrolled into separate groups for analysis.

An interim analysis was performed when 24 subjects in each of the four 2 × 2 crossover cohorts had completed both study periods, and Baseline and Day 84 visit data were available. The schedule of activities is presented in Table 1.

Table 1. Schedule of Activities

Protocol Activity	**Screen**	**Run-in**			**Period 1 Treatment**					**Wash-out**	**Period 2 Treatment**				**Run-out**	**Follow-Up**
Day	**-14**	**0±2**		**1-13 ±2**	**14±2**		**28±2**	**42±2**		**43-55 ±2**	**56±2**		**70±2**	**84±2**	**85-97 ±2**	**98±2**
Hour		**0**	**4-6[a]**		**0**	**4-6[a]**	**0**	**0**	**4-6[a]**		**0**	**4-6[a]**	**0**	**0**		
Informed consent	X															
General medical history including alcohol, smoking, and drug use	X															
Physical examination[b]	X	X			X			X	X		X		X	X		X
Raynaud's Phenomenon Attack Number Screen	X	X			X											
Modified Allen's test for SRP subjects	X															
Height and weight	X															
Laboratory assessments																
HbA1c[c], HIV antibody[d]	X															
HBsAg[e], HCV antibody[f]	X															
Hematology, blood chemistry	X				X				X		X			X		X
Urinalysis	X				X						X					X
Pregnancy test[g]	X				X						X					X
Assessments																
Supine BP and pulse rate measurement	X	X	X		X	X	X	X	X		X	X	X	X		X
Standing BP and pulse rate measurement	X	X	X		X	X		X	X		X	X				X
12-lead ECG	X	X	X		X	X		X	X		X	X				
Sample banking of plasma cGMP					X		X	X			X		X	X		
Treatments/pharmacokinetics																

Table 1. Schedule of Activities

Protocol Activity	**Screen**	**Run-in**			**Period 1 Treatment**					**Wash-out**	**Period 2 Treatment**				**Run-out**	**Follow-Up**
Day	**-14**	**0±2**		**1-13 ±2**	**14±2**		**28±2**	**42±2**		**43-55 ±2**	**56±2**		**70±2**	**84±2**	**85-97 ±2**	**98±2**
Hour		**0**	**4-6[a]**		**0**	**4-6[a]**	**0**	**0**	**4-6[a]**		**0**	**4-6[a]**	**0**	**0**		
Registration		X														
Randomization					X											
Study medication administration[h]		X		X	X		X	X		X	X		X	X	X	
PK/metabolite sample					X		X	X			X		X	X		
Efficacy assessment																
Daily diary[i]		X			X		X	X			X		X	X		X
Ulcer assessment[j]	X	X			X		X	X			X		X	X		X
Concomitant medication recording	X	X			X		X	X			X		X	X		X
Calcium channel blocker use	X	X			X		X	X			X		X	X		X
Adverse event recording	X----------→X															

BP = blood pressure; cGMP = cyclic guanosine 5'-monophosphate; ECG = electrocardiogram; HbA1c: glycosylated hemoglobin; HbaAG: hepatitis B surface antigen; HCV: hepatitis C virus; HIV: human immunodeficiency virus; IEC = Independent Ethics Committee; IRB: Institutional Review Board: PK = pharmacokinetics; SRP: secondary Raynaud's phenomenon.

a. Subjects remained at the study site while awaiting the postdose assessments.
b. Complete physical examination at the screening and follow-up visits; limited physical examination was done at all other time points.
c. On the screening day only for diabetic subjects.
d. On the screening day only for subjects without current (<1 year) documentation of HIV serology.
e. On the screening day only for subjects without current (<1 year) documentation of hepatitis B antigen levels.
f. On the screening day only for subjects without current (<1 year) documentation of hepatitis C serology.
g. Urine pregnancy tests were done in the study site; pregnancy tests might have been repeated at the Investigator's discretion, per request of IRB/IECs, or if required by local regulations.
h. The first dose of each 14-day cycle of study medications was administered in the study site. A medication diary was given to subjects at this time to record their study drug usage on subsequent days. Diaries were reviewed at each subsequent study site visit.
i. Raynaud's diaries were provided at each study site visit starting at the screening visit and were collected at each subsequent visit; diaries were reviewed at each study site visit for completeness and legibility.
j. A complete assessment was done for each ulcer by the same evaluator; if a subject developed an ulcer during the course of the study, an ulcer assessment was required to be initiated.

Number of Subjects (Planned and Analyzed): The planned enrollment was a total of 104 subjects with PRP and 104 subjects with SRP. In total 113 PRP and 130 SRP subjects were randomized and 102 PRP and 122 SRP subjects were treated and analyzed.

Diagnosis and Main Criteria for Inclusion: Male and female subjects aged 18 to 65 years with Active RP and stable disease and medication requirements over the previous 2 months. For SRP subjects, a diagnosis of scleroderma using the American College of Rheumatology criteria or by the presence of at least 3/5 features of calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia (CREST) syndrome was required.

Exclusion Criteria: Uncontrolled hypertension, diabetes mellitus, angina, or using oral nitrates. Smoking within 3 months or smoking cessation using nicotine products. Subjects currently taking sildenafil, tadalafil or vardenafil. Subjects with ulnar arterial occlusive disease as shown by a modified Allen test. Pregnant or breast feeding subjects or those considering pregnancy in next 4 months. Participation in a trial for an investigational drug within 30 days of study entry.

Study Treatment: All randomized subjects received PF-00489791 4 mg or 20 mg orally for 4 weeks either during Treatment Period 1 or Treatment Period 2. Subjects received placebo for the remainder of the study (ie, alternately with Treatment Period 1 or Treatment Period 2). To maintain the blind, subjects received 2 tablets of 2 mg, 2 tablets of 10 mg, or 2 tablets of matching placebo. Subjects were randomized to 1 of the 4 groups at a 1:1:1:1 ratio as noted on the study schema (Table 2).

Table 2. Study Schema

Group	Placebo Run-in	Treatment Period 1	Placebo Washout	Treatment Period 2	Placebo Run-out
1	X[a]	PF-00489791 4 mg	X[a]	X[a]	X[a]
2	X[a]	X[a]	X[a]	PF-00489791 4 mg	X[a]
3	X[a]	PF-00489791 20 mg	X[a]	X[a]	X[a]
4	X[a]	X[a]	X[a]	PF-00489791 20 mg	X[a]

a. Placebo administration.

The first dose of each 2-week allotment of study medication was taken at the study site. The subject was instructed to take the subsequent doses with water between 1700 and 2100 hours daily to minimize the potential for orthostatic hypotension.

Efficacy Endpoints:

Primary: Change in the RCS during the fourth week of treatment from Baseline, comparing active drug to placebo.

Secondary:

- Change in the number of RP attacks/week during the fourth week of treatment compared to the number of RP attacks/week at Baseline;

- Change in the total duration of RP attacks/week during the fourth week of treatment compared to the total duration of RP attacks/week at Baseline;
- Improvements in Raynaud's pain score comparing active to placebo;
- Decrease ulcer burden in SRP subjects by hastening healing or preventing new ulcer emergence;
- Plasma concentration of PF-00489791 and metabolites.
- Safety and tolerability of PF-00489791 as assessed by:
    - Incidences of treatment emergent adverse events (AEs);
    - Changes from Baseline for clinical laboratory tests, vital signs, orthostatic blood pressure measurements and 12-lead ECG parameters

Safety Evaluations: Safety evaluations included clinical monitoring, vital signs (heart rate, blood pressure), 12-lead ECGs, AEs, laboratory safety tests, and physical examinations at intervals specified in the protocol.

Statistical Methods:

The per-protocol (PP) population included all randomized subjects who had completed the study, receiving treatment until the end of treatment visit, who had been compliant with diary completion, and who were not serious protocol violators.

The intent-to-treat (ITT) population included all randomized subjects who had taken at least 1 dose of study medication and who had both a baseline and postbaseline efficacy assessment.

All efficacy analyses were performed on both PP and ITT populations and were performed separately for PRP and SRP.

The primary endpoint was the change from Baseline in the mean RCS at Week 4 comparing active drug to placebo. For each of the treatment periods, a new baseline was established using the mean RCS in the week prior to initiation of treatment. The scores ranged from 0 to 10, with higher score indicating worse condition.

The change from Baseline to Week 4 in the RCS was analyzed using a mixed effect analysis of variance (ANOVA) model with sequence, period, and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate. Estimates of the adjusted mean differences (PF-00489791 - placebo) and corresponding 80% confidence intervals (CIs) were obtained from the model. Similar analyses were conducted for the change from Baseline in the number of Raynaud's attacks, duration of each Raynaud's attack, and Raynaud's pain score.

RESULTS

Subject Disposition and Demography: Subject disposition is given in Table 3 for PRP and Table 4 for SRP. Demography is presented in Table 5 for PRP and Table 6 for SRP.

Table 3. Subject Evaluation Groups - PRP

Subject Evaluation Groups	PF-00489791 4 mg N=55 n (%)	PF-00489791 20 mg N=54 n (%)	Placebo N=102 n (%)
Screened: N=336[a]			
Assigned to study treatment: N=113			
Treated	55	54	102
Completed	49 (89.1)	46 (85.2)	96 (94.1)
Discontinued	6 (10.9)	8 (14.8)	6 (5.9)
Analyzed for pharmacokinetics			
PK concentration	55 (100.0)	54 (100.0)	0
Analyzed for efficacy			
PP	34 (61.8)	39 (72.2)	73 (71.6)
ITT	53 (96.4)	51 (94.4)	101 (99.0)
Analyzed for safety			
Adverse events	55 (100.0)	54 (100.0)	102 (100.0)
Laboratory data	50 (90.9)	48 (88.9)	98 (96.1)

Discontinuations were attributed to the last study treatment received.
ITT = intent to treat; N = number of subjects; n = number of subjects meeting prespecified criteria; PRP = primary Raynaud's phenomenon; PK = pharmacokinetics, PP = per protocol, SRP = secondary Raynaud's phenomenon.
a. Total number of subjects screened includes both PRP and SRP subjects.

Table 4. Subject Evaluation Groups - SRP

Subject Evaluation Groups	PF-00489791 4 mg N=61 n (%)	PF-00489791 20 mg N=64 n (%)	Placebo N=122 n (%)
Screened: N=336[a]			
Assigned to study treatment: N=130			
Treated	61	64	122
Completed	57 (93.4)	49 (76.6)	114 (93.4)
Discontinued	4 (6.6)	15 (23.4)	8 (6.6)
Analyzed for pharmacokinetics			
PK concentration	61 (100.0)	64 (100.0)	0
Analyzed for efficacy			
PP	47 (77.0)	36 (56.3)	83 (68.0)
ITT	61 (100.0)	63 (98.4)	121 (99.2)
Analyzed for safety			
Adverse events	61 (100.0)	64 (100.0)	122 (100.0)
Laboratory data	57 (93.4)	60 (93.8)	114 (93.4)

Discontinuations were attributed to the last study treatment received.
ITT = intent to treat; N = number of subjects; n = number of subjects meeting prespecified criteria; PK = pharmacokinetics, PP = per protocol; PRP = primary Raynaud's phenomenon; SRP = secondary Raynaud's phenomenon.
a. Total number of subjects screened includes both PRP and SRP subjects.

Table 5. Demographic Characteristics - PRP

Number of Subjects	PF-00489791 4 mg → Placebo			Placebo → PF-00489791 4 mg			PF-00489791 20 mg → Placebo			Placebo → PF-00489791 20 mg		
	Male N=4	Female N=25	Total N=29	Male N=2	Female N=25	Total N=27	Male N=2	Female N=26	Total N=28	Male N=4	Female N=25	Total N=29
Age (years):												
<18	0	0	0	0	0	0	0	0	0	0	0	0
18-44	0	12	12	0	14	14	0	14	14	2	12	14
45-64	4	12	16	2	11	13	2	12	14	2	13	15
≥65	0	1	1	0	0	0	0	0	0	0	0	0
Mean	56.5	43.3	45.1	57.0	40.7	41.9	56.0	42.2	43.2	46.8	43.7	44.1
SD	3.7	11.4	11.6	1.4	10.9	11.3	11.3	15.1	15.2	4.5	13.2	12.3
Range	53 – 61	20 – 65	20 – 65	56 – 58	20 – 56	20 – 58	48 – 64	18 – 64	18 – 64	43 – 52	22 – 61	22 – 61

N = number of subjects; PRP = primary Raynaud's phenomenon; SD = standard deviation.

Table 6. Demographic Characteristics - SRP

Number of Subjects	PF-00489791 4 mg → Placebo			Placebo → PF-00489791 4 mg			PF-00489791 20 mg → Placebo			Placebo → PF-00489791 20 mg		
	Male N=2	Female N=30	Total N=32	Male N=3	Female N=30	Total N=33	Male N=5	Female N=28	Total N=33	Male N=1	Female N=31	Total N=32
Age (years):												
<18	0	0	0	0	0	0	0	0	0	0	0	0
18-44	0	6	6	0	10	10	2	7	9	0	16	16
45-64	2	24	26	3	19	22	3	21	24	1	15	16
≥65	0	0	0	0	1	1	0	0	0	0	0	0
Mean	50.0	51.5	51.4	46.7	48.9	48.7	44.4	51.6	50.5	58.0	45.3	45.7
SD	7.1	9.3	9.1	1.2	9.7	9.3	12.3	10.6	11.0	0.0	9.2	9.3
Range	45 – 55	28 – 64	28 – 64	46 – 48	32 – 65	32 – 65	26 – 58	24 – 64	24 – 64	58 – 58	28 – 62	28 - 62

N = number of subjects; SD = standard deviation; SRP = secondary Raynaud's phenomenon.

Efficacy Results:

Change in RCS at Week 4:

PRP Cohort: The data for the change from Baseline in the mean RCS at Week 4 for the PRP Cohort are summarized by treatment sequence in Table 7. At Week 4, all treatments showed a decrease in mean RCS compared to Baseline. The largest decrease occurred in the PF-00489791 20 mg segment of the PF-00489791 20 mg → placebo sequence, which had a mean decrease in RCS of -1.05 compared to Baseline.

The summary of statistical analysis (analysis of covariance [ANCOVA]) of the change from Baseline of the RCS at Week 4 for the ITT population of the PRP Cohort is provided in Table 8. The estimated difference in RCS change from Baseline after 4 weeks of treatment following PF-00489791 4 mg compared to placebo was 0.2 (80% CI -0.08, 0.48) and was not statistically significant (p=0.3629). The difference following PF-00489791 20 mg compared to placebo was -0.65 (80% CI -0.93, -0.36) and was statistically significant at p=0.0046.

Table 7. Change From Baseline in the Mean RCS at Week 4 by Sequence - PRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=27)		Placebo → PF-00489791 4 mg (N=27)		PF-00489791 20 mg → Placebo (N=25)		Placebo → PF-00489791 20 mg (N=28)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	27	24	27	26	25	22	28	26
	Mean	3.02	2.02	3.21	2.31	3.01	2.28	2.74	2.26
	SD	1.808	1.440	2.026	1.978	2.088	1.959	1.882	1.995
	Median	2.71	1.79	3.43	1.86	2.86	2.29	2.57	2.21
	Min, max	(0.00, 6.14)	(0.00, 5.57)	(0.00, 8.57)	(0.00, 8.57)	(0.00, 8.43)	(0.00, 6.86)	(0.00, 8.14)	(0.00, 8.43)
	95% CI	(2.31, 3.74)	(1.41, 2.63)	(2.41, 4.01)	(1.51, 3.11)	(2.15, 3.88)	(1.41, 3.15)	(2.01, 3.47)	(1.46, 3.07)
Week 4	Observed value								
	N	25	23	26	25	23	22	27	24
	Mean	2.53	1.45	2.21	1.69	2.02	2.25	2.36	1.52
	SD	1.664	1.262	2.108	1.463	1.462	1.642	1.825	1.841
	Median	2.29	1.14	1.46	1.29	1.71	2.79	2.00	0.86
	Min, max	(0.00, 6.33)	(0.00, 4.43)	(0.00, 9.00)	(0.00, 5.29)	(0.00, 5.14)	(0.00, 4.86)	(0.00, 8.29)	(0.00, 7.57)
	95% CI	(1.84, 3.21)	(0.90, 2.00)	(1.36, 3.06)	(1.08, 2.29)	(1.39, 2.66)	(1.53, 2.98)	(1.63, 3.08)	(0.74, 2.30)
	Change from Baseline								
	N	25	23	26	25	23	22	27	24
	Mean	-0.63	-0.66	-0.99	-0.60	-1.05	-0.03	-0.41	-0.79
	SD	2.236	1.136	1.530	1.379	2.083	1.296	1.148	1.124
	Median	-0.57	-0.86	-0.79	-0.29	-0.57	0.00	-0.43	-0.71
	Min, max	(-5.57, 4.00)	(-2.29, 2.86)	(-4.82, 2.00)	(-4.71, 2.00)	(-7.43, 2.00)	(-2.14, 4.43)	(-2.51, 2.57)	(-4.86, 0.71)
	95% CI	(-1.55, 0.29)	(-1.15, -0.16)	(-1.61, -0.37)	(-1.17, -0.03)	(-1.95, -0.15)	(-0.60, 0.55)	(-0.86, 0.05)	(-1.27, -0.32)

CI = confidence interval; ITT = intent-to-treat; max = maximum; Min = minimum; N = number of subjects; PRP = primary Raynaud's phenomenon; RCS = Raynaud's condition score; SD = standard deviation.

Table 8. Summary of Statistical Analysis (ANCOVA) Change From Baseline of Mean RCS at Week 4 - PRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of treatment			
Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	53	-0.34	(-0.60, -0.08)
PF-00489791 20 mg	51	-1.19	(-1.45, -0.92)
Placebo	101	-0.54	(-0.71, -0.37)
Contrast of treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	0.20	(-0.08, 0.48)	0.3629
PF-00489791 20 mg vs placebo	-0.65	(-0.93, -0.36)	0.0046

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; PRP = primary Raynaud's phenomenon; RCS = Raynaud's Condition Score; vs = versus.

a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

SRP Cohort: The data for the change from Baseline in the mean RCS at Week 4 for the SRP Cohort are summarized by treatment sequence in Table 9. At Week 4, all treatments showed a decrease in mean RCS compared to Baseline. The largest decrease occurred in the PF-00489791 4 mg segment of the PF-00489791 4 mg → placebo sequence, which had a mean decrease in RCS of -1.02 compared to Baseline.

The summary of statistical analysis (ANCOVA) of the change from Baseline of the RCS at Week 4 for the ITT population of the SRP Cohort is provided in Table 10. The dose of PF-00489791 4 mg demonstrated efficacy relative to placebo on the RCS after 4 weeks of treatment, but minimal difference was observed in the dose of PF-00489791 20 mg compared to placebo. The estimated difference in RCS change from Baseline after 4 weeks of treatment following PF-00489791 4 mg compared to placebo was -0.36 (80% CI -0.65, -0.07) with p=0.1086. The difference following PF-00489791 20 mg compared to placebo was -0.13 (80% CI -0.42, 0.16) with p=0.5750.

Table 9. Change From Baseline in the Mean RCS at Week 4 by Sequence - SRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=32)		Placebo → PF-00489791 4 mg (N=33)		PF-00489791 20 mg → Placebo (N=32)		Placebo → PF-00489791 20 mg (N=31)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	32	30	33	29	32	27	31	31
	Mean	3.18	2.30	3.42	3.02	3.09	3.08	2.98	2.42
	SD	2.312	2.638	2.479	2.270	1.976	2.335	2.477	2.218
	Median	2.61	1.14	2.86	2.43	3.00	2.50	2.71	1.29
	Min, max	(0.00, 8.00)	(0.00, 8.60)	(0.14, 10.00)	(0.00, 7.57)	(0.00, 8.57)	(0.00, 8.29)	(0.00, 9.00)	(0.00, 7.86)
	95% CI	(2.35, 4.02)	(1.32, 3.29)	(2.54, 4.30)	(2.16, 3.88)	(2.37, 3.80)	(2.16, 4.01)	(2.07, 3.89)	(1.60, 3.23)
Week 4	Observed value								
	N	31	29	30	27	28	25	31	22
	Mean	2.20	1.94	3.14	2.43	2.59	2.74	2.86	2.34
	SD	2.389	2.192	2.297	2.246	1.724	2.346	2.330	2.86
	Median	1.14	1.14	3.08	1.86	2.29	2.57	2.43	1.71
	Min, max	(0.00, 7.20)	(0.00, 8.50)	(0.00, 8.17)	(0.00, 8.29)	(0.00, 7.57)	(0.00, 8.29)	(0.00, 8.20)	(0.00, 7.29)
	95% CI	(1.32, 3.08)	(1.11, 2.78)	(2.28, 3.99)	(1.54, 3.32)	(1.92, 3.26)	(1.77, 3.71)	(2.01, 3.72)	(1.24, 3.45)
	Change from Baseline								
	N	31	29	30	27	28	25	31	22
	Mean	-1.02	-0.21	-0.42	-0.51	-0.39	-0.23	-0.11	-0.08
	SD	1.768	0.831	1.677	1.430	1.233	0.900	1.748	0.844
	Median	-0.71	-0.10	-0.14	-0.14	-0.33	-0.29	0.00	0.00
	Min, max	(-5.71, 3.20)	(-2.14, 1.43)	(-5.86, 2.86)	(-4.43, 3.05)	(-3.14, 2.86)	(-2.17, 2.00)	(-4.29, 6.00)	(-1.43, 2.43)
	95% CI	(-1.67, -0.37)	(-0.53, 0.11)	(-1.04, 0.21)	(-1.08, 0.05)	(-0.87, 0.09)	(-0.61, 0.14)	(-0.76, 0.53)	(-0.46, 0.29)

CI = confidence interval; ITT = intent-to-treat; max = maximum; Min = minimum; N = number of subjects; SRP = secondary Raynaud's phenomenon; RCS = Raynaud's condition score; SD = standard deviation.

Table 10. Summary of Statistical Analysis (ANCOVA) Change From Baseline of Mean RCS at Week 4 - SRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of Treatment Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	60	-0.61	(-0.86, -0.35)
PF-00489791 20 mg	62	-0.37	(-0.63, -0.12)
Placebo	118	-0.25	(-0.40, -0.10)
Contrast of Treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	-0.36	(-0.65, -0.07)	0.1086
PF-00489791 20 mg vs placebo	-0.13	(-0.42, 0.16)	0.5750

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; SRP = secondary Raynaud's phenomenon; RCS = Raynaud's Condition Score; vs = versus.

a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

Change in Number of Raynaud's Attacks:

PRP Cohort: The data on the mean change and percentage change from Baseline in the number of Raynaud's attacks for the PRP Cohort are summarized for the ITT population by treatment in Table 11. At Week 4, all treatments except the placebo segment of the placebo → PF-00489791 20 mg sequence showed a decrease in the mean the number of Raynaud's attacks compared to Baseline. The largest decrease in terms of the percentage change from Baseline to Week 4 occurred in the PF-00489791 20 mg segment of the placebo → PF-00489791 20 mg sequence, which had a mean decrease of -32.98% in the number of Raynaud's attacks compared to Baseline.

The summary of statistical analysis (ANCOVA) of the change from Baseline of the number of Raynaud's attacks at Week 4 for the ITT population of the PRP Cohort is provided in Table 12. The dose of PF-00489791 20 mg resulted in a greater decrease in the number of Raynaud's attacks at Week 4 relative to placebo. The estimated difference in the change from Baseline after 4 weeks of treatment in the number of Raynaud's attacks following PF-00489791 4 mg compared to placebo was 0.67 (80% CI -1.40, 2.74) with p=0.6790. The difference following PF-00489791 20 mg compared to placebo was -3.04 (80% CI -5.15, -0.93) with p=0.0657.

Table 11. Change and Percent Change From Baseline in the Number of Raynaud's Attacks at Week 4 by Sequence - PRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=27)		Placebo → PF-00489791 4 mg (N=27)		PF-00489791 20 mg → Placebo (N=25)		Placebo → PF-00489791 20 mg (N=28)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	27	24	27	26	25	22	28	26
	Mean	17.78	13.96	23.85	19.58	16.12	16.09	16.36	14.85
	SD	9.349	8.249	23.605	23.693	9.658	13.986	12.368	11.284
	Median	16.00	13.50	16.00	11.00	15.00	13.50	13.50	14.00
	Min, max	(2.00, 48.00)	(1.00, 30.00)	(6.00, 102.00)	(1.00, 93.00)	(5.00, 50.00)	(0.00, 50.00)	(2.00, 51.00)	(1.00, 55.00)
	95% CI	(14.08, 21.48)	(10.48, 17.44)	(14.51, 33.19)	(10.01, 29.15)	(12.13, 20.11)	(9.89, 22.29)	(11.56, 21.15)	(10.29, 19.40)
Week 4	Observed value								
	N	25	23	26	25	23	22	27	24
	Mean	15.48	9.67	19.67	15.77	15.05	15.18	17.02	11.17
	SD	10.278	9.362	22.205	18.400	11.016	13.265	12.320	12.917
	Median	14.00	5.00	14.00	9.33	15.00	11.00	14.00	6.50
	Min, max	(4.00, 51.00)	(0.00, 35.00)	(2.00, 98.00)	(1.00, 89.00)	(1.00, 44.80)	(0.00, 46.00)	(6.00, 56.00)	(0.00, 56.00)
	95% CI	(11.24, 19.72)	(5.62, 13.72)	(10.70, 28.64)	(8.17, 23.36)	(10.29, 19.82)	(9.30, 21.06)	(12.14, 21.89)	(5.71, 16.62)
	Change from Baseline								
	N	25	23	26	25	23	22	27	24
	Mean	-2.52	-4.20	-4.71	-4.35	-1.82	-0.91	0.13	-4.04
	SD	11.237	5.729	13.517	13.240	7.277	8.326	10.929	6.623
	Median	-3.00	-3.00	-2.25	-2.00	-2.00	-1.00	0.00	-2.50
	Min, max	(-26.00, 26.00)	(-18.00, 5.00)	(-51.00, 10.00)	(-58.00, 10.00)	(-17.00, 9.00)	(-18.00, 19.00)	(-27.00, 28.00)	(-16.00, 11.00)
	95% CI	(-7.16, 2.12)	(-6.68, -1.73)	(-10.17, 0.75)	(-9.82, 1.11)	(-4.96, 1.33)	(-4.60, 2.78)	(-4.19, 4.45)	(-6.84, -1.24)
	Percent change from Baseline								
	N	25	23	26	25	23	20	27	24
	Mean	3.88	-22.00	-14.47	-12.25	-7.10	25.52	16.04	-32.98
	SD	77.543	78.967	37.862	38.626	55.147	221.052	62.452	42.401
	Median	-22.22	-42.86	-15.07	-10.00	-10.40	-19.05	0.00	-21.64
	Min, max	(-76.47, 257.14)	(-100.00, 300.00)	(-96.23, 83.33)	(-80.56, 76.92)	(-90.00, 114.29)	(-100.00, 950.00)	(-69.57, 157.14)	(-100.00, 47.83)
	95% CI	(-28.13, 35.89)	(-56.15, 12.15)	(-26.76, 0.82)	(-28.20, 3.69)	(-30.95, 16.75)	(-77.94, 128.97)	(-8.66, 40.75)	(-50.89, -15.08)

CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; PRP = primary Raynaud's phenomenon; SD = standard deviation.

Table 12. Summary of Statistical Analysis (ANCOVA) Change From Baseline of Number of Raynaud's Attacks at Week 4 - PRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of treatment			
Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	53	-1.65	(-3.50, 0.21)
PF-00489791 20 mg	51	-5.35	(-7.22, -3.48)
Placebo	101	-2.31	(-3.47, -1.15)
Contrast of treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	0.67	(-1.40, 2.74)	0.6790
PF-00489791 20 mg vs placebo	-3.04	(-5.15, -0.93)	0.0657

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; PRP = primary Raynaud's phenomenon; vs = versus.
a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

SRP Cohort: The data on the change from Baseline in the number of Raynaud's attacks at Week 4 of treatment for the SRP Cohort are summarized for the ITT population by treatment in Table 13. At Week 4, all treatments showed a decrease in the mean number of Raynaud's attacks compared to Baseline. The largest decrease in terms of the percentage change from Baseline to Week 4 occurred in the PF-00489791 4 mg segment of the PF-00489791 4 mg → placebo sequence, which had a mean decrease of -21.40% in the number of Raynaud's attacks compared to Baseline.

The summary of statistical analysis (ANCOVA) of the change from Baseline of the number of Raynaud's attacks at Week 4 for the ITT population of the SRP Cohort is provided in Table 14. The dose of PF-00489791 20 mg resulted in a greater decrease in the number of Raynaud's attacks at Week 4 relative to placebo. The estimated difference in the change from Baseline after 4 weeks of treatment in the number of Raynaud's attacks following PF-00489791 4 mg compared to placebo was -0.39 (80% CI -2.23, 1.44) with p=0.7834. The difference following PF-00489791 20 mg compared to placebo was -1.34 (80% CI -3.22, 0.53) with p=0.3567.

Table 13. Change and Percent Change From Baseline in the Number of Raynaud's Attacks at Week 4 by Sequence - SRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=32)		Placebo → PF-00489791 4 mg (N=33)		PF-00489791 20 mg → Placebo (N=32)		Placebo → PF-00489791 20 mg (N=31)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	32	30	33	29	32	27	31	31
	Mean	21.72	15.66	24.48	21.40	27.70	23.31	23.10	18.09
	SD	17.196	14.173	20.395	15.480	24.032	23.325	17.549	15.552
	Median	16.50	11.83	19.00	17.00	18.83	19.00	17.00	12.00
	Min, max	(6.00, 88.00)	(1.00, 55.00)	(0.00, 112.00)	(3.00, 60.00)	(7.00, 104.00)	(6.00, 112.00)	(2.00, 77.00)	(2.00, 62.00)
	95% CI	(15.52, 27.92)	(10.36, 20.95)	(17.25, 31.72)	(15.51, 27.29)	(19.03, 36.36)	(14.08, 32.54)	(16.66, 29.53)	(12.38, 23.79)
Week 4	Observed value								
	N	31	29	30	27	28	25	31	22
	Mean	16.72	14.14	21.13	20.65	20.53	23.31	20.94	19.00
	SD	15.892	12.555	12.853	17.746	15.395	26.156	17.222	16.937
	Median	13.00	11.00	20.50	16.00	14.00	17.00	16.00	14.50
	Min, max	(1.17, 75.00)	(1.00, 44.00)	(0.00, 53.00)	(0.00, 68.00)	(6.00, 67.00)	(2.00, 112.00)	(4.00, 68.00)	(0.00, 57.00)
	95% CI	(10.89, 22.55)	(9.36, 18.91)	(16.33, 25.93)	(13.63, 27.67)	(14.56, 26.50)	(12.51, 34.10)	(14.63, 27.26)	(11.49, 26.51)
	Change from Baseline								
	N	31	29	30	27	28	25	31	22
	Mean	-5.12	-1.82	-3.50	-1.41	-4.55	-1.15	-2.15	-0.06
	SD	9.269	4.533	13.326	5.473	10.111	7.550	10.933	8.426
	Median	-4.00	-2.00	-1.00	-1.50	-5.08	-1.00	-1.00	-1.00
	Min, max	(-23.00, 12.33)	(-11.00, 9.00)	(-65.33, 10.00)	(-13.00, 8.00)	(-30.00, 20.00)	(-15.33, 20.00)	(-26.00, 30.00)	(-25.00, 15.00)
	95% CI	(-8.52, -1.72)	(-3.54, -0.09)	(-8.48, 1.48)	(-3.57, 0.76)	(-8.47, -0.63)	(-4.26, 1.97)	(-6.16, 1.86)	(-3.80, 3.68)
	Percent change from Baseline								
	N	31	29	29	27	28	25	31	22
	Mean	-21.40	-1.64	-4.92	-14.75	-5.76	-7.83	5.82	2.98
	SD	43.678	57.699	39.260	31.560	45.815	35.322	89.554	68.080
	Median	-25.00	-13.33	-8.70	-7.89	-25.83	-10.71	-5.88	-7.40
	Min, max	(-91.03, 68.52)	(-85.71, 200.00)	(-100.00, 75.00)	(-100.00, 26.67)	(-58.82, 100.00)	(-75.00, 77.78)	(-66.67, 428.57)	(-100.00, 233.33)
	95% CI	(-37.43, -5.38)	(-23.59, 20.31)	(-19.86, 10.01)	(-27.24, -2.27)	(-23.53, 12.00)	(-22.41, 6.75)	(-27.03, 38.67)	(-27.21, 33.16)

CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; RCS = Raynaud's condition score; SD = standard deviation; SRP = secondary Raynaud's phenomenon.

Table 14. Summary of Statistical Analysis (ANCOVA) Change From Baseline of Number of Raynaud's Attacks at Week 4 - SRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of treatment			
Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	60	-2.52	(-4.15, -0.88)
PF-00489791 20 mg	62	-3.47	(-5.08, -1.85)
Placebo	118	-2.12	(-3.10, -1.14)
Contrast of treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	-0.39	(-2.23, 1.44)	0.7834
PF-00489791 20 mg vs placebo	-1.34	(-3.22, 0.53)	0.3567

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; SRP = secondary Raynaud's phenomenon; vs = versus.
a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

Change in Duration of Raynaud's Attacks:

PRP Cohort: The data for the change from Baseline in the mean duration of Raynaud's attacks at Week 4 of treatment for the PRP Cohort are summarized in Table 15. At Week 4, all treatments except the placebo segment of the PF-00489791 20 mg → placebo sequence showed a decrease in the mean duration of Raynaud's attacks compared to Baseline.

The summary of statistical analysis (ANCOVA) of the change from Baseline of the mean duration of Raynaud's attacks at Week 4 for the ITT population of the PRP Cohort is provided in Table 16. The dose of PF-00489791 20 mg approached a statistically significant greater decrease in the duration of Raynaud's attacks at Week 4 relative to placebo. The estimated difference in the change from Baseline after 4 weeks of treatment in the duration of Raynaud's attacks following PF-00489791 4 mg compared to placebo was -0.70 (80% CI -5.42, 4.02) with p=0.8486. The difference following PF-00489791 20 mg compared to placebo was -7.22 (80% CI -12.01, -2.42) with p=0.0550.

Table 15. Change and Percentage Change From Baseline in the Mean Duration of Raynaud's Attacks at Week 4 by Sequence - PRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=27)		Placebo → PF-00489791 4 mg (N=27)		PF-00489791 20 mg → Placebo (N=25)		Placebo → PF-00489791 20 mg (N=28)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	27	24	27	26	25	22	28	26
	Mean	20.24	14.53	34.29	28.12	18.27	12.60	28.86	26.51
	SD	14.996	11.192	68.196	56.755	13.544	10.566	64.150	47.210
	Median	15.29	13.86	14.41	12.38	16.07	8.61	15.62	10.68
	Min, max	(2.11, 50.23)	(1.23, 45.00)	(1.67, 360.00)	(1.31, 291.43)	(2.50, 50.00)	(0.00, 35.29)	(2.86, 351.43)	(2.88, 232.00)
	95% CI	(14.31, 26.17)	(9.80, 19.25)	(7.31, 61.27)	(5.20, 51.05)	(12.68, 23.86)	(7.92, 17.29)	(3.98, 53.73)	(7.44, 45.58)
Week 4	Observed value								
	N	25	23	26	25	23	22	27	24
	Mean	18.62	12.44	29.49	22.97	13.83	15.52	27.76	19.35
	SD	14.718	8.952	68.769	50.517	10.726	15.058	52.402	27.690
	Median	14.23	11.69	12.67	10.00	10.00	9.05	16.14	11.14
	Min, max	(2.33, 54.23)	(0.00, 32.17)	(1.38, 360.00)	(1.30, 257.14)	(1.67, 39.00)	(0.00, 56.78)	(2.78, 282.86)	(0.00, 137.00)
	95% CI	(12.55, 24.70)	(8.56, 16.31)	(1.72, 57.27)	(2.12, 43.83)	(9.19, 18.46)	(8.84, 22.20)	(7.03, 48.49)	(7.66, 31.04)
	Change from Baseline								
	N	25	23	26	25	23	22	27	24
	Mean	-2.19	-2.21	-5.17	-4.93	-3.05	2.92	-1.33	-8.82
	SD	10.458	9.270	10.541	10.571	5.716	12.649	14.999	56.331
	Median	-0.53	0.20	-1.72	-1.25	-1.75	-0.14	0.34	-1.38
	Min, max	(-23.63, 25.25)	(-33.75, 9.47)	(-46.00, 6.30)	(-35.00, 15.89)	(-24.00, 3.69)	(-6.61, 56.78)	(-68.57, 16.37)	(-232.00, 128.00)
	95% CI	(-6.51, 2.13)	(-6.21, 1.80)	(-9.43, -0.92)	(-9.29, -0.56)	(-5.52, -0.58)	(-2.69, 8.53)	(-7.27, 4.60)	(-32.61, 14.96)

Table 15. Change and Percentage Change From Baseline in the Mean Duration of Raynaud's Attacks at Week 4 by Sequence - PRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=27)		Placebo → PF-00489791 4 mg (N=27)		PF-00489791 20 mg → Placebo (N=25)		Placebo → PF-00489791 20 mg (N=28)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
	Percent change from Baseline								
	N	25	23	26	25	23	20	27	24
	Mean	-4.83	-4.23	-11.76	-12.63	-16.25	-8.01	14.80	49.91
	SD	53.009	39.251	35.839	38.726	25.839	41.205	47.626	297.061
	Median	-4.55	1.85	-16.72	-13.83	-12.17	-4.49	1.81	-12.57
	Min, max	(-75.91, 202.00)	(-100.00, 55.04)	(-71.35, 97.98)	(-65.78, 75.84)	(-72.22, 32.50)	(-100.00, 60.74)	(-50.44, 142.67)	(-100.00, 1422.22)
	95% CI	(-26.71, 17.05)	(-21.20, 12.75)	(-26.23, 2.72)	(-28.62, 3.35)	(-27.42, -5.08)	(-27.29, 11.28)	(-4.04, 33.64)	(-75.53, 175.35)

CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; PRP = primary Raynaud's phenomenon; RCS = Raynaud's condition score; SD = standard deviation.

Table 16. Summary of Statistical Analysis (ANCOVA) Change From Baseline of Mean Duration of Raynaud's Attacks at Week 4 - PRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of treatment			
Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	53	-2.36	(-6.46, 1.75)
PF-00489791 20 mg	51	-8.87	(-13.02, -4.72)
Placebo	101	-1.66	(-4.10, 0.79)
Contrast of treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	-0.70	(-5.42, 4.02)	0.8486
PF-00489791 20 mg vs placebo	-7.22	(-12.01, -2.42)	0.0550

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; PRP = primary Raynaud's phenomenon; vs = versus.
a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

SRP Cohort: The data for the change from Baseline in the mean duration of Raynaud's attacks at Week 4 of treatment for the SRP Cohort are summarized in Table 17. At Week 4, all treatments except the placebo segment of the PF-00489791 4 mg → placebo sequence and the PF-00489791 20 mg segment of the PF-00489791 20 mg → placebo sequence showed a decrease in the mean duration of Raynaud's attacks compared to Baseline.

The summary of statistical analysis (ANCOVA) of the change from Baseline of the mean duration of Raynaud's attacks at Week 4 for the ITT population of the SRP Cohort is provided in Table 18. The dose of PF-00489791 4 mg resulted in a greater decrease in the duration of Raynaud's attacks at Week 4 relative to placebo. The estimated difference in the change from Baseline after 4 weeks of treatment in the duration of Raynaud's attacks following PF-00489791 4 mg compared to placebo was -1.99 (80% CI -3.85, -0.13) with p=0.1710. The difference following PF-00489791 20 mg compared to placebo was -0.24 (80% CI -2.14, 1.65) with p=0.8684.

Table 17. Change and Percentage Change From Baseline in the Mean Duration of Raynaud's Attacks at Week 4 by Sequence - SRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=32)		Placebo → PF-00489791 4 mg (N=33)		PF-00489791 20 mg → Placebo (N=32)		Placebo → PF-00489791 20 mg (N=31)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	32	30	33	29	32	27	31	31
	Mean	16.81	15.03	18.83	17.15	18.37	21.34	21.42	18.80
	SD	17.872	16.837	19.193	17.391	16.861	27.827	22.133	19.564
	Median	10.04	9.75	11.48	12.65	13.74	15.39	13.05	11.84
	Min, max	(1.50, 73.57)	(1.92, 80.00)	(0.00, 82.24)	(1.00, 89.38)	(3.35, 91.36)	(3.60, 150.83)	(13.31,29.54)	(2.26, 86.67)
	95% CI	(10.36, 23.25)	(8.74, 21.32)	(12.03, 25.64)	(10.53, 23.76)	(12.29, 24.45)	(10.34, 32.35)	(2.68, 80.00)	(11.63, 25.98)
Week 4	Observed value								
	N	31	29	30	27	28	25	31	22
	Mean	13.40	15.34	16.41	14.43	19.64	15.39	19.58	18.13
	SD	13.836	16.310	15.915	13.787	24.696	11.229	18.589	17.280
	Median	8.75	9.09	14.38	11.88	14.78	13.45	13.46	10.63
	Min, max	(1.43, 61.67)	(1.00, 70.00)	(0.00, 85.40)	(0.00, 70.80)	(3.40, 133.33)	(2.00, 55.42)	(2.96, 88.42)	(0.00, 52.42)
	95% CI	(8.32, 18.47)	(9.14, 21.54)	(10.47, 22.35)	(8.97, 19.88)	(10.06, 29.22)	(10.76, 20.03)	(2.69, 80.00)	(10.47, 25.79)
	Change from Baseline								
	N	31	29	30	27	28	25	31	22
	Mean	-3.89	0.12	-2.07	-2.94	0.76	-1.05	-1.84	-3.73
	SD	11.146	7.632	10.369	9.391	10.733	4.279	12.836	11.431
	Median	-1.08	-0.49	0.41	-0.84	0.15	-1.91	0.02	-1.96
	Min, max	(-54.40, 11.75)	(-14.21, 31.00)	(-47.78, 8.17)	(-25.88, 13.54)	(-21.10, 41.97)	(-8.70, 9.36)	(-47.31, 20.92)	(-44.02, 14.72)
	95% CI	(-7.98, 0.20)	(-2.78, 3.02)	(-5.94, 1.80)	(-6.66, 0.77)	(-3.40, 4.92)	(-2.81, 0.72)	(-6.55, 2.86)	(-8.80, 1.34)
	Percent change from Baseline								
	N	31	29	29	27	28	25	31	22
	Mean	-9.58	5.04	-2.55	-4.60	1.53	-2.42	13.41	-12.32
	SD	51.061	53.294	38.808	44.150	35.857	33.717	64.649	35.548
	Median	-13.78	-6.98	2.27	-6.91	2.60	-7.17	0.15	-11.41
	Min, max	(-78.33, 166.67)	(-55.60, 206.67)	(-100.00, 71.20)	(-100.00, 92.86)	(-52.92, 94.44)	(-52.94, 112.26)	(-74.50, 203.13)	(-100.00, 75.56)
	95% CI	(-28.31, 9.15)	(-15.23, 25.31)	(-17.31, 12.21)	(-22.06, 12.87)	(-12.38, 15.43)	(-16.34, 11.50)	(-10.31, 37.12)	(-28.08, 3.44)

CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; SD = standard deviation; SRP = secondary Raynaud's phenomenon.

Table 18. Summary of Statistical Analysis (ANCOVA) Change From Baseline of Mean Duration of Raynaud's Attacks at Week 4 - SRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of treatment			
Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	60	-3.25	(-4.96, -1.54)
PF-00489791 20 mg	62	-1.51	(-3.19, 0.17)
Placebo	118	-1.26	(-2.34, -0.18)
Contrast of treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	-1.99	(-3.85, -0.13)	0.1710
PF-00489791 20 mg vs placebo	-0.24	(-2.14, 1.65)	0.8684

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; SRP = secondary Raynaud's phenomenon; vs = versus.
a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

Change in Raynaud's Pain Score:

PRP Cohort: The data for change from Baseline in the mean Raynaud's pain score at Week 4 for the PRP Cohort are summarized in Table 19. At Week 4, all treatments showed a decrease in the mean Raynaud's pain score compared to Baseline.

The summary of statistical analysis (ANCOVA) of the change from Baseline of the mean Raynaud's pain score at Week 4 for the ITT population of the PRP Cohort is provided in Table 20. The dose of PF-00489791 20 mg resulted in a statistically significant greater decrease in the Raynaud's pain score at Week 4 relative to placebo. The estimated difference in the change from Baseline after 4 weeks of treatment in the Raynaud's pain score following PF-00489791 4 mg compared to placebo was 0.20 (80% CI -0.10, 0.50) with p=0.3888. The difference following PF-00489791 20 mg compared to placebo was statistically significant: -0.71 (80% CI -1.01, -0.40) with p=0.0037.

Table 19. Change From Baseline in the Mean Raynaud's Pain Score at Week 4 by Sequence - PRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=27)		Placebo → PF-00489791 4 mg (N=27)		PF-00489791 20 mg → Placebo (N=25)		Placebo → PF-00489791 20 mg (N=28)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	27	24	27	26	25	22	28	26
	Mean	2.97	1.89	3.14	2.12	2.78	1.99	2.56	2.05
	SD	2.055	1.588	2.164	2.005	2.193	1.882	1.984	2.311
	Median	3.00	1.57	3.17	1.86	2.29	1.50	2.43	1.29
	Min, max	(0.00, 6.71)	(0.00, 5.43)	(0.00, 8.57)	(0.00, 8.57)	(0.00, 8.43)	(0.00, 6.71)	(0.00, 6.57)	(0.00, 7.71)
	95% CI	(2.16, 3.78)	(1.22, 2.56)	(2.28, 3.99)	(1.31, 2.93)	(1.88, 3.69)	(1.15, 2.82)	(1.79, 3.33)	(1.12, 2.99)
Week 4	Observed value								
	N	25	23	26	25	23	22	27	24
	Mean	2.31	1.23	2.03	1.52	1.66	1.96	2.24	1.50
	SD	1.853	1.166	2.097	1.368	1.256	1.658	2.076	2.030
	Median	2.29	0.71	1.43	1.14	1.57	1.71	2.00	0.93
	Min, max	(0.00, 7.17)	(0.00, 3.83)	(0.00, 9.00)	(0.00, 5.29)	(0.00, 5.00)	(0.00, 4.71)	(0.00, 8.00)	(0.00, 7.43)
	95% CI	(1.54, 3.07)	(0.73, 1.73)	(1.18, 2.87)	(0.96, 2.09)	(1.12, 2.21)	(1.23, 2.70)	(1.42, 3.06)	(0.64, 2.35)
	Change from Baseline								
	N	25	23	26	25	23	22	27	24
	Mean	-0.78	-0.74	-1.08	-0.59	-1.24	-0.03	-0.34	-0.73
	SD	2.194	1.313	1.411	1.339	2.058	1.346	1.103	1.353
	Median	-0.43	-0.43	-1.00	-0.43	-0.67	0.00	-0.33	-0.36
	Min, max	(-5.19, 4.14)	(-3.57, 1.14)	(-4.43, 2.00)	(-4.71, 1.57)	(-7.43, 0.86)	(-2.86, 4.43)	(-2.71, 1.86)	(-5.86, 0.86)
	95% CI	(-1.69, 0.12)	(-1.31, -0.17)	(-1.65, -0.51)	(-1.14, -0.04)	(-2.13, -0.35)	(-0.62, 0.57)	(-0.78, 0.10)	(-1.30, -0.16)

CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; PRP = primary Raynaud's phenomenon; SD = standard deviation.

Table 20. Summary of Statistical Analysis (ANCOVA) Change From Baseline of Mean Raynaud's Pain Score at Week 4 - PRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of treatment			
Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	53	-0.36	(-0.62, -0.09)
PF-00489791 20 mg	51	-1.27	(-1.54, -1.00)
Placebo	101	-0.56	(-0.72, -0.39)
Contrast of treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	0.20	(-0.10, 0.50)	0.3888
PF-00489791 20 mg vs placebo	-0.71	(-1.01, -0.40)	0.0037

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; PRP = primary Raynaud's phenomenon; vs = versus.
a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

SRP Cohort: The data for the change from Baseline in the mean Raynaud's pain score at Week 4 of treatment for the SRP Cohort are summarized in Table 21. At Week 4, all treatment segments showed a decrease in the mean Raynaud's pain score compared to Baseline.

The summary of statistical analysis (ANCOVA) of the change from Baseline of the mean Raynaud's pain score at Week 4 for the ITT population of the SRP Cohort is provided in Table 22. There was little difference between the results of either the PF-00489791 4 mg or 20 mg doses in change of the Raynaud's pain score at Week 4 relative to placebo. The estimated difference in the change from Baseline after 4 weeks of treatment in the Raynaud's pain score following PF-00489791 4 mg compared to placebo was -0.21 (80% CI -0.53, 0.11) with p=0.3919. The difference following PF-00489791 20 mg compared to placebo was -0.15 (80% CI -0.48, 0.17) with p=0.5455.

Table 21. Change From Baseline in the Mean Raynaud's Pain Score at Week 4 by Sequence - SRP, ITT Population

Visit		PF-00489791 4 mg → Placebo (N=32)		Placebo → PF-00489791 4 mg (N=33)		PF-00489791 20 mg → Placebo (N=32)		Placebo → PF-00489791 20 mg (N=31)	
		PF-00489791 4 mg	Placebo	Placebo	PF-00489791 4 mg	PF-00489791 20 mg	Placebo	Placebo	PF-00489791 20 mg
Baseline	Observed value								
	N	32	30	33	29	32	27	31	31
	Mean	3.53	2.68	3.67	3.00	3.29	3.19	2.65	2.11
	SD	2.692	2.998	2.717	2.165	2.181	2.467	2.672	2.140
	Median	2.67	1.55	2.86	2.71	3.00	2.57	1.57	1.25
	Min, max	(0.00, 10.00)	(0.00, 10.00)	(0.00, 10.00)	(0.00, 7.43)	(0.00, 9.71)	(0.00, 8.14)	(0.00, 9.00)	(0.00, 8.00)
	95% CI	(2.56, 4.50)	(1.56, 3.80)	(2.71, 4.63)	(2.18, 3.82)	(2.50, 4.08)	(2.21, 4.16)	(1.67, 3.63)	(1.32, 2.89)
Week 4	Observed value								
	N	31	29	30	27	28	25	31	22
	Mean	2.51	2.26	3.14	2.52	2.69	2.67	2.54	1.99
	SD	2.796	2.799	2.325	2.218	2.038	2.442	2.385	2.225
	Median	1.14	1.00	3.21	2.29	2.29	2.00	1.57	1.50
	Min, max	(0.00, 10.00)	(0.00, 10.00)	(0.00, 7.00)	(0.00, 8.86)	(0.00, 7.57)	(0.00, 8.71)	(0.00, 8.20)	(0.00, 7.29)
	95% CI	(1.49, 3.54)	(1.20, 3.33)	(2.28, 4.01)	(1.64, 3.39)	(1.90, 3.48)	(1.67, 3.68)	(1.66, 3.41)	(1.00, 2.97)
	Change from Baseline								
	N	31	29	30	27	28	25	31	22
	Mean	-1.06	-0.28	-0.68	-0.43	-0.48	-0.36	-0.11	-0.23
	SD	1.618	0.920	1.762	2.076	1.391	1.010	1.628	0.850
	Median	-0.71	-0.14	-0.18	-0.14	-0.59	-0.43	0.00	-0.05
	Min, max	(-5.19, 2.50)	(-2.43, 1.71)	(-6.29, 3.57)	(-5.43, 5.50)	(-3.86, 3.14)	(-1.83, 2.57)	(-4.57, 6.00)	(-1.57, 2.29)
	95% CI	(-1.66, -0.47)	(-0.63, 0.07)	(-1.34, -0.03)	(-1.26, 0.39)	(-1.02, 0.06)	(-0.77, 0.06)	(-0.71, 0.49)	(-0.60, 0.15)

CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; N = number of subjects; SRP = secondary Raynaud's phenomenon; SD = standard deviation.

Table 22. Summary of Statistical Analysis (ANCOVA) Change from Baseline of Mean Raynaud's Pain Score at Week 4 - SRP, ITT Population, and LOCF

Data Summary and Estimates of Treatment Difference			
End of treatment			
Treatment	N	Adjusted mean	80% CI
PF-00489791 4 mg	60	-0.56	(-0.84, -0.28)
PF-00489791 20 mg	62	-0.50	(-0.78, -0.23)
Placebo	118	-0.35	(-0.51, -0.19)
Contrast of treatments			
	Difference	80% CI	p-Value[a]
PF-00489791 4 mg vs placebo	-0.21	(-0.53, 0.11)	0.3919
PF-00489791 20 mg vs placebo	-0.15	(-0.48, 0.17)	0.5455

ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; N = number of subjects; SRP = secondary Raynaud's phenomenon; vs = versus.
a. p-Values are from ANCOVA with sequence, period and treatment as fixed effects and subject within sequence as a random effect, utilizing the baseline scores as covariate.

Decrease in Ulcer Burden: Because of the few digital ulcer (DU) numbers, no statistical inferences were drawn. In the PF-00489791 4 mg treatment group, a decrease in ulcers in subjects with DUs at Baseline (Baseline for each segment) occurred in 70.0% (7/10) of subjects at Day 14 and 81.8% (9/11) at Day 28 in the PF-00489791 4 mg segment and in 50.0% (5/10) of subjects at Day 14 and 50.0% (6/12) at Day 28 in the placebo segment. In the PF-00489791 20 mg treatment group, a decrease in ulcers in subjects with DUs at Baseline occurred in only 14.3% (1/7) of subjects at Day 14 but in 62.5% (5/8) at Day 28 in the PF-00489791 20 mg segment but in only 14.3% (1/7) of subjects at both Days 14 and 28 in the placebo segment.

Plasma Concentrations: Based on visual examination of the predose trough values, an approximately dose-proportional increase of mean PF-00489791 plasma concentration was observed going from 4 mg to 20 mg. Exposure in the PRP and SRP subjects was similar, with the SRP Cohort having a slightly higher mean PF-00489791 plasma concentration. The mean plasma concentrations by study day are presented in Table 23.

Table 23. Mean Plasma Concentrations by Study Day

Study Day	**PF-00489791 4 mg**		**PF-00489791 20 mg**	
	Mean µg/mL	**n**	**Mean µg/mL**	**n**
PRP Cohort				
Day 15	0.1523	27	0.5907	24
Day 57	0.1088	25	0.6890	24
SRP Cohort				
Day 15	0.1756	31	0.7718	28
Day 57	0.1167	27	0.7565	22

Summary statistics have been calculated by setting concentration values below the lower limit of quantification to 0. The lower limit of quantification is 0.0100 µg/mL.
n = number of observations (non-missing concentrations); PRP = primary Raynaud's phenomenon; SRP = secondary Raynaud's phenomenon.

Safety Results: Table 24 presents non-serious AEs observed during the study.

Table 24. Treatment Emergent Non-Serious Adverse Events

System Organ Class Preferred Term	PF-00489791 4 mg (PRP)	PF-00489791 20 mg (PRP)	Placebo (PRP)	PF-00489791 4 mg (SRP)	PF-00489791 20 mg (SRP)	Placebo (SRP)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number (%) of subjects						
Evaluable for adverse events	55	54	102	61	64	122
With adverse events	27 (49.1)	34 (63.0)	43 (42.2)	34 (55.7)	51 (79.7)	60 (49.2)
Blood and lymphatic system disorders	2 (3.6)	1 (1.9)	1 (1.0)	0	0	1 (0.8)
Anemia	0	1 (1.9)	0	0	0	1 (0.8)
Leukopenia	0	0	1 (1.0)	0	0	1 (0.8)
Lymphadenopathy	1 (1.8)	0	0	0	0	0
Neutropenia	1 (1.8)	0	0	0	0	0
Cardiac disorders	1 (1.8)	0	2 (2.0)	3 (4.9)	5 (7.8)	0
Bradycardia	0	0	0	1 (1.6)	0	0
Palpitations	1 (1.8)	0	2 (2.0)	2 (3.3)	1 (1.6)	0
Tachycardia	0	0	0	0	4 (6.3)	0
Congenital, familial and genetic disorders	0	0	0	0	0	1 (0.8)
Cystic fibrosis	0	0	0	0	0	1 (0.8)
Ear and labyrinth disorders	0	0	1 (1.0)	0	1 (1.6)	3 (2.5)
Ear pain	0	0	0	0	1 (1.6)	0
Tinnitus	0	0	0	0	0	3 (2.5)
Vertigo	0	0	1 (1.0)	0	0	0
Eye disorders	4 (7.3)	2 (3.7)	2 (2.0)	2 (3.3)	4 (6.3)	3 (2.5)
Conjunctivitis	0	0	1 (1.0)	1 (1.6)	1 (1.6)	0
Dry eye	1 (1.8)	0	0	1 (1.6)	1 (1.6)	0
Eye discharge	0	1 (1.9)	0	0	0	0
Eye oedema	1 (1.8)	0	0	0	0	0
Eye pruritus	0	0	0	0	0	2 (1.6)
Eyelid oedema	1 (1.8)	0	0	0	1 (1.6)	0
Lacrimation increased	0	0	0	1 (1.6)	0	0
Ocular hyperaemia	0	1 (1.9)	0	0	1 (1.6)	0
Periorbital oedema	1 (1.8)	0	0	0	0	0
Photophobia	0	0	0	0	1 (1.6)	0
Vision blurred	0	0	1 (1.0)	0	1 (1.6)	1 (0.8)
Gastrointestinal disorders	9 (16.4)	7 (13.0)	8 (7.8)	6 (9.8)	17 (26.6)	10 (8.2)
Abdominal discomfort	1 (1.8)	0	0	1 (1.6)	1 (1.6)	0
Abdominal distension	0	0	1 (1.0)	0	0	0
Abdominal pain	0	0	0	0	0	1 (0.8)
Abdominal pain upper	2 (3.6)	0	1 (1.0)	0	1 (1.6)	0
Diarrhoea	2 (3.6)	0	4 (3.9)	0	7 (10.9)	0
Dry mouth	0	0	2 (2.0)	1 (1.6)	0	0
Dyspepsia	1 (1.8)	5 (9.3)	0	2 (3.3)	0	1 (0.8)
Dysphagia	0	0	0	0	1 (1.6)	1 (0.8)
Flatulence	0	0	1 (1.0)	0	0	0
Gastritis	1 (1.8)	0	1 (1.0)	1 (1.6)	0	0
Gastrooesophageal reflux disease	0	1 (1.9)	0	1 (1.6)	1 (1.6)	0
Gingivitis	0	0	0	0	0	1 (0.8)
Nausea	5 (9.1)	0	0	0	3 (4.7)	2 (1.6)
Oesophageal pain	0	1 (1.9)	0	0	0	0
Oesophagitis	0	0	0	0	1 (1.6)	0
Salivary gland calculus	0	0	0	0	0	1 (0.8)
Stomatitis	0	0	0	0	0	1 (0.8)
Toothache	0	0	0	0	1 (1.6)	1 (0.8)
Vomiting	2 (3.6)	0	0	0	2 (3.1)	3 (2.5)

Table 24. Treatment Emergent Non-Serious Adverse Events

System Organ Class Preferred Term	PF-00489791 4 mg (PRP)	PF-00489791 20 mg (PRP)	Placebo (PRP)	PF-00489791 4 mg (SRP)	PF-00489791 20 mg (SRP)	Placebo (SRP)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
General disorders and administration site conditions	4 (7.3)	5 (9.3)	8 (7.8)	3 (4.9)	11 (17.2)	6 (4.9)
Adverse drug reaction	0	0	0	0	0	1 (0.8)
Asthenia	0	2 (3.7)	0	0	0	0
Chest pain	0	0	0	0	2 (3.1)	1 (0.8)
Face oedema	0	0	0	0	1 (1.6)	0
Fatigue	1 (1.8)	0	3 (2.9)	1 (1.6)	1 (1.6)	2 (1.6)
Feeling hot	0	0	3 (2.9)	0	0	1 (0.8)
Inflammation	0	0	0	0	0	1 (0.8)
Influenza like illness	1 (1.8)	0	0	0	0	0
Malaise	1 (1.8)	1 (1.9)	1 (1.0)	0	0	0
Oedema	0	0	0	0	3 (4.7)	0
Oedema peripheral	0	2 (3.7)	2 (2.0)	3 (4.9)	3 (4.7)	0
Pain	1 (1.8)	1 (1.9)	0	0	0	0
Pyrexia	1 (1.8)	0	1 (1.0)	0	1 (1.6)	0
Ulcer	0	0	0	0	1 (1.6)	0
Immune system disorders	0	0	1 (1.0)	0	1 (1.6)	0
Hypersensitivity	0	0	0	0	1 (1.6)	0
Seasonal allergy	0	0	1 (1.0)	0	0	0
Infections and infestations	6 (10.9)	8 (14.8)	17 (16.7)	8 (13.1)	11 (17.2)	24 (19.7)
Alveolar osteitis	0	0	0	0	1 (1.6)	0
Bacteriuria	0	0	0	1 (1.6)	0	0
Bronchitis	0	1 (1.9)	0	0	1 (1.6)	1 (0.8)
Cystitis	0	1 (1.9)	0	0	0	1 (0.8)
Furuncle	0	0	0	0	0	1 (0.8)
Gastroenteritis viral	1 (1.8)	0	1 (1.0)	0	0	0
Gastrointestinal infection	1 (1.8)	0	0	0	0	0
Influenza	0	1 (1.9)	0	1 (1.6)	0	4 (3.3)
Laryngitis	0	0	0	0	1 (1.6)	0
Localised infection	0	0	0	1 (1.6)	0	0
Nasopharyngitis	3 (5.5)	2 (3.7)	3 (2.9)	1 (1.6)	3 (4.7)	4 (3.3)
Oesophageal candidiasis	0	0	0	0	1 (1.6)	0
Oral herpes	0	1 (1.9)	0	0	0	1 (0.8)
Otitis externa	0	0	0	0	0	1 (0.8)
Otitis media	0	0	0	1 (1.6)	0	0
Pharyngotonsillitis	0	0	1 (1.0)	0	0	0
Rash pustular	0	0	0	0	0	1 (0.8)
Respiratory tract infection	0	0	0	0	1 (1.6)	1 (0.8)
Sialoadenitis	0	0	0	0	0	1 (0.8)
Sinusitis	2 (3.6)	1 (1.9)	2 (2.0)	0	2 (3.1)	2 (1.6)
Tonsillitis	0	1 (1.9)	0	0	0	0
Tooth abscess	0	0	0	1 (1.6)	0	0
Tooth infection	0	0	0	0	0	2 (1.6)
Upper respiratory tract infection	0	0	10 (9.8)	2 (3.3)	1 (1.6)	5 (4.1)
Urinary tract infection	0	0	0	0	1 (1.6)	0
Vaginitis bacterial	0	0	0	0	1 (1.6)	0
Viral infection	0	0	0	1 (1.6)	0	0
Injury, poisoning and procedural complications	0	1 (1.9)	1 (1.0)	0	0	2 (1.6)
Fall	0	0	1 (1.0)	0	0	1 (0.8)
Frostbite	0	1 (1.9)	0	0	0	0
Laceration	0	0	0	0	0	1 (0.8)
Limb injury	0	0	0	0	0	1 (0.8)
Thermal burn	0	0	0	0	0	1 (0.8)
Investigations	1 (1.8)	1 (1.9)	1 (1.0)	2 (3.3)	1 (1.6)	4 (3.3)

Table 24. Treatment Emergent Non-Serious Adverse Events

System Organ Class Preferred Term	PF-00489791 4 mg (PRP)	PF-00489791 20 mg (PRP)	Placebo (PRP)	PF-00489791 4 mg (SRP)	PF-00489791 20 mg (SRP)	Placebo (SRP)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alanine aminotransferase increased	0	0	0	1 (1.6)	0	0
Blood creatine phosphokinase increased	0	1 (1.9)	0	0	0	0
Blood potassium increased	0	0	0	0	0	1 (0.8)
Blood pressure increased	0	0	0	0	0	1 (0.8)
Electrocardiogram abnormal	0	0	0	0	1 (1.6)	0
Gamma-glutamyltransferase increased	0	0	0	0	0	1 (0.8)
Haemoglobin decreased	0	0	0	0	0	1 (0.8)
Heart rate increased	0	0	0	1 (1.6)	0	0
Transaminases increased	0	0	1 (1.0)	0	0	0
Weight increased	1 (1.8)	0	0	0	0	0
Metabolism and nutrition	0	0	0	0	2 (3.1)	1 (0.8)
Decreased appetite	0	0	0	0	1 (1.6)	0
Fluid retention	0	0	0	0	1 (1.6)	1 (0.8)
Musculoskeletal and connective tissue disorders	5 (9.1)	10 (18.5)	6 (5.9)	8 (13.1)	11 (17.2)	9 (7.4)
Arthralgia	1 (1.8)	2 (3.7)	0	2 (3.3)	1 (1.6)	0
Back pain	0	2 (3.7)	1 (1.0)	2 (3.3)	5 (7.8)	0
Fibromyalgia	0	0	1 (1.0)	0	0	0
Joint swelling	0	1 (1.9)	0	0	0	0
Muscle spasms	1 (1.8)	1 (1.9)	0	2 (3.3)	0	2 (1.6)
Musculoskeletal pain	0	0	2 (2.0)	0	0	0
Musculoskeletal stiffness	0	1 (1.9)	0	0	0	0
Myalgia	2 (3.6)	3 (5.6)	1 (1.0)	4 (6.6)	7 (10.9)	3 (2.5)
Neck pain	0	0	1 (1.0)	0	0	1 (0.8)
Pain in extremity	2 (3.6)	3 (5.6)	2 (2.0)	0	2 (3.1)	1 (0.8)
Pain in jaw	0	0	0	1 (1.6)	0	0
Polyarthritis	1 (1.8)	0	0	0	0	1 (0.8)
Sensation of heaviness	0	0	0	0	0	1 (0.8)
Synovitis	1 (1.8)	0	0	0	0	0
Tendonitis	0	0	0	1 (1.6)	0	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1.8)	0	0	0	0	0
Benign neoplasm of cornea	1 (1.8)	0	0	0	0	0
Nervous system disorders	9 (16.4)	17 (31.5)	14 (13.7)	12 (19.7)	24 (37.5)	19 (15.6)
Balance disorder	0	0	0	0	0	1 (0.8)
Dizziness	1 (1.8)	1 (1.9)	1 (1.0)	3 (4.9)	3 (4.7)	4 (3.3)
Headache	8 (14.5)	14 (25.9)	9 (8.8)	9 (14.8)	21 (32.8)	12 (9.8)
Hypoaesthesia	0	1 (1.9)	0	0	0	1 (0.8)
Migraine	0	1 (1.9)	1 (1.0)	0	0	0
Paraesthesia	0	1 (1.9)	1 (1.0)	1 (1.6)	1 (1.6)	0
Parosmia	0	0	0	1 (1.6)	0	0
Sciatica	0	0	0	0	1 (1.6)	0
Sinus headache	0	0	2 (2.0)	0	0	0
Syncope	0	0	0	0	1 (1.6)	0
Tremor	0	0	0	0	0	1 (0.8)
Psychiatric disorders	0	1 (1.9)	2 (2.0)	1 (1.6)	2 (3.1)	1 (0.8)
Anxiety	0	0	1 (1.0)	0	1 (1.6)	0
Depression	0	0	0	1 (1.6)	1 (1.6)	1 (0.8)
Insomnia	0	0	1 (1.0)	0	1 (1.6)	0
Mood swings	0	1 (1.9)	0	0	0	0
Orgasm abnormal	0	0	0	0	1 (1.6)	0
Renal and urinary disorders	1 (1.8)	0	0	1 (1.6)	1 (1.6)	0

Table 24. Treatment Emergent Non-Serious Adverse Events

System Organ Class Preferred Term	PF-00489791 4 mg (PRP)	PF-00489791 20 mg (PRP)	Placebo (PRP)	PF-00489791 4 mg (SRP)	PF-00489791 20 mg (SRP)	Placebo (SRP)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Proteinuria	0	0	0	0	1 (1.6)	0
Renal impairment	0	0	0	1 (1.6)	0	0
Urinary incontinence	1 (1.8)	0	0	0	0	0
Reproductive system and breast disorders	0	1 (1.9)	0	2 (3.3)	5 (7.8)	0
Erection increased	0	0	0	1 (1.6)	1 (1.6)	0
Menstruation irregular	0	0	0	0	1 (1.6)	0
Metrorrhagia	0	0	0	0	1 (1.6)	0
Nipple pain	0	0	0	1 (1.6)	0	0
Spontaneous penile erection	0	0	0	0	2 (3.1)	0
Vaginal haemorrhage	0	1 (1.9)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	4 (7.3)	5 (9.3)	1 (1.0)	1 (1.6)	6 (9.4)	6 (4.9)
Allergic bronchitis	0	0	0	0	1 (1.6)	0
Cough	1 (1.8)	0	1 (1.0)	0	1 (1.6)	2 (1.6)
Dysphonia	0	0	0	0	1 (1.6)	0
Dyspnoea	0	0	0	0	0	1 (0.8)
Epistaxis	0	0	0	0	2 (3.1)	0
Nasal congestion	1 (1.8)	0	0	0	0	0
Nasal obstruction	0	1 (1.9)	0	0	0	0
Nasal ulcer	1 (1.8)	0	0	0	0	0
Oropharyngeal pain	1 (1.8)	2 (3.7)	0	0	0	2 (1.6)
Pleuritic pain	1 (1.8)	0	0	0	0	0
Productive cough	0	0	0	1 (1.6)	0	1 (0.8)
Respiratory disorder	0	1 (1.9)	0	0	0	0
Rhinorrhoea	0	1 (1.9)	0	1 (1.6)	1 (1.6)	0
Sinus congestion	0	1 (1.9)	0	0	0	0
Vasomotor rhinitis	0	0	0	0	1 (1.6)	0
Wheezing	0	0	1 (1.0)	0	1 (1.6)	0
Skin and subcutaneous tissue disorders	3 (5.5)	1 (1.9)	3 (2.9)	2 (3.3)	10 (15.6)	5 (4.1)
Acne	0	0	0	0	0	1 (0.8)
Acne cystic	0	0	1 (1.0)	0	0	0
Alopecia	0	0	0	0	1 (1.6)	0
Dry skin	0	0	0	1 (1.6)	1 (1.6)	0
Eczema	0	0	0	0	2 (3.1)	0
Erythema	1 (1.8)	0	0	0	2 (3.1)	0
Increased tendency to bruise	1 (1.8)	0	0	0	0	0
Nail bed inflammation	0	0	0	0	0	1 (0.8)
Pain of skin	0	0	0	1 (1.6)	0	0
Pruritus	0	0	1 (1.0)	1 (1.6)	0	0
Rash	1 (1.8)	0	0	0	0	0
Rash erythematous	0	0	0	0	1 (1.6)	1 (0.8)
Rash pruritic	0	0	0	0	0	1 (0.8)
Skin burning sensation	0	0	0	0	1 (1.6)	0
Skin disorder	0	0	0	0	1 (1.6)	0
Skin lesion	0	0	1 (1.0)	0	0	0
Skin ulcer	0	0	0	0	1 (1.6)	0
Urticaria	0	1 (1.9)	0	0	0	1 (0.8)
Vascular disorders	4 (7.3)	4 (7.4)	1 (1.0)	5 (8.2)	4 (6.3)	4 (3.3)
Flushing	3 (5.5)	2 (3.7)	1 (1.0)	3 (4.9)	4 (6.3)	1 (0.8)
Haematoma	0	0	0	0	0	1 (0.8)
Hot flush	0	1 (1.9)	0	1 (1.6)	0	0
Hypertension	0	0	0	0	0	2 (1.6)
Hypotension	1 (1.8)	0	0	0	0	0
Peripheral ischaemia	0	0	0	1 (1.6)	0	0

Table 24. Treatment Emergent Non-Serious Adverse Events

System Organ Class Preferred Term	PF-00489791 4 mg (PRP)	PF-00489791 20 mg (PRP)	Placebo (PRP)	PF-00489791 4 mg (SRP)	PF-00489791 20 mg (SRP)	Placebo (SRP)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Phlebitis superficial	1 (1.8)	0	0	0	0	0
Raynaud's phenomenon	0	1 (1.9)	0	0	0	0

Subjects are only counted once per treatment for each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; PRP = primary Raynaud's phenomenon; SRP = secondary Raynaud's phenomenon.

The incidences of treatment-related AEs that occurred in ≥5% of subjects in any treatment group, by MedDRA preferred term are presented for the PRP and SRP Cohort in Table 25 and Table 26 respectively.

Table 25. Summary of Treatment-Emergent AEs (Treatment-Related) That Occurred in ≥5% of Subjects by Preferred Term - PRP

No. of Subjects	PF-00489791 4 mg n (%)	PF-00489791 20 mg n (%)	Placebo n (%)
Subjects evaluable for AEs[a]	55	54	102
Headache	7 (12.7)	12 (22.2)	4 (3.9)
Dyspepsia	1 (1.8)	4 (7.4)	0
Flushing	3 (5.5)	1 (1.9)	1 (1.0)

Included data up to 7 days after the last dose of study drug.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; No. = Number; n = number of subjects meeting prespecified criteria; PRP = primary Raynaud's phenomenon.
a. MedDRA (version 14.1) coding dictionary applied.

Table 26. Summary of Treatment-Emergent AEs (Treatment-Related) That Occurred in ≥5% of Subjects by Preferred Term - SRP

No. of Subjects	PF-00489791 4 mg n (%)	PF-00489791 20 mg n (%)	Placebo n (%)
Subjects evaluable for AEs[a]	61	64	122
Diarrhoea	0	4 (6.3)	0
Back pain	2 (3.3)	5 (7.8)	0
Myalgia	2 (3.3)	6 (9.4)	2 (1.6)
Headache	6 (9.8)	17 (26.6)	8 (6.6)
Flushing	3 (4.9)	4 (6.3)	1 (0.8)

Included data up to 7 days after the last dose of study drug.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; No. = Number; n = number of subjects meeting prespecified criteria; SRP = primary secondary Raynaud's phenomenon.
a. MedDRA (version 14.1) coding dictionary applied.

One (1) subject had a treatment-emergent SAE which was not considered treatment-related (Table 27).

Table 27. Treatment-Emergent Serious Adverse Events

System Organ Class Preferred Term	PF-00489791		Placebo (PRP)	PF-00489791		Placebo (SRP)
	4 mg (PRP)	20 mg (PRP)		4 mg (SRP)	20 mg (SRP)	
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Number (%) of subjects						
Evaluable for AEs	55	54	102	61	64	122
With AEs	0	0	0	0	0	1 (0.8)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	0	0	0	0	1 (0.8)
Oesophageal adenocarcinoma	0	0	0	0	0	1 (0.8)

Subjects are only counted once per treatment for each row.
Includes data up to 7 days after last dose of study drug.
MedDRA (version 14.1) coding dictionary applied.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects with adverse events; PRP = primary Raynaud's phenomenon; SRP = secondary Raynaud's phenomenon.

There was 1 death which occurred during the placebo run-in period. One (1) subject in the SRP cohort with prior relevant past history of malnutrition experienced hypoglycemia and "mixed shock" resulting in death.

Discontinuations due to AEs are presented in Table 28 and Table 29 for the PRP and SRP cohorts, respectively.

Table 28. Discontinuations Due to AEs - PRP

Subject Serial Number	System Organ Class[a]	Preferred Term[a]	Severity/ Ouctome	Causality
Treatment group: PF-00489791 4 mg				
1	Musculoskeletal and connective tissue disorders	Polyarthritis*	Mild/ still present	Other illness (inflammatory process)
2	Vascular disorders	Phlebitis*	Moderate/ resolved	Other (unknown)
Treatment group: PF-00489791 20 mg				
3	Gastrointestinal disorders	Esophageal pain*	Mild/ resolved	Study drug
4	Nervous system disorders	Headache*	Moderate/ resolved	Study drug
5	Nervous system disorders	Headache*	Moderate/ resolved	Study drug
6	Nervous system disorders	Migraine*	Moderate/ resolved	Study drug

Age of subject was at the time of screening.
*Treatment-emergent.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; PRP = primary Raynaud's syndrome.
a. MedDRA (version 14.1) coding dictionary applied.

Table 29. Discontinuations Due to AEs - SRP

Subject Serial Number	System Organ Class[a]	Preferred Term[a]	Severity/ Ouctome	Causality
Treatment group: Placebo				
1	Gastrointestinal disorders	Impaired gastric emptying[b]	Moderate/ resolved	Study drug
2	Nervous system disorders	Dizziness*	Moderate/ resolved	Study drug
3	Investigations	Alanine aminotransferase increased	Moderate/ still present	Other (unknown)
Treatment group: PF-00489791 4 mg				
4	Musculoskeletal and connective tissue disorders	Arthralgia	Mild/ resolved	Other illness (scleroderma related)
5	Musculoskeletal and connective tissue disorders	Myalgia*	Moderate/ resolved	Study drug
6	Infections and infestations	Localized infection*	Moderate/ still present	Disease under study
	Vascular disorders	Peripheral ischemia*	Severe/ still present	Disease under study
Treatment group: PF-00489791 20 mg				
7	Nervous system disorders	Headache*	Moderate/ resolved	Study drug
8	Nervous system disorders	Headache*	Moderate/ resolved	Study drug
9	Cardiac disorders	Tachycardia*	Mild/ resolved	Study drug
10	Eye disorders	Eyelid edema*	Moderate/ resolved	Study drug
11	Nervous system disorders	Syncope*	Moderate/ resolved	Study drug
12	Nervous system disorders	Headache*	Mild/ resolved	Study drug
13	Musculoskeletal and connective tissue disorders	Myalgia	Moderate/ resolved	Study drug
14	Musculoskeletal and connective tissue disorders	Myalgia*	Severe/ resolved	Study drug
15	Musculoskeletal and connective tissue disorders	Myalgia*	Severe/ resolved	Study drug
16	Nervous system disorders	Headache*	Moderate/ resolved	Study drug
17	Gastrointestinal disorders	Dysphagia*	Mild/ resolved	Study drug
18	Investigations	ECG abnormal*	Moderate/ resolved	Other (aortic calcium deposits; including sinus bradycardia, T-wave abnormality, and possible anterior ischemia)

Table 29. Discontinuations Due to AEs - SRP

Age of subject was at the time of screening.
*Treatment-emergent.
AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities; SRP = secondary Raynaud's syndrome.
a. MedDRA (Version 14.1) coding dictionary applied.
b. Serious adverse event according to Investigator's assessment.

The only laboratory parameter in either cohort to show notable differences in the change from Baseline was creatine kinase (CK) which in the PRP Cohort resulted in the following changes: PF-00489791 4 mg = no change, PF-00489791 20 mg = +2 U/L, placebo = +9 U/L, and demonstrated the following changes in the SRP Cohort: PF-00489791 4 mg = -10 U/L, PF-00489791 20 mg = -6 U/L, placebo = no change.

ALT or AST increases to higher than 3 times ULN (repeated and verified); CPK increases to higher than 10 times of ULN (repeated and verified), and causality was unknown; and serum creatinine values higher than 1.8 mg/dL (repeated and verified), and the repeated value had not decreased to its Baseline within 1 week.

Normal variability was observed in vital signs among the treatment groups over time, but none of the mean values in any treatment group or at any timepoint were notable. In the PRP Cohort, 11/211 (5.2%) and 12/211 (5.7%) subjects had a maximum increase from Baseline (rebaselined) of ≥30 mmHg in SBP and standing SBP, respectively, and 7/211 (3.3%) and 1/211 (0.5%) subjects had a maximum decrease from Baseline of ≥30 mmHg in supine SBP and standing SBP, respectively. In the SRP Cohort, 8/246 (3.3%) and 9/246 (3.7%) subjects had a maximum increase from Baseline (rebaselined) of ≥30 mmHg in supine SBP and standing SBP, respectively, and 7/246 (2.8%) and 4/246 (1.6%) subjects had a maximum decrease from Baseline of ≥30 mmHg in supine SBP and standing SBP, respectively.

CONCLUSIONS:

- This study was a proof-of-concept study for the treatment of vasospasm in PRP and SRP for PF-00489791, a long acting and selective inhibitor of PDE5. This was a 4-cohort placebo controlled crossover (2x2) study to compare the efficacy and safety of PF-00489791 in subjects with PRP and SRP using 2 dose levels, 4 mg and 20 mg, of PF-00489791 administered orally QD.
- The demographics of the subjects enrolled in this study were typical for a RP population in terms of gender, age, race, weight, and body mass index. All treatment sequences were comparable with respect to demographic variables and Baseline RCS scores.
- In the PRP population, PF-00489791 20 mg demonstrated statistically significant efficacy relative to placebo on the RCS after 4 weeks of treatment (p=0.0046). There was no difference between PF-00489791 4 mg and placebo in the RCS scores after 4 weeks of treatment.
- In the SRP population, PF-00489791 4 mg demonstrated efficacy relative to placebo on the RCS after 4 weeks of treatment (p=0.1086), however it was not statistically significant. There was no difference between PF-00489791 20 mg and placebo in the RCS scores after 4 weeks of treatment.
- Thus, the results of this study demonstrated effective treatment with PF-00489791 20 mg in the PRP and PF-00489791 4 mg in the SRP.
- The statistical analyses of the secondary endpoints of mean change from Baseline to Week 4 in number and duration of Raynaud's attacks and in Raynaud's pain score indicated no statistically significant differences between PF-00489791 and placebo in

most analyses. The only analysis that did show statistical significance was comparison PF-00489791 20 mg with placebo in the change in Raynaud's pain score in the PRP Cohort (p=0.0037). However, the decreases in the PF-00489791 treatment groups tended to be greater than in the placebo group for most endpoints.

- The results demonstrating the decrease of DUs showed a trend in favor of both doses of PF-00489791 over placebo.

- Plasma concentrations of PF-00489791 were analyzed and a dose-proportionate increase of mean PF-00489791 plasma concentration was observed.

- PF-00489791 was safe and well tolerated in the PRP population with headaches and gastrointestinal (dyspepsia and nausea) AEs being the most commonly observed. In the SRP population, PF-00489791 4 mg was safe and well tolerated. However, the 20 mg treatment group had a higher number of discontinuations and AEs compared to other treatment groups.

- Statistically significant efficacy relative to placebo was demonstrated in the PRP population at the PF-00489791 20 mg dose on the RCS after 4 weeks of treatment (p=0.0046). The higher rates of discontinuation and AEs confound the response seen in the SRP PF-00489791 20 mg treatment group.