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COMPOUND NUMBER: PF-00489791

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00853112

PROTOCOL NO.: A7331009

PROTOCOL TITLE: A Phase 2a, Randomized, Double Blind, Placebo-Controlled, Parallel Group Study Investigating the Dose-Response of PF-00489791 on Acute Hemodynamics in Subjects With Idiopathic and Familial Pulmonary Arterial Hypertension

Study Centers: A total of 17 centers enrolled and treated subjects in the study, including 2 in Canada, 1 in Germany, 4 in India, 2 in the Russian Federation, 2 in Spain, 2 in Sweden, and 4 in the United States.

Study Initiation Date and Primary Completion or Completion Dates: 16 April 2009 to 28 July 2010. The study was terminated prematurely.

Phase of Development: Phase 2a

Study Objectives: Primary: To evaluate the effect of different doses of PF-00489791 on pulmonary vascular resistance index (PVRI) in subjects with idiopathic pulmonary arterial hypertension (IPAH) and familial pulmonary arterial hypertension (FPAH).

Secondary: To evaluate the effect of different doses of PF-00489791 on systemic vascular resistance index (SVRI) and other systemic hemodynamic parameters; To evaluate specificity of different doses of PF-00489791 for pulmonary versus systemic hemodynamics; To evaluate the effect of different doses of PF-00489791 on cardiac index, mean pulmonary artery pressure (mPAP) and other pulmonary hemodynamic parameters and blood gases, assessed by right heart catheterization (RHC); To evaluate safety of different doses of PF-00489791 after a single-dose administration; and to characterize pharmacokinetics (PK) of PF-00489791 in subjects with pulmonary arterial hypertension (PAH). Other: To evaluate the effect of PF-00489791 on a target biomarker, cyclic guanosine monophosphate (cGMP), and explore its relationship to pulmonary hemodynamic response in subjects with primary pulmonary hypertension and to investigate the PK/pharmacodynamic (PD) relationship between PF-00489791 and sildenafil exposure and pulmonary and systemic hemodynamic parameters.

METHODS

Study Design:

This was a randomized, double-blind, placebo-controlled, parallel-group study investigating different oral doses of PF-00489791; it also included a 20 mg sildenafil arm for observational comparison. In Stage 1 subjects were to be randomized to placebo, sildenafil, or PF-00489791 1 mg, 2 mg, 4 mg, 10 mg, or 20 mg. Following an interim analysis (IA), up to 30 additional subjects were to be randomized to placebo, sildenafil, or doses of PF-00489791 in Stage 2. The study consisted of a pretreatment Screening period (up to 30 days), dosing/hemodynamic assessment visit (for single-dose administration), Follow-up visit (2 to 4 days after dosing), and a phone call follow-up (9 to 13 days after dosing). This adaptive-design study was terminated upon completion of planned enrollment of subjects into Stage 1; neither the IA nor enrollment into Stage 2 were conducted. As a result of the decision to terminate the study early, the final statistical analyses were based on a smaller sample size than originally planned and therefore the statistical power of this study was lower than originally estimated.

Number of Subjects (Planned and Analyzed): The study planned to enroll 42 subjects in the 7 arms (6 subjects per arm) in Stage 1 and up to 30 subjects in Stage 2. The study was stopped upon completion of Stage 1 and did not enroll in Stage 2. Forty-eight subjects were randomized and 44 were treated: 6 each in the placebo and sildenafil arms, and 6, 7, 6, 6, and 7 subjects in the PF-00489791 1, 2, 4, 10, and 20 mg arms, respectively.

Diagnosis and Main Criteria for Inclusion: Male or female subjects ≥18 years of age with IPAH or FPAH, mPAP ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) <15 mm Hg who also fulfilled the other inclusion and exclusion criteria defined in the protocol.

Study Treatment: The study drug was supplied by the Sponsor. PF-00489791 was supplied in tablets of 1 mg, 2 mg, and 10 mg and placebo to match. Sildenafil was supplied as 20 mg tablets and placebo to match. Subjects took 1 dose of study medication (total of 3 tablets) orally; the study drug was administered at the center by center personnel with approximately 240 mL of ambient water.

Efficacy Evaluations: Hemodynamic measurements collected at the dosing/assessment visit (Baseline and 1, 2, 3, and 4 hours postdose) included cardiac output (CO), right atrial pressure (RAP), mPAP, systolic PAP (sPAP), diastolic PAP (dPAP), PCWP, mean systemic arterial pressure (SAP) (mSAP), systolic SAP (sSAP), diastolic SAP (dSAP), and heart rate (HR). The following efficacy hemodynamic parameters were calculated: cardiac index, pulmonary vascular resistance, systemic vascular resistance, PVRI, and SVRI.

The primary efficacy endpoint was defined as the mean change from Baseline in PVRI during the 4 hours immediately postdose. Secondary endpoints included changes from Baseline over 4 hours postdose in the above-mentioned hemodynamic parameters and greatest reduction from Baseline in PVRI and SVRI.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Evaluations: Blood samples (3 mL) to measure plasma levels of PF-00489791, sildenafil and desmethyl sildenafil (UK-103,320) were collected at 1, 2, 3, 4, 5, 6, and 8 hours postdose, and at the Follow-up visit (Days 3 to 5). Blood samples (up to 5 mL) for the analysis of plasma cGMP were collected at Baseline and at 1, 2, 3, 4, 5, 6, and 8 hours postdose, and at the Follow-up visit. In addition, a blood sample for pharmacogenomic research was taken for subjects consenting for this additional optional research activity (to be reported separately).

Safety Evaluations: Safety evaluations included clinical monitoring, physical examinations, vital signs (HR, blood pressure), 12-lead electrocardiograms (ECGs), adverse events (AEs), and safety laboratory tests, conducted from Screening (up to 13 days before dosing) through Follow-up (up to 13 days after dosing). Partial arterial pressure of oxygen (PaO_2) and carbon dioxide ($PaCO_2$) were also assessed at Baseline, 1 and 4 hours postdose.

Statistical Methods:

Data Sets Analyzed: All parameters were analyzed with the full analysis set (FAS), which included all randomized and treated subjects except for 1 subject excluded due to significant study conduct issues at the site; in addition, some analyses were conducted using the FAS Observed data set, from which 3 subjects' data were excluded. The PK analysis set included all randomized and treated subjects with at least 1 measured PF-00489791 or sildenafil concentration. The PD analysis set included all randomized and treated subjects with at least 1 measured concentration of target biomarker cGMP postdose.

Efficacy Analysis Methods: The primary analysis modeled the dose-response curve for the change from Baseline in PVRI using a 4-parameter Bayesian E_{max} model. Doses were compared to placebo and the PF-00489791 20 mg dose (ie, the highest dose used in the study) using the model. The dose that yielded 75% of the PF-00489791 20 mg dose effect was also estimated along with its 95% credible interval. Sensitivity analyses were performed to assess the influence of the priors in the primary analysis. The primary and secondary hemodynamic assessment endpoints were analyzed using analysis of covariance (ANCOVA), fitting a fixed effect term for treatment and Baseline as a covariate. The differences between each active treatment and placebo were estimated, along with 95% confidence intervals (CIs). The other PF-00489791 doses were also compared to the PF-00489791 20 mg dose. The changes from Baseline in PVRI, SVRI, cardiac index, and mean PAP at 1, 2, 3, and 4 hours postdose were also analyzed using a longitudinal model.

Safety Analysis Methods: All the safety data were summarized descriptively through appropriate data tabulations, descriptive statistics, and graphical presentations according to the Sponsor's standards.

Pharmacokinetics: To assess the PK profile of PF-00489791, sildenafil, and UK-103,320, PK plasma concentrations were listed and plotted.

Pharmacodynamics: Plasma cGMP values were listed and summarized; changes from Baseline were listed and plotted.

RESULTS

Subject Disposition and Demography: Table 1 summarizes subject disposition and evaluation groups during the study.

Table 1. Subject Disposition and Evaluation Groups

	Placebo	PF-00489791					Sildenafil 20 mg
		1 mg	2 mg	4 mg	10 mg	20 mg	
Screened 66[a]							
Assigned to Study Treatment	6	7	7	8	6	7	7
Derandomized[b]	0	1	0	2	0	0	1
Treated	6	6	7	6	6	7	6
Completed	6	6	7	6	6	7	6
Discontinued	0	0	0	0	0	0	0
Analyzed for Efficacy:							
Full Analysis Set	6	6	7	6	6	6[c]	6
Full Analysis Set Observed	6	6	7	6	6	5[c,d]	5[d]
Analyzed for Safety:							
Adverse events	6	6	7	6	6	7	6
Laboratory data	6	6	7	6	6	7	6
Safety Analysis Set	6	6	7	6	6	7	6

Abbreviations: PVRI=pulmonary vascular resistance index, PCWP=pulmonary capillary wedge pressure
[a]2 subjects were allowed to enter Screening 2 times (1 subject was a screen failure 2 times and 1 subject was randomized after the 2nd Screening).
[b]Subjects were allowed to be derandomized per protocol; the randomization number was then made available again.
[c]Subject excluded due to study conduct issues at study site.
[d] Subject excluded due to missing PVRI data; could not be computed for these subjects postbaseline due to missing PCWP data

The majority of subjects were female (30/44, 68.2%) and Asian (26/44, 59.1%). The mean age of subjects ranged from 39.1 to 59.3 years across the 7 treatment groups (range 21 to 80 years). The mean weight ranged from 59.6 to 71.8 kg across the 7 treatment groups (range 25 to 102 kg), and the mean body mass index (BMI) ranged from 21.7 to 28.0 kg/m^2 across the 7 treatment groups (range 11.6 to 40.3 kg/m^2).

Efficacy Results:

Primary endpoint

Mean changes from Baseline in PVRI over 4 hours postdose in the PF-00489791 groups ranged from -335.3 (4 mg) to 11.6 $dyne \cdot s \cdot m^2/cm^5$ (2 mg). The PF-00489791 4 mg, 10 mg, and 20 mg doses had the largest mean reductions in PVRI from Baseline over the 4 hourly time points. The mean change from Baseline in PVRI in the placebo group was -47.3 $dyne \cdot s \cdot m^2/cm^5$. The mean change from Baseline in the sildenafil group was 304.9 $dyne \cdot s \cdot m^2/cm^5$; this large increase was due to 1 subject with outlier values who also had a low plasma concentration of sildenafil.

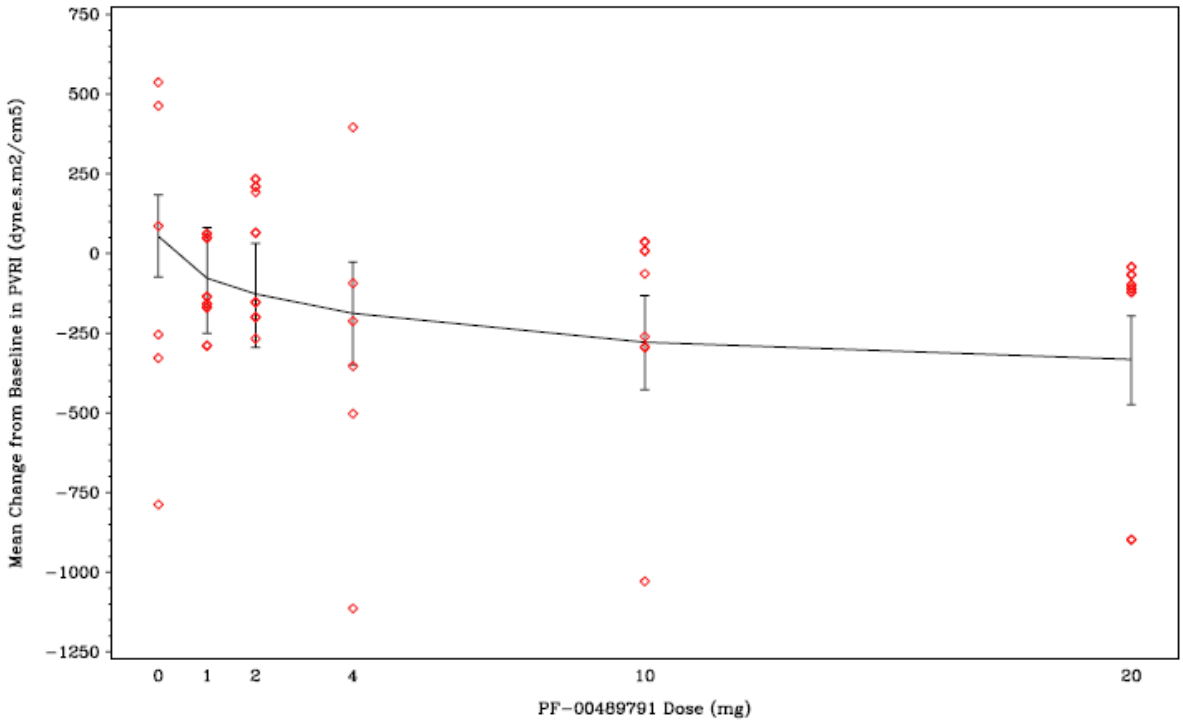
The posterior probability for PF-00489791 dose decreasing PVRI by at least 240 dyne•s•m^2/cm^5 over placebo was ≥0.25 for doses 2 mg and higher (0.250, 0.485, 0.810, and 0.974 for the PF-00489791 2 mg, 4 mg, 10 mg, and 20 mg groups, respectively; Table 2). Figure 1 displays the PF-00489791 dose-response curve and associated credible intervals for the mean change from Baseline in PVRI over 4 hours using a Bayesian 4-parameter E_{max} model, where missing data were imputed.

Table 2. Bayesian 4-Parameter E_{max} Model: Mean Changes From Baseline in PVRI (dyne•s•m^2/cm^5) for Placebo and PF-00489791 – FAS

	Placebo	PF-00489791				
		1 mg	2 mg	4 mg	10 mg	20 mg
	N=6	N=6	N=7	N=6	N=6	N=6
Predicted Mean	51.9	-63.1	-118.7	-188.3	-276.0	-327.5
SD	65.55	81.66	83.22	82.44	74.68	71.13
95% Credible Interval	(-73.3, 183.4)	(-249.7, 80.4)	(-295.0, 31.9)	(-349.2, -26.4)	(-427.5, -132.4)	(-474.6, -195.4)
Comparison to Placebo:						
Predicted Mean Estimate	N/A	-115.0	-170.6	-240.2	-327.9	-379.4
SD	N/A	98.36	107.84	109.28	92.41	73.61
95% Credible Interval	N/A	(-371.5, -1.1)	(-409.2, -7.1)	(-444.8, -33.8)	(-492.9, -148.0)	(-520.6, -238.8)
Posterior Probabilities:						
(PF-00489791 – Placebo) ≥240 dyne•s•m^2/cm^5	N/A	0.120	0.250	0.485	0.810	0.974

Abbreviations: FAS=full analysis set, PVRI=pulmonary vascular resistance index, SD=standard deviation, N=number of subjects, N/A=not applicable, E_{max}=difference between maximum achievable response (at infinite dose) and Baseline
The response was the mean change from Baseline in PVRI over 4 hours.
Data analyzed using a Bayesian 4-parameter E_{max} model. Missing data were imputed.
The predicted means and SD are the posterior means and standard deviation from the Bayesian analysis.

Figure 1. Dose-Response Curve (With 95% Credible Intervals): Mean Change From Baseline in PVRI (dyne•s•m^2/cm^5) for Placebo and PF-00489791 – FAS



Abbreviations: PVRI= pulmonary vascular resistance index, FAS=full analysis set, E_{max}=difference between maximum achievable response (at infinite dose) and Baseline
Dose=0 represents the placebo group.
The response was mean change from Baseline in PVRI over 4 hours.
Data analyzed using a Bayesian 4-parameter Emax model. Missing data were imputed.

The ANCOVA model showed that PF-00489791 doses 4 mg and higher achieved at least 240 dyne•s•m^2/cm^5 decrease in PVRI compared to placebo (-276.3, -297.4, and -247.4 dyne•s•m^2/cm^5 for the PF-00489791 4 mg, 10 mg, and 20 mg groups, respectively; Table 3). None of the comparisons to placebo was statistically significant at the 5% level.

Table 3. ANCOVA: Mean Changes From Baseline in PVRI (dyne•s•m^2/cm^5) for Placebo and PF-00489791 – FAS

	Placebo	PF-00489791				
		1 mg	2 mg	4 mg	10 mg	20 mg
	N=6	N=6	N=7	N=6	N=6	N=6
Adjusted Mean	5.3	-163.7	17.0	-271.0	-292.1	-242.1
SE	152.06	152.73	137.04	150.63	148.91	148.52
Comparison to Placebo						
Adjusted Mean	N/A	-169.0	11.6	-276.3	-297.4	-247.4
SE	N/A	221.59	204.08	209.36	215.56	214.66
95% CI	N/A	(-621.6, 283.5)	(-405.2, 428.4)	(-703.9, 151.3)	(-737.7, 142.8)	(-685.8, 191.0)
p-value	N/A	0.452	0.955	0.197	0.178	0.258

Abbreviations: ANCOVA=analysis of covariance, FAS=full analysis set, PVRI=pulmonary vascular resistance index, SE=standard error, N=number of subjects, N/A=not applicable, CI=confidence interval
The response was the mean change from Baseline in PVRI over 4 hours.
Baseline was defined as the measurement taken prior to Nitric Oxide administration (where administered).
The analysis was performed using ANCOVA with Baseline fitted as a covariate. Missing data were imputed.

Secondary endpoints

The mean greatest reduction from Baseline in PVRI over 4 hours for the PF-00489791 doses ranged from -600.9 (4 mg) to -143.4 dyne•s•m^2/cm^5 (2 mg). The mean greatest reduction from Baseline in PVRI over 4 hours in the placebo and sildenafil groups was -180.8 and 55.8 dyne•s•m^2/cm^5, respectively. The greatest reduction from Baseline in PVRI over 4 hours for the PF-00489791 4 mg dose was statistically significant at the 5% level compared to placebo (difference in adjusted mean [PF-00489791 – placebo] = -435.7 dyne•s•m^2/cm^5 with 95% CI [-835.9, -35.6], p-value=0.034). The PF-00489791 10 mg and 20 mg doses showed differences from placebo in greatest reduction in PVRI of -334.7 and -278.0 dyne•s•m^2/cm^5, respectively; neither of these comparisons was statistically significant at the 5% level.

The longitudinal analysis of hourly changes in PVRI for all PF-00489791 doses except 2 mg, showed decreases compared to placebo in hourly changes in PVRI at each of the 4 hourly time points; none of the comparisons was statistically significant at the 5% level.

The mean hourly changes from Baseline in mPAP across the PF-00489791 groups over 4 hours postdose ranged from -6.33 (20 mg at Hours 3 and 4) to 2.10 mm Hg (10 mg at Hour 3). The mean hourly changes from Baseline in mPAP in the placebo group ranged from 2.17 (Hour 1) to 2.83 mm Hg (Hour 3) and in the sildenafil group ranged from -2.67 (Hour 1) to -0.67 mm Hg (Hours 3 and 4). The longitudinal analysis of hourly changes in mPAP showed that all doses had a decrease compared to placebo at all time points. The comparisons with placebo for the PF-00489791 20 mg group were statistically significant at the 5% level at each of the 4 hourly time points (p-values=0.040, 0.021, 0.020, and 0.026 at Hours 1, 2, 3, and 4, respectively) and ranged from -8.01 mm Hg at Hour 1 to -9.01 mm Hg at Hour 3.

Cardiac index generally increased with PF-00489791 dose over 4 hours postdose compared to placebo. The mean hourly changes from Baseline in cardiac index across the PF-00489791 groups ranged from -0.15 (2 mg at Hour 3) to 0.59 L/min/m^2 (10 mg at Hour 2). The mean hourly changes from Baseline in cardiac index in the placebo group ranged from 0.12 (Hour 1) to 0.22 L/min/m^2 (Hour 2) and in the sildenafil group ranged from -0.27 (Hour 4) to -0.11 L/min/m^2 (Hour 2). The results of longitudinal analysis of hourly changes in cardiac index were not consistent across PF-00489791 doses; none of the comparisons with placebo was statistically significant at the 5% level.

The mean changes from Baseline in SVRI across the PF-00489791 groups over 4 hours postdose ranged from -704.7 (10 mg) to -145.7 dyne•s•m^2/cm^5 (2 mg). The mean changes from Baseline for the placebo and sildenafil groups were -486.8 and 97.6 dyne•s•m^2/cm^5, respectively. The PF-00489791 4 mg, 10 mg, and 20 mg doses showed a decrease from Baseline in SVRI over 4 hours compared to placebo (-82.6, -325.6, and -61.2 dyne•s•m^2/cm^5, respectively), with the 1 mg group showing no change compared to placebo (-0.4 dyne•s•m^2/cm^5), and the 2 mg group showing an increase compared to placebo (72.2 dyne•s•m^2/cm^5). None of the comparisons was statistically significant at the 5% level.

The PF-00489791 10 mg group had the greatest reduction from Baseline in SVRI compared to placebo, -329.4 dyne•s•m^2/cm^5. None of the comparisons with placebo was statistically significant at the 5% level.

The mean hourly changes from Baseline in SVRI across the PF-00489791 groups over 4 hours postdose ranged from -893.81 (10 mg at Hour 2) to -48.54 dyne•s•m^2/cm^5 (20 mg at Hour 1). The mean hourly changes from Baseline in SVRI in the placebo group ranged from -660.98 (Hour 4) to -278.74 dyne•s•m^2/cm^5 (Hour 1) and in the sildenafil group ranged from 34.44 (Hour 2) to 151.18 dyne•s•m^2/cm^5 (Hour 4). The longitudinal analysis of hourly changes in SVRI showed that all PF-00489791 doses had a decrease compared to placebo at 1 hour postdose; none of the comparisons with placebo was statistically significant at the 5% level.

The mean hourly changes from Baseline in PVRI/SVRI ratio across the PF-00489791 groups over 4 hours postdose ranged from -0.06 (20 mg at Hours 1 and 4) to 0.06 (10 mg at Hour 2). The mean hourly changes from Baseline in PVRI/SVRI ratio in the placebo group ranged from 0.04 (Hour 1) to 0.08 (Hour 4) and in the sildenafil group ranged from -0.01 (Hour 1) to 0.08 (Hour 3). Mean changes from Baseline in the PVRI/SVRI ratio were small and there were no consistent changes across the treatment groups in the PVRI/SVRI ratio over time.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Results: Mean PF-00489791 concentrations were in the expected range for the PF00489791 doses administered in the study. In the sildenafil group, 5 subjects had concentrations of sildenafil in the expected range for the dose used and 1 subject had low concentrations of sildenafil. Mean cGMP values in the PF-00489791 groups at Baseline ranged from 3.27 (4 mg) to 3.82 ng/mL (20 mg). Mean cGMP values at Baseline in the placebo and sildenafil groups were 5.20 and 3.03 ng/mL, respectively. Mean hourly cGMP values in the PF-00489791 groups ranged from 2.64 (10 mg at Hour 1) to 5.50 ng/mL (20 mg at Hour 5). Mean hourly values in the placebo group ranged from 3.86 (Hour 2) to 5.05 ng/mL (Hour 1) and in the sildenafil group ranged from 2.81 (Hour 5) to 5.18 ng/mL (Hour 3). Overall the changes from Baseline in cGMP were small and not clinically significant. PK/PD and pharmacogenomic results will be presented in separate reports.

Safety Results:

One subject experienced serious adverse events (SAEs) of vomiting and acute diarrhea during Screening (the subject did not undergo RHC as part of the Screening assessment and was not randomized or treated) and later died of cardio-respiratory arrest.

Two subjects in the placebo group and 1 subject in the PF-00489791 20 mg treatment group experienced a total of 5 treatment-emergent SAEs during the study; none was considered related to study medication (Table 4).

Table 4. Treatment-Emergent Serious Adverse Events

Treatment	MedDRA System Organ Class/ Preferred Term/	Severity	Outcome	Causality
Placebo	**General disorders and administration site conditions/** Edema peripheral	Severe	Resolved	Concomitant treatment
Placebo	**General disorders and administration site conditions/** Chest pain	Moderate	Resolved	Disease under study
	Gastrointestinal disorders/ Hemorrhoids	Mild	Resolved	Concomitant treatment
PF-00489791 20 mg	**Cardiac disorders/** Cardiac failure congestive	Severe	Resolved	Disease under study
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)/ Vulval cancer	Moderate	Still present	Other illness

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities (Version 13.0), incl=including

No subjects withdrew from the study.

Overall the incidence of AEs (all causalities and treatment-related) did not appear to be dose-dependent. Twenty-five (57%) subjects reported at least 1 AE (all causalities) and 13 (29.5%) subjects reported at least 1 treatment-related AE. The PF-00489791 2 mg group had the lowest percentage (2/7 subjects, 28.6%) of subjects experiencing AEs (all causalities), while the PF-00489791 4 mg group had the highest percentage (5/6 subjects, 83.3%) of subjects experiencing AEs. All AEs in the PF-00489791 groups except for the SAE noted above were of mild or moderate severity. No sildenafil-treated subject experienced an SAE or a severe AE. None of the SAEs or severe AEs in any treatment group was treatment-related.

Table 5 summarizes all treatment-emergent AEs that occurred in at least 2 subjects overall; nausea (4 subjects overall) and hematoma (3 subjects overall) were the most frequent AEs; 2 of the AEs of nausea and none of the AEs of hematoma were considered related to study treatment.

Table 5. Treatment-Emergent Adverse Events Occurring in ≥2 Subjects Overall (All Causalities)

No. of Subjects	Placebo	PF-00489791					Sildenafil
		1 mg	2 mg	4 mg	10 mg	20 mg	20 mg
	N=6	N=6	N=7	N=6	N=6	N=7	N=6
Nausea	1	2	0	1	0	0	0
Hematoma	0	0	0	2	0	1	0
Asthenia	0	0	0	1	1	0	0
Proteinuria	0	0	1	0	1	0	0
Hypotension	0	1	0	0	1	0	0
Headache	0	0	0	2	0	0	0
Vomiting	0	1	0	1	0	0	0
Pyrexia	0	0	0	1	0	0	1
Chest pain	1	0	0	0	0	0	1

Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities, N=number of subjects, No.=number
MedDRA Version 13.0 coding dictionary applied.
Includes data up to 999 days after last dose of study drug.
Results are sorted by total frequency and then by decreasing frequency in descending order of the PF-00489791 dose groups.

A decrease from Baseline in mean arterial partial pressure of oxygen was observed for the PF-00489791 4 mg, 10 mg, and 20 mg doses. At 1 hour postdose the changes increased with PF-00489791 dose; at 4 hours postdose the 10 mg dose had the greatest change.

There were no clinically meaningful changes from Baseline in other clinical laboratory parameters, ECGs, vital signs, or physical examinations during the study.

CONCLUSIONS:

- The dose response for the change from Baseline in PVRI was not able to be fully characterized based on the data from Stage 1 of the study. An effect on change from Baseline in PVRI for PF-00489791 doses 4 mg and above was observed. The ANCOVA showed changes in PVRI compared to placebo of -276.3, -297.4, and -247.4 dyne•s•m^2/cm^5 for the PF-00489791 4 mg, 10 mg, and 20 mg groups, respectively. None of the comparisons to placebo was statistically significant at the 5% level.

- The analysis of SVRI showed a decrease in the adjusted mean SVRI change from Baseline over 4 hours compared to placebo for the PF-00489791 4 mg, 10 mg, and 20 mg doses. None of the comparisons was statistically significant at the 5% level.

- All PF-00489791 groups had mean decreases from Baseline in sSAP from 1 to 4 hours postdose, except for the PF-00489791 2 mg group at 3 hours postdose. All PF-00489791 groups had mean decreases from Baseline in dSAP from 1 to 4 hours postdose. Mean decreases in sSAP and dSAP did not exceed 10 mm Hg in any PF-00489791 treatment group.

- Changes from Baseline in the PVRI/SVRI ratio were small over the 4 hours postdose. There did not appear to be consistent changes across the treatment groups in the PVRI/SVRI ratio or percentage change in PVRI versus percentage change in SVRI.

- Cardiac index generally increased with PF-00489791 compared to placebo; however, there were no consistent changes across PF-00489791 doses.

- Decreases from Baseline in mPAP were observed with all PF-00489791 doses. The dose with the largest mean decreases was PF-00489791 20 mg; the decreases compared to placebo ranged from -8.01 mm Hg at Hour 1 to -9.01 mm Hg at Hour 3 and were statistically significant at all time points during 4 hours postdose.

- During 4 hours postdose, consistent mean increases in cGMP compared to Baseline were seen in the PF-00489791 20 mg group.

- Overall PF-00489791 in single doses used in the study was safe and well-tolerated.

- No dose proportionality was observed with respect to frequency of AEs.

- There were no AEs of concern.

- There were no significant decreases or large orthostatic changes in systemic arterial blood pressure for subjects treated with PF-00489791.

- A decrease from Baseline in mean arterial partial pressure of oxygen was observed for the PF-00489791 4 mg, 10 mg, and 20 mg doses. At 1 hour postdose the changes increased with PF-00489791 dose; at 4 hours postdose the 10 mg dose had the greatest change.

- No safety concerns regarding other laboratory data, ECGs, or vital signs were observed through 4 days of follow-up postdose.

- The study successfully achieved the objectives of Stage 1. If the study had not been terminated it would have continued into Stage 2, with subjects receiving PF-00489791 4 mg, 10 mg, 20 mg, placebo, or sildenafil based on the results of Stage 1 analyses.