Phosphodiesterase-5

Blood Pressure Lowering Effects of a New Long-Acting Inhibitor of Phosphodiesterase 5 in Patients With Mild to Moderate Hypertension

Robert Wolk, William B. Smith, Joel M. Neutel, John Rubino, Dawei Xuan, James Mancuso, James Gilbert, Milton L. Pressler

Abstract—Inhibition of phosphodiesterase 5 is an attractive candidate mechanism for blood pressure (BP) lowering. In this study, a novel long-acting phosphodiesterase 5 inhibitor, PF-00489791, was evaluated in 133 patients with mild to moderate hypertension, randomized into 1 of 4 groups: placebo, 4 mg, 10 mg, and 20 mg titrated after 14 days of dosing to 40 mg. Study medication was administered once daily for 28 days. Ambulatory BP monitoring was used. There was a statistically significant decrease (compared with placebo) in mean daytime systolic BP on day 28 at the 10 and 20/40 mg doses (by \(\approx 5\) and \(\approx 7\) mm Hg, respectively). Changes in mean daytime diastolic BP corresponded with those in systolic BP. The magnitude of BP lowering was greater on day 1 than on days 14 and 28, but the response was sustained between days 14 and 28. PF-00489791 also exerted BP lowering effects on mean 24-hour ambulatory BP. There was a dose-related increase in plasma cGMP concentration (statistically significant at the 20/40 mg dose). There was an increased incidence of headaches at the 10 and 20/40 mg doses (22% and 21%, respectively, compared with 12% with placebo) and an increased incidence of dyspepsia/gastroesophageal reflux disease and musculoskeletal adverse events at the 20/40 mg dose. In conclusion, PF-00489791 causes a clinically meaningful and sustained BP lowering in patients with hypertension. It is generally safe and well tolerated at the clinically efficacious doses. (Hypertension. 2009;53:1091-1097.)

Key Words: hypertension ■ phosphodiesterase 5 ■ PDE-5 inhibition ■ PF-00489791 ■ ABPM ■ cGMP ■ blood pressure

Inhibition of phosphodiesterase 5 (PDE-5) is an attractive candidate mechanism for blood pressure (BP) lowering. PDE-5 is an enzyme that, among several other tissues, is also expressed in human arterial and venous vascular smooth muscle (VSM) cells,1,2 where it mediates the breakdown of cGMP by metabolizing it to inactive 5’-GMP. Elevated cGMP reduces levels of intracellular calcium and thereby produces relaxation of arterial VSM cells and hence a decrease in arterial vascular resistance. Thus, inhibition of PDE-5 should lead to an increase in intracellular cGMP, arterial and venous vasorelaxation, and a consequent reduction in systemic arterial BP. In the present study, we evaluated BP lowering effects of a novel long-acting PDE-5 inhibitor, PF-00489791, in patients with mild to moderate hypertension.

Methods

Study Subjects and Study Design

Patients were recruited and the study was conducted at 17 participating study centers in the United States. Written informed consent was obtained from each study participant. The final protocol and informed consent documentation were reviewed and approved by the institutional review board at each of the investigational centers. The study was registered on ClinicalTrials.gov.

Study subjects included males and females of nonchildbearing potential, between the ages of 18 and 70 years, who had a history of mild to moderate hypertension that was currently controlled with antihypertensive medication, or, if untreated, a mean seated cuff BP reading with a diastolic BP (DBP) of 140 to 179 mm Hg, taken in duplicate reading with a diastolic BP (DBP) of 90 to 109 mm Hg and/or a antihypertensive medication, or, if untreated, a mean seated cuff BP reading with a diastolic BP (DBP) of 90 to 109 mm Hg and/or a systolic BP (SBP) of 140 to 179 mm Hg, taken in duplicate \(\approx 5\) minutes apart. Major exclusion criteria included secondary hypertension and malignant hypertension, type 1 and type 2 diabetes mellitus on prescribed medications (diet and exercise control were not exclusions), any major cardiovascular event within the last 12 months of enrollment, and congestive heart failure or known left ventricular ejection fraction <40%. Nitrates or NO donors were to be discontinued \(\approx 21\) days before the treatment period and were not to be taken during the study.

Subjects were randomized in a double-blind manner into one of the following parallel treatment arms: 4 mg of PF-00489791, 10 mg of PF-00489791, 20 mg of PF-00489791 titrated after 14 days of dosing to 40 mg, and placebo. Oral PF-00489791 or placebo was administered once daily for 28 days, in the morning.

The study consisted of 3 periods: a 1-week screening period, a 3- to 4-week single-blind placebo run-in period, and a 4-week double-
blind treatment period (PF-00489791 or placebo). During the placebo run-in period, subjects on active antihypertensive medications were required to discontinue their use for ≥3 weeks before randomization to the treatment period. To qualify for the treatment period, subjects had to demonstrate mean seated cuff SBP and DBP of ≥140/90 mm Hg (but <180/110 mm Hg) on 2 consecutive occasions, at least 1 week apart, during the placebo run-in period. They also had to participate in the ambulatory BP monitoring (ABPM) assessments and had to demonstrate a mean daytime ABPM reading with both SBP of ≥135 mm Hg and DBP ≥85 mm Hg.

Study Evaluations

Ambulatory BP Monitoring

ABPM was performed at the end of the placebo run-in period while the subject was still taking placebo (day 0; baseline) and then on study days 1, 14, and 28. The ABPM device (90207 ABP Monitor; Spacelabs Healthcare) was automatically programmed to inflate every 20 minutes from 5 AM until 9:59 PM. From 10 PM to 4:59 AM, the device inflated every 60 minutes. Mean 24-hour, daytime (between 8 AM and 3:59 PM), and nighttime (between 10 PM to 5:59 AM) SBP and DBP were derived from 24-hour ABPM as the average of measurements taken over the respective time period. ABPM recordings were downloaded, evaluated, and analyzed in a blinded manner at Spacelabs Healthcare, and the data were provided to Pfizer.

Cyclic Guanosine Monophosphate

Blood samples for cGMP analysis were collected before dosing on days 1, 14, and 28. Blood samples (3 mL) to provide a minimum of 1 mL plasma for cGMP analysis were collected into prechilled tubes containing ethylenediamine tetraacetic acid (EDTA). Plasma was separated from the whole blood within ~30 minutes of collection. Plasma samples were kept frozen until analysis with a validated high-performance liquid chromatography–tandem mass spectrometry method with a lower limit of quantification of 0.5 ng/mL.

Safety

Adverse events, laboratory tests (hematology, clinical chemistry, urinalysis), vital signs (BP and heart rate [HR]), and 12-lead ECG were assessed periodically during the study and complemented by physical examinations.

Statistical Analyses

The primary end point was the change from predose baseline (day 0) to day 28 in mean daytime SBP as measured by ABPM. The primary statistical analysis consisted of a 3-parameter E_max nonlinear dose-response model fit to the primary end point. Analysis of covariance (ANCOVA) was also performed. The baseline value of the response variable was included as a covariate in each of the models, and the investigative center was included as a covariate in the ANCOVA model.

The secondary efficacy end points included the following: change from baseline to day 28 in mean daytime DBP; change from baseline to day 28 in mean 24-hour SBP and DBP; and change from baseline to day 28 in mean 24-hour pulse pressure. The change in mean daytime DBP was analyzed using the same methods as the primary end point, whereas all other secondary end points were analyzed by ANCOVA. Changes from baseline to day 28 in cGMP were analyzed using the ANCOVA model. For all statistical analyses, a 2-sided P value was used.

Results

Study Subjects

A total of 133 subjects received at least 1 dose of study medication. The subjects’ baseline characteristics are summarized in Table 1. There were no significant differences between the study groups with respect to a variety of demographic parameters, including past or current medical history or concomitant treatment.

Effects of PF-00489791 on Mean Daytime ABPM

The primary end point was the change from predose baseline to day 28 in mean daytime SBP. Changes in mean daytime SBP (unadjusted for any covariates) are presented in Figure 1A as profiles over time. Using the nonlinear dose-response model, there was a statistically significant decrease in mean daytime SBP at day 28 between each of the 2 higher doses of PF-00489791 (10 and 20/40 mg) and placebo (Table 2). To evaluate for robustness of the finding, a second analysis was done using an ANCOVA model, and similar results were obtained. The change from baseline to day 28 in mean daytime SBP in the placebo group was small, suggesting that the study was adequately controlled and that the washout of previous antihypertensive medications was adequate.

The change in mean daytime ambulatory DBP was considered a secondary end point. As shown in Figure 1B, changes in mean daytime ambulatory DBP corresponded with those in SBP. All PF-00489791 dose levels resulted in a statistically significant DBP lowering at day 28 compared with placebo using the nonlinear dose-response model (Table 2). Similar results were obtained using the ANCOVA model.

Based on the graphical summary of the changes from baseline in mean daytime ambulatory SBP and DBP presented in Figure 1, the magnitude of BP lowering achieved at the 10 and 20/40 mg doses of PF-00489791 was greater on day 1 than on days 14 and 28, but the response was sustained between days 14 and 28. This suggests either the possibility of an adaptive response to continued dosing between day 1 and day 14 or a more prominent BP lowering effect of the first dose on day 1.

Effects of PF-00489791 on Mean 24-Hour ABPM

Changes in mean 24-hour ambulatory SBP and DBP are presented in Figure 2. Results of the statistical analysis are summarized in Table 3. Only the 10 mg PF-00489791 dose resulted in a statistically significant DBP lowering at day 28 compared with placebo. However, both the 10- and 20/40 mg PF-00489791 doses significantly lowered the mean 24-hour ambulatory DBP. None of the PF-00489791 doses resulted in a statistically significant effect on mean 24-hour pulse pressure compared with placebo.

Effects of PF-00489791 on Plasma cGMP Levels

The time course of changes from baseline in plasma cGMP concentration is shown in Figure 3. There appeared to be a dose-related and continuous increase in plasma cGMP concentration over the 28-day treatment period. Using the ANCOVA model, only the 20/40 mg PF-00489791 dose resulted in a statistically significant effect on plasma cGMP (P value was 0.6637, 0.1565, and 0.0005 for the 4-, 10-, and 20/40 mg dose groups, respectively).
Clinical Safety of PF-00489791

Overall, PF-00489791 was safe and well tolerated at all doses investigated. The majority of the reported adverse events were mild or moderate in intensity. The most frequent adverse events, by body system, were nervous system disorders (28 adverse events), gastrointestinal disorders (19 adverse events), and musculoskeletal disorders (11 adverse events). Adverse events of all causality that occurred in subjects in any treatment group are presented in Table 4. The most common single adverse event was headache. Headache appeared to occur in a dose-dependent manner, with a higher incidence at the PF-00489791 doses of 10 and 20/40 mg (22% and 21%, respectively) compared with placebo (12%). Dyspepsia/gastroesophageal reflux disease and musculoskeletal adverse events occurred most often in the 20/40 mg group.

There were no reported cases of clinical significance of orthostatic hypotension during the study or rebound hypertension after drug withdrawal at the end of dosing. None of the observed changes in BP after the first dose met the predefined criterion of symptomatic hypotension (defined as SBP <100 mm Hg accompanied by symptoms of lightheadedness, dizziness, or syncope).

Five subjects were permanently discontinued from the study because of adverse events (1 subject in the placebo group, 2 subjects in the 4 mg group, 1 subject in the 10 mg group, and 1 subject in the 20/40 mg group), and 1 subject had a temporary discontinuation because of an adverse event.

There were no clinically significant postdose laboratory test abnormalities or changes in ECG or vital signs. Effects on HR were not modeled, and no formal statistical analysis was performed. However, based on the graphical summary (data not shown), there appeared to be an early increase in mean HR in the 10 mg group relative to placebo that was not sustained over time. A modest but sustained increase in mean

### Table 1. Summary of Subjects' Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo n=34</th>
<th>PF-00489791 4 mg n=34</th>
<th>PF-00489791 10 mg n=32</th>
<th>PF-00489791 20/40 mg n=33</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male, n</td>
<td>20</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>Female, n</td>
<td>14</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Age, y</td>
<td>Mean (SD)</td>
<td>57 (6)</td>
<td>57 (9)</td>
<td>58 (7)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>44 to 68</td>
<td>36 to 70</td>
<td>42 to 69</td>
</tr>
<tr>
<td>Race</td>
<td>White, n</td>
<td>21</td>
<td>23</td>
<td>17</td>
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<tr>
<td></td>
<td>Black, n</td>
<td>6</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Asian, n</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td></td>
<td>Other, n</td>
<td>6</td>
<td>5</td>
<td>7</td>
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<tr>
<td>Weight, kg</td>
<td>Mean (SD)</td>
<td>90 (18)</td>
<td>91 (19)</td>
<td>88 (17)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>52 to 129</td>
<td>56 to 137</td>
<td>54 to 132</td>
</tr>
<tr>
<td>Height, cm</td>
<td>Mean (SD)</td>
<td>171 (11)</td>
<td>170 (10)</td>
<td>171 (11)</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>152 to 189</td>
<td>142 to 186</td>
<td>147 to 191</td>
</tr>
</tbody>
</table>
| Duration of hypertension since first diagnosis, y
| Mean                                  | 10.1         | 10.6                   | 11.7                   | 9.8                      |
| Range                                 | 1.0 to 28.0  | 0.8 to 38.0            | 0.0 to 32.0            | 0.2 to 23.2              |
| Mean daytime SBP (mm Hg) by ABPM      | Mean (SD)    | 151 (9)                | 151 (9)                | 155 (11)                 | 151 (12)                 |
|                                       | Range        | 137 to 173             | 136 to 177             | 139 to 175               | 134 to 171               |
| Mean daytime DBP (mm Hg) by ABPM      | Mean (SD)    | 97 (7)                 | 93 (7)                 | 96 (9)                   | 96 (8)                   |
|                                       | Range        | 82 to 111              | 82 to 108              | 84 to 114                | 82 to 116                |
| Mean 24-hour SBP (mm Hg) by ABPM      | Mean (SD)    | 148 (9)                | 147 (10)               | 152 (10)                 | 147 (11)                 |
|                                       | Range        | 131 to 171             | 132 to 176             | 136 to 170               | 128 to 166               |
| Mean 24-hour DBP (mm Hg) by ABPM      | Mean (SD)    | 94 (7)                 | 89 (6)                 | 94 (9)                   | 92 (7)                   |
|                                       | Range        | 80 to 109              | 78 to 104              | 80 to 111                | 78 to 108                |
HR (not exceeding 6 bpm at any time point) appeared to be associated with the dose of 20/40 mg, but it was not accompanied by any apparent symptoms, such as palpitations or rapid heart beat. There was no apparent effect of the dose of 4 mg on mean HR when juxtaposed to the change with placebo.

**Discussion**

**BP Lowering Effects**

The results from this study demonstrated statistically significant differences in BP lowering (measured by ABPM) for the 2 doses of PF-00489791 (10 and 20/40 mg) compared with placebo, for the primary end point of mean daytime SBP. Both the 10 mg and 20/40 mg PF-00489791 doses resulted in similar and clinically meaningful decreases in daytime SBP. The 4 mg dose did not result in a significant effect on daytime ambulatory SBP, although the mean reduction was $\approx 3$ mm Hg ($P=0.08$). These results suggest that the minimally efficacious dose of PF-00489791 with respect to SBP is between 4 mg and 10 mg for a 4-week period of exposure. Changes in mean daytime DBP corresponded with the changes in mean daytime SBP. PF-00489791 did not have any statistically significant effect on mean ambulatory pulse pressure compared with placebo, consistent with the observation that the magnitude of BP lowering was similar for SBP and DBP.

It is interesting to note that the effect of PF-00489791 on BP appeared to be similar for the 10 mg and 20/40 mg doses, which may indicate that the maximum BP lowering response was already achieved at the dose of 10 mg. This may be consistent with a steeply rising dose response or with a response that is near maximal once a threshold level of enzymatic inhibition is reached. Alternatively, the sustained increase in HR at higher doses (20/40 mg) may have counterbalanced the peripheral vasodilator response by increasing cardiac output. However, investigation of this finding was beyond the scope of the study.

The magnitude of mean daytime SBP and DBP lowering was less on days 14 and 28 than on day 1. This may suggest some degree of adaptation in BP response to continued exposure.

**Table 2. Analysis of Change From Baseline to Day 28 (vs Placebo) in Mean Daytime Ambulatory SBP and DBP Using the Nonlinear Dose-Response Model**

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Change in Mean Daytime Ambulatory SBP (mm Hg)</th>
<th>Change in Mean Daytime Ambulatory DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS Mean (SE) 95% CI</td>
<td>$P$ Value</td>
</tr>
<tr>
<td>PF-00489791 4 mg</td>
<td>$-2.80 (1.60)$</td>
<td>$(-5.97, 0.36)$</td>
</tr>
<tr>
<td>PF-00489791 10 mg</td>
<td>$-4.66 (1.92)$</td>
<td>$(-8.47, -0.85)$</td>
</tr>
<tr>
<td>PF-00489791 20/40 mg</td>
<td>$-6.97 (2.26)$</td>
<td>$(-11.45, -2.48)$</td>
</tr>
</tbody>
</table>

LS indicates least squares.
dosing compared with day 1, as might be expected from a vasodilatory drug acting through NO. However, the magnitude of BP lowering was maintained between days 14 and 28, indicating that the adaptive response might be self-limited and that a sustained effect of PF-00489791 on BP was achieved. This is in contrast to organic nitrates, which act as NO donors that relax VSM, but because they rapidly desensitize guanylyl cyclase, their hypotensive effects are attenuated rapidly during chronic therapy.

BP lowering effects have also been recognized with other PDE-5 inhibitors. For example, in healthy normotensive subjects, sildenafil (100 mg), vardenafil (20 mg), and tadalafil (20 mg) reduce supine cuff BP by −8.4/−5.5 mm Hg, −7.5/−8 mm Hg, and −1.6/−0.8 mm Hg, respectively. Greater decreases in BP may be observed in treated or untreated hypertensive patients. Acute BP reductions have also been observed after single-dose administration of sildenafil (50 mg) or tadalafil (20 mg) when measured with ABPM. Of particular relevance to our study of PF-00489791 is a study of multiple-dose administration of sildenafil in untreated hypertensive patients. In that study, 50 mg of sildenafil or placebo was administered 3 times daily for 16 days in 25 subjects, in a crossover design. Mean daytime BP (measured by ABPM) decreased by −8/−6 mm Hg, and mean 24-hour BP decreased by −7/−5 mm Hg (the effects similar in magnitude to those in our study). However, no PDE-5 inhibitors are approved for treatment of hypertension. A short duration of action and variation in bioavailability make some of the PDE-5 inhibitors less favorable as antihypertensive drugs. Conversely, an agent with a longer duration of action, such as PF-00489791, may potentially prove clinically useful.

As one druggable attribute, the human pharmacokinetics of PF-00489791 are consistent with once-daily dosing (half-life = 12 to 15 hours; Pfizer, unpublished data, 2006). Second, the BP lowering effects of PF-00489791 were maintained despite repeated dosing. Third, PF-00489791 had a very favorable safety profile at the BP lowering doses, with no reported cases of first-dose hypotension, orthostatic hypotension, or rebound hypertension after withdrawal of study drug. Fourth, PF-00489791 may be unique in the armamentarium of antihypertensive drugs by its involvement in the vascular NO–cGMP pathway and thereby its ability to improve endothelial function and endothelium-dependent vasodilation. And finally, PDE-5 inhibition may potentially offer additional beneficial effects on hypertensive end-organ damage, independent of and beyond the BP lowering effect, including effects on nephropathy, stroke, or myocardial hypertrophy. That said, it has to be recognized that the overall magnitude of the maximum sustained BP lowering effect of PF-00489791 in the present study was relatively modest.

### Mechanism of Action

The highest dose of PF-00489791 tested in this study, 20/40 mg, resulted in a statistically significant increase in plasma cGMP values from baseline to day 28 compared with placebo. Overall, there appeared to be a dose-related effect of PF-00489791 on plasma cGMP. Therefore, the most straightforward explanation of the BP lowering effect observed in the present study is inhibition of VSM PDE-5 by PF-00489791, with a consequent increase in intracellular VSM cGMP, a decrease in intracellular calcium, and a resultant VSM relaxation, leading to a decrease in systemic BP (the similar degree of SBP and DBP reduction may reflect effects on both the arterial and venous vasculature). This explanation is consistent with the observed increases in plasma cGMP, although intracellular cGMP was not measured in our study.

However, it is of note that the BP effects of the 10 mg and the 20/40 mg doses of PF-00489791 were relatively similar in magnitude, whereas the 10 mg dose had a much less pronounced effect on plasma cGMP. Therefore, it is conceivable that the BP effects of PF-00489791 may, at least in part, be independent of cGMP. One such mechanism is the blockade of the calcium channels, which has been demonstrated for some other PDE-5 inhibitors. Another possibility is an increased expression of endothelial NO synthase or inhibition of and beyond the BP lowering effect, including effects on nephropathy, stroke, or myocardial hypertrophy. That said, it has to be recognized that the overall magnitude of the maximum sustained BP lowering effect of PF-00489791 in the present study was relatively modest.

### Table 3. Analysis of Change From Baseline to Day 28 (vs Placebo) in Mean 24-Hour Ambulatory SBP and DBP Using the ANCOVA Model

<table>
<thead>
<tr>
<th>Treatment Arm</th>
<th>Change in Mean 24-h Ambulatory SBP (mm Hg)</th>
<th>Change in Mean 24-h Ambulatory DBP (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LS Mean (SE) 95% CI P Value</td>
<td>LS Mean (SE) 95% CI P Value</td>
</tr>
<tr>
<td>PF-00489791 4 mg</td>
<td>0.13 (1.98) (−3.79, 4.05) 0.9479</td>
<td>−1.45 (1.44) (−4.30, 1.41) 0.3173</td>
</tr>
<tr>
<td>PF-00489791 10 mg</td>
<td>−4.75 (2.03) (−8.78, −0.72) 0.0215</td>
<td>−3.81 (1.42) (−6.64, −0.99) 0.0087</td>
</tr>
<tr>
<td>PF-00489791 20/40 mg</td>
<td>−3.43 (2.00) (−7.39, 0.53) 0.0886</td>
<td>−3.95 (1.41) (−6.76, −1.15) 0.0062</td>
</tr>
</tbody>
</table>

LS indicates least squares.

### Figure 3. Changes from baseline (mean ± SE) in plasma cGMP.

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The role of PF-00489791 in the treatment of hypertension and well tolerated at the clinically efficacious doses of 10 to 20 mg and lower, indicating that a sustained BP lowering effect can be achieved at PF-00489791 doses that are very well tolerated during chronic therapy. It is safe and well tolerated at the clinically efficacious doses of 10 to 20 mg per day. The role of PF-00489791 in the treatment of hypertension and hypertension-associated diseases awaits further clinical investigation.

**Source of Funding**

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**Disclosures**

R.W., D.X., J.M., J.G., and M.L.P. are employed by Pfizer, and R.W., J.M., J.G., and M.L.P. own stock or stock options in the company. W.B.S., J.M.N., and J.R. were contracted by Pfizer as investigators for patient recruitment into this study. J.N. is a Speakers’ Bureau member for Pfizer and received honoraria from the Speakers’ Bureau. J.R. owns Pfizer stock.

**References**


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