A CCR2/5 Inhibitor, PF-04634817, Is Inferior to Monthly Ranibizumab in the Treatment of Diabetic Macular Edema

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PURPOSE. Ligands for the proinflammatory C-C chemokine receptor types 2 and 5 (CCR2 and CCR5) are elevated in the eyes of patients with diabetic macular edema (DME). We evaluated the efficiency and safety of PF-04634817, an oral CCR2/5 dual antagonist, versus intravitreal ranibizumab, in adult subjects with DME.

METHODS. In this phase II, randomized, placebo-controlled, double-masked study, eligible subjects (>18 years of age) had type 1 or 2 diabetes and DME with best-corrected visual acuity (BCVA) of 20/32 or worse (letter score ≤78), and up to 20/520 or better (≥24 letter score), in the study eye. Subjects were assigned randomly 1:1 to once-daily (QD) oral PF-04634817 200 mg plus masked sham therapy as placebo or monthly intravitreal ranibizumab 0.3/0.5 mg plus masked sham therapy as placebo or monthly intravitreal ranibizumab 0.3/0.5 mg plus QD oral placebo. The primary objective was to evaluate the efficacy of PF-04634817 compared with ranibizumab in change from baseline in BCVA after 12 weeks in a noninferiority design. Noninferiority was based on BCVA 80% confidence interval (CI): there had to be a less than three letter loss in the PF-04634817 arm compared with the ranibizumab arm.

RESULTS. A total of 199 subjects were randomized. Least squares mean difference in change in BCVA from baseline to week 12 in the study eye for the PF-04634817 arm was −2.41 letters (80% CI: −3.91, −0.91; P = 0.04) compared with ranibizumab. PF-04634817 was well tolerated.

CONCLUSIONS. Treatment with oral CCR2/5 receptor dual antagonist PF-04634817 was associated with a modest improvement in BCVA, but did not meet the predefined noninferiority criteria compared with intravitreal ranibizumab.

Keywords: CCR2, CCR5, diabetes, diabetic macular edema, visual acuity

In 2014, it was reported that diabetes mellitus affects ~422 million adults worldwide.1 If not appropriately controlled, diabetes is linked with several serious complications, including visual impairment.1,2 Diabetic retinopathy, a microvascular complication of diabetes3 associated with various risk factors including poor glycemic control,5 is a leading cause of acquired vision loss in adults,4,5 and in 2010 was attributed to 2.6% of global blindness.6 Anatomical and biochemical changes resulting from retinopathy may lead to diabetic macular edema (DME) in up to a third of patients with diabetes7,8 and is characterized clinically by swelling of the macula due to increased permeability of blood vessels.4 DME accounts for the majority of vision loss in diabetics, and has a major impact on the US working population in terms of productivity losses and absenteeism.9,10 Focal or grid photocoagulation has been used for the treatment of DME since the 1980s.5,11,12 Although effective, this is limited to treating the pathology, but not the underlying biochemical changes, and results in permanent retinal scarring.13 Intravitreal administration of corticosteroids is beneficial for some patients with DME.14 The mechanisms of action of these agents include nonspecific anti-inflammatory properties14. VEGF is the primary mediator of the breakdown in blood–retinal barrier characteristic of DME.2,15,16 The intravitreal anti-VEGF therapies, ranibizumab (Lucentis; Genentech, Inc., San Francisco, CA, USA) and aflibercept (Eylea; Regeneron, Inc., Tarrytown, NY, USA), have become the standard of care for DME, with functional and anatomical benefits evident in terms of improved visual acuity and associated decreases in retinal thickness.17–20 Nevertheless, intravitreal therapy has limitations, and patients risk pain, short- and long-term increases in intraocular pressure (IOP), subconjunctival/vitreal hemorrhages, vitreous floaters, retinal detachment, and endophthalmitis.5,21–24

Although VEGF is an important mediator, the pathogenesis of DME is multifaceted,4,27 involving various underlying angiogenic and inflammatory pathways* that may serve as drug targets. The concentration of ligands for C-C chemokine receptor types 2 (CCR2; primary ligand: monocyte chemo-attractant protein-1 [MCP-1]) and 5 (CCR5; primary ligand:
RANTES are elevated in the vitreous and aqueous humors of patients with diabetic retinopathy/DME. CCR2 and CCR5, expressed on the surface of monocytes, play a key role in inflammation and in the homing of inflammatory cells to their target tissues. Preclinical studies have linked the CCR2 pathway with vascular leakage from, and monocyte infiltration into, the retina in experimental diabetes. Furthermore, CCR2 has been implicated in modulating VEGF production, suggesting that CCR2 antagonism might be an indirect mechanism for modulating VEGF levels. Thus, antagonism of CCR2 and CCR5 receptors represent credible targets for reducing vascular leakage and inflammation in the retina in patients with diabetic retinopathy and DME.

PF-04634817 is a small molecule CCR2/5 chemokine receptor dual antagonist. To test the hypothesis that inhibition of CCR2/5 pathways could reduce DME and vascular leakage and lead to improved visual acuity, the efficacy and safety of oral PF-04634817 were compared with intravitreal ranibizumab in adult subjects with DME (NCT01994291).

METHODS

Subjects

Subjects were enrolled in 49 centers across nine countries (Bulgaria, Czech Republic, Germany, Hungary, Israel, Poland, Republic of Moldova, Romania, United States). Eligible subjects were ≥18 years of age; had received no anti-angiogenic therapy within 3 months of screening; had a clinical diagnosis of diabetes mellitus (type 1 or 2), with a serum glycosylated hemoglobin A1c (HbA1c) level of <10.5%; had a best corrected visual acuity (BCVA) of 20/32 or worse (≤78 letters) and up to 20/520 or better (≥24 letters) in the study eye as measured with the early treatment diabetic retinopathy study-BCVA (ETDRS-BCVA) eye chart; and had DME affecting the fovea of the study eye as measured by fluorescein angiography and also demonstration of a central retinal thickness ≥250 μm using optical coherence tomography (OCT; measured by CIRRUS [Zeiss, Jena, Germany] or SPECTRALIS [Heidelberg, MA, USA]). BCVA in the fellow (nonstudy) eye had to be 20/400 or better (≥19 letters); if both eyes met inclusion criteria, the most severely affected was selected as the study eye. Subjects were excluded from the study if they had a history of active/untreated Mycobacterium tuberculosis infection; severely impaired renal function; and any intraocular condition or previous surgery, or high risk of proliferative diabetic retinopathy, in either eye. Medications that were prohibited during the study included moderate-to-strong cytochrome P450 3A4 (CYP3A4) inducers/inhibitors and intraocular/periocular steroids in either eye.

All subjects provided written informed consent. This study was conducted in compliance with the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice Guidelines and was approved by the Institutional Review Boards (IRBs) and/or Independent Ethics Committees at each of the investigational centers participating in the studies or a central IRB.

Study Design and Treatment

This was a 16-week, multicenter, randomized, placebo-controlled, double-masked, parallel-group phase II study based on a noninferiority design (Fig. 1).

Following stratification according to baseline kidney function, eligible subjects were randomized 1:1 to one of two treatment arms. The PF-04634817 plus masked sham therapy arm comprised oral PF-04634817 (200 mg once daily [QD], supplied as bottled 50-mg tablets) plus masked sham therapy (monthly), which comprised a capped, sterile, empty syringe without needle that otherwise was identical to that used to administer ranibizumab in the other study arm. The ranibizumab plus placebo arm comprised intravitreal administration of ranibizumab (0.3 mg [supplied as 6 mg/mL in a single-use vial] or 0.5 mg [supplied as 10 mg/mL in a 0.2-mL vial] per month, as per the approved label relevant to the study site) plus oral placebo (QD) that matched PF-04634817.

Doses of PF-04634817 were selected based on data from healthy volunteers that demonstrated daily doses of up to 300
mg to be safe and well-tolerated in four phase 1 studies: NCT01098877, evaluating a single oral dose (fed and fasted state); NCT011140672, evaluating multiple doses; NCT01247883, a comparison of tablet versus oral solution formulation; and NCT01791855, a study in patients with renal impairment. In addition, the use of pharmacokinetic/pharmacodynamic modeling approaches, using biomarker data generated from these studies, confirmed high levels of CCR2 receptor-blocking activity with the 200 mg QD dose of PF-04634817. Population-based pharmacokinetic modeling was used to simulate the possible effect of renal impairment on PF-04634817 exposure (clearance occurs via a combination of CYP3A4 metabolism and renal clearance), with results predicting that exposure would be increased in patients with renal impairment. These simulations were verified by a renal impairment study (NCT01791855). Thus, subjects with significant levels of renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m²) were ineligible for participation.

An Interactive Voice Response System (IVRS) or equivalent, which assigned subjects a single identifying number at screening, was used to manage enrollment and medication supplies. Following randomization, all study medications were administered as assigned by the IVRS. All study investigators and participants were masked to treatment allocation; efficacy and safety evaluations were conducted by an investigator separate from the one who prepared and administered intravitreal injections and sham therapy.

**Efficacy and Safety Evaluations**

The primary objective was to evaluate whether the clinical efficacy of PF-04634817 is noninferior to ranibizumab, as measured by change in BCVA from baseline after 12 weeks of treatment.

Secondary objectives included the following: effects of PF-04634817 on macular edema and diabetic retinopathy; safety and tolerability; and systemic effects on several biomarkers. Primary and secondary efficacy analyses were calculated for the study eye; as ranibizumab was only injected into one eye, all analyses of the fellow eye were calculated and reported separately.

The effects of PF-04634817 on BCVA (ETDRS), central retinal thickness (CCT), vascular leakage (fluorescein angiography), and diabetic retinopathy (changes in four-wide field digital color fundus photography) were assessed. Changes from baseline in biomicroscopic and ophthalmoscopic parameters, together with IOP, physical attributes, blood pressure/pulse, electrocardiogram (ECG), clinical laboratory test results (including serum creatinine and estimates of glomerular filtration), and adverse event (AE) profiles were evaluated to assess safety and tolerability of PF-04634817. In addition, a 4-mL blood sample from each subject was collected and analyzed to determine systemic exposure of PF-04634817 (Covance Bioanalytical Services, Shanghai, China).

**Statistical Analyses**

The full analysis set (FAS) included all subjects who received at least one dose of randomized treatment and had at least one postbaseline measurement of BCVA. Sample size calculations were based on the primary efficacy end point, with the study planned to enroll ~100 subjects per arm (~10% dropout assumed). This sample size provided ~76% power assuming no difference between PF-04634817 and standard of care, and an SD of 10 letters. The study was considered successful if PF-04634817 was noninferior to ranibizumab. Noninferiority was determined at the end of the study via the use of an 80% confidence interval (CI) for the treatment difference δ. If the lower limit of the interval is less than −4 letters (e.g., −4.0 or −5 letters), then PF-04634817 was to be declared noninferior to ranibizumab. All other comparisons and end points were descriptive.

Analysis of the primary end point was based on a mixed model repeated-measures (MMRM) analysis using all postbaseline time points. This model included fixed effects for treatment (PF-04634817, ranibizumab 0.3 mg/0.5 mg), time (all postdose visits, including follow-up where applicable), previous treatment status (naïve or received prior ranibizumab), baseline kidney function, and treatment by time interaction. The baseline values of BCVA were included as covariates, and the differences between all posttreatment changes and baseline were included as dependent variables. Secondary end points were analyzed with an MMRM as per the primary end point, aside from the area of vascular leakage and severity steps of diabetic retinopathy, which were assessed with an analysis of covariance (ANCOVA) model. The ANCOVA included the baseline values of BCVA as covariates and the fixed effects for treatment, previous treatment status, and baseline kidney function.

Binary end points, including the proportion of subjects gaining ≥15 ETDRS letters from baseline, were analyzed using a generalized linear mixed model, including covariates for treatment, previous treatment status, and baseline kidney function.

Summary statistics were obtained for pharmacokinetic PF-04634817 concentrations and all safety data.

**RESULTS**

**Subjects**

The study was terminated early for business reasons. All subjects who were in screening at the time of this decision were allowed to complete the screening process, and if found to be eligible for inclusion and randomization, were allowed to enter the study if they so wished. This resulted in 199 of the intended 200 subjects entering the study. In total, 167 of 199 randomized subjects completed the study (Fig. 2). Rates and reasons for study discontinuation were similar between treatment arms.

Subject demographics and disease characteristics were generally balanced between treatment arms (Table 1). The presence of DME at baseline in the study population is confirmed in Table 1.

**Efficacy**

**BCVA.** Least squares (LS) mean changes from baseline in BCVA for the study eye are shown in Figure 3A. For the primary comparison of the change from baseline in BCVA in the study eye at week 12, the LS mean difference between the PF-04634817 plus masked sham therapy arm versus the ranibizumab 0.3/0.5 mg plus placebo arm was −2.41 letters (80% CI: −3.91 to −0.91; P = 0.0399). The lower two-sided 80% CI limit for the difference in LS means was <−3 letters, and the upper bound of the CI was <0 letters; therefore, PF-04634817 was inferior to ranibizumab.

LS mean changes from baseline in BCVA for the fellow eye (in subjects with baseline BCVA in the eye of between 24 and 78 letters, inclusive) are shown in Figure 3B. In the fellow eye at week 12, the LS mean difference between the PF-04634817...
FIGURE 2. Subject disposition. FAS: all subjects who received at least one dose of randomized treatment and had at least one postbaseline measurement of BCVA. Safety analysis set: all subjects who received at least one dose of study medication (data are reported for subjects analyzed for AEs); one subject in each of the ranibizumab 0.3 mg plus placebo and 0.5 mg plus placebo arms were not analyzed for laboratory data. One subject was randomized but discontinued prior to dosing.
and ranibizumab arms was not statistically significant (LS mean difference 0.66 letters; 80% CI: −1.06, 2.38; P = 0.6213).

The proportion of subjects in the PF-04634817 arm gaining 15 ETDRS letters in BCVA from baseline to week 12 was also numerically inferior to the ranibizumab arm (LS mean difference −0.0849; 80% CI: −0.1516, −0.0168; P = 0.0778) in the study eye. There was also no statistically significant difference in the fellow eye between treatment arms (LS mean difference −0.0104; 80% CI: −0.0441, 0.0250; P = 0.6823).

**Central Subfield Retinal Thickness.** LS mean changes from baseline in central subfield retinal thickness are shown in Figures 4A and 4B for the study/fellow eye. In the study eye, at week 12 compared with baseline, there was a small increase in central subfield retinal thickness in the PF-04634817 arm (LS mean 1.75 μm; 80% CI: −50.41, 53.77), whereas in the ranibizumab arm, central subfield retinal thickness decreased (LS mean −85.59 μm; 85% CI: −136.8, 34.45). The difference between the treatment arms was statistically significant (LS mean difference 87.32 μm; 80% CI: 67.45, 107.19; P < 0.0001). In the fellow eye, there was no statistically significant difference between treatment arms (LS mean difference −13.26 μm; 80% CI: −26.59, −0.12; P = 0.1960).

**Vascular Leakage.** In the study eye (data not reported for fellow eye), the LS mean difference in change from baseline at week 12 in area of vascular leakage was slightly increased in the PF-04634817 arm (mean change from baseline 1.02 mm²), whereas it decreased in the ranibizumab arm (mean change from baseline −6.05 mm²; LS mean difference 7.07 mm²; 80% CI: 5.66, 8.48; P < 0.0001).

**Diabetic Retinopathy.** In the study eye (data not reported for fellow eye), there was also a small increase in severity steps of diabetic retinopathy (ETDRS severity scale) in the PF-04634817 arm (mean change from baseline at week 12 was 0.11 steps), compared with a decrease in the ranibizumab arm (mean change from baseline at week 12 was −0.35 steps; LS mean difference 0.46 steps; 80% CI: 0.30, 0.63; P = 0.0004).

**Secondary and Exploratory Analyses.** Spearman correlations between the changes from baseline at week 12 in key secondary and exploratory efficacy outcomes are summarized in Supplementary Table S1.

**Pharmacokinetic and Pharmacodynamic Findings.** Observed plasma PF-04634817 concentrations over time indicated that steady state was achieved after ~1 week of treatment (data not shown).

There was no statistically significant difference in the mean percentage change in plasma HbA1c concentration from baseline at week 12 between the PF-04634817 (−0.091; SD, 8.8289) and ranibizumab (0.497; SD, 10.5857) arms. The time

### TABLE 1. Subject Demographics and Baseline Disease Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PF-04634817 200 mg QD</th>
<th>Ranibizumab 0.3 mg</th>
<th>Ranibizumab 0.5 mg</th>
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<tr>
<td><strong>Demographics</strong></td>
<td></td>
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<tr>
<td>Male, n (%)</td>
<td>N = 99</td>
<td>N = 43</td>
<td>N = 56</td>
<td>N = 99</td>
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<tr>
<td>Age, mean (SD), y</td>
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<td>60.4 (7.5)</td>
<td>64.3 (8.4)</td>
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<td>Race, n (%) white</td>
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<td>31 (72.4)</td>
<td>56 (100)</td>
<td>87 (87.9)</td>
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<td>95.5 (17.3)</td>
<td>87.5 (15.0)</td>
<td>90.1 (16.2)</td>
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<tr>
<td>BMI, mean (SD) kg/m²</td>
<td>30.9 (6.2)</td>
<td>32.7 (6.3)</td>
<td>30.1 (4.2)</td>
<td>31.2 (5.4)</td>
</tr>
</tbody>
</table>

- N: Not applicable
- SD: Standard deviation
- CI: Confidence interval
- P: Probability
- LS: Least squares
- ETDRS: Early Treatment Diabetic Retinopathy Study
- SD: Standard deviation
- CI: Confidence interval
- P: Probability
FIGURE 3. (A) LS mean (80% CI) change from baseline in BCVA scores: study eye (FAS) and (B) LS mean (80% CI) change from baseline in BCVA scores: fellow eye (FAS). MMRM analysis. Baseline defined as the most recent nonmissing value prior to dosing. For subjects who discontinued the study, all available data up to the first assessment post-treatment withdrawal were reported. Fellow eye data shown only for subjects with a baseline value between 24 and 78 letters (inclusive).
Figure 4. (A) LS mean (80% CI) change from baseline in central subfield retinal thickness: study eye (FAS) and (B) LS mean (80% CI) change from baseline in central subfield retinal thickness: fellow eye (FAS). MMRM analysis. Baseline defined as the most recent nonmissing value prior to dosing. For subjects who discontinued the study, all available data up to the first assessment post-treatment withdrawal were reported.
course of plasma HbA1c did not appear to differ substantially between treatment arms.

Mean percentage changes in serum MCP-1 concentrations from baseline at weeks 4, 8, and 12 were increased in the PF-04634817 arm, with essentially no change in the ranibizumab arm. At week 12, the differences from baseline were 842.876 (SD, 551.5534) and -0.493 (SD, 31.9379), respectively. Following completion of PF-04634817 dosing, the MCP-1 concentrations returned toward baseline levels.

Safety

The overall incidences of all-cause (data not reported) and treatment-related AEs, serious AEs, and severe AEs were similar between treatment groups (Table 2), with the majority of AEs mild or moderate in severity.

The system organ class with the highest frequency of reported AEs was eye disorders (PF-04634817 arm, n = 4; ranibizumab arm, n = 3). In all, four subjects in the PF-04634817 arm and four subjects in the ranibizumab arm permanently discontinued from the study due to AEs. Two of these in the PF-04634817 arm were considered treatment-related (n = 2; diabetic retinal edema and cardiac failure) versus none in the ranibizumab arm; three in the PF-04634817 arm were reported as a serious AE (aortic valve stenosis, ischemic stroke, and cardiac failure [treatment-related]), as was one in the ranibizumab arm (diabetic ketoacidosis).

Laboratory anomalies that were prespecified for potential clinical concern (including hematology, liver function, clinical chemistry, electrolyte, and renal function indicators) occurred in 45% (45 of 99) of subjects in the PF-04634817 arm and 41% (40 of 97) of subjects in the ranibizumab arm. Of interest, white blood cell counts (10^3/mm^3) 1.5× the upper limit of normal (ULN) occurred in 0% of subjects in the PF-04634817 arm and 2.1% (2/97) of subjects in the ranibizumab arm. Absolute monocytes (10^3/mm^3) >1.2× ULN similarly occurred in 0% of subjects in the PF-04634817 arm and 1% (1/97) of subjects in the ranibizumab arm.

No discernible trends were observed in vital signs or ECG data in any treatment arm. Most subjects across all treatment arms had no changes in the anterior/posterior segments of the study eye at week 12/week 8. The mean maximum increases in IOP in the study eye in the PF-04634817 and ranibizumab arms were 2.5 (SD, 2.58) and 4.3 (SD, 4.24) mm Hg, respectively.

Discussion

Although small improvements in BCVA in the study eye were associated with treatment with PF-04634817 200 mg QD, the treatment was inferior to monthly intravitreal injections of ranibizumab (with data similar for ranibizumab 0.3 and 0.5 mg [not reported separately] and 0.3/0.5 mg combined). Following PF-04634817 treatment, there was a small increase in mean central subfield retinal thickness in the study eye at week 12 compared with baseline, and changes from baseline in other efficacy end points were close to zero. Consistent with this apparent lack of PF-04634817 efficacy, there were no changes that we would deem clinically significant observed in the fellow eye. PF-04634817 was generally well tolerated when administered for 12 weeks, with a favorable ocular safety profile versus intravitreal therapies. Pharmacokinetic analyses showed that subjects achieved plasma concentrations of PF-04634817 that were predictable from previous studies of healthy volunteers (NCT01098877 and NCT01140672). Notably, increases in serum MCP-1 (primary CCR2 ligand) were observed in subjects in the PF-04634817 arm versus the ranibizumab arm; indicating that, although efficacy of PF-04634817 was not clearly demonstrated, a high level of CCR2 antagonism was apparent throughout treatment. This suggests that the mechanism of action was thoroughly tested in this study.

The ability of robust pharmacologic antagonism of CCR2 receptors (and by extension, of CCR5 receptors) by PF-04634817 to deliver only modest efficacy in terms of BCVA improvement, may be due to various factors. As the relative contributions of multiple angiogenic and inflammatory factors associated with diabetic retinopathy/DME remain to be fully elucidated, it is possible that CCR2/5 antagonism by PF-04634817 does not result in inhibition of a key pathway, or that the pathophysiologic function of these specific populations of receptors can be taken on by other mechanisms once CCR2/5 receptors are blocked.

A combination of redundancy among the many chemokine pathways, and the dominance of certain pathways in animal models not reflected in humans, is a possible scenario. The former reflects the conclusions of Lehre et al., who sought to explain the failure of previous clinical trials with CCR2 and CCR5 antagonists in patients with rheumatoid arthritis. Researchers have also considered inadequate levels of receptor occupancy by an antagonist to be a potential further explanation for the failure of CCR2/5 antagonism to provide therapeutic benefit. It should be acknowledged that levels of PF-04634817 and resulting pharmacology were not measured directly in the eye in this study. However, the target CCR2 and CCR5 receptors are expressed on circulating cells and therefore are freely accessible to blockade by PF-04634817; nonhuman pharmacokinetic data (Pfizer data on file, 2012) support the belief that PF-04634817 freely penetrates the eye. The key pharmacologic biomarker of CCR2 receptor antagonism, increases in MCP-1, was measured from peripheral blood samples, rather than sampling from vitreous fluid (vitrectomy), which in this study would have exposed the patient to risk. However, the substantial rise in MCP-1 levels observed throughout the dosing period were similar to the maximum observed in healthy volunteers, which did not increase with higher doses of PF-04634817 (Pfizer data on file [NCT01098877 and NCT01140672]). Recent evaluation of another CCR2 inhibitor, CCX140-B, by de Zeeuw et al. in patients with type 2 diabetes and nephropathy also showed increases in serum MCP-1, but only at the highest dose seen. This observation was associated with a lesser reduction in albuminuria (primary end point) than that seen with lower doses of CCX140-B. Researchers hypothesized that increased MCP-1 concentrations may compete with the antagonist at the CCR2 receptor, thus reducing the effectiveness of pharmacologic blockade. In the present study, we cannot exclude the possibility that the high circulating concentrations of MCP-1 might compete against PF-04634817 at the CCR2 receptor. However, in clinical studies of healthy volunteers, the maximum increase in circulating MCP-1 was achieved at doses lower than the 200 mg PF-04634817 QD selected in the present study, suggesting that this dose is at the plateau of the exposure–response curve. If this assumption is correct, then the high concentration of the antagonist would reduce the likelihood of competition from the agonist ligand MCP-1.

The effectiveness of PF-04634817 in the present study may also have been limited by the relatively short duration of treatment. The possibility exists that the small improvement in BCVA observed at 12 weeks may have continued to increase with longer treatment as implied by the upward slope of the BCVA plot versus time; however, this may simply reflect
variability that cannot be properly assessed in view of the absence of a separate placebo group.

**Conclusions**

In this phase II study of subjects with DME, treatment with the oral CCR2/5 receptor dual antagonist PF-04634817 was associated with a modest improvement in BCVA, which was inferior to intravitreal ranibizumab.

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