Reduction of Diabetic Macular Edema by Oral Administration of the Kinase Inhibitor PKC412

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PURPOSE. To evaluate the efficacy and safety of PKC412, an orally administered kinase inhibitor, in subjects with diabetic macular edema.

METHODS. This was a randomized (1:1:1:1), multicenter, double-masked, parallel-group study in which subjects (n = 141) received placebo or PKC412 (50, 100, or 150 mg/d) for up to 3 months. Subjects were 18 to 85 years of age and had retinal thickening that met predefined criteria and best corrected visual acuity of 55 letters or more. Efficacy was based on changes in retinal thickening measured by grading of fundus photographs and optical coherence tomography (OCT) and changes in visual acuity.

RESULTS. Grading of fundus photographs showed a statistically significant decrease in the area of greatest retinal thickening in patients receiving 150 mg/d of PKC412 (P = 0.032). OCT demonstrated that the two higher doses of PKC412 caused a significant decrease in thickening in the region of greatest thickening and in the fovea (P ≤ 0.039), with response in the high-dose group significantly different from that in the placebo group (difference = −66.69 μm [95.2% CI: −128.57 to −4.81]; P = 0.030). Retinal volume for all locations also showed a significant decrease from baseline in the 100- and 150-mg/d PKC412 groups (P ≤ 0.004), and the 150-mg/kg group showed significantly less retinal volume than the placebo group at 3 months (difference = −0.40 mm³ [95.2% CI: −0.86–0.06]; P = 0.019). There was a small (4.36 letters), but significant (P = 0.007), improvement in visual acuity at 3 months compared with baseline in the 100-mg/d PKC412 group. Gastrointestinal side effects (diarrhea, nausea, and vomiting) were the most common adverse events attributed to the drug. Dose-related effects were observed for tolerability, glycemic control, and liver toxicity.

CONCLUSIONS. Orally administered PKC412 at doses of 100 mg/d or higher may significantly reduce macular edema and improve visual acuity in diabetic subjects. However, concern regarding liver toxicity with systemic therapy makes local delivery an appealing approach.

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RESULTS. Several strategies for inhibiting VEGF are being tested. Some target VEGF-A (Rosenfeld PJ, et al. IOVS 2003;44:ARVO E-Abs 970), but other members of the VEGF family may also be involved. One way to neutralize several members of the VEGF family is to block VEGF receptors 1 and 2. PKC412 is a nonspecific kinase inhibitor that blocks VEGF receptors 1 and 2, PDGF receptors, the receptors for stem cell factor, and several isoforms of PKC. Oral administration of PKC412 strongly suppresses VEGF-induced retinal neovascularization and VEGF-induced retinal vascular leakage. In this study, we investigated the effect of orally administered PKC412 in patients with DME.

MATERIALS AND METHODS

Study Design

This was a randomized, multicenter, double-masked, parallel-group, dose-finding study that compared the efficacy and safety of PKC412 (50, 100, and 150 mg/d) versus matching placebo in subjects with DME. Each subject attended the clinic for 10 visits, with the primary efficacy endpoint at month 3 and then 12 months of follow-up off drug (see online supplement at http://www.iovs.org/cgi/content/full/45/3/922/DC1 for details).

Study Population

The main inclusion criteria for the study were as follows: (1) male or female (any ethnicity) between 18 and 85 years of age; (2) diabetes type 1 or type 2 diabetes mellitus with nonproliferative diabetic retinopathy or no more than mild proliferative diabetic retinopathy, as defined by ETDRS level 61⁴; (3) retinal thickening in the study eye within 3000 μm of the foveal center with an area of at least 0.5 disc areas or a posterior edge of retinal thickening (or of hard exudates adjacent to the retinal thickening) 500 μm or less from the foveal center; and (4) best corrected visual acuity score of at least 55 letters on the ETDRS chart (approximately equivalent to 20/80 or better). Exclusion criteria are listed in an online supplement.

From the ¹Departments of Ophthalmology and Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, Maryland. ²Group members are listed in the Appendix. Supported by Novartis Ophthalmics. PAC is the George S. and Dolores Dore Eccles Professor of Ophthalmology and Neuroscience. Submitted for publication September 2, 2003; revised October 30, 2005; accepted November 11, 2003. Disclosure: P.A. Campochiaro, Novartis Ophthalmics (F, C)

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Treatment Assignment, Drug Administration, and Masking

Subjects were randomized in a 1:1:1:1 ratio to one of four treatment groups: placebo or one of three doses of PKC412 (50, 100, or 150 mg/d). The randomization schedule was computer generated (Proc Plan, SAS, ver. 6.12; SAS Institute, Cary, NC) and prepared by Ingenix Pharmaceutical Services (Basking Ridge, NJ). The study population was randomized as a unit and was not stratified by investigator. Individual subjects were assigned the next randomization number available at their site.

Subjects took three capsules of masked study medication with food and water twice daily for 3 months, with the first dose taken on the morning of visit 2 after baseline assessments were performed and the last dose taken the evening before visit 5 (month 3 visit). Placebo capsules lacked PKC412, but appeared identical with drug capsules, which contained 25 mg of PKC412. Subjects randomized to one of the PKC412 groups received an appropriate mixture of PKC412 and placebo capsules to maintain the treatment mask. Identity of masked study medication was concealed by storing the medication in individually sealed envelopes at the study sites. During the course of the study, treatment was unmasked for only one subject who was withdrawn because of two serious adverse events (AEs; see safety results for details).

Efficacy Assessments

The primary efficacy variable was change from baseline in the area of retinal thickening (measured in disc areas), as determined by a central reading center (University of Wisconsin-Madison Fundus Photograph Reading Center) from stereoscopic fundus photographs. Secondary efficacy variables were change in (1) retinal thickness (in micrometers) and volume (in cubic millimeters) measured by optical coherence tomography (OCT; selected investigative sites only; Carl Zeiss Meditec, Dublin, CA); (2) best corrected visual acuity; (3) involvement of optic nerve to the center of the fovea; (4) amount of leakage assessed by fluorescein angiograms; (5) diabetic retinopathy classification, and (6) requirement for rescue focal or scatter laser photocoagulation. Efficacy assessments were performed on both eyes, but if each met the inclusion criteria, the investigator designated the study eye at baseline.

Retinal thickening was assessed by photographic grading in 13 locations of the retina, a circle with radius of 200 μm centered on the foveola and three concentric rings with radii of 500, 1500, and 3000 μm, each divided into four quadrants. Data were analyzed by location, for all locations combined, and for the location with greatest retinal thickening at baseline.

Six sites measured retinal thickness by OCT. The average thickness and volume were calculated by the OCT software for the fovea (central circle with radius of 200 μm), and the other retinal areas were assessed by photographic grading.

Investigators measured best corrected distance visual acuity with the ETDRS protocol. Seven field stereoscopic fundus photographs and fluorescein angiograms were obtained with the techniques used in the ETDRS and were graded in masked fashion at the University of Wisconsin Reading Center, according to standard ETDRS protocols. Diabetic retinopathy was assessed with the ETDRS scale of diabetic retinopathy severity (a modified Airlie House classification scheme). Safety assessments are listed in the online supplement.

RESULTS

Disposition, Demographics, and Baseline Characteristics

The study was conducted from April 28, 2000 (first subject, first visit) to October 29, 2002 (last subject, last visit). A total of 142 subjects from 12 centers in the United States and Europe were randomized (32-38 subjects per treatment group). All but one subject (placebo group) received at least one dose of study drug; this patient was not included in the efficacy analysis. Most subjects in each treatment group completed the study, but 28 (20%) of 141 subjects were withdrawn, most from the higher PKC412 dose groups (12 subjects, 100 mg/d; 10 subjects, 150 mg/d). The most common reason for discontinuation was AEs, and each occurred in subjects who received PKC412.

The average duration of exposure to the study drug ranged from 73.5 days in the 150-mg/d PKC412 group to 90.1 days in the placebo group. As many as 22% of subjects in each treatment group took drug for less than 60 days. All randomized subjects who received at least one dose of study drug were included in the safety analyses (n = 141), but three of these patients withdrew with no efficacy visits after baseline, so that 138 subjects were included in the intent-to-treat (ITT) efficacy group (placebo, 54; 50 mg/d, 32; 100 mg/d, 37; 150 mg/d, 35). None of the subjects was withdrawn from the study because of lack of efficacy.

Treatment groups were balanced with regard to demographic and baseline characteristics (Table 1). Mean age of the study population was 59.3 years (range: 22-80 years). Average duration of diabetes mellitus from the time of diagnosis was 14.8 years and average duration of DME was 1.3 years. The mean baseline visual acuity in study eyes was 73.3 letters. Concomitant use of both diabetic and nondiabetic medications was comparable among treatment groups during the active treatment and follow-up periods.

Effect of PKC412 on Area of Retinal Thickenening by Fundus Photograph Grading

All Locations Combined. The mean area of retinal thickening differed among treatment groups at baseline (Table 2). Summing across all locations of the retina, mean area of retinal thickening ranged from 2.54 (placebo) to 4.82 (50 mg/d PKC412) disc areas. Subjects who received 50 mg/d or 100 mg/d PKC412 had significantly more edema at baseline than did placebo-treated subjects (P ≤ 0.005, Dunnett method).

Approximately 40% to 60% of subjects in each treatment group showed no change from baseline (same ≥ 0.49 disc areas) in area of retinal thickening in the study eye. The percentage of subjects who showed any degree of improvement in the area of retinal thickening was more than two times greater in the PKC412 groups than in the placebo group (online supplement, Fig. 1). Furthermore, the degree of improvement was more marked in the PKC412 groups, with 9% (50 and 100 mg/d) to 15% (150 mg/d) of subjects showing a decrease in the area of retinal thickening of at least 2 disc areas. The percentage of subjects who had a 50% or greater reduction in the area of retinal thickening was higher in the 150-mg/d PKC412 group (15%) than in the other treatment groups (6% each). Although statistical comparisons were not made between individual treatment groups, the Fisher exact test revealed no significant differences among the treatment groups.

Area of Greatest Retinal Thickening. Patients vary with regard to location of retinal thickness, and although changes in thickness outside the foveal region may not affect their vision, such changes still provide important information regarding the efficacy of a drug. The mean area of greatest retinal thickening was significantly higher at baseline in the 50-mg/d PKC412 group than in the placebo (P = 0.003, Dunnett method) and 150-mg/d PKC412 (P = 0.036, Tukey-Kramer method; Table 2) groups. Subjects in the 150-mg/d PKC412 group showed a significant reduction from baseline in mean area of greatest retinal thickening (difference = −0.17 disc areas; P = 0.032), representing a 15.1% improvement in macular edema. No other significant differences were observed during active therapy.
Retinal Thickness and Volume by OCT

Average retinal thickness in the center–center location represents foveal thickness, a measurement that when elevated indicates clinically significant macular edema. At baseline, foveal thickness was significantly greater in the 100-mg/d PKC412 group than in each of the other groups (P ≤ 0.035), indicating that subjects in the 100-mg/d PKC412 group had considerably more foveal edema at baseline (Table 3). Average foveal thickness was numerically reduced in each treatment group and reached statistical significance in the 100-mg/d (P = 0.015, paired t-test) and 150-mg/d (P = 0.039) groups (Fig. 1). The reduction in foveal thickness was significantly greater in the 150-mg/d PKC412 group than in the placebo group (difference = −66.69 μm [95.2% CI: −128.57 to −4.81]; P = 0.030, Dunnett method).

The average retinal thickness in the region of greatest thickness increased from baseline to month 3 in the placebo group and decreased in all the PKC412 groups. There was a signifi-
cant decrease from baseline to month 3 in the 100-mg/d (−60.20 μm, P = 0.009, paired t-test) and 150-mg/d (−58.00 μm, P = 0.032) groups. None of the placebo-treated subjects showed a 20% or more reduction in average retinal thickness. With active therapy, 20% reductions in retinal thickness ranged from 14% (2/14) in the 50-mg/d PKC412 group to 33% (4/12) in the high-dose group.

The OCT software uses an integration algorithm to compute the retinal volume from the average thickness measurements within a given location. As expected, the results for foveal volume mirrored those for average foveal thickness (Table 4). Volume in all locations combined provides a global measure of macular edema. At baseline, total retinal volume was significantly smaller in the placebo group than in the 100-mg/d PKC412 group (P = 0.005; Dunnett method). At month 3, an increase in retinal volume was observed in the placebo group, whereas decreases were observed in each of the treatment groups and were statistically significant in the 100- and 150-

Table 2. Mean Change from Baseline in Area of Retinal Thickening: ITT Group and OCT Subset (Study Eye)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Placebo (n = 34)</th>
<th>50 mg/d PKC412 (n = 32)</th>
<th>100 mg/d PKC412 (n = 38)</th>
<th>150 mg/d PKC412 (n = 37)</th>
<th>Total (n = 141)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All locations combined (ITT Group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>n</td>
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<td>Mean Δ</td>
<td>n</td>
<td>BL</td>
</tr>
<tr>
<td>34</td>
<td>2.44</td>
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<td>4.82</td>
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<tr>
<td>34</td>
<td>2.34</td>
<td>0.42</td>
<td>0.22</td>
<td>32</td>
<td>4.82</td>
</tr>
<tr>
<td>Area of greatest retinal thickening (ITT Group)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>n</td>
<td>BL</td>
<td>Mean Δ</td>
<td>n</td>
<td>BL</td>
</tr>
<tr>
<td>33</td>
<td>0.99</td>
<td>−0.01</td>
<td>0.02</td>
<td>30</td>
<td>1.61</td>
</tr>
<tr>
<td>34</td>
<td>0.97</td>
<td>0.02</td>
<td>0.01</td>
<td>30</td>
<td>1.61</td>
</tr>
<tr>
<td>All locations combined (OCT subset)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>n</td>
<td>BL</td>
<td>Mean Δ</td>
<td>n</td>
<td>BL</td>
</tr>
<tr>
<td>14</td>
<td>2.49</td>
<td>0.20</td>
<td>0.18</td>
<td>14</td>
<td>4.22</td>
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<tr>
<td>14</td>
<td>2.49</td>
<td>0.31</td>
<td>0.22</td>
<td>14</td>
<td>4.22</td>
</tr>
<tr>
<td>Area of greatest retinal thickening (OCT subset)</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>n</td>
<td>BL</td>
<td>Mean Δ</td>
<td>n</td>
<td>BL</td>
</tr>
<tr>
<td>14</td>
<td>1.02</td>
<td>0.03</td>
<td>0.11</td>
<td>13</td>
<td>1.51</td>
</tr>
<tr>
<td>14</td>
<td>1.02</td>
<td>−0.01</td>
<td>0.31</td>
<td>15</td>
<td>1.51</td>
</tr>
</tbody>
</table>

Bold type indicates a statistically significant (P ≤ 0.048) change from baseline (paired t-test). BL, baseline; Δ, change. Data are expressed in disc areas.
mg/d groups (Table 4; P ≤ 0.004, paired t-tests). Significant differences were observed between the placebo and 150-mg/d PKC412 groups for change in retinal volume (difference = −0.46 mm³ [95.2% CI: −0.86 to −0.06]; P = 0.019).

**Effect of PKC412 on Visual Acuity**

Visual acuity in the study eye was comparable among treatment groups at baseline (Table 5). At 3 months, a mean decrease in the visual acuity score was observed in placebo-treated subjects (−0.21 letters), whereas mean increases up to 4.36 letters were observed with PKC412 treatment (Fig. 2), reaching significance in the 100-mg/d PKC412 group (P = 0.007, paired t-test).

**Fluorescein Angiography**

Most of the subjects in each treatment group (range: 78%–100%) showed no change from baseline in the foveal avascular zone size of the study eye (online supplement, Fig. 2A), and the majority (range: 64%–91%) showed no change in zone outline (online supplement, Fig. 2B). Increases from baseline in foveal avascular zone size generally occurred at the same frequency as decreases in zone size, whereas frequencies of worsening zone...
respectively. Similar results were generally observed at other
treatment groups at any retinal location for the
cystoid formation.

Across treatment groups, frequencies of improvement in
subjects showed no shift in cystoid accumulation of dye.
The majority of subjects in each treatment group (range: 63%–
73%) exhibited no shift in diabetic retinopathy classi-
cation among treatment groups throughout the
15-month evaluation period. Mean changes from
baseline; Placebo 50 mg/d PKC412 100 mg/d PKC412 150 mg/d PKC412

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Placebo</th>
<th>50 mg/d PKC412</th>
<th>100 mg/d PKC412</th>
<th>150 mg/d PKC412</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average retinal volume at</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>center-center location</td>
<td>n  BL Mean Δ</td>
<td>n  BL Mean Δ</td>
<td>n  BL Mean Δ</td>
<td>n  BL Mean Δ</td>
</tr>
<tr>
<td>Month 1</td>
<td>14  0.029 0.002</td>
<td>14  0.032 −0.001</td>
<td>14  0.049 −0.003</td>
<td>12  0.030 −0.004</td>
</tr>
<tr>
<td>Month 3</td>
<td>14  0.029 0.002</td>
<td>14  0.032 −0.001</td>
<td>15  0.047 −0.008</td>
<td>12  0.030 −0.006</td>
</tr>
<tr>
<td>Average retinal volume for all locations combined</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>14  7.060 0.034</td>
<td>14  7.687 −0.090</td>
<td>14  8.772 −0.402</td>
<td>12  7.594 −0.288</td>
</tr>
<tr>
<td>Month 3</td>
<td>14  7.060 0.107</td>
<td>14  7.687 −0.132</td>
<td>15  8.750 −0.513</td>
<td>12  7.594 −0.432</td>
</tr>
<tr>
<td>Average retinal volume at location of greatest retinal volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>14  1.380 −0.010</td>
<td>14  1.600 −0.050</td>
<td>14  1.750 −0.100</td>
<td>12  1.580 −0.100</td>
</tr>
<tr>
<td>Month 3</td>
<td>14  1.38 −0.01</td>
<td>14  1.60 −0.02</td>
<td>15  1.75 −0.10</td>
<td>12  1.58 −0.13</td>
</tr>
</tbody>
</table>

Bold type indicates a statistically significant (P ≤ 0.048) change from baseline (paired t-test). Data are expressed in cubic millimeters. BL, baseline; Δ, change.

outline were typically greater than frequencies of improve-

ment. No statistically significant differences were observed among treatment groups for frequency distributions of change in these parameters.

Approximately 50% to 75% of subjects in each treatment
group showed no shift from baseline in fluorescein leakage
from the center location, and approximately 65% to 85% of
subjects showed no shift in cystoid accumulation of dye.
Across treatment groups, frequencies of improvement in flu-
orescein leakage at the center location (range: 8%–25%) were
similar to those observed for worsening (range: 12%–30%).
Likewise, frequencies of improvement and worsening in cystoid appearance ranged from 13% to 16% and from 4% to 22%,
respectively. Similar results were generally observed at other
locations of the retina. No significant differences were ob-
served among treatment groups at any retinal location for the
frequency distribution of change in fluorescein leakage or
cystoid formation.

Classification of Diabetic Retinopathy

The majority of subjects in each treatment group (range: 63%–
75%) exhibited no shift in diabetic retinopathy classification of
the study eye, and 13% to 20% of subjects in each group
showed a favorable shift from the initial screening (online
supplement, Fig. 3). The percentage of subjects who showed a
worsening in diabetic retinopathy varied among treatment
groups (range: 7%–20%), with the lowest incidence occurring in
subjects who received 150 mg/d PKC412. No statistically
significant differences were observed in the frequency distri-
bution of change in diabetic retinopathy classification among
treatment groups.

Subjects Requiring Rescue Focal and/or Grid Laser Treatment

None of the subjects required panretinal photocoagulation in
the study eye during active therapy, and very few subjects
(one, placebo; one, 50 mg/d PKC412) required focal and/or
grid laser therapy. In the fellow eye, three PKC412-treated
subjects (two, 100 mg/d; one, 150 mg/d) required panretinal
photocoagulation during active therapy, and two subjects in
the 50-mg/d PKC412 group had focal and/or grid laser treat-
ment.

Ocular Safety Findings

Most subjects in each treatment group showed no shift from
screening in the slit lamp or dilated ophthalmoscopy findings
in either eye after 3 months of therapy. Mean changes from
baseline in IOP were small and comparable among treatment
groups throughout the 15-month evaluation period. Mean
changes from baseline in manifest refraction findings were also
small and comparable among treatment groups throughout the
study, with the largest change observed in the left eye of the
100-mg/d PKC412 group at month 15 (+0.37 spherical equiva-

Adverse Events

During the treatment period, the majority of subjects in each
treatment group experienced at least one AE, ranging from

TABLE 5. Mean Change from Baseline in Best corrected Visual Acuity: ITT Group (Study Eye)

<table>
<thead>
<tr>
<th>Evaluation</th>
<th>Placebo</th>
<th>50 mg/d PKC412</th>
<th>100 mg/d PKC412</th>
<th>150 mg/d PKC412</th>
</tr>
</thead>
<tbody>
<tr>
<td>All evaluable subjects</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>34  75.41 0.53</td>
<td>32  70.56 −0.16</td>
<td>34  70.12 3.71</td>
<td>34  77.53 1.21</td>
</tr>
<tr>
<td>Month 3</td>
<td>34  75.41 −0.21</td>
<td>32  70.56 1.13</td>
<td>36  71.50 4.36</td>
<td>34  77.53 0.15</td>
</tr>
<tr>
<td>Subjects with visual acuity &lt;70 letters at baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 1</td>
<td>10  60.20 4.10</td>
<td>14  61.29 −0.07</td>
<td>12  51.25 8.17</td>
<td>9   63.00 2.89</td>
</tr>
<tr>
<td>Month 3</td>
<td>10  60.20 2.80</td>
<td>14  61.29 2.14</td>
<td>12  51.25 8.42</td>
<td>9   63.00 −2.33</td>
</tr>
</tbody>
</table>

Bold type indicates a statistically significant (P ≤ 0.048) change from baseline (paired t-test). Data are expressed in number of letters. BL, baseline; Δ, change.
77% in the placebo group to 100% in the 150-mg/d PKC412 group (Table 6). Most events were nonocular in nature, with only 12% to 19% of subjects in each group experiencing an ocular event. Most AEs were mild or moderate in intensity; only 7% of the 406 events reported across treatment groups were severe in intensity. AEs were generally transient in duration, although nausea persisted in some subjects. The overall incidence of treatment-emergent events with an investigator-suspected relationship to study drug was lowest in the placebo group (24%) and highest in the 150-mg/d PKC412 group (68%). Drug-related events that occurred in 5% or more of subjects in any treatment group are listed in Table 7. AE profiles were generally comparable among treatment groups, although placebo-treated subjects had a lower incidence of gastrointestinal (GI) events and aminotransferase abnormalities than did those who received PKC412. In PKC412-treated subjects, the most common events with a suspected relationship to study drug were nausea, diarrhea, and vomiting, and these appeared to be dose related. Subjects in the 150-mg/d PKC412 group had the highest incidence of these events. Fifteen subjects experienced a total of 19 AEs that met the criteria for serious (Table 7). No serious events were fatal, and most events (15/19, 79%) were nonocular in nature. Except for two events (elevated alanine and aspartate aminotransferase [ALT/AST]) that occurred in the same subject (150 mg/d PKC412), none of the serious events had an investigator-suspected relationship to study drug. Serious ocular events consisted of substantial worsening of macular edema (two subjects, 50 mg/d PKC412) and vitreous hemorrhage (one subject, 100 mg/d PKC412; one subject, 150 mg/d PKC412); each of these events occurred at least 5 months after cessation of drug.

Fourteen PKC412-treated subjects were withdrawn from the study because of an AE, with the highest incidence occurring in the 150-mg/d group (22%). All events that led to discontinuation were nonocular. The most common withdrawal event was vomiting (one subject, 50 mg/d PKC412; three subjects, 150 mg/d PKC412), and all cases were attributed to study drug by the investigator. Other withdrawal events with a suspected relationship to study drug were nausea (one subject, 150 mg/d PKC412) and urticaria (one subject, 100 mg/d PKC412). No placebo-treated subjects withdrew because of an AE.

**Laboratory Findings**

For most laboratory parameters, the most subjects in each treatment group had normal laboratory results at baseline and showed no shift to abnormally high or low values at the

![Figure 2. Oral PKC412 improves visual acuity in patients with DME. Points represent the change in number of letters read with best correction on ETDRS chart at each time point. Patients treated with 100 mg/d of PKC412 showed a small, but statistically significant, improvement in number of letters read at 1 and 3 months. The treatment period was from months 0 to 3. Probabilities are based on a paired t-test for within-treatment effect.](https://iovs.arvojournals.org/article-pdf/45/3/927/2157386/i0156-9567-45-3-927.pdf)

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**Table 6. Overall Summary of Adverse Events**

<table>
<thead>
<tr>
<th>Category</th>
<th>Placebo (n = 34)</th>
<th>50 mg/d (n = 32)</th>
<th>100 mg/d (n = 38)</th>
<th>150 mg/d (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one txt-emergent AE</td>
<td>26 (77)</td>
<td>29 (91)</td>
<td>32 (84)</td>
<td>37 (100)</td>
</tr>
<tr>
<td>Ocular event</td>
<td>4 (12)</td>
<td>6 (19)</td>
<td>5 (13)</td>
<td>6 (16)</td>
</tr>
<tr>
<td>Nonocular event</td>
<td>24 (71)</td>
<td>28 (88)</td>
<td>31 (82)</td>
<td>36 (97)</td>
</tr>
<tr>
<td>At least one txt-emergent, drug-related AE*</td>
<td>8 (24)</td>
<td>11 (34)</td>
<td>19 (50)</td>
<td>25 (68)</td>
</tr>
<tr>
<td>Ocular event</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Nonocular event</td>
<td>8 (24)</td>
<td>10 (31)</td>
<td>19 (50)</td>
<td>25 (68)</td>
</tr>
<tr>
<td>At least one SAE</td>
<td>1 (3)</td>
<td>7 (22)</td>
<td>2 (5)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>At least one drug-related SAE*</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Deaths</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Withdrawal due to an AE</td>
<td>0 (0)</td>
<td>3 (9)</td>
<td>3 (8)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>Withdrawal due to a drug-related AE*</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

Data are number of patients with percentage of total patient group in parentheses. SAE, serious adverse event; txt, treatment.

* Events with a suspected relationship to masked study medication (per the investigator).
Liver toxicities were generally transient and resolved after therapy. Three subjects (one, 50 mg/d; two, 150 mg/d) had an ALT and/or AST level higher than three times the upper limit of normal (ULN) during active treatment. Each of these toxicities occurred in subjects with normal liver function at baseline. Except for one bilirubin abnormality, each of these toxicities was withdrawn from the study. At that time, the abnormalities were detected, and no further follow-up was possible. The subject was taking concomitant medications that may have contributed to the hepatotoxicity.

Subjects in the placebo and 50-mg/d PKC412 groups showed little change from baseline in mean total cholesterol or low-density lipoprotein cholesterol (LDL-C) during active treatment (online supplement, Figs. 5A, 5B, respectively). However, in the higher dose PKC412 groups, clinically relevant reductions in total cholesterol and LDL-C were observed during therapy. In each case, levels returned to baseline when subjects entered the follow-up phase. None of the treatments had a notable effect on mean high-density lipoprotein cholesterol (HDL-C) or triglyceride levels during active therapy, except for a slight, yet consistent, increase in mean HDL-C in the 150-mg/d PKC412 group (online supplement, Fig. 5C).

PKC412 had no clinically significant effect on mean changes from baseline or shifts from baseline in any hematologic parameter. In the 150-mg/d PKC412 group, a slight, yet progressive, decrease in mean total white blood cell count was observed during active therapy, although mean counts remained within normal range at each evaluation.

**Electrocardiograms**

PKC412 had no clinically significant effect on mean changes from baseline in heart rate, QRS axis, or intervals for PR, QRS, QT, and QTc. Most subjects showed no shift from baseline in electrocardiogram (ECG) findings during the active treatment and follow-up periods. At month 3, the percentage of subjects in each treatment group who shifted from normal at baseline to abnormal after baseline was generally comparable to those who shifted from abnormal at baseline to normal at month 3. Three subjects (one per PKC412 group) withdrew from the study because of an abnormal ambulatory ECG. None of the ECG abnormalities that resulted in discontinuation was attributed to the study drug.

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**Table 7. Most Common Treatment-Emergent Adverse Events with a Suspected Relationship to Study Drug**

<table>
<thead>
<tr>
<th>Term</th>
<th>Placebo (n = 34)</th>
<th>PKC412 Dose</th>
<th>PKC412 Dose</th>
<th>PKC412 Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 mg/d (n = 32)</td>
<td>100 mg/d (n = 38)</td>
<td>150 mg/d (n = 37)</td>
<td></td>
</tr>
<tr>
<td>Anemia NOS</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Constipation</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Decreased white blood cell</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>count</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>6 (16)</td>
<td>7 (19)</td>
</tr>
<tr>
<td>Dizziness (excluding vertigo)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Headache NOS</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Increased ALT</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>3 (8)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>Increased AST</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>3 (8)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Increased blood glucose</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Increased lacrimation</td>
<td>0 (0)</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (3)</td>
<td>2 (6)</td>
<td>8 (21)</td>
<td>14 (38)</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>2 (6)</td>
<td>1 (3)</td>
<td>2 (5)</td>
<td>1 (5)</td>
</tr>
<tr>
<td>Vomiting NOS</td>
<td>0 (0)</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>7 (19)</td>
</tr>
</tbody>
</table>

Events that occurred in 5% or more of subjects in any treatment group during active treatment. Data are expressed as the number of patients, with the percentage of the total patient cohort in parentheses. NOS, not otherwise specified.
DISCUSSION

Laser photocoagulation has been shown to be the only beneficial treatment for DME, but its usefulness is limited by side effects, inability to restore lost vision, and frequent lack of efficacy. Therefore, development of drug therapy is a high priority. In this multicenter, phase I/II placebo-controlled, dose-ranging study, we investigated the safety and efficacy of the oral kinase inhibitor, PKC412.

Ultimately, the usefulness of any drug is judged by its ability to improve and maintain visual acuity in patients with DME. However, the challenge for early-stage trials is to identify surrogate outcome measures that can accurately assess drug efficacy, often in patients with advanced disease (who may have a substantial component of visual loss that is permanent), in a short period, and provide predictive information on the likely effect on visual acuity with long-term treatment in patients with reversible visual loss from DME. Retinal thickness is such an outcome measure for DME. Increase in retinal thickness correlates well with loss of visual acuity and decrease in retinal thickness is necessary, but not always sufficient for improvement in visual acuity. There are several possible reasons why some patients may not experience improvement in visual acuity despite improvement in retinal thickness including: (1) permanent loss of visual acuity from irreversible structural changes due to severity and chronicity of edema, (2) lag time between restoration of normal thickness and restoration of function, (3) lack of improvement in function from partial improvement in thickening (decrease in thickening in the fovea from 500 to 300 μm is a large effect with regard to thickening, but may not be sufficient to cause improvement in vision), and (4) decreases in retinal thickening in regions outside the center of the macula have no effect on visual acuity. Therefore, retinal thickness is a more sensitive short-term outcome measure for efficacy in DME trials than visual acuity.

In past interventional trials, including the ETDRS, retinal thickness was assessed by masked grading of stereoscopic fundus photographs using a categorical scale. It essentially represents the gold standard, although it involves subjective assessments by highly trained graders. OCT is a new objective technique that provides highly reproducible measurements of retinal thickness in micrometers, using a continuous scale. It is reasonable to assume that the objectivity, continuous scale, and high reproducibility of OCT make it more sensitive than photographic grading for assessment of retinal thickening, but this proposition has never been tested.

In this study, we used both photographic grading by the Wisconsin Reading Center and OCT to assess retinal edema. Both techniques demonstrated a PKC412 treatment effect providing cross-validation of the techniques, but it is clear that OCT is more sensitive and provides a much more robust signal. Direct comparison of the techniques provides insight as to why this is the case. Graders make an assessment of the presence or absence of retinal thickening at all points within various regions of the retina to arrive at the area of thickening within that region. The areas within each of the regions are summed to calculate the total area of retinal thickening. To detect a change, a sufficiently large area of retina must return to normal appearance to distinguish the treatment effect from noise due to inconsistency in grading. Even with completely consistent grading, partial resolution of edema is not assessed. Graders gather categorical information (thickening or no thickening) from a small area of the macula, the peripheral rims of mounds of edema, and gather no information from the remainder of the macula. In the region of greatest thickening in patients treated with 150 mg/d of PKC412, graders were able to detect a decrease in the area of thickening that could reliably be attributed to the drug and not chance, possibly because the slope was steep enough so that as the mound decreased, changes at the border of the mound were easily detectable.

In contrast, OCT assesses the severity of edema at numerous points throughout the macula using a continuous scale. The ability to assess partial resolution of edema quantitatively is a major advantage of OCT. As a result, OCT not only detected significant decreases in thickness in regions of greatest thickness at 3 months compared with baseline in both the 100- and 150-mg/d groups, but in these two groups, OCT also detected highly significant decreases in foveal thickening and total macular volume, which provides a global assessment of macular edema. Several internal consistencies bolster confidence in the OCT results. (1) The results were strongly dose dependent, with no treatment effect in the placebo or 50-mg/d groups and a significant effect at the two higher doses. (2) The results were time dependent. The two high-dose groups showed a trend toward decreased thickening at 1 month and definite decreases at 3 months. (3) There was strong agreement among multiple OCT parameters. (4) Thickening worsened after stopping the PKC412. We conclude from these data that oral treatment with PKC412 reduces retinal thickness in patients with DME and therefore is beneficial and that OCT is more sensitive and robust than photographic grading as an outcome measure in DME trials and should replace it as a gold standard.

We also conclude that 3 months is sufficient for treatment duration to detect a treatment effect by OCT in patients with DME. We did not determine the optimum duration of PKC412 treatment, but it is reasonable to assume that it is likely to be longer than 3 months, because patients experienced only partial resolution of retinal thickening with 3 months of treatment.

Although visual acuity was assessed as a secondary outcome measure, the trial was not designed to identify an effect on visual acuity. Investigators attempted to avoid patients who were judged likely to need focal laser during the trial, and therefore most patients had persistent edema despite one or more focal laser treatments with the last treatment at least 4 months before baseline, or they had edema that was outside the central region of the macula. There is no potential for visual improvement in the latter, and the potential for improvement in the former is unknown. It is likely that some patients had a component of permanently decreased visual acuity, because the edema was chronic with an average duration of 1.3 years. Finally, the treatment duration was predicted to be too short to detect maximal effects on visual acuity. This prediction is likely to be correct because, as noted earlier, only partial resolution of retinal thickness was achieved by 3 months of treatment with 100 or 150 mg/d PKC412. Despite this and the other design shortcomings regarding assessment of visual acuity, significant improvement in visual acuity was observed in the 100-mg/d group. Compared with the 150-mg/d group, more patients in the 100-mg/d group had thickening in the center of the fovea, and this may be why the latter group, but not the former, showed improvement in visual acuity.

Fluorescein angiography is not a quantitative technique, and assessment of leakage is dependent on overall exposure of the film, which can vary greatly from angiogram to angiogram in the same patient due to differences during acquisition of images (e.g., level of pupillary dilation and squinting) and differences during film processing. Despite these shortcomings, large differences in leakage can be detected. These were not seen suggesting that there was still substantial leakage after 3 months of oral administration of 100 or 150 mg/d of PKC412. This suggests that a significant reduction in retinal thickness can be achieved without a dramatic shutdown in leakage. It is likely that PKC412 reestablishes a favorable balance between fluid removal by endogenous pumps and leakage. Whether it does this by stimulating pump function or by decreasing permeability by an amount that is not detectable by fluorescein...
angiography at 3 months, but is still sufficient to tip the balance in favor of fluid egress (which is a wide range), or a combination of both is unknown. These data, along with the partial resolution of excess retinal thickening at 3 months, suggests that sustained long-term oral administration of PKC412 may be necessary to achieve optimal effects in patients with DME.

Oral administration is the preferred route for most medicines in most individuals, particularly for drugs that require long-term administration; however, it results in systemic exposure and requires a reasonable safety profile. In this study, we found that PKC412 was well tolerated by most patients, with GI side effects of diarrhea, nausea, and vomiting the most common. These side effects were generally mild or moderate in intensity and transient, although nausea persisted in some subjects. Four patients (11%) in the 150-mg/d group (three vomiting and one nausea) and one patient in the 50-mg/d group (vomiting) withdrew from the study because of GI symptoms. GI events were commonly reported in two multiple-dose Phase I/II cancer studies in which patients with advanced solid tumors or lymphoproliferative disease received PKC412 at doses up to 300 mg/d.22,23

Signs of liver toxicity, primarily manifested as elevations in serum transaminases, were observed in some patients during treatment with the higher doses of PKC412, especially the 150 mg/d dose. In the lymphoproliferative cancer study, these toxicities were generally asymptomatic, mild to moderate in intensity, and resolved after cessation of therapy. In contrast to our findings, investigators in the solid tumor cancer study reported no significant effects of PKC412 on liver function, despite doses up to 300 mg/d.22 Further investigation is warranted to evaluate the potential hepatic toxicity of orally administered PKC412 in diabetic subjects.

Elevated serum lipids (especially total cholesterol and LDL-C) are often considered to be risk factors for the progression of DME because of their association with development of hard exudates.24,25 In this study, PKC412 had no adverse effect on serum lipids, indicating that the drug does not exacerbate the risk of hyperlipidemia. In fact, PKC412 appears to have a favorable effect on serum cholesterol levels. Neither cancer study reported any effects of PKC412 on serum lipids.22,23 The safety data indicate that orally administered PKC412 is safe and well-tolerated in diabetic subjects in doses up to 100 mg/d. Because this dose also caused significant improvement in retinal thickening and visual acuity, additional trials investigating the effects of PKC412 at 100 mg/d would be reasonable with careful monitoring of liver enzymes. Another alternative is sustained, local delivery of PKC412 which has recently been shown to result in high intraocular levels of PKC412 that are sufficient to provide strong suppression of choroidal neovascularization in a porcine model.20

References


**APPENDIX**

**The PKC412 Study Group**

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