Conbercept for Treatment of Neovascular Age-related Macular Degeneration: Results of the Randomized Phase 3 PHOENIX Study

KUN LIU, YANPING SONG, GEZHI XU, JIAN YE, ZHIFENG WU, XIAOLING LIU, XIAOGUANG DONG, MINGZHI ZHANG, YIQIAO XING, SHAOPING ZHU, XIA CHEN, YINCHEN SHEN, HENGYE HUANG, LIYUN YU, ZUNHONG KE, PHILIP J. ROSENFELD, PETER K. KAISER, GUISHUANG YING, XIAODONG SUN, AND XUN XU, FOR THE PHOENIX STUDY GROUP

• PURPOSE: Age-related macular degeneration (AMD) can cause irreversible vision loss leading to blindness. We aim to evaluate the efficacy and safety of intravitreal injections of 0.5 mg conbercept, a new anti–vascular endothelial growth factor (anti-VEGF) drug, for treatment of AMD on a schedule more manageable for patients.

• DESIGN: A prospective, double-masked, multicenter, sham-controlled, phase III randomized trial.

• METHODS: PATIENTS: Patients with choroidal neovascularization (CNV) secondary to AMD were enrolled and randomized to the conbercept group or the sham control group. INTERVENTION: The conbercept group received intravitreal injections of conbercept (0.5 mg) once monthly for the first 3 months, then once quarterly until month 12 (3 + Q3M). The sham group received first 3 monthly sham injections and then 3 monthly injections of conbercept (0.5 mg) followed by quarterly administrations until month 12. MAIN OUTCOME MEASURES: The primary endpoint was mean change from baseline in best-corrected visual acuity (BCVA) at month 3.

• RESULTS: A total of 114 patients (91.9%) from 9 sites in China completed the 12-month study. At the 3-month primary endpoint, the mean changes in BCVA from baseline were +9.20 letters in the conbercept group and +2.02 letters in the sham group, respectively ($P < .001$). At 12 months, the mean changes from baseline in BCVA letter score were +9.98 letters in the conbercept group and +8.81 letters in the sham group ($P = .64$). The most common ocular adverse events were associated with intravitreal injections, such as conjunctival hemorrhage, and increased intraocular pressure.

• CONCLUSIONS: A conbercept dosing regimen of 3 initial monthly administrations followed by quarterly treatments is effective for treatment of AMD. In previous reports, other anti-VEGF agents were unable to maintain similar clinical benefits with the same regimen. (Am J Ophthalmol 2019;197:156–167. © 2018 Elsevier Inc. All rights reserved.)

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Aug 17, 2018.

From the Department of Ophthalmology, Shanghai Key Laboratory of Ocular Fundus Diseases, Shanghai General Hospital, Shanghai Engineering Center for Visual Science and Photomedicine, Shanghai, China (K.L., S.Z., X.C., Y.S., X.S., X.X.); Department of Ophthalmology, Wuhan General Hospital of Guangzhou Military, Wuhan, Hubei, China (Y.S.); Department of Ophthalmology, Eye & ENT Hospital of Fudan University, Shanghai, China (G.X.); Department of Ophthalmology, Institute of Surgery Research, Daping Hospital, Third Military Medical University, Chongqing, China (J.Y.); Department of Ophthalmology, Wuxi No. 2 People's Hospital, Nanjing Medical University, Wuxi, Jiangsu, China (Z.W.); School of Optometry and Ophthalmology and Eye Hospital, Wenzhou Medical University, Wenzhou, Zhejiang, China (X.L.); Department of Ophthalmology, Qingdao Eye Hospital, Shandong Eye Institute, Qingdao, Shandong, China (X.D.); Joint Shantou International Eye Centre, Shantou, Guangdong, China (M.Z.); Department of Ophthalmology, Renmin Hospital of Wuhan University, Wuhan, Hubei, China (Y.X.); School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China (H.H.); Company, Chengdu Kanghong Biotechnology Inc, Chengdu, Sichuan, China (L.Y., Z.K.); Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami, Florida, USA (P.J.R.); Cole Eye Institute, Cleveland Clinic, Cleveland, Ohio, USA (P.K.K.); and Department of Ophthalmology, Center for Preventative Ophthalmology and Biostatistics, University of Pennsylvania, Philadelphia, Pennsylvania, USA (G.Y.).

Inquiries to Xun Xu, Department of Ophthalmology, Shanghai Key Laboratory of Ocular Fundus Diseases, Shanghai General Hospital, Shanghai Engineering Center for Visual Science and Photomedicine, 100 Haining Rd, Shanghai 200080, China; e-mail: drxuxun@sjtu.edu.cn

AGE-RELATED MACULAR DEGENERATION (AMD) IS the leading cause of irreversible blindness among the >50 age group, with incidence increasing steadily with age. Owing to increase in life expectancy, the population affected by AMD is estimated to at least double by the year 2020.[1,2] An epidemiologic investigation in China found that 15.5% of Shanghai residents (aged ≥50 years) suffered from AMD, of which 11.9% developed neovascular (exudative) AMD.[3] The high cost and mandatory frequent monitoring visits generate a problematic burden for both the patients and the healthcare system in China.

Vascular endothelial growth factor (VEGF) was identified as the key trigger in the proliferation and maintenance of choroidal neovascularization (CNV) in neovascular AMD.[4,5] Therefore, VEGF has become a main target in the treatment of CNV. Several anti-VEGF agents have been developed that bind to VEGF,

0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.08.026

thereby inhibiting angiogenesis. Intraocular injection of these anti-VEGF agents is now the standard of care in AMD and has provided substantial visual benefits to patients with CNV. The commonly used anti-VEGF drugs include ranibizumab (Lucentis; Genentech, South San Francisco, California, USA), bevacizumab (Avastin; Genentech), and aflibercept (Eylea; Regeneron, Tarrytown, New York, USA).[6–11] The suggested therapy for the above drugs are monthly (ranibizumab, bevacizumab) or bimonthly (aflibercept) treatment after 3 monthly loading doses. Any delay in injection administration during the maintenance phase may cause reduction in visual benefits or even vision loss.[6,9,11] For these reasons, frequent follow-up for monitoring disease activity and for treatment is needed every 1–2 months. These mandatory visits can cause considerable burden for patients undergoing anti-VEGF treatment, particularly for AMD patients who are typically older and may require assistance in obtaining treatment, leading to noncompliance.[12] Compliance is vital in managing this chronic disease; however, frequent intraocular injections and visits may result in poor compliance. In addition, considering the increasing prevalence of AMD and the huge aging population, treatment costs may pose great challenges to healthcare systems.

Conbercept (Lumitin; Chengdu Kanghong Biotech Co, Ltd, Chengdu, China), an anti-VEGF agent developed in China, successfully improved visual acuity (VA) and reduced central retinal thickness(CRT) and CNV area in patients with neovascular AMD in our previous phase I and II studies.[13,14] Conbercept is a 141-kDa engineered fusion protein produced by the gene recombination of VEGF receptor domains with the Fc fragment of human immunoglobulin. Compared with former VEGF-trap, aflibercept, which was reported to be effective with bimonthly treatment after 3 initial monthly doses, conbercept was added with the fourth binding domain of VEGFR2, which was demonstrated to stabilize the receptor-ligand complex and further extend the half-life of conbercept.[14–16] In China, it is now covered by the national basic medical insurance. In the United States, it was given permission to begin phase III clinical trials by the FDA without repeating the phase II trials.

The main focus of this study was to evaluate the efficacy of less-frequent maintenance dosing intervals in patients with AMD. In our previous animal experiments, conbercept displayed longer half-life and stronger bioavailability than did ranibizumab. Using a mathematical model, we predicted that a prolonged dosing interval (Supplemental Appendix 1; Supplemental Material available at AJO.com) would be effective. These lines of evidence were the basis for developing an optimized treatment paradigm with conbercept. Herein, we report the results of the pivotal phase III Chinese registration study, the PHOENIX trial, conducted to assess the safety and efficacy of intravitreal injections of conbercept administered in 3 monthly loading doses followed by a quarterly dosing regimen in patients with CNV secondary to AMD.

METHODS

• **STUDY DESIGN:** The PHOENIX trial was a 12-month prospective, randomized, double-masked, multicenter, sham-controlled, phase III clinical trial conducted at 9 sites in the People's Republic of China. It was designed to assess the safety and efficacy of multiple intravitreal injections of conbercept in patients with CNV secondary to AMD compared to sham injections. It should be noted that there were no approved anti-VEGF therapies in China when the trial was initiated. This trial was registered at ClinicalTrials.gov, number NCT01436864 (A Randomized, Double-masked, Multicenter, Sham-controlled, Safety and Efficacy Study of KH902 in Patients with Wet AMD). The study protocol (Supplemental Appendix 2; Supplemental Material available at AJO.com) was approved by the Ethics Committees of Shanghai General Hospital affiliated with Shanghai Jiaotong University (2011[9]). There were no deviations from the trial and no changes to trial outcomes after the trial commenced. All human participants provided written informed consent.

• **PARTICIPANTS:** Patients were enrolled in the study if they met the following key inclusion criteria: age at least 50 years old; active, primary, or recurrent subfoveal or juxtafoveal CNV secondary to AMD with lesion size less than 30 mm^2; and a best-corrected visual acuity (BCVA) letter score between 73 (20/40 Snellen equivalent) and 19 (20/400 Snellen equivalent) letters. The BCVA score was measured as the total number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) VA chart when assessed at a starting distance of 4 meters.

Patients were excluded if any of the following ocular conditions were present: significant subfoveal atrophy or scarring; presence of other causes of CNV in either eye; history of previous AMD drug treatment (such as anti-VEGF drugs and/or steroids) within the last 6 months of screening visit in the study eye; and previous laser therapy or other ocular surgery in the study eye, such as macular translocation surgery, cataract surgery, pars plana vitrectomy, glaucoma filtering operation, verteporfin ocular photodynamic therapy, subfoveal focal laser photocoagulation, and transpupillary thermotherapy. Patients with active ocular inflammation or infection were also excluded from the study. Furthermore, the patients were not eligible for the study if any of the following systemic conditions was present: uncontrolled diabetes mellitus (defined as fasting blood glucose ≥ 7 mmol/L or 2-hour postprandial blood glucose ≥ 11.1 mmol/L); uncontrolled hypertension (defined as blood pressure greater than 150/95 mm Hg after

the treatment with antihypertensive drugs); history of a cerebrovascular accident or myocardial infarction within 6 months prior to study entry; renal failure requiring dialysis or renal transplant; pregnancy or lactation.

It should be noted that patients with polypoidal choroidal vasculopathy (PCV) and typical neovascular AMD were pooled in this study. PCV was initially intended to be excluded at the beginning of the study, but unexpectedly, the supply of indocyanine green (ICG) agents ran out in the year 2012 in China, which made it impossible to give patients ICG examinations. Without ICG, PCV could not be accurately diagnosed.

• **RANDOMIZATION AND MASKING:** Random number tables were generated by a third-party statistics company using a stratified method. All the patients were randomized before receiving conbercept or sham injection on day 0. Randomization was stratified by baseline BCVA letter score ($\leq$48 or $>$48) and study center with an adequate number of envelopes to maintain a 2:1 ratio between conbercept and sham injection for ethical consideration, based on the hypothesis that the conbercept group may see greater clinical benefit. The randomly assigned numbers were kept in opaque envelopes to avoiding selection bias by ensuring that neither clinicians nor participants would know the treatment assignment. In order to restrict performance and detection bias, the study was double-masked. Treatment assignment was masked from patients, VA assessor, and evaluating investigators. An unmasked investigator performed the injection of sham or study drug. Study drugs were dispensed by pharmacy staff who were unmasked but played no other role in the study. Unmasking was performed after all the patients had completed treatment. If patients experienced serious adverse events (SAE) requiring the knowledge of drug use, the patient was unmasked and the sponsor notified. Unmasked patients were withdrawn from this study.

• **INTERVENTION:** Patients, investigators, outcome assessors, and caregivers were masked to treatment assignment. Eligible patients (1 study eye per patient) were randomized in a 2:1 ratio into the conbercept group or the sham control group. During the 3-month loading phase, patients in the conbercept group received monthly intravitreal injections of conbercept (0.5 mg). After 3 sequential monthly injections, additional injections were given once every 3 months until month 12 (3 + Q3M). Patients in the sham group first received 3 sequential monthly sham injections. After the first 3 months, conbercept was given to the sham group for 3 months, followed by an injection every 3 months until month 12. Rescue therapy was not offered in this study, as there were no approved anti-VEGF therapies in China at the start of this study (2011). In 2012, the first agent, ranibizumab, was approved. If a patient elected to receive any other AMD therapy, he or she was withdrawn from the study.

The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments, China's Good Clinical Practices regulations, and applicable institutional regulatory requirements. Before the initiation of the study, relevant institutional review boards and ethics committees from the respective study centers approved the research protocol and its amendments. All patients provided written informed consent for study participation. The trial was registered at ClinicalTrials.gov, number NCT01436864 and under the name "A Randomized, Double-masked, Multicenter, Sham-controlled, Safety and Efficacy Study of KH902 in Patients with Wet AMD."

• **PROCEDURES:** The primary outcome of this study was the mean change in BCVA score from baseline to month 3. The secondary outcomes included the mean change in BCVA score from baseline to month 12, as well as from month 3 to month 12. We also assessed the proportion of patients who gained more than 0 letters, gained at least 15 letters, gained at least 30 letters, or lost fewer than 15 letters from baseline at month 3; the mean change in CRT on optical coherence tomography (OCT) imaging; the mean change in leakage area on fluorescein angiography (FA) imaging over time; and the incidence rate of adverse events (AE) over time. The primary endpoint was evaluated at the end of the loading dose phase at month 3. Results of the maintenance phase were assessed at month 12.

All patients were evaluated monthly. Evaluations included BCVA measured with an ETDRS chart (4 m starting distance), visual function assessments, intraocular pressure measurements, slit-lamp examinations, imaging with color fundus photography (CFP), OCT, and FA. OCT imaging was performed at every visit while FA and CFP were performed only at baseline and at months 3, 6, and 12. OCT imaging was performed with either the Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA) or the Heidelberg Spectralis spectral-domain OCT (SD-OCT) (Heidelberg Engineering, Heidelberg, Germany). For all patients, the same OCT device used at baseline was used throughout the study. When the Stratus OCT was used, the following scan patterns were performed on both eyes and centered on the fovea: 2 7-mm posterior pole custom scans positioned 5 degrees below horizontal from the temporal edge of the optic nerve toward the fovea (512 A-scans per B-scan), 1 3-mm high-resolution cross-hair scan (512 A-scans per B-scan), 1 6-mm high-resolution cross-hair linear scan (512 A-scans per B-scan), and 2 fast macular thickness map scans consisting of 6 radial line scans (128 A-scans per B-scan). When the Heidelberg Spectralis SD-OCT was used, the following scan patterns were performed on both eyes and centered on the fovea: a single 30-degree horizontal section scan with an Automatic Real-Time (ART) setting of 15 (1536 A-scans per B-scan) and a volume scan over a 20 degree $\times$ 20 degree area consisting of 49 B-scans (512 A-scans per

B-scan) with each B-scan separated by 120 μm and an ART setting of 15. Fluorescein angiography was performed using either the Topcon TRC.50-DX or the Heidelberg HRA2. Color fundus photography was performed using Topcon TRC.50-DX, Topcon TRC-50EX, and Zeiss FF 450plus. The OCT, FA, and CFP images were graded at a central reading center (Fundus Photograph Reading Center, University of Wisconsin-Madison). Study visits were scheduled every 30 ± 7 days.

• **SAFETY ASSESSMENTS:** Safety was assessed through collection and summary of ocular and nonocular AEs, SAEs, ocular assessments, deaths, laboratory results, and vital signs. At each study visit, nondirective questioning was used to elicit AE reports from patients. All AEs and SAEs, whether volunteered by the patient, discovered by study site personnel during questioning, or detected by examination, laboratory testing, or other means, were recorded in the patient record and case report forms. Safety analysis was based on the safety data set, which included all the patients who participated in the study. Safety data were evaluated using summary statistics. Only the AEs, treatment-related AEs, incidence of AEs, and SAEs emerging within the first 3 months were compared between groups using the χ^2 test/Fisher exact method. AEs were recorded at each visit and coded with MedDRA 15.1.

• **STATISTICAL ANALYSIS:** According to our previous phase I and phase II study results, a sample size of 120 patients (ratio of 2:1) was determined to provide 80% power to detect an 8-letter difference between the conbercept group and the sham-control group at month 3, assuming a standard deviation of 10 letters per group, with a 2-sided *t* test at a significance level of 5%.

Unless otherwise specified, the intent-to-treat principle was used for efficacy analyses and the full analysis data set was used, which included all randomized patients who received any study medication, had baseline assessments, and had at least 1 postbaseline assessment. Missing data were imputed using the last-observation-carried-forward method. Patients were analyzed according to the group at randomization. In addition, we performed the safety analyses based on safety set for investigating the AEs and SAEs.

For continuous variables with an approximately normal distribution, means and standard deviations are reported. Otherwise, medians and interquartile ranges (IQRs) are reported. Binary endpoints were analyzed with the use of the Cochran-Mantel-Haensel test (≤48 letters vs >48 letters). Mean changes from baseline were analyzed with the use of analysis of variance for endpoints with respect to an analysis of covariance for morphologic endpoints.

All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, North Carolina, USA). All statistical tests were 2-sided test. A *P* value of less than .05 was considered statistically significant.

• **STUDY APPROVAL:** The study protocol (Supplemental Appendix 2) was approved by the Ethics Committees of Shanghai General Hospital affiliated with Shanghai Jiaotong University (2011[9]). There are no deviations from the trial and no changes to trial outcomes after the trial commenced. All human participants gave written informed consent.

RESULTS

ELIGIBLE PARTICIPANTS WERE RECRUITED FROM AUGUST 29, 2011, to September 27, 2013. Overall, 124 patients were enrolled in the PHOENIX trial and randomized in a 2:1 ratio to the conbercept (n = 81) and sham-control groups (n = 43).

Among the 124 patients, 123 patients (99.2%) completed the study at the primary endpoint (3 months), with 1 patient in the sham group discontinuing the study owing to continued loss of VA. All 123 patients entered into the maintenance phase and 113 patients (91.1%) completed the 12-month study (Figure 1). Reasons for withdrawal during the whole phase included loss of VA (n = 1, 0.81%), SAEs (n = 5, 4.03%), investigator discretion (n = 4, 3.22%) and loss to follow-up (n = 1, 0.81%).

The patients in the conbercept and sham groups were generally well balanced with respect to baseline demographics and the studied eye characteristics, including the history of prior treatment (Table 1).

At the primary endpoint, the mean numbers of conbercept injections were 3 and 0 in the treatment and sham groups, respectively. The mean number of conbercept injections at 12 months was 5.8 in the conbercept group and 4.8 in the sham group.

At the 3-month primary endpoint, patients in the conbercept group saw a mean change in BCVA score from baseline of +9.20 letters in the conbercept group (95% confidence interval [CI], 6.93 to 11.53; standard deviation [SD], 9.22), while the sham group experienced a mean change of +2.02 (95% CI, −1.20 to 5.12; SD, 12.67), respectively. Improvement in the conbercept group was statistically significant compared to that in the sham group (mean difference, +7.27 letters, 95% CI, 3.36 to 11.18; $P < .001$). From month 3 to month 12, the mean changes in BCVA was +0.78 letters in the conbercept group (95% CI, −1.85 to 3.40; SD, 11.87) and +6.76 letters in the sham group (95% CI, 3.62 to 9.90; SD, 10.08), and there was a statistically significant difference between the 2 groups (mean difference, −5.62 letters; 95% CI, −9.99 to −1.26; $P = .01$). When comparing month 12 to baseline, the mean change in BCVA was +9.98 letters in the conbercept group (95% CI, 6.89 to 13.06; SD, 13.95) and +8.81 letters in the sham group (95% CI 4.47 to 13.15, SD 13.92), respectively (Figure 2), and these

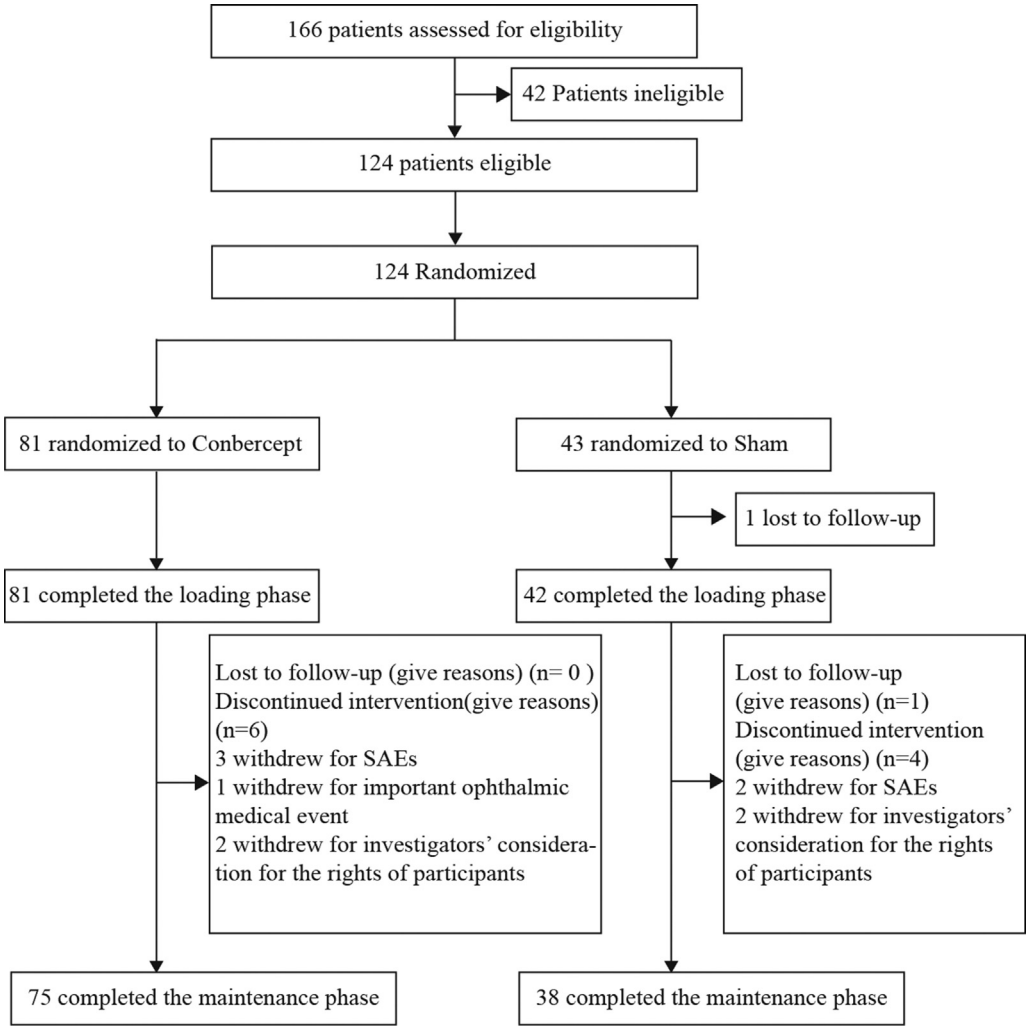

FIGURE 1. Flowcharts describing treatment allocation and patient disposition during the enrollment process in the PHOENIX study using conbercept for the treatment of neovascular age-related macular degeneration. In total, 124 patients were enrolled in the PHOENIX trial and randomized in a 2:1 ratio to the conbercept (n = 81) and sham-control groups (n = 43). SAE = serious adverse event.

differences were not statistically significant (mean difference, +1.24 letters; 95% CI, −4.01 to 6.50; $P = .64$).

To supplement the analysis, we also conducted the per-protocol set analysis. For our main outcome measurement, the visual benefit of the conbercept group was also significant over the sham group (mean difference, +7.27 letters; 95% CI, 3.27 to 11.26; $P < .001$).

At the 3-month endpoint, the proportion of patients in the conbercept group and the sham groups losing fewer than 15 letters were 100.0% and 93.0% ($P = .02$), respectively. Those losing fewer than 5 letters at this time point were 93.8% and 76.7% ($P = .006$) for the conbercept and the sham group, respectively. In the conbercept group, 49.4% of patients gained 10 or more letters by month 3, and 23.5% gained 15 or more letters. In comparison, for sham group patients at month 3, 18.6% ($P < .001$) gained 10 or more letters, and 16.3% ($P = .34$) gained 15 or more letters (Figure 3).

There was a statistically significant difference in the mean decrease in CRT between conbercept and sham groups from baseline to month 3 (mean difference −83.29 μm, 95% CI, −125.92 to −40.67; $P < .001$). However, no significant difference remained between the 2 groups when comparing month 3 to month 12 (mean difference, 14.08 μm; 95% CI, −19.75 to 47.90; $P = .41$) (Figure 4). Additional changes in other anatomic outcomes, such as total macular volume, leakage area, and CNV area, can be found in Table 2.

Intravitreal conbercept was generally well tolerated. From baseline to month 3, 40 patients (49.4%) in the conbercept group (81 patients) reported AEs, including 23 (28.4%) ocular AEs and 23 (28.4%) nonocular AEs. There were no reports of cataract, vitreous hemorrhage,

TABLE 1. Patient Demographic and Baseline Characteristics of Conbercept and Sham Group in PHOENIX Study (Full Analysis Set)

Characteristics	Conbercept Group (N = 81)	Sham Group (N = 43)
Sex		
Male	52 (64.2%)	32 (74.4%)
Female	29 (35.8%)	11 (25.6%)
Age (y)	66.9 (7.6)	64.6 (8.1)
Study eye		
Right eye	44 (54.3%)	26 (60.5%)
Left eye	37 (45.7%)	17 (39.5%)
Previous treatment for AMD		
Yes	24 (29.6%)	8 (18.6%)
No	57 (70.4%)	35 (81.4%)
BCVA (letters)	49.0 (17.1)	48.0 (14.1)
Snellen	20/100	20/100
CRT (μm)	328.3 (126.8)	374.4 (142.4)
Leakage area (mm^2)	7.1 (6.8)	6.3 (4.4)
Lesion type		
Predominantly classic	38 (46.9%)	23 (53.5%)
Minimally classic	17 (21.0%)	12 (27.9%)
Occult	24 (29.6%)	7 (16.3%)
No CNV	2 (2.5%)	0 (0.0%)
Cannot classify/missing	0 (0.0%)	1 (2.3%)

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; CNV = choroidal neovascularization; CRT = central retinal thickness.
Data are n (%) or mean (SD) unless otherwise indicated.

or serious ocular inflammation (sterile or infectious endophthalmitis) in the study eyes of the conbercept group. Sixteen patients (37.2%) in the sham group reported AEs, including 8 (18.6%) with ocular AEs and 11 (25.6%) with nonocular AEs. The incidence of nonocular AEs was similar in both groups (28.4% vs 25.6%).

During the 12-month period in the conbercept group, there were 42 (51.9%) ocular AEs. The most common ocular AEs was injection site hemorrhage associated with intravitreal injections (22; 27.2%). The incidences of other ocular AEs of study eyes included increased intraocular pressure, reduced VA, and vitreous floaters and were 5 (6.2%), 7 (8.6%), and 3 (3.7%), respectively. The proportion of nonocular AEs was 56.8%. Moreover, in the sham group, the total of ocular AEs was 22 (52.4%) during 9 months with the beginning of injection. The rate of injection site hemorrhage associated with intravitreal injections was 12 (28.6%). The other ocular AEs of study eyes included increased intraocular pressure, reduced VA, and vitreous floaters, with 5 (11.9%), 1 (2.4%), and 1 (2.4%) occurrences, respectively. The total of nonocular AEs was 19 (45.2%).

The incidence of Antiplatelet Trialists' Collaboration arterothrombolic events was 1.2% in the conbercept group (1 anterior myocardial infarction) and 2.4% in the sham group (1 mild cerebral infarction) during the entire study period. There were no apparent allergic reactions and no deaths during the study period. Major ocular AEs and SAEs (including ocular and nonocular) are summarized in Table 3.

DISCUSSION

AS GLOBAL LIFE EXPECTANCY INCREASES, THE ELDERLY POPulation continues to grow. Likewise, AMD and other age-related diseases continue to be potentially significant challenges to the healthcare system. Currently, intravitreal injection of anti-VEGF is considered the first-line therapy for neovascular AMD. However, frequent visits and time-consuming examinations are required for adequate treatment and pose a risk of noncompliance and treatment burden, particularly in elderly patients with limited healthcare access. Aside from these social considerations, repeated injections are associated with a risk of SAEs, such as endophthalmitis, whose prevalence is 0.3% per injection and 0.9% per eye.[17] When one considers that more than 160 000 intravitreal injections for neovascular AMD are administered each year in China, the impact of decreased injection frequency becomes ever more apparent. Ideally, an improvement over current therapeutic options should reduce the frequency of injections and visits while maintaining a similar efficacy and tolerance profile.

Conbercept, as a new VEGF-trap developed in China, was predicted to have strong bioactivity.[18,19] Efforts have been made to explore a more patient-friendly treatment by using this new agent. Here, we reported the results of the PHOENIX trial, which demonstrated promising results of using conbercept for targeting neovascular AMD. As a prospective, randomized, sham-controlled, phase III study, the PHOENIX was conducted not only to assess the safety and efficacy of intravitreal administration of conbercept for patients with neovascular AMD, but also to evaluate the utility of a regimen with fewer injections. The results demonstrated a significant and rapid improvement in visual and anatomic outcomes at the 3-month endpoint (after 3 monthly treatments) for patients in the conbercept group than in the sham group. Although the sham treatment produced a mean change of +2.02 ETDRS letters from baseline to 3 months, an improvement of at least 5 letters (a line in ETDRS chart) was normally considered functional.[20,21] At 12 months, both the conbercept and sham groups had received 3 monthly doses of conbercept and had started receiving quarterly injections. Obvious visual improvements from baseline were noted in both groups, suggesting the effectiveness of the injections throughout the treatment period. The VA and CRTs at 12 months showed no statistically significant differences between the

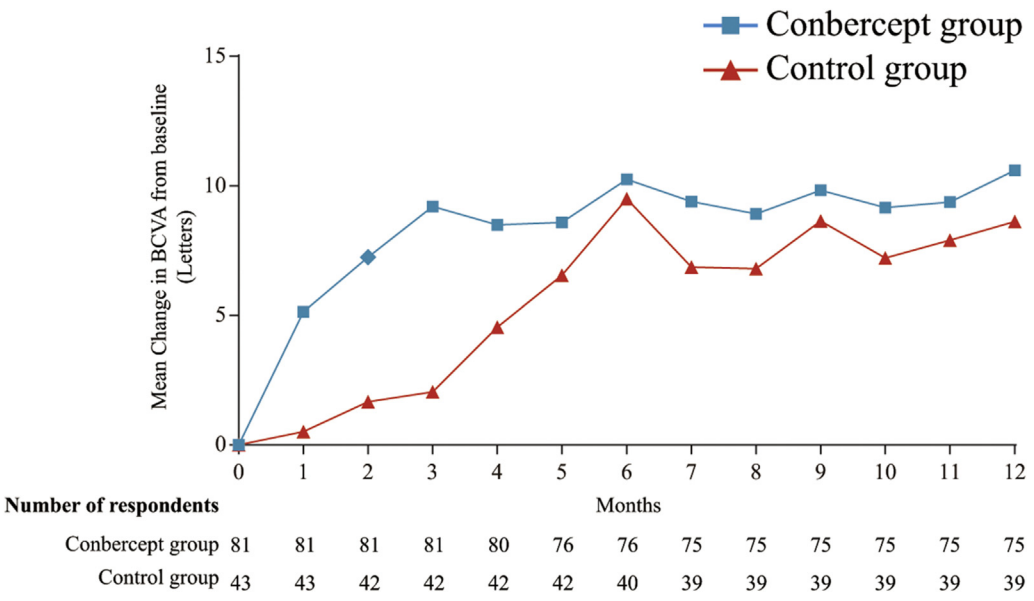

FIGURE 2. Mean change in best-corrected visual acuity (BCVA) when using conbercept for the treatment of neovascular age-related macular degeneration from baseline over time up to month 12. At the 3-month primary endpoint, the conbercept group showed statistically significant improvements over the sham group. When comparing month 12 to baseline, the mean changes in BCVA were +9.98 letters in the conbercept group and +8.81 letters in the sham group. Data shown are mean ± SD, as determined using covariance analysis. Conbercept group, n = 81. Control group, n = 43.

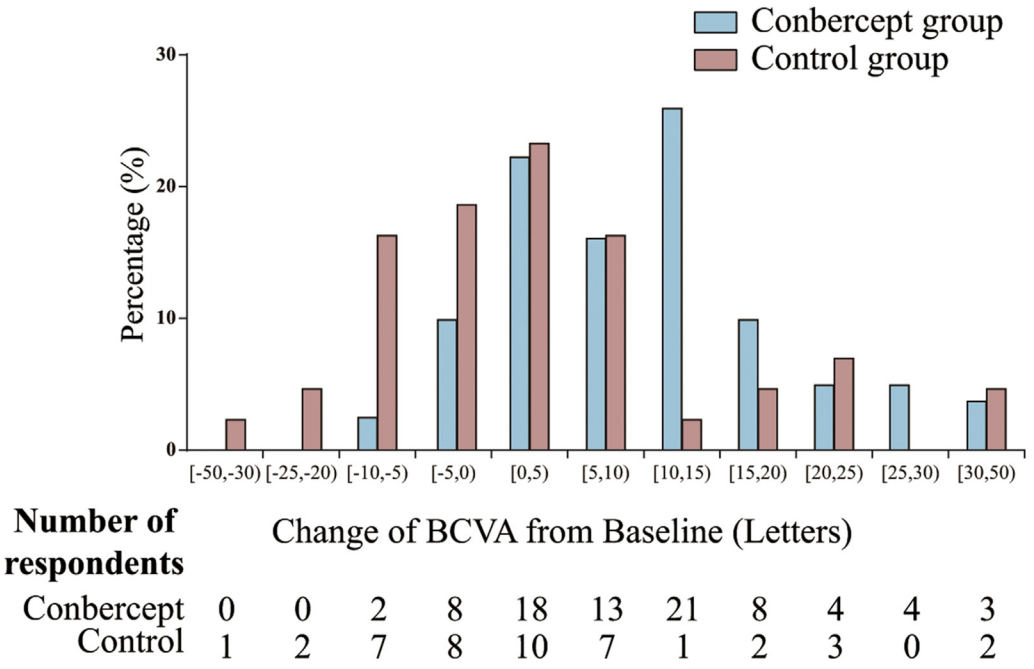

FIGURE 3. The percentage of patients with a change in best-corrected visual acuity (BCVA) when using conbercept or sham injections for the treatment of neovascular age-related macular degeneration in the 2 groups from baseline over time up to month 3, as determined using Fisher exact test. At the 3-month endpoint, the proportion of patients in the conbercept and sham groups losing fewer than 15 letters were 100.0% and 93.0%, respectively. Conbercept group, n = 81. Control group, n = 43.

conbercept and sham groups, probably because the 2 groups had already received the 3 monthly injections, which were intended to improve the impaired visual function. Therefore, it is important to compare the 2 groups at month 3 when the conbercept group had received 3 monthly loading injections, whereas the sham group

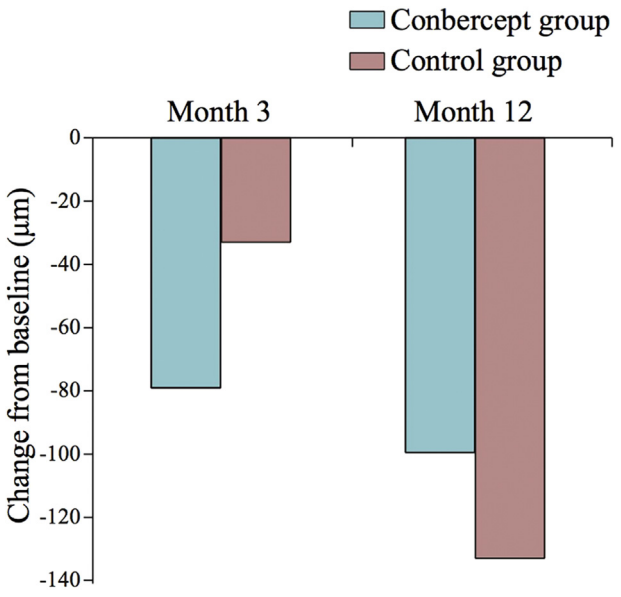

FIGURE 4. Mean change in central retinal thickness (CRT) when using conbercept for the treatment of neovascular age-related macular degeneration from baseline over time up to month 12. A statistically significant difference was observed in the mean decrease in CRT between the conbercept and sham groups from baseline to month 3. No significant difference remained between the 2 groups when comparing CRT from month 3 to month 12. Data shown are mean ± SD, as determined using covariance analysis. Conbercept group, n = 81. Control group, n = 43.

had received none. The difference at 3 months between the 2 groups indicated the efficiency of conbercept treatment. The following quarterly injections were mostly intended as maintenance treatment to prevent the VA from decreasing. In other words, the stabilization of VA after the first 3 loading injections is a good sign. Therefore, the 2 groups showed little difference in VA and CRTs at 12 months, since patients in both groups had all completed the loading dose phase.

Moreover, the clinical benefit in the conbercept group was maintained through 12 months when maintenance treatment was administered quarterly. To enhance the generalizability of the findings, 9 representative centers from different regions of China were chosen for this study. To the authors' knowledge, this is the first report of the efficacy of an anti-VEGF treatment at this quarterly maintenance dosing schedule. We hypothesized that with the decreased injection frequency, noncompliance will decrease in the clinical practice. In previous studies (PIER, EXCITE, and VIEW 1 and 2), a quarterly maintenance dosing schedule was tested for anti-VEGF agents. These regimens failed to achieve satisfactory efficacy, and thus highlight the importance of the findings of the PHOENIX study.[6,9,11] In the PIER study, ranibizumab resulted in a BCVA score of −0.2 letters at month 12 by using 3 initial monthly doses followed by quarterly maintenance treatment, which was the same dosing regimen as that used in the PHOENIX study. In the EXCITE study, noninferiority criteria for quarterly vs monthly dosing regimen of ranibizumab were not met; this indicated the clinical superiority of a monthly treatment regimen using this anti-VEGF drug. The VIEW 1 and VIEW 2 studies provided efficiency data for aflibercept when using bimonthly injections following 3 initial monthly doses, which was a more frequent dosing interval than that used in the PHOENIX study. However, aflibercept had not yet been approved for use in China to treat ocular diseases. Although head-to-head studies are still needed, the PHOENIX study shows that conbercept is an effective and well-tolerated treatment for AMD with the potential to provide health outcome advantages over other anti-VEGF treatments. Since anti-VEGF treatment plays an increasingly important role in treating neovascular ocular diseases, decreasing the treatment frequency and compliance burden would yield considerable social benefits and probably make a difference in promoting vision healthcare.

Conbercept was specifically designed for enhanced bioactivity and stability on the basis of in vitro, in vivo, and in silico data with the goal of decreasing the dosing frequency for a more patient-friendly treatment regimen. The distinctive molecular design of this novel VEGF-trap mimics multiple human VEGFR domains, and hence, it can bind to several VEGF family members including VEGF-A, VEGF-B167, and PLGF. Compared to ranibizumab, conbercept contains an additional antigen-binding fragment (Fab) with specificity for VEGF-A, which confers a wider range of targets and higher binding affinity to VEGF-A165.[16,22] We previously assessed the bioactivity of conbercept in an exploratory animal experiment in which ranibizumab was used as a reference (Supplemental Appendix 1). The results of that study showed that compared to ranibizumab, conbercept had a longer half-life and greater bioavailability after a single intravitreal injection (conbercept was present at 0.47 ng/mL in the retina on day 56, but ranibizumab was undetectable since day 45). After detecting this significant difference in an in vivo animal model, we used a mathematical model to predict similar measures in humans (Supplemental Appendix 2). The model suggested that the increased bioavailability and half-life of conbercept could support a prolonged dosing interval. Moreover, when compared with another VEGF-trap, aflibercept, conbercept has improved biological activity owing to its extra functional domain (VEGFR2 domain 4), which can stabilize the receptor-ligand complex and enhance dimerization. In a study evaluating the anti-angiogenic effects among different VEGF-traps in human

TABLE 2. Comparison of the Mean Changes in Anatomic Outcomes Between the Conbercept and Sham Groups at Different Time Points During the Treatment for Neovascular Age-related Macular Degeneration

	Anatomic Outcome							
	Central Retinal Thickness (μm)		Total Macular Volume (mm^3)		Leakage Area (mm^2)		CNV Area (mm^2)	
	Conbercept	Sham	Conbercept	Sham	Conbercept	Sham	Conbercept	Sham
Baseline to month 3								
Means (SD)	−79.16 (136.03)	−33.03 (163.04)	−1.12 (1.69)	−0.23 (1.58)	−1.93 (4.14)	0.93 (4.77)	0.07 (3.97)	1.53 (4.16)
Adjusted means (SD)	−91.54 (12.29)	−8.25 (17.48)	−1.14 (0.12)	−0.20 (0.18)	−1.89 (0.47)	0.84 (0.66)	0.09 (0.45)	1.47 (0.64)
Comparison[a]								
Mean difference (95% CI)	−83.29 (−125.92 to −40.67)		−0.94 (−1.37 to −0.51)		−2.73 (−4.34 to −1.12)		−1.38 (−2.92 to 0.16)	
P value	<.001		<.001		.001		.08	
Baseline to month 12								
Means (SD)	−99.63 (168.83)	−132.93 (160.60)	−1.16 (1.92)	−1.03 (1.05)	−2.21 (4.96)	−0.09 (6.03)	−0.03 (4.74)	2.23 (6.20)
Adjusted means (SD)	−115.058 (10.25)	−103.573 (16.54)	−1.149 (0.11)	−1.056 (0.16)	−2.148 (0.58)	−0.213 (0.80)	0.028 (0.60)	2.129 (0.83)
Comparison[a]								
Mean difference (95% CI)	−11.486 (−46.31 to 23.34)		−0.093 (−0.48 to 0.29)		−1.935 (−3.90 to 0.03)		−2.100 (−4.12 to −0.08)	
P value	.47		.63		.05		.04	
Month 3 to 12								
Means (SD)	−12.92 (100.21)	−96.63 (161.42)	−0.02 (0.75)	−0.94 (1.33)	−0.40 (3.86)	−1.03 (5.41)	0.00 (2.97)	0.78 (4.37)
Adjusted means (SD)	−37.12 (9.69)	−51.19 (13.52)	−0.15 (0.10)	−0.68 (0.13)	−0.55 (0.49)	−0.74 (0.68)	−0.02 (0.40)	0.81 (0.55)
Comparison[a]								
Mean difference (95% CI)	14.08 (−19.75 to 47.90)		0.52 (0.18 to 0.86)		0.20 (−1.47 to 1.87)		−0.84 (−2.19 to 0.52)	
P value	.41		.003		.81		.22	

CNV = choroidal neovascularization.
[a]Comparison was calculated via adjusted data.

TABLE 3. All Ocular Adverse Events and Serious Adverse Events (including Nonocular Ones) From Baseline to Months 3 and 12 for the 2 Groups of Eyes During Treatment for Neovascular Age-related Macular Degeneration

	Month 1–3		Month 1–12	Month 4–12
	Conbercept Group (N = 81)	Sham Group (N = 43)	Conbercept Group (N = 81)	Sham Group (N = 42)
Ocular AEs of study eye				
Injection site hemorrhage	14 (17.3)	1 (2.3)	22 (27.2)	12 (28.6)
Reduced visual acuity	2 (2.5)	2 (4.7)	7 (8.6)	1 (2.4)
Conjunctivitis	2 (2.5)	3 (7.0)	7 (8.6)	0
Increased intraocular pressure	4 (4.9)	0	5 (6.2)	5 (11.9)
Vitreous floaters	-	-	3 (3.7)	1 (2.4)
Injection site injury	1 (1.2)	0	0	0
Cataract	-	-	1 (1.2)	0
Allergic conjunctivitis	-	-	1 (1.2)	0
Macular hemorrhage	-	-	1 (1.2)	0
Macular edema	-	-	1 (1.2)	0
Retinal edema	1 (1.2)	0	1 (1.2)	0
Polypoidal choroidal vasculopathy	-	-	1 (1.2)	0
Dry eye	-	-	0	1 (2.4)
Retinal detachment	-	-	0	1 (2.4)
Retinal hemorrhage	0	1 (2.3)	-	-
SAEs				
Retinal detachment	-	-	0	1 (2.4)
Cataract	-	-	1 (1.2)	0
Cervical disorder	-	-	0	1 (2.4)
Pancreatic cancer	-	-	2 (2.5)	0
Femoral fracture	-	-	1 (1.2)	0
Rectal cancer	-	-	1 (1.2)	0
Chronic obstructive pulmonary disease	-	-	1 (1.2)	0
Myocardial infarction	-	-	1 (1.2)	0

AE = adverse events; SAE = serious adverse events.

Conbercept group received a loading dose of 3 monthly injections followed by injections every 3 months until month 12 (3 + Q3M). Control group received 3 monthly sham injections, then at month 3 received 3 monthly injections of conbercept followed by quarterly administration until month 12.

umbilical vein endothelial cells, conbercept was found to be superior to aflibercept.[19] These data supported our hypothesis that the bioactivity of conbercept could support the quarterly dosing regimen assessed in the PHOENIX study.

Despite these strengths, the PHOENIX study has some limitations. First, the stock of ICG agents ran out in China during the research period, and this made it difficult to distinguish patients with PCV and other diseases. Therefore, we cannot rule out the possibility of some patients with PCV being present in the current study sample. However, recent evidence has indicated the efficiency of anti-VEGF monotherapy in patients with PCV, which reduced subretinal fluid levels and caused vision stabilization.[23,24] Moreover, the subgroup analysis of the Aurora study proved the efficacy of conbercept in PCV.[25] To further confirm this effect, we actively participated in the prospective clinical trial accessing the efficacy of intravitreal injection of conbercept in patients with PCV (STAR study, NCT03159884, ClinicalTrials.gov).

Conbercept was well tolerated, with no systemic AEs or SAEs in this study. The most common ocular AEs were associated with intravitreal injections, such as conjunctival hemorrhage, and increased intraocular pressure. The reduced incidence of systemic AEs and prolonged activity of conbercept may be attributed to its large molecular size (143 kDa), which likely limits its permeability through blood-ocular barriers with little systemic exposure compared to that of systemically administered drugs.[15] Other ocular AEs, including endophthalmitis, uveitis, and retinal detachment, were not detected in the current study, which is consistent with the findings of previous preclinical and clinical studies. Although no new AE was detected, owing to the limited sample size, the PHOENIX study was not adequately powered to detect all drug-related AEs. Postmarketing studies will continue to monitor the long- and short-term drug safety.

In conclusion, the phase III PHOENIX study demonstrated that 3 initial monthly doses of intravitreal conbercept (0.5 mg) followed by quarterly dosing of conbercept

(0.5 mg) resulted in clinically and statistically significant visual and anatomic benefits for patients with neovascular AMD at 3 and 12 months. Because other anti-VEGF agents cannot support this dosing regimen, treatment using conbercept has the potential to be a more patient-friendly treatment than are existing treatments.

FUNDING/SUPPORT: THIS WORK WAS SUPPORTED BY CHENGDU KANGHONG BIOTECHNOLOGY INC (CHENGDU, SICHUAN, China). The sponsor participated in the design of the study, conducting the study, data collection, data management, and preparation of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. Financial Disclosures: Liyun Yu and Zunhong Ke are employees of Chengdu Kanghong Biotechnology, Company, Ltd. Philip J. Rosenfeld is a consultant to Chengdu Kanghong Biotech. He also received research support from Acucela, Apellis, Carl Zeiss Meditec, Inc, Genentech, GlaxoSmithKline, Ocata Therapeutics/Astellas Institute for Regenerative Medicine, and Tyrogenex. He is also a consultant to Carl Zeiss Meditec, Achillion Pharmaceuticals, Acucela, Alcon, Boehringer-Ingelheim, Cell Cure Neurosciences, Genentech, Healios K.K., F. Hoffmann-La Roche Lt., MacRegen Inc, NGM Biopharmaceuticals, Ocunexus Therapeutics, Regeneron, and Tyrogenex. He has equity interests in Apellis and Digisight. Peter K. Kaiser is a consultant to Chengdu Kanghong Biotech, Bayer, Regeneron, Allergan, Alcon, and Novartis. Guishuang Ying is a consultant to Janssen Research & Development and Chengdu Kanghong Biotech, Inc. The following authors have no financial disclosures: Kun Liu, Yanping Song, Gezhi Xu, Jian Ye, Zhifeng Wu, Xiaoling Liu, Xiaoguang Dong, Mingzhi Zhang, Yiqiao Xing, Shaoping Zhu, Xia Chen, Yinchen Shen, Hengye Huang, Xiaodong Sun, and Xun Xu. All authors attest that they meet the current ICMJE criteria for authorship.

Other Acknowledgments: The authors thank Qiao Sun, Chong Chen, Xiaolu Yang, Ying Zheng, Qi Yu, Yupeng Xu, and Jing Wang (Department of Ophthalmology, Shanghai General Hospital, Shanghai, China) for their help during manuscript preparation.

The PHOENIX Study Group: Members of the PHOENIX Study Group not listed as article authors: Rong Li, Quan Wu, Xinguo Wang, Fenglei Kuang, Jing Lv, and Zhili Niu, from Company, Chengdu Kanghong Biotechnology Inc, Chengdu, Sichuan, China.

REFERENCES

1. Friedman DS, O'Colmain BJ, Munoz B, et al. Prevalence of age-related macular degeneration in the United States. *Arch Ophthalmol* 2004;122(4):564–572.
2. Kawasaki R, Yasuda M, Song SJ, et al. The prevalence of age-related macular degeneration in Asians: a systematic review and meta-analysis. *Ophthalmology* 2010;117(5):921–927.
3. Zou HD, Zhang X, Xu X, Wang FH, Zhang SJ. Prevalence study of age-related macular degeneration in Caojiadu blocks, Shanghai. *Zhonghua Yan Ke Za Zhi* 2005;41(1):15–19.
4. Spilsbury K, Garrett KL, Shen WY, Constable IJ, Rakoczy PE. Overexpression of vascular endothelial growth factor (VEGF) in the retinal pigment epithelium leads to the development of choroidal neovascularization. *Am J Pathol* 2000;157(1):135–144.
5. van Lookeren Campagne M, LeCouter J, Yaspan BL, Ye W. Mechanisms of age-related macular degeneration and therapeutic opportunities. *J Pathol* 2014;232(2):151–164.
6. Regillo CD, Brown DM, Abraham P, et al. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. *Am J Ophthalmol* 2008;145(2):239–248.
7. Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, Giraldez J. Ranibizumab for neovascular age-related macular degeneration. *Am J Health Syst Pharm* 2008;65(19):1805–1814.
8. Brown DM, Michels M, Kaiser PK, Heier JS, Sy JP, Ianchulev T. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: two-year results of the ANCHOR study. *Ophthalmology* 2009;116(1):57–65.e55.
9. Schmidt-Erfurth U, Eldem B, Guymer R, et al. Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration: the EXCITE study. *Ophthalmology* 2011;118(5):831–839.
10. Martin DF, Maguire MG, Ying GS, Grunwald JE, Fine SL, Jaffe GJ. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med* 2011;364(20):1897–1908.
11. Heier JS, Brown DM, Chong V, et al. Intravitreal aflibercept (VEGF trap-eye) in wet age-related macular degeneration. *Ophthalmology* 2012;119(12):2537–2548.
12. Haller JA. Current anti-vascular endothelial growth factor dosing regimens: benefits and burden. *Ophthalmology* 2013;120(5 Suppl):S3–S7.
13. Zhang M, Zhang J, Yan M, et al. A phase 1 study of KH902, a vascular endothelial growth factor receptor decoy, for exudative age-related macular degeneration. *Ophthalmology* 2011;118(4):672–678.
14. Li X, Xu G, Wang Y, et al. Safety and efficacy of conbercept in neovascular age-related macular degeneration: results from a 12-month randomized phase 2 study: AURORA study. *Ophthalmology* 2014;121(9):1740–1747.
15. Li H, Lei N, Zhang M, Li Y, Xiao H, Hao X. Pharmacokinetics of a long-lasting anti-VEGF fusion protein in rabbit. *Exp Eye Res* 2012;97(1):154–159.
16. Zhang M, Yu D, Yang C, et al. The pharmacology study of a new recombinant human VEGF receptor-fc fusion protein on experimental choroidal neovascularization. *Pharm Res* 2009;26(1):204–210.
17. Jager RD, Aiello LP, Patel SC, Cunningham ET Jr. Risks of intravitreous injection: a comprehensive review. *Retina* 2004;24(5):676–698.
18. Mordenti J, Cuthbertson RA, Ferrara N, et al. Comparisons of the intraocular tissue distribution, pharmacokinetics, and safety of 125I-labeled full-length and Fab antibodies in rhesus monkeys following intravitreal administration. *Toxicol Pathol* 1999;27(5):536–544.
19. Yu DC, Lee JS, Yoo JY, et al. Soluble vascular endothelial growth factor decoy receptor FP3 exerts potent antiangiogenic effects. *Mol Ther* 2012;20(5):938–947.
20. Gonzalez VH, Campbell J, Holekamp NM, et al. Early and long-term responses to anti-vascular endothelial growth factor therapy in diabetic macular edema: analysis of protocol I data. *Am J Ophthalmol* 2016;172:72–79.

21. Jaffe GJ, Ciulla TA, Ciardella AP, et al. Dual antagonism of PDGF and VEGF in neovascular age-related macular degeneration: a phase IIb, multicenter, randomized controlled trial. *Ophthalmology* 2017;124(2):224–234.
22. Lu X, Sun X. Profile of conbercept in the treatment of neovascular age-related macular degeneration. *Drug Des Devel Ther* 2015;9:2311–2320.
23. Wolff B, Vasseur V, Cahuzac A, et al. Aflibercept treatment in polypoidal choroidal vasculopathy: results of a prospective study in a Caucasian population. *Ophthalmologica* 2018;1–5.
24. Hikichi T. Six-year outcomes of antivascular endothelial growth factor monotherapy for polypoidal choroidal vasculopathy. *Br J Ophthalmol* 2018;102(1):97–101.
25. Qu J, Cheng Y, Li X, Yu L, Ke X. Efficacy of intravitreal injection of conbercept in polypoidal choroidal vasculopathy: subgroup analysis of the Aurora Study. *Retina* 2016;36(5):926–937.