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Intravitreal conbercept for diabetic macular oedema: 2-year results from a randomised controlled trial and open-label extension study

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/bjophthalmol-2020-318690>).

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Received 7 January 2021
Revised 31 March 2021
Accepted 13 April 2021
Published Online First
17 May 2021



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To cite: Liu K, Wang H, He W, et al. *Br J Ophthalmol* 2022;**106**:1436–1443.

ABSTRACT

Background To demonstrate the efficacy and safety of intravitreal injections of conbercept versus laser photocoagulation in the treatment of diabetic macular oedema (DME).

Methods A 12-month multicentre, randomised, double-masked, double-sham, parallel controlled, phase III trial (Sailing Study), followed by a 12-month open-label extension study. Patients with centre-involved DME were randomly assigned to receive either laser photocoagulation followed by pro re nata (PRN) sham intravitreal injections (laser/sham) or sham laser photocoagulation followed by PRN 0.5 mg conbercept intravitreal injections (sham/conbercept). Patients who entered the extension study received PRN conbercept treatment. The primary endpoint was the changes in best-corrected visual acuity (BCVA) from baseline.

Results A total of 248 eyes were included in the full analysis set and 157 eyes continued in the extension study. Significant improvement in mean change in BCVA from baseline to month 12 was observed in the sham/conbercept group (8.2±9.5 letters), whereas no improvement was observed in the laser/sham group (0.3±12.0 letters). Patients in the laser/sham group showed a marked improvement in BCVA after the switch to conbercept in the extension study, and there was no difference in BCVA between the two groups at the end of the extension study.

Conclusion The use of a conbercept PRN intravitreal injection regimen improved the BCVA of patients with DME, and its efficacy was better than that of laser photocoagulations, and the same efficacy was observed when the eyes treated with laser alone were switched to conbercept.

Trial registration number NCT02194634.

INTRODUCTION

Diabetic retinopathy and diabetic macular oedema (DME) are the most common causes of preventable blindness worldwide,^{1–3} and the worldwide prevalence of DME is 4.7%–10.1%.^{4–6} Retinal thickening and hard exudates that threaten or involve the centre of the macula are considered to have clinical significance.^{7,8}

For decades, focal and grid laser photocoagulation has been the mainstay treatment to prevent vision loss. However, the intraocular administration of anti-vascular endothelial growth factor (VEGF) agents reduces DME without tissue damage and is more effective in improving vision.^{1–3} Due to its advantages, currently, anti-VEGF agents has become the gold standard for the treatment of DME.

VEGF has been shown to have a major role in promoting exudation and neovascularisation,^{9–11} and the inhibition of VEGF can stabilise or even reverse the retinal damage due to DME.¹² Over the past two decades, anti-VEGF agents such as pegaptanib, bevacizumab, ranibizumab and aflibercept were approved for the treatment of ocular diseases that involve retinal neovascularisation and exudation, including DME.^{13–17}

Conbercept (KH902; Chengdu Kanghong Biotech Co., China) is a recombinant fusion protein with key domains 2, 3 and 4 from VEGF receptors 1 and 2. It has a high affinity for all VEGF isoforms and for placental growth factor.¹⁸ In 2013, it was approved in China for the treatment of neovascular (wet) age-related macular degeneration.¹⁸ In addition, conbercept is approved for the treatment of choroidal neovascularisation secondary to pathological myopia. The objective of the Sailing Study was to compare the efficacy and safety of intravitreal conbercept injections versus laser for the treatment of DME. This report includes the 1-year results of the Sailing Study and the 1-year results of its extension study in which patients crossed over to conbercept therapy.

METHODS

Study design and patients

The Sailing Study was a multicentre, randomised, double-masked, double-sham, parallel controlled, phase III trial (registered at ClinicalTrials.gov) conducted at 18 centres in China. An open-label extension study was conducted after patients completed the Sailing Study.

For each patient, only one eye was enrolled in the study. If both eyes of a subject met the inclusion criteria, the investigators determined the target eye from the medical perspective, with the eye with poorer vision selected in principle. The

key inclusion criteria were (1) >18 years of age; (2) type I or II diabetes mellitus; (3) haemoglobin A1c (HbA1c) of <10%; and (4) the study eye had to meet the following criteria: (i) DME involving the central fovea, (ii) ETDRS best-corrected visual acuity (BCVA) between 73 and 24 letters (Snellen equivalent of 20/40–20/320), (iii) central retinal thickness (CRT) of >300 μm according to optical coherence tomography (OCT) imaging, (iv) clear ocular media and adequate pupil dilation for examination and imaging and (5) the ETDRS BCVA of the subject's non-target eye of ≥ 24 letters (equivalent to 20/320 of the Snellen vision). The key exclusion criteria were (1) active eye infection in either eye; (2) any ophthalmic conditions leading to macular oedema or alterations in vision other than diabetic retinopathy; (3) panretinal photocoagulation within 6 months prior to screening or local/grid retinal photocoagulation within 3 months prior to screening; (4) treatment with anti-VEGF drugs (eg, aflibercept, pegaptanib sodium, ranibizumab, bevacizumab, etc) within 6 months prior to screening; (5) any type of intraocular surgery (eg, cataract surgery, yttrium aluminium garnet (YAG) posterior capsulotomy, etc) within 3 months prior to screening; (6) uncontrolled hypertension; and (7) stroke, transient ischaemic attack, myocardial infarction or acute congestive heart failure within 6 months prior to screening. The detailed exclusion criteria are shown in the online supplemental appendix.

Randomisation and masking

During the Sailing Study, the eligible patients were randomly assigned in a 1:1 ratio to receive either sham laser followed by conbercept (sham/conbercept group) or laser followed by a sham injection (laser/sham group) according to the interactive web response system. Masking was performed for the patients, masked investigators and statisticians. Treatments were performed by unmasked investigators who were not involved in any other study work. The extension study was an open-label study, so no masking was necessary.

Treatments

During the Sailing Study, the patients in the sham/conbercept group received sham laser and then an intravitreal injection of conbercept (0.5 mg, Chengdu Kanghong Biotech Co.) on day 0, followed by pro re nata (PRN) conbercept treatments and sham laser treatments during the monthly follow-up per predefined criteria. Patients in the laser/sham group received modified ETDRS grid photocoagulation and then a sham intravitreal injection on day 0. Starting at month 3, the laser group received PRN sham injections and active laser treatments during the monthly follow-up per predefined criteria, but the retreatment of laser will not be evaluated if less than 12 weeks from the last sham or active laser treatment. When the patients received active PRN conbercept or laser, the sham laser or sham injection was performed on the same day. An interval of at least 2 hours was ensured between the active or sham laser treatment and the active or sham intravitreal injection.

PRN laser was performed if any of the following criteria was met: (1) retinal thickening within a radius of 500 μm around the centre of the macula; (2) hard exudates with adjacent retinal thickening within a radius of 500 μm around the centre of the macula (for hard exudates left behind after retinal thickening regression, no treatment is required); (3) the total area of one or multiple regions with retinal thickening is no less than that of one optic disk (2.54 mm^2); and the distance from a part of the region of retinal thickening to the centre of the macula is below a diameter of the optic disk (1800 μm).

The criteria for repeated conbercept treatments were (any of the following criteria satisfied): (1) CRT increased by at least 50 μm if compared with the previous minimum value; (2) CRT of ≥ 300 μm ; (3) cystoid degeneration of retina, subretinal fluid or pigment epithelial detachment in the macular region; (4) ETDRS BCVA was improved by at least five letters if compared with that during the previous visit; and (5) ETDRS BCVA declined by at least five letters if compared with the maximum number of letters previously, combining with CRT increase, in comparison with that when ETDRS BCVA is at its optimum level.

Other treatments forbidden from the study included (1) anti-VEGF drugs other than conbercept; (2) any other antiangiogenic drugs; (3) ocular or systemic steroids; (4) drugs with toxicity to the lens, retina or nerves; (5) anticoagulant or antiplatelet therapy, except for low-dose prophylactic use; or (6) treatments to the study eye with impact on the efficacy and safety assessments of the present study, such as panretinal photocoagulation, verteporfin photodynamic therapy, external beam radiotherapy, vitrectomy, transpupillary thermotherapy and macular surgery.

Starting at month 6, whether the patients needed rescue treatment was assessed monthly. If patients met either one of the criteria for rescue treatment: (1) ETDRS BCVA declined by at least 15 letters compared with the maximum number of letters previously and lowered to a degree below the baseline; or (2) ETDRS BCVA decreased to a level that at least 10 letters fewer than the baseline during visits of two consecutive months, and the investigators believed that the visual impairment was caused by the persistent or worsening oedema from the DME, then their sham designation was switched to active treatment in whatever group they were assigned.

During the extension study, patients in both groups received PRN conbercept treatment with monthly follow-up.

Assessment

The primary endpoint of the Sailing Study was the mean change in BCVA from baseline to month 12. Secondary endpoints included the change in CRT from baseline to month 12 and safety. Safety assessments included both ocular and non-ocular adverse events (AEs) and serious adverse events (SAEs). Other endpoints included changes in CRT, total macular volume (TMV), fluorescein angiographic leakage area, BCVA and the total score of 25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25) from baseline to month 12, as well as the proportion of ≤ 5 , 10 and 15 letters vision gain or loss from baseline to months 6 and 12.

The primary outcome of the extension study was the mean change in BCVA from month 12 to 24. Secondary outcomes included the long-term safety of conbercept, change in BCVA from month 12 to 24, change in CRT from month 12 to 24, change in TMV from month 12 to 24, change in leakage area from month 12 to 24 and the number of injections in the extension study.

Patients were followed up monthly for ophthalmological examinations, including ETDRS protocol BCVA, intraocular pressure, slit-lamp examination and OCT. Colour fundus photography (CFP) and fundus fluorescein angiography (FFA) were performed every 3 months. NEI VFQ-25 was completed every 6 months. Protocol BCVA was measured by using the standard ETDRS visual acuity chart (starting at the 4 m testing distance). All study-related image acquisitions were certificated by EyeKor, LLC (online supplemental table 1). OCT, CFP and FFA images were assessed by the reading centre of the University of Wisconsin–Madison.

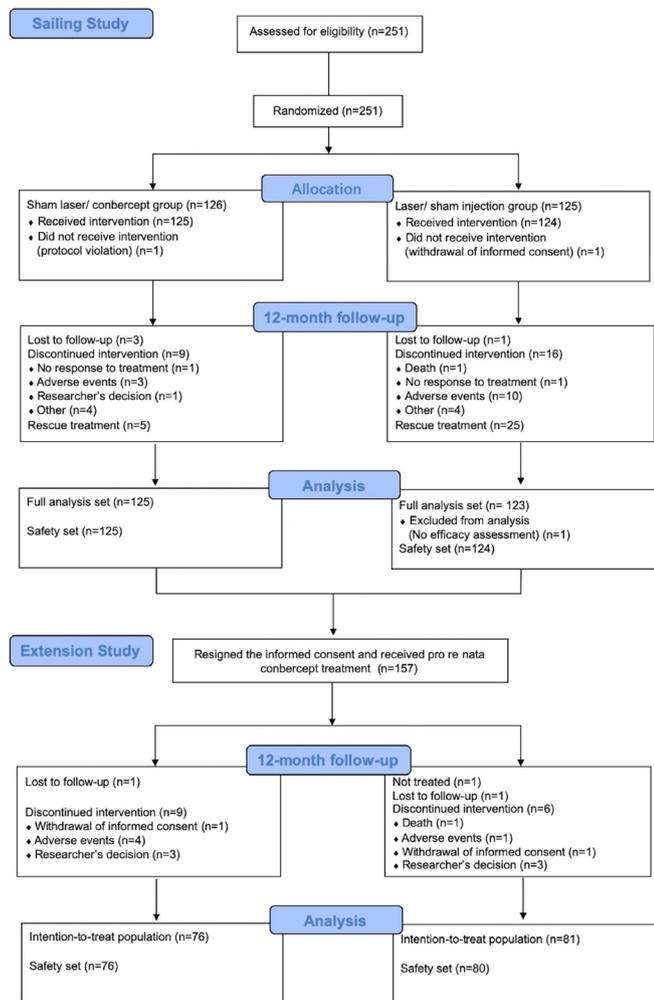


Figure 1 Study flowchart.

Statistical analysis

Assuming that the changes in BCVA from baseline to month 12 had a difference of five letters between the two groups, the SD of the two groups was 10 and 12 letters, respectively. A total of 208 patients (104 in each group) were calculated with a one-sided significance level of 2.5% and a power of 90%. Assuming the drop-out rate of 20%, 124 patients were needed in each group.

The full analysis set in the Sailing Study included all randomised patients who received at least one treatment with the corresponding efficacy assessment. The safety set (SS) in the Sailing Study included all patients who received at least one treatment and at least one safety assessment. The intention-to-treat population in the extension study included all patients who agreed to continue the follow-up and received at least one extension assessment. The SS in the extension study included all patients who received at least one conbercept treatment during the 2-year period. For the primary endpoint of the Sailing Study, the missing values were imputed using the last observation carried forward (LOCF) method. For patients who had a rescue treatment, the missing values were imputed using LOCF method prior to the first rescue treatment. Missing values for the secondary endpoints in the Sailing Study and all outcomes in the extension study were not imputed.

Statistical analyses were performed using SAS V.9.4. Continuous variables were presented as means±SD. The analysis of covariance was used for the primary outcome comparison. For

secondary efficacy outcomes, the independent t-test was used for intergroup comparisons and a paired t-test was used for comparisons between two time points. Categorical variables were presented as frequencies (percentages) and compared with the Cochran-Mantel-Haenszel χ^2 test or Fisher's exact test, as appropriate. A two-sided p value of <0.05 was considered statistically significant.

RESULTS

Patient disposition, baseline characteristics and treatment experience

Between August 2014 and December 2015, a total of 251 eligible patients were randomised. After completing the Sailing Study, 157 patients enrolled in the extension study. Figure 1 shows the study flowchart and analysis sets.

The baseline characteristics of the patients in the Sailing Study were well balanced between groups (table 1). The patient disposition in the extension study is shown in online supplemental table 2. Eyes in the Sailing Study received an average of 2.6 and 2.7 sham or laser treatments in the sham/conbercept group and laser/sham groups, respectively, and 9.5 and 9.7 intravitreal or sham injections, respectively. More patients in the laser group required a rescue treatment compared with the conbercept group in the Sailing Study (20.3% vs 4.0%, $p<0.001$). During the extension study, the numbers of conbercept treatments were 8.5 ± 3.5 and 8.6 ± 3.4 in the conbercept and laser groups, respectively (online supplemental table 3).

Efficacy

Significant improvement in BCVA from baseline to month 12 was observed in the conbercept group (8.2 ± 9.5 letters, $p<0.001$), whereas no improvement was observed in the laser group (0.3 ± 12.0 letters, $p=0.810$) (figure 2A). The changes in BCVA from baseline were significantly different between the two groups at all time points during the first year (all $p<0.001$). The subset of eyes that continued in the extension study also showed a similar result during the first year (figure 2B). During the extension study, after patients in the laser group crossed over to receiving PRN conbercept treatment, there was a significant improvement in BCVA at all time points of the second year (vs month 12, all $p<0.05$) (figure 2B). The change in BCVA at month 24 in the laser group was 4.9 ± 9.4 letters from month 12 ($p<0.001$) and 8.0 ± 11.4 letters from baseline ($p<0.001$). For patients in the conbercept group, 2-year results showed that they continued to maintain visual acuity gains from intravitreal injection. The changes in BCVA at month 24 in the sham conbercept group were 2.3 ± 8.8 letters from month 12 ($p=0.030$) and 8.3 ± 12.4 letters from baseline ($p<0.001$).

Both the results of 6 months and those of 12 months showed that significantly more eyes treated with conbercept gained vision from baseline, whereas significantly more eyes treated with laser lost letters from baseline (all $p<0.001$) (online supplemental table 4). The proportion of eyes with vision gain of ≥ 15 letters from baseline were 17.4% (21/121) and 25.0% (28/112) at months 6 and 12 in the sham/conbercept group compared with 6.8% (8/118) and 14.9% (13/87) in the laser/sham group, respectively, at the same time points. The proportion of eyes with vision loss of ≥ 15 letters from baseline were 1.7% (2/121) and 3.4% (4/112) at months 6 and 12 in the sham/conbercept group compared with 0% (0/118) and 1.1% (1/87) in the laser/sham group, respectively.

Significant differences in CRT were observed between the two groups at all time points in the first 12 months (all $p<0.01$)

Table 1 Baseline characteristics of patients in the Sailing Study

Variables	Conbercept (95% CI)		Laser (95% CI)		P value
	(n=125)	(57.43 to 60.42)	(n=123)	(57.18 to 60.30)	
Age (years)	58.9±8.5	(57.43 to 60.42)	58.7±8.8	(57.18 to 60.30)	0.863
Sex, n (%)					0.527
Male	66 (52.8)	(51.31 to 53.27)	60 (48.8)	(47.27 to 49.23)	
Female	59 (47.2)	(46.73 to 48.69)	63 (51.2)	(50.77 to 52.73)	
BMI (kg/m ²)	24.2±3.4	(24.13 to 24.50)	25.0±4.5	(24.83 to 25.32)	0.095
Duration of diabetes (years)	12.3±7.0	(12.16 to 12.92)	11.0±6.3	(10.77 to 11.44)	0.138
HbA1c	7.06±1.19	(6.85 to 7.27)	7.13±1.192	(6.92 to 7.35)	0.646
Study eye, n (%)					0.881
Right	72 (57.6)	(56.21 to 58.16)	72 (58.5)	(57.19 to 59.13)	
Left	53 (42.4)	(41.84 to 43.79)	51 (41.5)	(40.87 to 42.81)	
BCVA (ETDRS letter)	56.6±11.5	(54.50 to 59.19)	57.6±11.5	(54.59 to 59.62)	0.505
IOP (mm Hg)	15.2±3.0	(14.62 to 15.68)	15.1±3.4	(14.45 to 15.66)	0.819
CRT (µm)	480.0±180.0	(476.36 to 495.90)	470.0±160.0	(464.09 to 481.28)	0.753
TMV (mm ³)	9.9±1.2	(9.45 to 10.39)	10.1±1.4	(9.68 to 10.72)	0.534
Leakage area (mm ²)	28.2±11.0	(26.20 to 30.11)	27.8±10.8	(25.92 to 29.76)	0.820
NEI VFQ-25 total score	65.9±17.1	(62.88 to 68.93)	66.7±17.9	(63.47 to 69.85)	0.733
History of laser treatments, n (%)					0.622
Yes	77 (61.60)	(60.14 to 62.06)	72 (58.54)	(57.25 to 59.19)	
No	48 (38.40)	(37.94 to 39.86)	51 (41.46)	(40.81 to 42.75)	
History of ocular anti-VEGF treatments, n (%)					0.098
Yes	14 (11.20)	(10.08 to 11.30)	23 (18.70)	(17.61 to 19.13)	
No	111 (88.80)	(88.70 to 89.92)	100 (81.30)	(80.87 to 82.39)	

BCVA, best-corrected visual acuity; BMI, Body Mass Index; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; HbA1c, haemoglobin A1c; IOP, intraocular pressure; NEI VFQ-25, 25-Item National Eye Institute Visual Function Questionnaire; TMV, total macular volume; VEGF, vascular endothelial growth factor.

(figure 3A). The mean reduction of CRT from baseline to month 12 was $200\pm 210\ \mu\text{m}$ ($p<0.001$) in the sham/conbercept group and $130\pm 190\ \mu\text{m}$ ($p<0.001$) in the laser/sham group. Significant reduction of TMV from baseline was observed by month 3

($1.3\pm 0.9\ \text{mm}^3$, $p<0.001$) in eyes treated with sham/conbercept, whereas this reduction was observed at month 6 ($0.6\pm 0.7\ \text{mm}^3$, $p=0.004$) in eyes treated with laser/sham (figure 3C). There was a significant difference in TMV between the two groups at months 3 and 6 (both $p<0.05$), but not at months 9 and 12. The trends of the leakage area changes were similar to those of the CRT changes. The mean reduction of leakage area from baseline to month 12 was $7.9\ \text{mm}^2$ ($p<0.001$) in the sham/conbercept group and $3.9\ \text{mm}^2$ ($p<0.001$) in the laser/sham group, and the leakage area was significantly decreased in the sham/conbercept group compared with the laser/sham group ($p<0.001$). The mean change in the NEI VFQ-25 total score from baseline was significantly different between the sham/conbercept group and the laser/sham groups at months 6 (4.4 ± 16.0 vs -1.5 ± 15.5 , $p=0.004$) and 12 (4.3 ± 19.5 vs -3.8 ± 17.7 , $p=0.001$) (figure 3E). During the extension study, the improvements in anatomical outcomes (CRT, TMV and leakage area) were maintained in both groups (figure 3B,D), and the laser group did better in reducing fluorescein leakage area.

Safety

In the Sailing Study, the proportion of total AEs (87.2% vs 87.1%) and SAEs (17.6% vs 19.4%) were similar between the sham/conbercept and laser/sham groups (table 2). The most common AEs were visual impairment (20.0%), upper respiratory tract infection (20.0%), intraocular hypertension (12.8%), hypertension (12.0%), elevated blood pressure (12.0%) and subconjunctival haemorrhage (12.0%) in patients treated with conbercept. The most common AEs were visual impairment (19.4%), upper respiratory tract infection (17.7%), hypertension (10.5%) and diabetic nephropathy (10.5%) in patients treated with laser. More patients reported ocular AEs (57.6%) in the

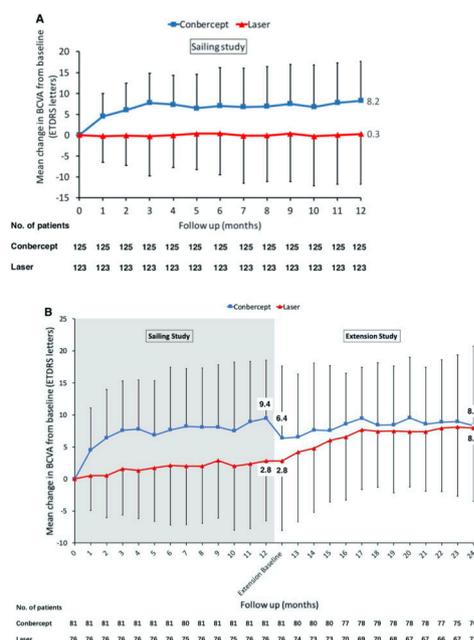


Figure 2 Mean changes in BCVA for laser and conbercept study groups in the Sailing Study. (A) One-year results compared with baseline. (B) Two-year results compared with baseline for the subset of eyes that continued in the extension study. Error bars denote SD. BCVA, best-corrected visual acuity.

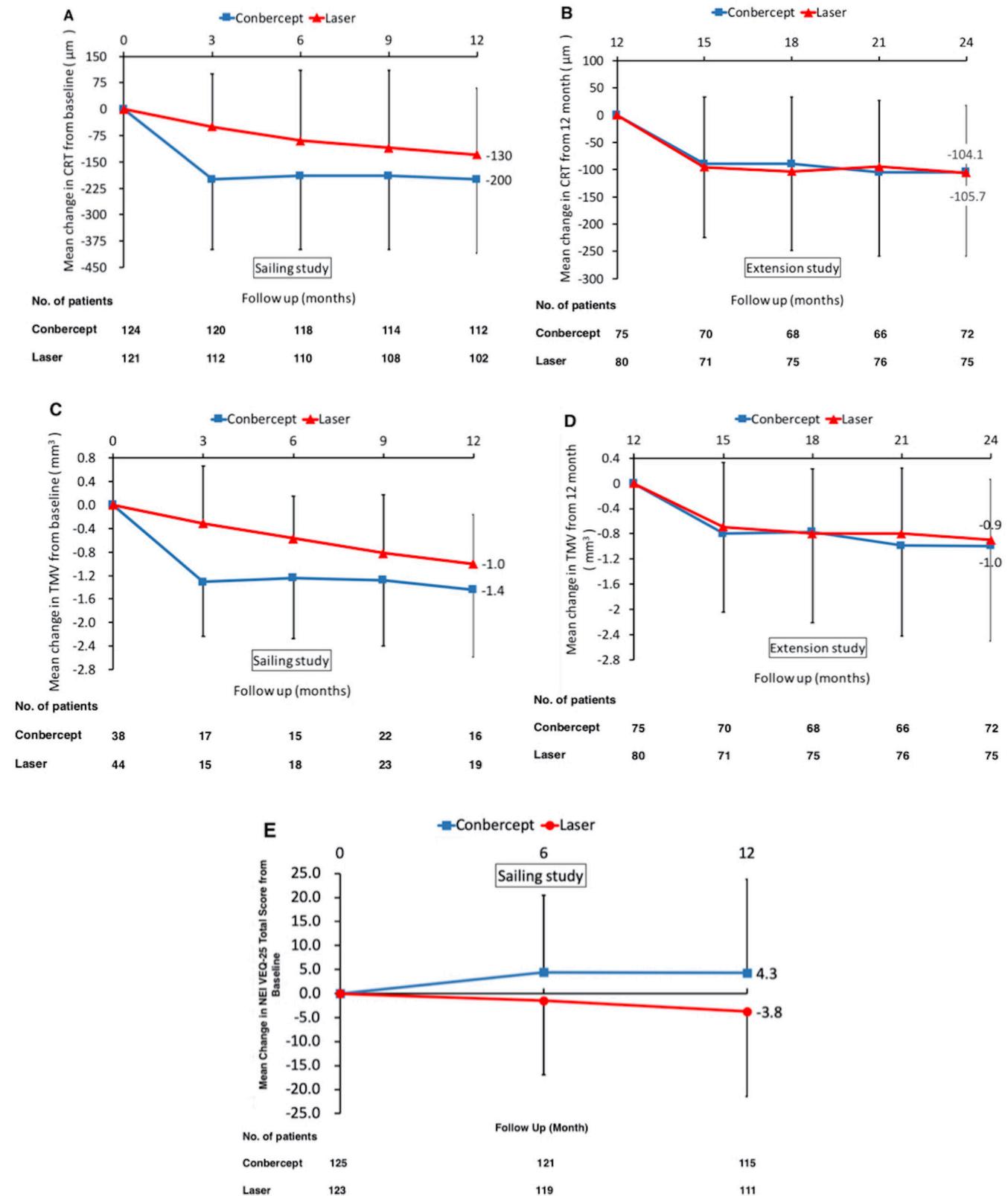


Figure 3 Mean changes of secondary endpoints for laser and conbercept study groups in the Sailing Study. (A) One-year results of mean CRT changes compared with baseline. (B) Extension study results of mean CRT changes from 12 to 24 months. (C) Mean changes in TMV compared with baseline (1-year results). (D) Mean changes in TMV from 12 to 24 months (extension study results). (E) Mean change in NEI VFQ-25 total score from baseline to month 12 of the Sailing Study. Error bars denote SD. CRT, central retinal thickness; NEI VFQ-25, 25-Item National Eye Institute Visual Function Questionnaire; TMV, total macular volume.

Table 2 AEs in the Sailing Study and extension study

Events	Sailing Study		Extension study	
	Conbercept (n=125)	Laser (n=124)	Conbercept (n=76)	Laser (n=80)
All AEs	109 (87.2)	108 (87.1)	61 (80.3)	75 (93.8)
Treatment-related AEs	45 (36.0)	19 (15.3)	30 (39.5)	34 (42.5)
SAEs	22 (17.6)	24 (19.4)	11 (14.5)	16 (20.0)
Death	0	1 (0.8)	0	1 (1.3)
All ocular AEs	72 (57.6)	49 (39.5)	39 (51.3)	50 (62.5)
Treatment-related ocular AEs	40 (32.0)	12 (9.7)	27 (35.5)	31 (38.8)
Ocular SAEs	6 (4.8)	2 (1.6)	7 (9.2)	4 (5.0)
AEs occurring in >5% of patients in either group				
Visual impairment	25 (20.0)	24 (19.4)	3 (3.9)	5 (6.3)
Upper respiratory tract infection	25 (20.0)	22 (17.7)	9 (11.8)	15 (18.8)
Intraocular hypertension	16 (12.8)	6 (4.8)	11 (14.5)	13 (16.3)
Systemic hypertension	15 (12.0)	13 (10.5)	5 (6.6)	5 (6.3)
Elevated blood pressure*	15 (12.0)	7 (5.6)	3 (3.9)	10 (12.5)
Subconjunctival haemorrhage	15 (12.0)	4 (3.2)	2 (2.6)	4 (5.0)
Diabetic nephropathy	9 (7.2)	13 (10.5)	1 (1.3)	5 (6.3)
Hyperlipaemia	7 (5.6)	9 (7.3)	3 (3.9)	3 (3.8)
Urinary tract infection	7 (5.6)	6 (4.8)	2 (2.6)	3 (3.8)
Elevated blood glucose	6 (4.8)	7 (5.6)	6 (7.9)	2 (2.5)
Vitreous haemorrhage	6 (4.8)	7 (5.6)	4 (5.3)	4 (5.0)
Nasopharyngitis	6 (4.8)	6 (4.8)	4 (5.3)	2 (2.5)
Elevated blood urea	5 (4.0)	7 (5.6)	1 (1.3)	2 (2.5)
Detected urine protein	2 (1.6)	12 (9.7)	1 (1.3)	1 (1.3)
Xerophthalmia	2 (1.6)	7 (5.6)	3 (3.9)	2 (2.5)
Vitreous opacity	0	6 (4.8)	4 (5.3)	2 (2.5)

*Elevated blood pressure but not enough to diagnose hypertension.
AE, adverse event; SAE, serious adverse event.

sham/conbercept group compared with 39.5% in the laser/sham group. Most of the additional ocular AEs with conbercept treatment were intraocular hypertension (12.8% vs 4.8% with laser) and subconjunctival haemorrhage (12.0% vs 3.2% with laser). Endophthalmitis occurred in two patients treated with conbercept and one thereof was non-infectious intraocular inflammation. Endophthalmitis did not occur in patients treated with laser. The incidence of non-ocular SAEs in the laser/sham group (16.9%) was higher than in the sham/conbercept (12.0%). The incidences of Anti-Platelet Trialists' Collaboration-defined arterial thromboembolic events (APTC-ATEs) were equal (3.2%) in both groups.

The AEs that occurred during the extension study were similar to those in the Sailing Study. Intraocular hypertension (24/156, 15.4%) and upper respiratory tract infection (24/156, 15.4%) were the most frequently reported AEs in the second year. For APTC-ATEs, rates were 7.7% (12/156) in the extension study. No death occurred in the conbercept group during the 2-year period. One patient in the laser group died from cerebral haemorrhage during the first year, and another patient died from ischaemic cardiomyopathy in the second year.

DISCUSSION

The Sailing Study was designed to evaluate the use of conbercept for the management of patients with centre-involved DME. The primary endpoint of the Sailing Study was the mean change in BCVA from baseline to month 12. The primary outcomes of the extension study were safety and mean change in BCVA from

month 12 of the Sailing Study to month 12 of the extension study. The results of the study show that conbercept can improve the BCVA in patients with centre-involved DME, and its efficacy was better than that of traditional ETDRS laser photocoagulation. The safety of conbercept was good with the total occurrence of AEs being similar between the two groups.

In the present study, the sham/conbercept group followed a PRN regimen of conbercept injections after the first injection at baseline and over 12 months, the actual number of injections was 9.5 with a mean improvement of +8.2 letters. The results of the 1-year open-label extension study showed that the efficacy of conbercept was maintained for 24 months, but the number of injections was not significantly reduced. In the extension study after 12 months, patients in the laser/sham group were crossed over and received conbercept PRN. The laser/sham group showed a significant improvement in BCVA after crossing over to conbercept therapy, and there was no difference in BCVA between the two groups at the end of the extension study. This is a different result from other studies where anti-VEGF was delayed and the delayed anti-VEGF group did not catch up to the group treated with anti-VEGF from baseline.

Several studies have demonstrated that anti-VEGF treatment is superior to laser in DME.^{15–17, 19} The RISE and RIDE trials compared the efficacy of ranibizumab for DME with PRN laser photocoagulation, and the results showed that ranibizumab improved BCVA, reduced the risk of vision loss and improved the parameters of macular oedema.¹⁹ The VISTA and VIVID studies examined two regimens of aflibercept versus laser photocoagulation for DME and showed that aflibercept was superior to laser photocoagulation in terms of visual acuity and anatomic changes.^{15–17} Despite using a different anti-VEGF agent, the Sailing Study showed similar results to the RISE, RIDE, VISTA and VIVID trials. Conbercept, which is similar to aflibercept, is a recombinant fusion protein composed of VEGF binding domain from human VEGF receptors 1 and 2.²⁰ However, conbercept may have a higher potency and a longer half-life compared with aflibercept because of an additional portion in the fourth binding domain of VEGF receptor 2, which enhances the rate of binding and the stability of the binding complex.²¹ In the 12-month results of aflibercept in the phase III studies, the mean injection numbers of 2q4 and 2q8 groups were 11.8 and 8.4 in VISTA, and 12.2 and 8.7 in VIVID, respectively.¹⁵ In our Sailing Study, the number of conbercept injections was 9.5, which is similar to the number of injections in 2q8 group. While this number is lower, it is important to recognise that the injection frequency in VIVID and VISTA were fixed not PRN. Of note, at the time of the study, aflibercept and ranibizumab had not been approved for the treatment of DME in China. Thus, additional clinical studies are needed to compare the efficacy of conbercept with other anti-VEGF agents in DME.

The efficacy of laser photocoagulation in improving BCVA during the Sailing Study was similar to that in VISTA and VIVID, with +0.3±12.0, +0.2±12.5 and +1.2±10.6 letters in BCVA, respectively. In our study, the percentage of eyes that had BCVA improvement in the laser group was greater than similar laser groups in other clinical trials. The reason for this is unknown but may depend on external factors such as the investigators' operational approaches and the type of laser used, as well as the patient population. The factors associated with differences in visual acuity outcomes in eyes treated with panretinal photocoagulation include the HbA1c levels and the severity of the diabetic retinopathy in these patients.²² However, our results do indicate that the standard treatment of laser photocoagulation is still a good therapeutic option for some patients, but it is noteworthy

that the laser group had a higher proportion of eyes with vision loss than the conbercept group. However, the proportion of patients with loss of ≥ 15 letters in the laser therapy group was 1.1%, far less than the 9.1% and 10.6% observed in the VIVID and VISTA trials.^{15–17}

During the extension study, patients in the laser group had significant improvement in visual acuity after crossing over to receive PRN conbercept injections and reached similar mean change in BCVA levels compared with patients in the conbercept group at 24 months, suggesting the promising efficacy of conbercept in DME. However, it took 2 months to demonstrate a four-letter BCVA improvement in the laser group, while the conbercept group achieved it in the first month. The delayed benefit from conbercept injection in the laser group could be due to the longer duration of the oedema and resulting outer retinal changes due to the prolonged oedema in the macular tissue. Nonetheless, compared with the RESTORE extension study of ranibizumab where it took nearly 12 months to gain +4 letters after switching to ranibizumab,²³ conbercept cross-over patients exhibited a faster visual acuity improvement. The rapid and sustained effect of conbercept could improve the quality of life and reduce the risk of vision loss for patients with DME.

With respect to the anatomical outcomes (CRT, TMV and leakage area) and the vision-related quality of life scores (NEI VFQ-25 total score), rapid and sustained improvements were observed in the conbercept group over the first 12 months. The laser group showed worse vision-related quality of life results, despite steady but slow improvement in anatomical indices. In the extension study, CRT in the laser group decreased to a similar level as that in the conbercept group. This supports the fact that conbercept improved the pathological changes in the eye, resulting in better visual acuity and better vision-related quality of life. This was also observed in the RISE, RIDE, VISTA, VIVID and RESTORE trials.^{15–17 19 23}

In the Sailing Study, the major AEs in the conbercept group were intraocular hypertension and subconjunctival haemorrhage (mostly mild), which were consistent with the AEs reported in previous studies.^{15–20 23–25} Endophthalmitis occurred in two patients after the injection of conbercept, which was aligned with the low incidence of endophthalmitis reported after the injection of saline,²⁶ bevacizumab,²⁷ ranibizumab^{19 28} and aflibercept.¹⁷ The incidence of non-infectious intraocular inflammation was 0.12% (1/861) of all injections, within the range of 0.09%–0.37% reported in the literature.²⁹ These AEs were predominantly associated with any routine intravitreal injection. The 2-year results of safety were similar to the safety profile of conbercept in the 1-year Sailing Study. No new ocular and non-ocular AEs were identified. Overall, the safety of conbercept treatment was similar to other anti-VEGF agents.

A limitation of the extension study is that only 62.6% (157/251) of the initial patients entered the study. Of the 157 subjects enrolled, 142 completed the extension study and 15 withdrew before completing the study. Due to the limited sample size, it is hard to identify the significance of infrequent SAEs that occurred across groups, such as cerebrovascular accident and myocardial infarction.

In conclusion, the 0.5 mg conbercept PRN treatment regimen significantly improved the functional and anatomical outcomes of patients with centre-involved DME, compared with laser photocoagulation. The evidence from the Sailing extension study confirms that conbercept was well tolerated and its efficacy was sustained through 24 months. Intravitreal injections of conbercept can be considered an additional option in the management of patients with DME.

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Contributors Conception and design, obtained funding and overall responsibility: KL and XX; data collection: KL, WH, JiYe, YS, YW, XLiu, ZW, SC, KF, YL, FZ, ZL, LL, JZ, XZ, JuYe, XLia and XLI; analysis, interpretation and writing: HW, XK, QW, XW, JL and ST; manuscript revision: PR, JSH and PK.

Funding The study was supported by National Key R&D Program of China (2016YFC0904800 and 2019YFC0840607) and Chengdu Kanghong Biotechnology Inc. (number 36 ShuxiRoad, JinniuDistrict, Chengdu, China).

Competing interests XK, QW, JL, ST and XW are employees of Chengdu Kanghong Biotechnology, Company, Ltd. PR and PK are consultants to Chengdu Kanghong Biotech.

Patient consent for publication Not required.

Ethics approval The protocols and amendments (including the Sailing Study and its extension study) were approved by the ethics committees of all participating centres and in accordance with Good Clinical Practice and the Declaration of Helsinki. Written informed consent was obtained from each patient. The patients who completed the 12-month Sailing Study signed an additional informed consent form to enter the extension study and had another 12 months of follow-up. The study protocol is available from the authors at drxuxun@sjtu.edu.cn.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement No data are available. This study is under the supervision of the Ministry of Science and Technology of China, and data sharing cannot be provided temporarily.

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Supplementary Table 1. Image acquisitions at each center

No.	Center	FFA	FFA-serial	4 wide-field CFP	CFP-serial	Spectral domain OCT	OCT-serial
1	Shanghai General Hospital	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(HRA2-KT-00641)	Topcon Corporation 50DX	Serial #(947899)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(KT-01003)
2	He Eye Hospital	Topcon Corporation 50DX	Serial #(948122)	Topcon Corporation 50DX	Serial #(948122)	Topcon Corporation 3D-OCT 1000	Serial #(209079)
3	The Third Affiliated Hospital of Third Military Medical University	Heidelberg Engineering, Inc. HRA2	Serial #(KT-00285)	Carl Zeiss Meditec, Inc. Visucam	Serial #(1103225)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(TR-KT-00525)
4	Wuhan General Hospital of Guangzhou Military	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(HRA2-KT-01419)	Topcon Corporation NW7SF	Serial #(677290)	Topcon Corporation 3D-OCT 1000	Serial #(209032)
5	The First Affiliated Hospital of the Fourth Military Medical University	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(04734-S1600)	Topcon Corporation 50DX	Serial #(948084)	Topcon Corporation 3D-OCT 2000	Serial #(688057)
6	The Eye Hospital of Wenzhou Medical University	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(HRA2-00445)	Topcon Corporation 50DX	Serial #(947590)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(H2E-12052-010-005)

7	Wuxi No. 2 People's Hospital	Topcon Corporation 50IX	Serial #(175258)	Topcon Corporation 50IX	Serial #(175258)	Carl Zeiss Meditec, Inc. Cirrus	Serial #(4000- 12023)
8	Southwest Hospital	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(H2E- 11774-004-002)	Kowa Company, Ltd nonmyd a-DIII	Serial #(1579000 605)	Topcon Corporation 3D-OCT 1000	Serial #(209032)
9	The Ophthalmological Research Institute of Henan	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(TSP- 02572)	Carl Zeiss Meditec, Inc. FF450 Plus	Serial #(988819)	Carl Zeiss Meditec, Inc. Cirrus	Serial #(4000- 6040)
10	Peking University Third Hospital	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(HRA2 00093)	Carl Zeiss Meditec, Inc. FF450 Plus	Serial #(2019990 88)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(TR- KT1248)
11	Beijing Tongren Hospital, Capital Medical University	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(04768- S3600)	Topcon Corporation 50DX	Serial #(870707)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(04768- S3600)
12	TianJin University Medical Eye Hospital	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(H2E- 15131-003-001)	Topcon Corporation 50EX	Serial #(274768)	Topcon Corporation 3D-OCT 2000	Serial #(608102)
13	Shanghai Renji Hospital	Carl Zeiss Meditec, Inc. Visucam 500	Serial #(1100811)	Carl Zeiss Meditec, Inc. Visucam 500	Serial #(1100811)	Carl Zeiss Meditec, Inc. Cirrus	Serial #(4000- 8143)

14	West China Hospital, Sichuan University	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(HRA2-00617)	Topcon Corporation 50DX	Serial #(948400)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(01596-S2000)
15	The First Affiliated Hospital of Chongqing Medical University	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(01848-S1300)	Canon, Inc. CR-DGi	Serial #(DGI311808 - BX00271)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(03721-S2000)
16	Peking Union Medical College Hospital	Topcon Corporation 50DX	Serial #(8710039)	Topcon Corporation 50DX	Serial #(8710039)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(03986-S3600)
17	Zhongshan Ophthalmic Center, Sun Yat-Sen University	Heidelberg Engineering, Inc. Spectralis (cSLO)	Serial #(HRA2-KT-03251)	Topcon Corporation 50DX	Serial #(948133)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(2867-5-3600)
18	Peking University People's Hospital	Topcon Corporation 50DX	Serial #(945906)	Carl Zeiss Meditec, Inc. FF450 Plus	Serial #(1076503)	Heidelberg Engineering, Inc. Spectralis (OCT)	Serial #(01225-S3300)

CFP, Color fundus photography; FFA, fundus fluorescein angiography; OCT, optical coherence tomography.

Supplementary Table 2. Patient disposition in the extension study

	Conbercept	Laser	Total
Enrolled, n	76	81	157
Enrolled but not treated, n (%)	1 (1.3)	1 (1.2)	2 (1.3)
Completed the study, n (%)	67 (88.2)	75 (92.6)	142 (90.4)
Withdrew from the study, n (%)	9 (11.8)	6 (7.4)	15 (9.6)
Adverse event	4 (5.3)	1 (1.2)	5 (3.2)
Investigator judgement	3 (3.9)	3 (3.7)	6 (3.8)
Withdrawal of consent	1 (1.3)	1 (1.2)	2 (1.3)
Lost to follow up	1 (1.3)	0	1 (0.6)
Death	0	1 (1.2)	1 (0.6)

Supplementary Table 3. Treatment experience

	Sailing study (baseline to month 12)			Extension study (month 12 to month 24)		
	Conbercept (n=125)	Laser (n=123)	P	Conbercept (n=76)	Laser (n=81)	P
Number of intravitreal injections	9.5±2.8	9.7±3.1 ^a	0.538	8.5±3.5	8.6±3.4	
Number of laser photocoagulation treatments	2.6±1.3 ^b	2.7±1.3	0.604	NA	NA	NA
Rescue treatment	5 (4.0)	25 (20.3)	<0.001	NA	NA	NA

NA, not applicable.

a. In the laser group, the number of sham injections was counted and did not include all treatments after the first rescue treatment.

b. In the conbercept group, the number of sham laser treatment was counted and did not include all treatments after the first rescue treatment.

Supplementary Table 4. Visual distribution in the Sailing Study

Variables	6 months		P	12 months		P
	Conbercept (n=121)	Laser (n=118)		Conbercept (n=112)	Laser (n=87)	
Vision gain						
≥0 letter	110(90.9)	65(55.1)	<0.001	104(92.9)	62(71.3)	<0.001
≥5 letters	81(66.9)	40(33.9)	<0.001	81(72.3)	46(52.9)	0.005
≥10 letters	51(42.1)	20(16.9)	<0.001	56(50.0)	26(29.9)	0.004
≥15 letters	21 (17.4)	8 (6.8)	0.012	28 (25.0)	13 (14.9)	0.082
Vision loss						
≥0 letter	11(9.1)	53(44.9)	<0.001	8(7.1)	25(28.7)	<0.001
≥5 letters	7(5.8)	25(21.2)	0.001	4(3.6)	6(6.9)	0.287
≥10 letters	6(5.0)	15(12.7)	0.034	3(2.7)	3(3.4)	0.753
≥15 letters	2 (1.7)	4 (3.4)	0.391	0	1 (1.1)	0.255

Subjects

Subjects can be included in this study if they meet all of the following inclusion criteria and do not meet any of the exclusion criteria during the screening.

1.1 Inclusion criteria:

- 1) The subjects have provided the written informed consent, and are willing to receive the follow-up at the time points as specified in the trial;
- 2) The subjects are males or females at least 18 years of age;
- 3) The subjects have confirmed Type 1 or type 2 diabetes;
- 4) The glycated hemoglobin (HbA1c) is $\leq 10\%$;
- 5) The target eye shall meet the following requirements:
 - DME involving the fovea and leading to decreased vision is present;
 - BCVA measured ≥ 24 letters and ≤ 73 letters at the 4m/1m ETDRS eye chart (equivalent to 20/40 to 20/320 of the Snellen eye chart);
 - The OCT examination shows CRT ≥ 300 μm (using spectral domain OCT, the measured values of CRT shall be subject to confirmation by the imaging reading center);
 - There is absence of opaque opacity of the refractive medium and pupil contraction affecting fundus examination.
- 6) The BCVA of the subject's non-target eye ≥ 24 letters (equivalent to 20/320 of the Snellen vision).

Note: Only one target eye of a subject can be selected in the study. If both eyes of a subject meet the inclusion criteria, the investigators shall determine the target eye from the medical perspective.

1.2 Exclusion criteria

1.2.1 Patients with any of the following eye diseases:

- 1) Active eye infection occurs in either eye (e.g., blepharitis, keratitis, scleritis, and conjunctivitis, etc.);
- 2) Proliferative diabetic retinopathy (PDR) occurs in the target eye, with the exception of PDR resolving after full retina photocoagulation, and inactive, and fibrotic PDR;
- 3) The target eye has a history of vitreous bleeding within 2 months prior to screening;
- 4) The target eye has structural damage of the retina that involves the fovea (e.g., retinal pigment epithelium (RPE) atrophy, retinal fibrosis, laser scar, and dense hard exudation), or the investigators believe that there are other retinal damage in the target eye that may prevent vision improvement following resolution of macular edema.
- 5) The target eye, in addition to DR, has other ophthalmic conditions leading to macular edema or alterations in vision (e.g., retinal vein occlusion (RVO), CNV, retinal detachment, macular hole, traction of macular retina, and preretinal membrane, etc.);
- 6) The target eye contains iris neovascularization;

- 7) The target eye has uncontrolled glaucoma (which is defined as an intraocular pressure ≥ 25 mmHg) after the treatment with anti-glaucoma drugs, or a history of glaucoma filtering surgery.
- 8) The investigators believe that cataract of the target eye may affect the examination or judgment of the trial results, or surgical treatment is required within the next 6 months; or
- 9) The target eye has no crystal (inclusion is acceptable if there is artificial lens).

1.2.2 Patients having undergone any of the following eye treatment

- 10) Either eye has been intraocularly injected with corticosteroids (e.g., triamcinolone) within 3 months prior to screening, or particularly injected with corticosteroids within 1 month prior to screening;
- 11) The target eye has a history of vitrectomy;
- 12) The target eye has undergone panretinal photocoagulation within 6 months prior to screening, or there is a possibility of panretinal photocoagulation during the study;
- 13) The target eye has undergone ≥ 2 times of local/grid retinal photocoagulation, or local/grid retinal photocoagulation within 3 months prior to screening;
- 14) The target eye or the general system has been treated with anti-VEGF drugs (e.g., aflibercept, pegaptanib sodium, ranibizumab, and bevacizumab, etc.) within 6 months prior to screening, or the non-target eye has been treated with anti-VEGF drugs within the first 3 months prior to screening;

- 15) The target eye has received any type of intraocular surgery (e.g., cataract surgery, and YAG posterior capsulotomy, etc.) within 3 months prior to screening; or
- 16) The target eye has undergone eye surgery that involves the macular region (e.g., PDT, and macular transposition, etc.), except for local/grid retinal photocoagulation;

1.2.3 Patients with any of the following systemic diseases

- 17) The blood glucose is not well controlled within 3 months prior to screening (which is defined as the switch from the oral administration of hypoglycemic drugs to the insulin therapy, initiation of the insulin pump therapy, or an increase in the number of daily insulin injections);
- 18) Impaired renal function (Crea is 2-fold the upper limit of the normal value in the laboratory of this center) or abnormal hepatic function (ALT and AST are 2-fold the upper limit of the normal value in the laboratory of this center) are identified;
- 19) Poor control of blood pressure (which is defined as systolic blood pressure \geq 150 mmHg or diastolic blood pressure \geq 95 mmHg following treatment with antihypertensive medications) is noted;
- 20) Patients are now developing systemic infections requiring oral, intramuscular or intravenous administration;
- 21) Patients have stroke, transient ischemic attack, myocardial infarction or acute

congestive heart failure within 6 months prior to screening;

- 22) Patients have abnormal blood coagulation function (prothrombin time $\geq 3s$ above the upper limit of the normal value, activated partial thromboplastin time $\geq 10s$ above the upper limit of the normal value);
- 23) Patients are currently receiving drugs toxic to the lens, retina or optic nerve or may do so during the study (e.g., deferoxamine, chloroquine, hydroxychloroquine (chloroquinine), tamoxifen, phenothiazine or ethambutol, etc.);
- 24) Patients have confirmed systemic immune diseases (e.g., ankylosing spondylitis, and systemic lupus erythematosus, etc.) or any uncontrollable clinical conditions (e.g., AIDS, malignancies, active hepatitis, and severe mental, neurological, cardiovascular and respiratory diseases, etc.); or
- 25) Patients have allergic reactions or a history of allergy to sodium fluorescein, a history of allergy to therapeutic or diagnostic protein products, allergy to two or more drugs and/or non-drug factors, or allergic diseases currently;

1.2.4 Others

- 26) Subjects who have not undergone effective contraception;

Note: the following circumstances do not fall into the scope of exclusion.

- i. Amenorrhea for 12 months under the natural conditions, or amenorrhea for 6 months with the level of serum follicle stimulating hormone > 40 mIU/ml;
- ii. Bilateral ovariectomy with or without hysterectomy received 6 weeks ago;

- iii. One or several acceptable contraception means as follows haven been used:
 - Sterilization (bilateral vasoligation or vasectomy in males)
 - Hormonal contraception (implanted, patch, and oral)
 - Intrauterine contraceptive devices, double blocking
 - iv. Use of reliable contraceptives throughout the study until 30 days after the discontinuation of the study drug (The unacceptable contraceptive methods include regular abstinence - by calendar, ovulation period, temperature measurement, post-ovulation, and coitus interruptus).
- 27) Pregnant (pregnancy is defined as a positive testing of the urine pregnancy in this trial) and lactating women;
- 28) Patients participating in any drug (not including vitamins and minerals) clinical trials within 3 months prior to screening (If the study drug has a long half-life and the duration of 5 half-life is > 3 months, then the 5 half-life is used); or
- 29) Patients whose exclusion investigators deem necessary.