SUPPLEMENTARY MATERIALS

Supplementary Methods

Ethics

The study was approved by the independent ethics committee (IEC) for each centre (one IEC for all sites in the UK) and was conducted according to the ethical principles in the Declaration of Helsinki. All patients provided written, IEC-approved informed consent.

Sample size and power analysis

The sample size was recalculated by protocol amendment based on the pooled data from three published studies.[1-3] For the primary efficacy variable (change in central subfield retinal thickness [CSRT] from baseline to Day 90), it was calculated that a sample size of 124 patients would have 90% power to detect a difference in means of 30 µm, assuming a standard deviation (SD) of differences of 102 µm, using a paired t-test with a 0.050 2-sided significance level.

Permitted SD-OCT instruments

During the study, from the screening visit onwards, OCT parameters were assessed by one of the following instruments: Spectralis OCT, Spectralis OCT plus or Spectralis HRA+OCT (with Spectralis Software Version 5.7 or newer); Topcon 3D OCT-1000, 3D OCT 2000; Carl Zeiss Meditec Cirrus HD-OCT 400/4000, Cirrus HD-OCT 500/5000 or Cirrus Photo 600/800.

Summary statistics

The summary statistics for continuous variables presented include: n (the number of non-missing observations), mean, SD, minimum, median, maximum, and, where appropriate, the 95% confidence interval (CI). If data were not normally distributed, the median was presented instead of the mean. For categorical variables, the summary statistics include: frequencies and percentages, and, where appropriate, 95% CI. Unless otherwise specified, all statistical tests were 2-sided and used the 0.05 level of significance. Statistical analyses were conducted using SAS version 9.4.

Analysis sets

All efficacy evaluations were carried out on the Full Analysis Set (FAS), which consisted of all patients who received at least one application of study treatment in the study eye and had a baseline and at least one post-baseline assessment for CSRT. 'Baseline' was defined as the last available non-missing value collected prior to the start of treatment in the study eye. Following the intent-to-treat principle, patients were analysed according to the treatment assigned. No data were excluded from the FAS analyses because of protocol deviations.

All safety evaluations were carried out on the Safety Set (SS), which consisted of all patients who received at least one application of study treatment in the study eye and had at least one post-baseline safety assessment.

A sensitivity analysis was also performed, by repeating the primary analysis using the Per Protocol Set (PPS). The PPS consisted of all patients in the FAS who followed the assigned treatment and completed the study without clinically significant protocol deviations.

Regression analyses

The change over time in CSRT and best corrected visual acuity (BCVA) from baseline to Day 90 (and Day 180) was analysed using separate ANCOVAs including 'duration of aflibercept treatment' and 'number of aflibercept injections prior to switch', and the following baseline retinal morphology parameters as independent variables: presence of intra-/subretinal or sub-RPE haemorrhage (study eye), haemorrhage including the fovea (study eye), presence of active leakage in the sense of a neovascular membrane (study eye), atrophy outside the active choroidal neovascularisation (CNV) lesion, age-related macular degeneration location (study eye), CNV subtype (study eye), presence of intraretinal fluid, presence of intraretinal cysts (IRCs), presence of subretinal fluid, presence of intra-/subretinal fluid within the central subfield, presence of a pigment epithelial detachment (PED), presence of central retinal pigment epithelium atrophy, presence of macular geographic atrophy, presence of vitreomacular traction, area of macular CNV lesion, area of leakage, area of total lesion (including CNV, blood, scar), area size of atrophy (total area, calculated), CSRT, central subfield retinal volume, foveal centre point (FCP) thickness, maximum height of IRC, maximum height of PED, maximum diameter of PED, subfoveal choroidal thickness, and BCVA. The same models were performed including only baseline retinal morphology parameters as independent variables. Stepwise regression was employed to select the final model. Only variables which had data for ≥50% of patients were entered into the stepwise regression procedure. In addition, only patients who had baseline data available for all variables in the model were included in the analyses.

Supplementary Results

Regression analyses

When the model assessing the change in CSRT was run with 'duration of aflibercept treatment' and 'number of aflibercept injections prior to switch', these parameters were not selected by the stepwise procedure. Similarly, when the same model was run for change in BCVA, although 'duration of aflibercept treatment' was selected by the stepwise procedure, it was not found to be significant and the overall results were very similar when the prior treatment history parameters were excluded. Therefore, only the results of the analyses excluding these parameters from the baseline variables are considered.

After adjusting for the baseline risk factors reported, a statistically significant association was found between change from baseline to Day 90 in CSRT and each of the following baseline parameters: area of leakage (based on n=65, p=0.0220; this was also the case at Day 180 [n=59, p=0.0131]), maximum PED diameter (n=65, p=0.0151), BCVA in the study eye (n=65, p<0.0001; this was also the case at Day 180 [n=59]) and FCP thickness (n=65, p=0.0169). There was no statistically significant relationship between baseline CSRT and change in CSRT at Day 90 after adjusting for the baseline risk factors selected by the stepwise procedure.

Regression analyses assessing change in BCVA indicated no effects of baseline parameters apart from BCVA itself, whereby for every letter increase in baseline BCVA, a decrease from baseline in BCVA at Day 90 and Day 180 was predicted (−0.20 letters [n=85, p=0.0050] and −0.34 letters [n=87, p=0.0079], respectively).

Supplementary References

1. Chang AA, Li H, Broadhead GK, et al. Intravitreal aflibercept for treatment resistant neovascular age-related macular degeneration. Ophthalmology 2014; 121(1):188-192.
2. He L, Silva RA, Moshpeghi DM, et al. Aflibercept for the treatment of retinal pigment epithelial detachments. Retina 2016; 36:492-498.
3. Kent JS, Iordanous Y, Mao A, et al. Comparison of outcomes after switching treatment from intravitreal bevacizumab to ranibizumab in neovascular age-related macular degeneration. Can J Ophthalmol. 2012; 47:159-164.

Supplementary Table 1. Key study exclusion criteria

Key exclusion criteria
Systemic medical history and conditions
▪ History of cerebrovascular accident, transient ischemic attack, or myocardial infarction within 3 months of the screening visit ▪ Uncontrolled blood pressure
Ocular medical history and conditions
Either eye
▪ Evidence of bilateral active CNV during the screening period or at baseline requiring bilateral anti-VEGF injections[a] ▪ Prior IVT injection of ranibizumab or bevacizumab into the study eye and/or prior IVT injection of bevacizumab into the fellow eye
Study eye
▪ At screening and baseline: • Cataract (if causing significant visual impairment) • Aphakia • Severe vitreous haemorrhage • Rhegmatogenous retinal detachment • Proliferative retinopathy • **Or** choroidal neovascularisation of any cause other than nAMD (e.g. ocular histoplasmosis, pathologic myopia [≥−6 dioptres]) ▪ Irreversible structural damage involving the centre of the fovea (e.g. advanced fibrosis or geographic atrophy) which in the opinion of the Investigator is sufficient to irreversibly impair visual acuity ▪ Polypoidal choroidal vasculopathy, RPE tear, central serous retinopathy, or significant vitreomacular traction identified during the screening period or within 4 months of the baseline visit. Note that small vitreomacular adhesions that do not result in deformity of the retina are permitted ▪ Unable to obtain OCT images at screening of sufficient quality to be analysed

[a]Patients with active CNV in the study eye with quiescent CNV in the fellow eye who may have received IVT aflibercept or ranibizumab injections into the fellow eye >40 days prior to screening, were not excluded from the study. However, if the fellow eye required anti-VEGF treatment during the study, only ranibizumab was utilised. CNV: choroidal neovascularisation; IVT: intravitreal; nAMD: neovascular age-related macular degeneration; OCT: optical coherence tomography; RPE: retinal pigment epithelium; VEGF: vascular endothelial growth factor.

Supplementary Table 2. Change from baseline in foveal centre point thickness and central subfield retinal thickness through to Day 180

		Overall N= 100	
		FCP thickness, µm	**CSRT,** µm
Baseline	n	100	97
	Mean (SD)	378.59 (161.7)	409.41 (142.8)
	Median (min, max)	346.00 (69.0, 944.5)	384.00 (154.0, 975.0)
Change to Day 30	n	95	92
	Mean (SD)	−50.63 (75.1)	−49.23 (60.7)
	Median (min, max)	−38.00 (−350.0, 180.0)	−35.00 (−261.0, 58.0)
Change to Day 60	n	95	91
	Mean (SD)	–52.09 (92.0)	−50.28 (73.2)
	Median (min, max)	–35.50 (–567.0, 219.0)	−33.00 (−405.0, 147.0)
Change to Day 90	n	93	88
	Mean (SD)	−55.04 (94.4)	−51.64 (75.6)
	Median (min, max)	−35.50 (−578.0, 99.5)	−29.25 (−386.0, 78.0)
Change to Day 120	n	90	89
	Mean (SD)	−40.01 (100.8)	−39.11 (82.0)
	Median (min, max)	−18.75 (−575.0, 190.5)	−17.50 (−412.5, 136.0)
Change to Day 150	n	89	87
	Mean (SD)	−45.61 (97.2)	−42.58 (74.4)
	Median (min, max)	−19.00 (−389.5, 213.5)	−21.50 (−242.5, 99.0)
Change to Day 180	n	93	85
	Mean (SD)	−34.75 (102.4)	−35.38 (83.7)
	Median (min, max)	−23.50 (−464.0, 306.5)	−28.00 (−271.0, 171.0)

At each time point, only patients with a value at both baseline and that time point were included in the change from baseline. CSRT: central subfield retinal thickness; FCP: foveal centre point; SD: standard deviation.

106 **Supplementary Table 3.** Change from baseline in morphology parameters

		Overall N= 100		
		IRC height, µm	**PED height,** µm	**PED diameter,** µm
Baseline	n	42	93	93
	Mean (SD)	131.99 (81.5)	255.69 (146.3)	2159.83 (1097.9)
	Median (min, max)	121.50 (21.0, 280.5)	236.00 (66.5, 674.0)	2205.00 (0.0, 4877.0)
Change to Day 30	n	21	81	79
	Mean (SD)	−45.52 (78.8)	7.90 (354.4)	−54.47 (390.3)
	Median (min, max)	−22.00 (−178.5, 103.0)	−16.00 (−292.5, 3098.5)	−37.00 (−1806.0, 1164.0)
Change to Day 60	n	20	84	83
	Mean (SD)	−39.93 (76.2)	−20.77 (80.3)	33.15 (567.1)
	Median (min, max)	−33.50 (−224.5, 64.0)	−24.25 (−467.5, 226.0)	7.00 (−1440.0, 2171.0)
Change to Day 90	n	22	77	75
	Mean (SD)	−41.82 (76.0)	−22.27 (74.0)	37.39 (716.1)
	Median (min, max)	−30.25 (−163.5, 118.5)	−12.00 (−413.5, 159.0)	17.00 (−3351.0, 2364.0)
Change to Day 120	n	29	79	78
	Mean (SD)	−19.00 (80.6)	−22.17 (78.0)	60.51 (678.5)
	Median (min, max)	−10.50 (−166.0, 159.5)	−4.50 (−480.5, 141.5)	−3.00 (−2028.0, 2105.0)
Change to Day 150	n	24	75	74
	Mean (SD)	−25.56 (90.4)	−17.87 (67.6)	126.96 (647.1)
	Median (min, max)	−12.50 (−183.0, 182.0)	−6.00 (−315.0, 129.5)	−12.50 (−1410.0, 2507.0)
Change to Day 180	n	29	80	80
	Mean (SD)	−12.78 (87.9)	−18.44 (80.6)	262.21 (764.4)
	Median (min, max)	0.00 (−223.5, 235.0)	−2.50 (−336.5, 131.0)	59.50 (−1007.0, 2756.0)

107 IRC: intra-retinal cyst; PED: pigment epithelial detachment; SD: standard deviation.

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Supplementary Table 4. Change from baseline in BCVA (letters) in the study eye

		Overall N= 100
Baseline	n	100
	Mean (SD)	68.7 (12.65)
	Median (min, max)	71.5 (36, 90)
Change to Day 30	n	96
	Mean (SD)	0.9 (7.91)
	Median (min, max)	−1.0 (−23, 31)
Change to Day 60	n	97
	Mean (SD)	1.4 (8.03)
	Median (min, max)	0.0 (−16, 35)
Change to Day 90	n	94
	Mean (SD)	1.9 (8.50)
	Median (min, max)	1.0 (−22, 34)
Change to Day 120	n	92
	Mean (SD)	1.9 (8.40)
	Median (min, max)	1.0 (−33, 34)
Change to Day 150	n	93
	Mean (SD)	0.5 (10.86)
	Median (min, max)	0.0 (−44, 35)
Change to Day 180	n	97
	Mean (SD)	1.9 (10.93)
	Median (min, max)	1.0 (−31, 35)

BCVA: best corrected visual acuity; SD: standard deviation.

Supplementary Table 5. Summary of treatment-emergent adverse events

	Overall N= 100	
	Events	n (% of participants affected)
TEAEs	180	73 (73.0)
Common TEAEs:[a]		
Blepharitis		6 (6.0)
Cough		7 (7.0)
Lower respiratory tract infection		7 (7.0)
Nasopharyngitis		9 (9.0)
Serious TEAEs	23	10 (10.0)
Ocular TEAEs	48	32 (32.0)
Study eye	36	26 (26.0)
Common ocular TEAEs:[b]		
Blepharitis		2 (2.0)
Eye pain		3 (3.0)
Intraocular pressure		3 (3.0)
Posterior capsule opacification		2 (2.0)
Visual impairment		3 (3.0)
Fellow eye	4	4 (4.0)
Both eyes	8	6 (6.0)
TEAEs leading to study discontinuation	-	2 (2.0)
TEAEs leading to death	-	0
Severity[c]		
Mild	122	44 (44.0)
Moderate	47	22 (22.0)
Severe	11	7 (7.0)
Relationship to study treatment[c]		
Not related	164	62 (62.0)
Related	16	11 (11.0)
Blepharitis		1 (1.0)
Eye pain		1 (1.0)
Eyelid oedema		1 (1.0)
Intraocular pressure increased		2 (2.0)
Ocular hypertension		1 (1.0)
Photopsia		1 (1.0)
Procedural pain		1 (1.0)
Rash pruritic		1 (1.0)
Vision blurred		1 (1.0)
Visual impairment		1 (1.0)

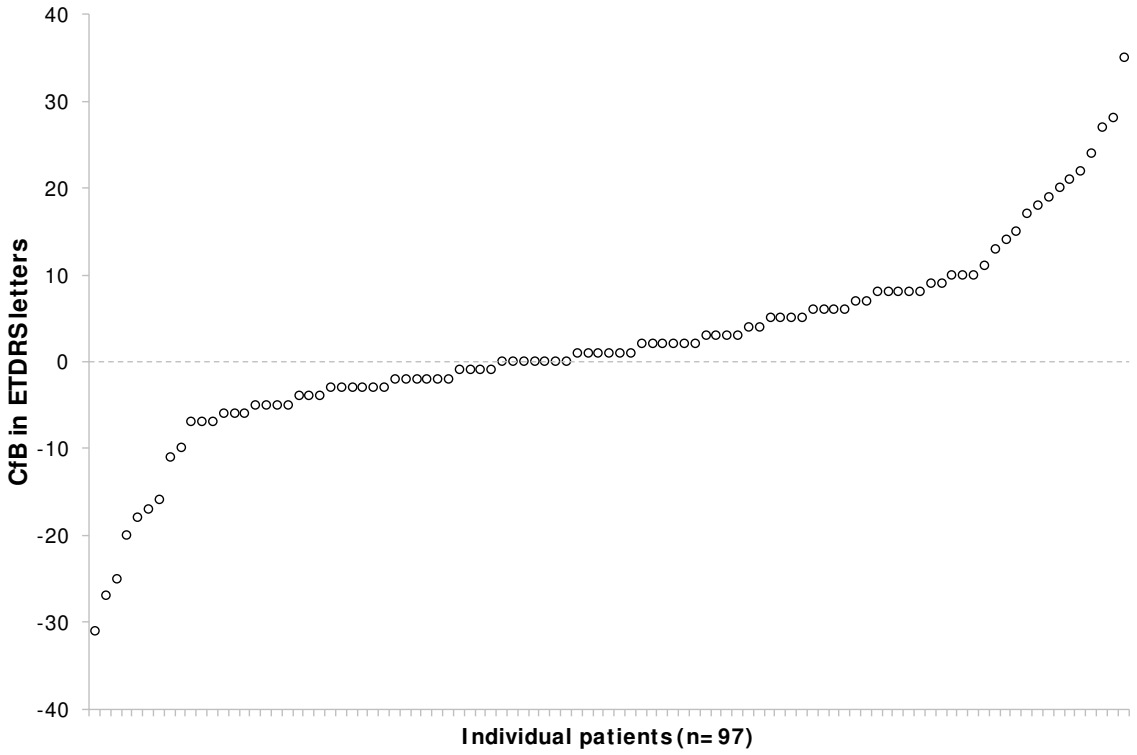
Safety Set. Adverse events were coded using MedDRA Version 20.1. [a]Common TEAEs, by preferred term, reflect those reported by ≥5% of patients overall; [b]Common ocular TEAEs in the study eye, by preferred term, reflect those reported by ≥2% patients overall; [c]If a patient experienced more than one TEAE, the patient was counted once at the most severe or most related event. TEAE: treatment-emergent adverse event.

Supplementary Table 6. Change from baseline or screening to Day 180 in exploratory efficacy variables

		Overall N=100			
		SFC thickness, µm	**Total lesion area**, mm^2	**Area of leakage**, mm^2	**Macular CNV area**, mm^2
Screening /Baseline[a]	n	49	78	78	79
	Mean (SD)	174.24 (50.0)	8.9599 (6.482)	3.3708 (3.676)	1.2417 (1.615)
	Median (min, max)	178.00 (77.0, 265.0)	7.7175 (0.000, 42.420)	2.1350 (0.000, 18.636)	0.6950 (0.000, 6.840)
Change to Day 180	n	36	45	46	46
	Mean (SD)	−8.26 (40.5)	−0.1557 (3.619)	0.5259 (3.845)	0.6858 (2.495)
	Median (min, max)	−3.50 (−129.0, 77.5)	−0.1000 (−7.550, 13.225)	0.0145 (−7.051, 16.215)	0.3765 (−6.385, 8.005)

[a]Change from baseline is shown for SFC thickness data; change from screening is shown for total lesion area, area of leakage, and macular CNV area. CNV: choroidal neovascularisation; SD: standard deviation; SFC: subfoveal choroidal thickness.

Supplementary Figure 1. Waterfall plot of change from baseline to Day 180 in ETDRS letters (study eye)



CfB: change from baseline; ETDRS: Early Treatment Diabetic Retinopathy Study.