ONLINE APPENDIX

RESOLVE investigators

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Randomization procedure

Eligible patients were randomised 1:1:1 to either ranibizumab (0.3 mg or 0.5 mg) or sham treatment according to a computer-generated randomised allocation schedule (kept at a secure site and accessible only to the injecting physician; stratification by center and by the thickness of macular edema as assessed by the central reading center at Visit 1 [≤400 µm *vs.* >400 µm]). Based on the patient strata the injecting physician would take the treatment allocation card and tear-off the cover and follow instructions to choose vial from the box as indicated (3 boxes, randomisation block size 3). The randomisation data were kept strictly confidential until database lock; not accessible to anyone involved in the study with the exception of injecting physician(s) and drug accountability monitor. Masking was maintained through appointment of a minimum of 2 investigators at each study site; unmasked injecting physician and a masked evaluating physician (roles could not be switched). The injecting physician performed the injection procedures and immediate safety assessments following the injection, but was not involved in the evaluations. The evaluating physician conducted all ocular assessments (BCVA and CRT), overall safety assessments and determined the need for dose doubling and/or laser photocoagulation as rescue treatment (as of month 3). To ensure the integrity of masking, the first

assessment by the evaluating physician was conducted one month after first injection and then at subsequent visits; one month after injection it would not be evident if the patient was injected with the study drug or sham.

Study design: details on interim analysis and protocol amendments

This study involved a planned interim analysis at month 6 on a subset of patients (n=42, Group A) with the objective to facilitate early decisions on dose, treatment ratio, sample adjustments, or futility assessments. The interim analysis revealed that ranibizumab led to a clinically and statistically significant treatment effect on macular edema. It also revealed a clinically and statistically significant treatment effect on the originally specified primary parameter central retinal thickness (CRT). Both groups receiving ranibizumab showed efficacy with a rapid onset and sustained effects throughout the 6 months time period. The macular edema started to decrease by an average of 27% and 33% in the ranibizumab 0.3 to 0.6 mg and ranibizumab 0.5 to 1.0 mg group, respectively, 7 days after first treatment, and reached a mean % reduction at Month 6 of 45% and 58% in the ranibizumab 0.3 to 0.6 mg and ranibizumab 0.5 to 1.0 mg group, respectively. In contrast, the macular edema for the sham-treated patients, on average, increased between 4% to 15% over the same period.

Furthermore, ranibizumab led to significant improvements in mean BCVA (secondary objective of the interim analysis) compared with sham (descriptive $p< 0{\cdot}05$) (21). It was decided to extend the purpose of this study from a pure exploratory assessment of the efficacy (BCVA) to confirmatory hypothesis testing. The study protocol was amended and the study comprised a pilot part (Group A, n=49) and a confirmatory part (Group B, n=109). The primary objective of the confirmatory part was to demonstrate superiority of ranibizumab over sham in terms of the mean average change in BCVA from baseline from month 1 to month 12. There was a clear demarcation between data sets used for hypothesis generation (Group A, 42 patients) and data used for confirmatory hypothesis testing in a prospective manner (Group B, 109 patients), i.e. independence between hypothesis generation and hypothesis confirmation. Results from the analysis of Group B confirmed the favourable findings of Group A (Results of Group A and B, presented in this apendix). Group (A+B) was then considered for assessment of overall treatment effects.

Statistical Analysis

Originally RESOLVE was planned as an exploratory study to provide data for the future development of ranibizumab in DME, but promising 6 months interim results from 42 patients offered the opportunity to actually incorporate the next step of this development, i.e. the confirmatory proof of efficacy on the visual acuity (VA) outcome, directly into this trial by implementing a protocol amendment.

This interim analysis revealed not only a clinically and statistically significant treatment effect on the originally specified primary parameter CRT, but also on Best Corrected Visual Acuity

(BCVA) (p-values of corresponding comparisons ranibizumab *vs.* sham control at Month 6 less than 0.01).

BCVA, the key clinical efficacy parameter in DME, was specified in the original protocol only as the key secondary endpoint because at that time the expected effect on VA was stabilization, but not improvement. With the robust observations of the interim analysis, particularly for VA improvement under ranibizumab treatment there was both a justification and an obligation to extend the purpose of this study from a pure exploratory assessment of the efficacy to a confirmatory approach, with the primary objective to demonstrate superiority of ranibizumab in terms of the change in BCVA.

To avoid possible questions regarding the integrity of this confirmatory approach, confirmatory hypothesis testing was based only on those patients not having participated in the interim analysis. Proceeding this way led to a clear demarcation between data sets used for hypothesis generation (Group A, 42 patients) and data used for confirmatory hypothesis testing in a prospective manner (Group B, 109 patients), i.e. independence between hypothesis generation and hypothesis confirmation. Group (A+B) was then considered a powerful basis for assessment of treatment effects.

For clarity the efficacy results for Group A, Group B and Group A+B are presented separately in this webappendix.

In the first step of hypothesis testing according to a Closed Testing Procedure approach, the global one-sided hypothesis 'ranibizumab was superior to sham' was tested at the alpha-level of 0.025:

H_{01}: $\mu_{ranibizumab} - \mu_{sham} \leq 0$ versus H_{A1}: $\mu_{Ranibizumab} - \mu_{sham} > 0$

Where $\mu_{ranibizumab}$ was the unknown mean value of the primary variable for the pooled two ranibizumab treatment groups and μ_{sham} was the corresponding value for the sham treatment group.

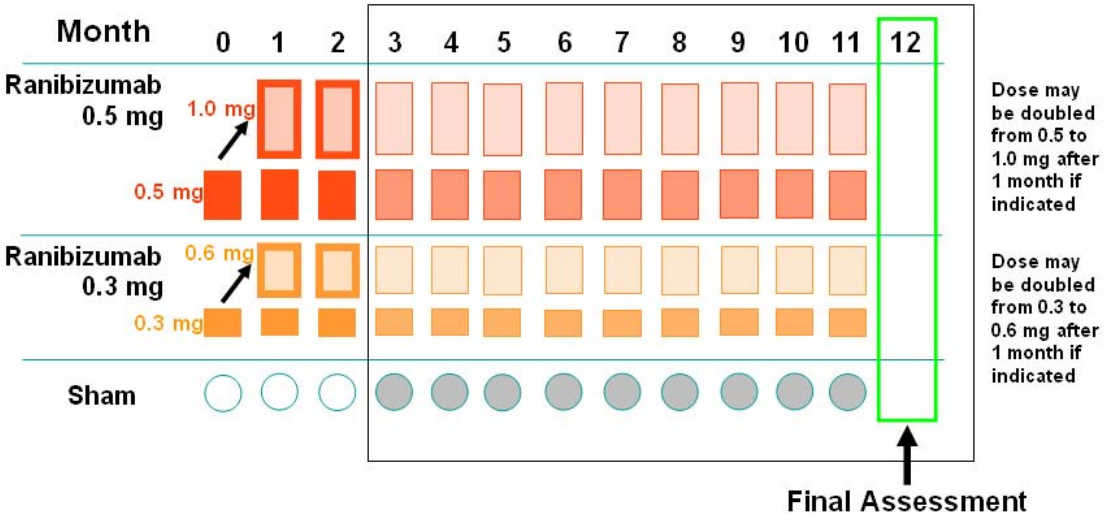
Following the concept of the Closed Testing Procedure approach a second step of hypotheses testing was followed only if H_{A1} could be claimed, i.e. the superiority of the pooled ranibizumab treatments to sham treatment. In this second step each of the two ranibizumab treatment groups were compared separately against the sham treatment group with a one-sided alpha-level of 0.025 for each of the two comparisons:

H_{02}: $\mu_{ranibizumab\text{-}6} - \mu_{sham} \leq 0$ versus H_{A2}: $\mu_{ranibizumab\text{-}6} - \mu_{sham} > 0$
H_{03}: $\mu_{ranibizumab\text{-}10} - \mu_{sham} \leq 0$ versus H_{A3}: $\mu_{ranibizumab\text{-}10} - \mu_{sham} > 0$

Where $\mu_{ranibizumab\text{-}6}$ and $\mu_{ranibizumab\text{-}10}$ were the unknown mean values of the primary variable for the two ranibizumab treatment groups with the concentrations of 0.3 to 0.5 mg and 0.5 to 1.0 mg. According to the Closed Testing Procedure superiority was claimed for each of these two comparisons H_{02} and H_{03} separately once the corresponding one-sided p-value was ≤ 0.025.

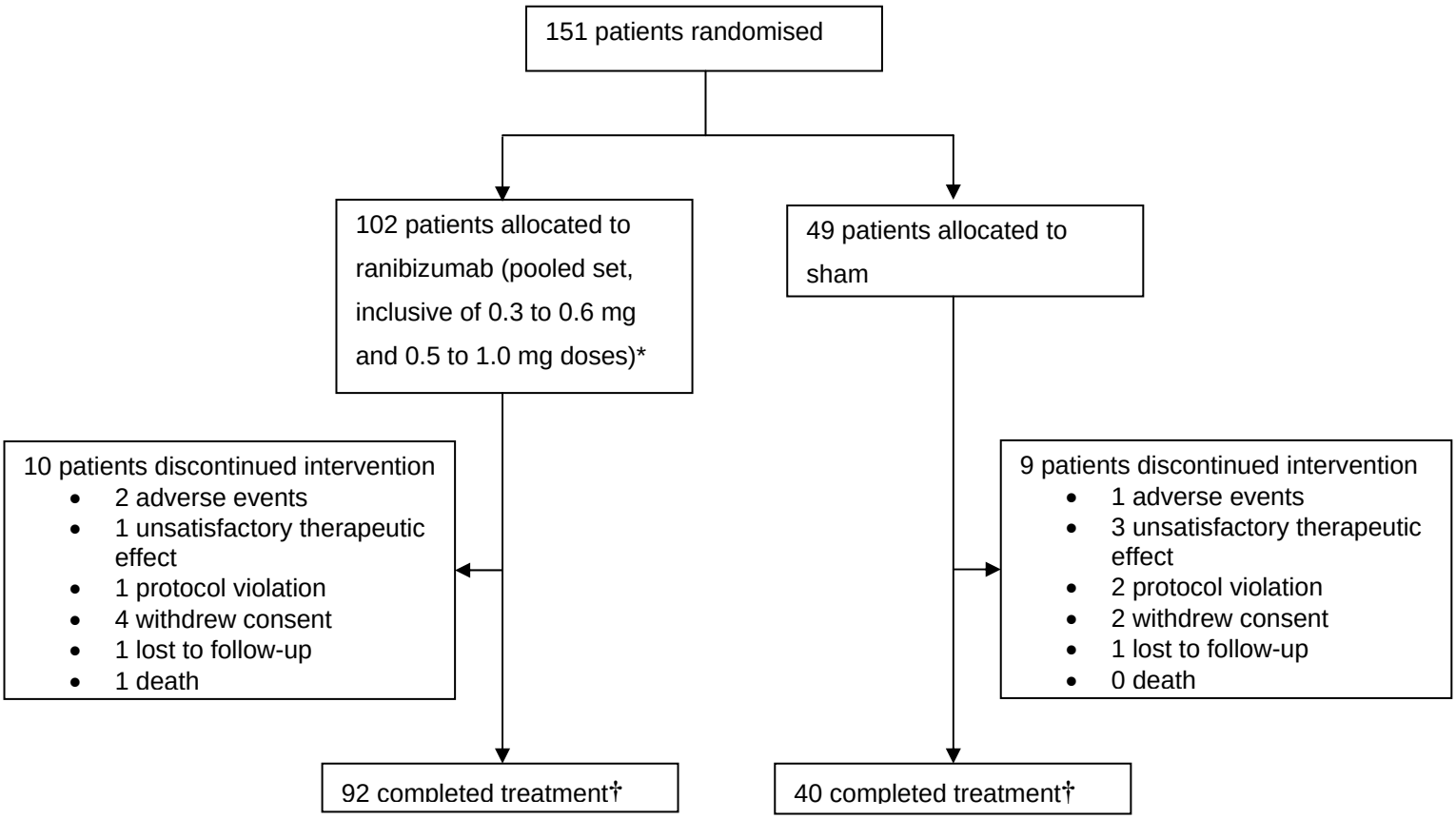
Due to the conditional ordering of the first and second step of hypothesis testing the overall type one error maintains the one-sided level of 0.025. The statistical hypothesis testing of the mean average changes from baseline in BCVA was based on a stratified Cochran-Mantel-Haenszel test using the observed values (permutation test) as scores. The statistical software package StatXact was used to compute the exact test. Based on the interim data, the 12-month analysis was stratified by categories of VA (≤ 60 letters *vs.* >60 letters) and CRT (≤ 400 µm *vs.* > 400 µm), both as assessed in the study eye at baseline. The primary analysis was performed on the Full Analysis Set (FAS).

Supplementary Figure 1: Treatment schedule for RESOLVE study



From month 3-11, treatment was stopped/re-initiated based on pre-specified criteria, as follows. ***Treatment success:*** Study treatment was to be discontinued if the central retinal thickness (CRT) in the study eye was ≤225 µm and best-corrected visual acuity (BCVA) was ≥79 letters and re-initiated if the CRT increased by ≥50 µm or BCVA decreased by ≥5 letters and was <74 letters; ***Futility*:** Treatment was to be discontinued if on 3 consecutive injections had not produced at least borderline improvements in the study eye (decrease in CRT of at least 50 µm and represents at least a 20% reduction in average CRT or increase in BCVA of ≥5 letters). ***Toxicity:*** Treatment was to be discontinued in case of adverse events (e.g. intraocular inflammation [≥+1]; BCVA loss related to study drug [≥30 letters]; Intra ocular pressure (IOP) in the study eye [≥30 mmHg]; vitreous haemorrhage [≥2+ and a ≥ 30 letters decrease in BCVA]; retinal break or detachment; subfoveal haemorrhage; local or systemic infection and intraocular surgery). ***Rescue therapy:*** Laser photocoagulation was permitted if after 3 consecutive monthly injections, BCVA in the study eye had decreased from baseline by >10 letters at 2 consecutive visits at least 1 month apart or if the investigator considered the macula not to be flat as assessed by OCT (flat being defined as ≤225 µm).

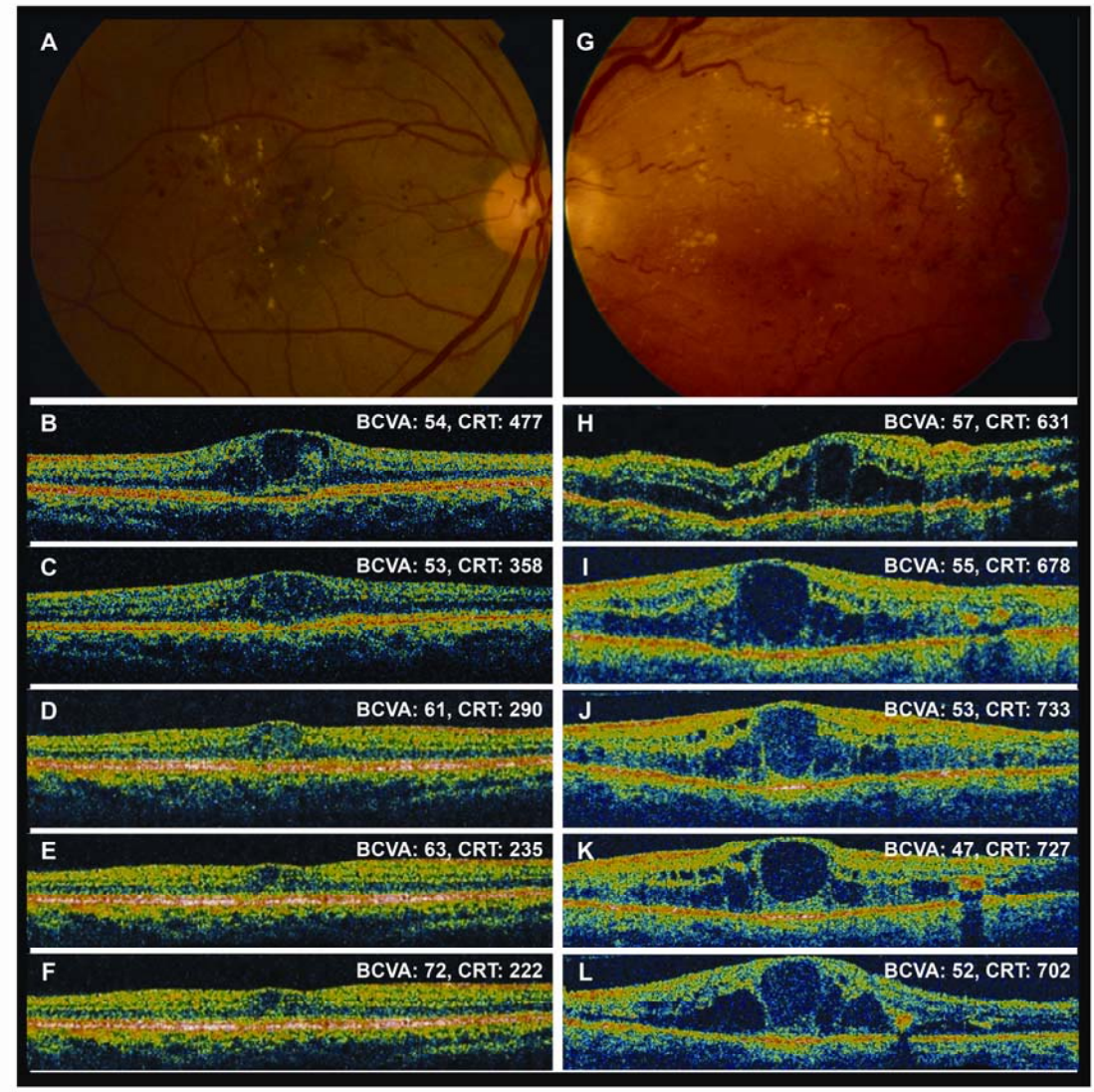
Supplementary Figure 2: Consort flow of the study patients



*ranibizumab 0.3 to 0.6 mg and 0.5 to 1.0 mg: Completed: both 46 (90.2%); Discontinued: both 5 (9.8%); Adverse events: both 1(2.0%); Unsatisfactory therapeutic effect: 0 and 1 (2.0%); protocol violation: 0 and 1 (2.0%) Subject withdrew consent: both 2 (3.9%); Lost to follow-up: 1 (2.0%) and 0; Death: 1 (2.0%) and 0

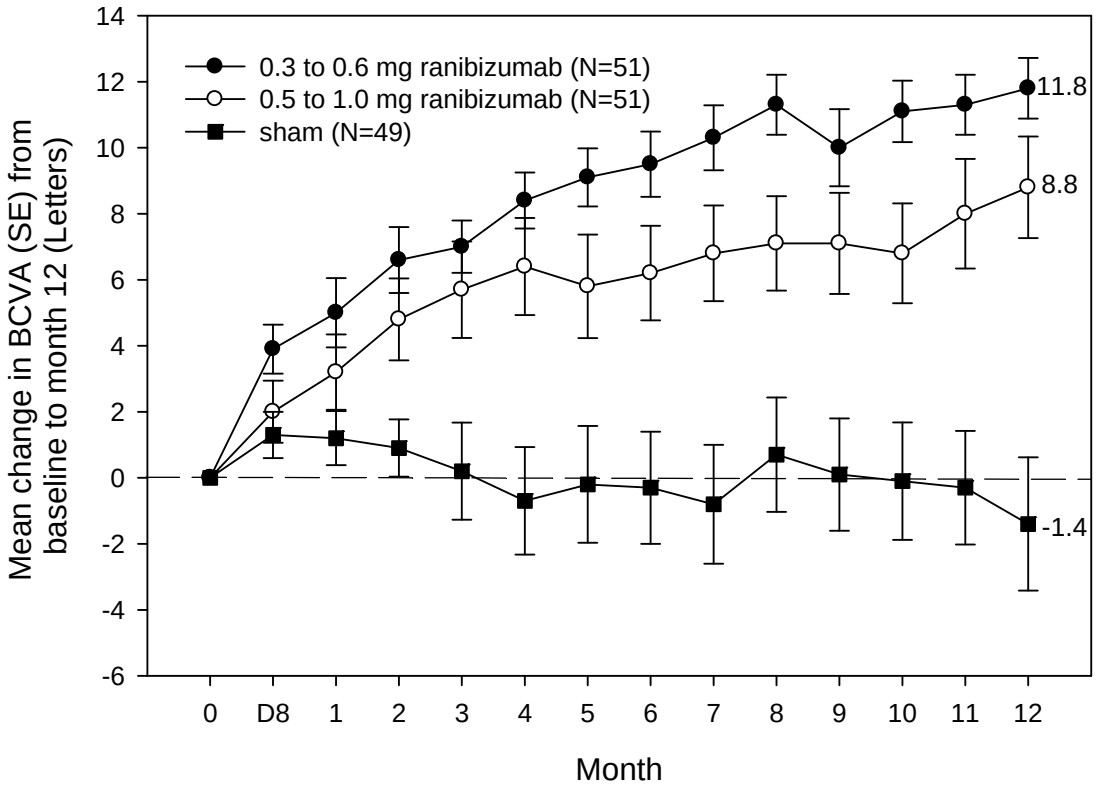
†Number of patients with rescue laser treatment: 5 (4.9%) for ranibizumab and 17 [34.7%] for sham

Supplementary Figure 3 (A-L): Representative case studies of transfoveal optical coherence tomography in a patient on ranibizumab (0.3 to 0.6 mg) (left, A-F) and sham (right, G-L) at baseline and month 1, 3, 6 and 12.



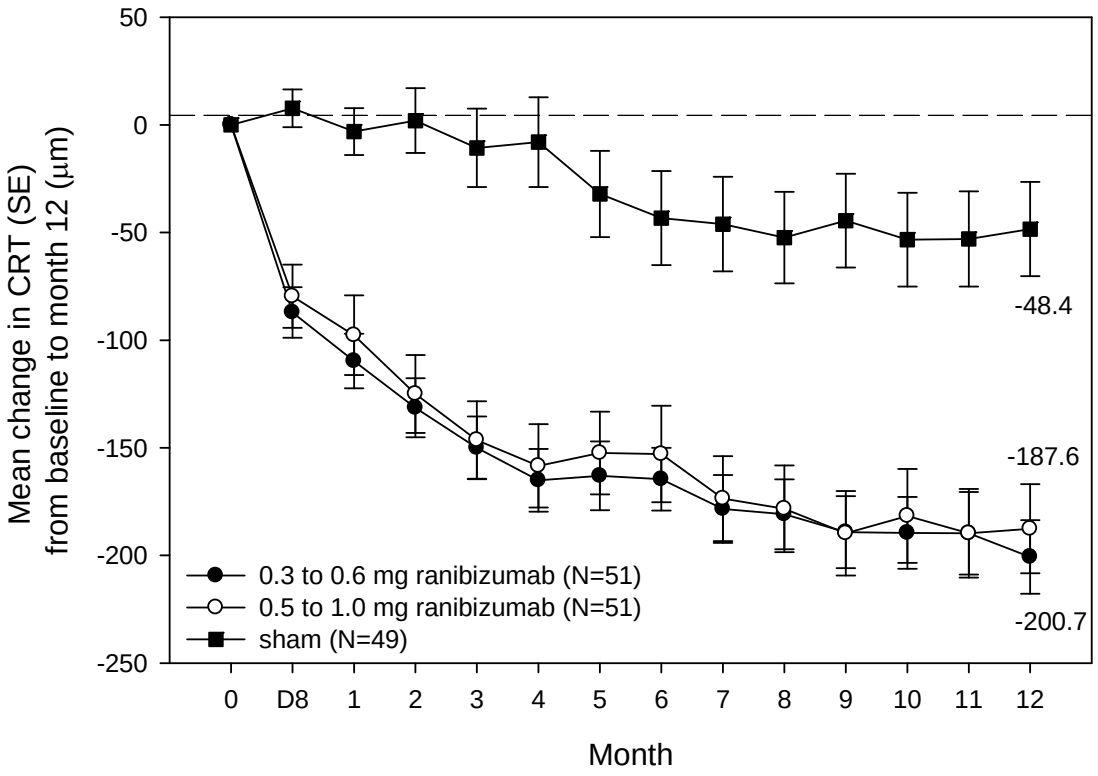
The patient on ranibizumab showed substantial macular edema before injection (central retinal thickness, CRT=477 µm). As observed from the images the macular edema significantly decreased from months 3 to 12, reducing CRT to 222 µm at month 12. The decrease in CRT was also paralleled by an increase in best-corrected visual acuity (BCVA) from 54 to 72 letters from baseline to month 12 (left, A-F). The sham case also showed substantial macular edema at baseline (CRT= 631 µm; BCVA=57 letters). The edema worsened over the 12-month study period, increasing the CRT to 702 µm while BCVA decreased from 57 to 52 letters (right, G-L).

Supplementary Figure 4A. Mean change in BCVA (letters) from baseline to Month 12, by ranibizumab dose (0.3 to 0.6 mg and 0.5 to 1.0 mg) *vs.* sham (Group A+B)



Full analysis set, last observation carried forward (LOCF)
BCVA, best-corrected visual acuity; SE, standard error of the mean

Supplementary Figure 4B. Mean change in CRT (µm) from baseline to Month 12, by ranibizumab dose (0.3 to 0.6 mg and 0.5 to 1.0 mg) *vs.* sham (Group A+B)



Full analysis set, last observation carried forward (LOCF)
CRT, central retinal thickness; SE, standard error of the mean

Supplementary Table 1- Key inclusion and exclusion criteria

Inclusion criteria	• Age >18 years • Type 1 or type 2 diabetes mellitus, • Stable Hb_{A1c} levels (≤12%) and • DME with centre involvement in at least one eye
Eligibility criteria of study eye	• CRT ≥300 µm (Stratus Zeiss Meditec) • BCVA score between 73 and 39 letters inclusively, using ETDRS charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/40 to 20/160) • Decreased vision attributed to foveal thickening from DME, that was not explained by any other causes in the opinion of the investigator • Patients for whom, in the opinion of the investigator, laser photocoagulation, additional or first treatment, could be withheld for at least 3 months after randomisation. • If both eyes were eligible, the eye with the worse BCVA was selected for study treatment unless, for medical reasons, the investigator deemed the other eye as more appropriate.
Exclusion criteria	• Panretinal, focal peripheral laser photocoagulation performed within 6 months prior to study entry. Grid/central laser photocoagulation was excluded except for patients with only mild laser burns at least 1000 µm from the center of the fovea performed more than 6 months preceding Day 1. • Proliferative DR in the study eye, with the exception of tufts of neovascularization less than one disc area with no vitreous hemorrhage. As well as those with area of retinal ischemia ≥500 µm and located ≤500 µm from the center of the macula of the study eye as assessed by fluorescein angiography at Visit 1 and confirmed by a central reading center. • Patients with unstable medical conditions like poor glycaemic or blood pressure control. Patients with hypertension for whom a change in antihypertensive treatment was initiated within 2 months preceding Day 1 were not enrolled unless blood pressure was maintained for at least 1 month prior Day 1 below 160/100 mmHg by antihypertensive treatment. • History of treatment with systemic corticosteroids within 4 months prior to randomisation or topical, rectal or inhaled corticosteroids in current use more than 2 times per week • Previous participation in a study on anti-angiogenic drugs • Ocular disorders and history of any condition that may confound the interpretation of study results or might render patient at high-risk for treatment complications • Ocular inflammation in either eye or history of cataract surgery in the study eye within 6 months before study initiation • Pre-menopausal women not using adequate contraception and pregnant or nursing women were excluded from the study.

CRT: central retinal thickness; DME: diabetic macular edema; BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; DR: diabetic retinopathy

Supplementary Table 2: Demographics and baseline characteristics

Characteristics	Ranibizumab 0·3 to 0·6 mg N=51	Ranibizumab 0·5 to 1·0 mg N=51	Ranibizumab (pooled) N=102	Sham N=49
Demographics				
Age, years				
Mean (range)	63.2 (37-85)	62.8 (32-84)	63.0 (32-85)	65.0 (41-82)
Gender n (%)				
Male	29 (56.9)	27 (52.9)	56 (54.9)	25 (51.0)
Female	22 (43.1)	24 (47.1)	46 (45.1)	24 (49.0)
Race, n (%)				
Caucasian	47 (92.2)	44 (86.3)	91 (89.2)	41 (83.7)
Asian	4 (7.8)	4 (7.8)	8 (7.8)	5 (10.2)
Others	0 (0.0)	3 (5.9)	3 (3.0)	3 (6.0)
Diabetes				
Type 2	50 (98.0)	49 (96.1)	99 (97.1)	48 (98.0)
Hb_{A1c}				
Mean (Range)	7.3 (5.5-11.1)	7.6 (5.6-10.0)	7.4 (5.5-11.1)	7.5 (5.3-9.7)
Time since first diagnosis of diabetes, years	14.4 (1.4-36.0)	13.9 (0.7-46.0)	14.2 (0.7-46.0)	15.1 (2.1-45.8)
Mean (Range)				
DME				
Time since first diagnosis, years				
Mean (Range)	1.2 (0.0-7.2)	1.1 (0.0-7.2)	1.2 (0.0-7.2)	1.4 (0.0-19.8)
Ocular				
VA, ETDRS				
Mean (SD)	59.2 (10.2)	61.2 (9.5)	60.2 (9.9)	61.1 (9.0)
Range	37-73	39-79	37-79	39-76
CRT, μm				
Mean (SD)	459.5 (109.1)	451.3 (120.1)	455.4 (114.2)	448.9 (102.8)
Range	278-753	290-758	278-758	282-650
FA characteristics				
Macular edema: definite	51 (100.0)	51 (100.0)	102 (100.0)	49 (100.0)
Macular edema: center involvement	51 (100.0)	50 (98.0)	101 (99.0)	49 (100.0)
Leakage	51 (100.0)	50 (98.0)	101 (99.0)	49 (100.0)
Prior laser photocoagulation treatment				

Yes	10 (19.6)	9 (17.6)	19 (18.6)	9 (18.4)
No	41 (80.4)	42 (82.4)	83 (81.4)	40 (81.6)

DME: Diabetic macular edema; VA: Visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CRT: Central retinal thickness; FA: Fluorescein angiography

Supplementary Table 3A. Mean change in best-corrected visual acuity (BCVA, letters) and central retinal thickness (CRT, µm) from baseline to Month 12 (Group A)

Mean change	**Ranibizumab 0.3 to 0.6 mg N=14**	**Ranibizumab 0.5 to 1.0 mg N=11**	**Ranibizumab Pooled N=25**	**Sham N=17**
BCVA				
Baseline mean (SD)	60.0 (9.1)	52.9 (10.0)	56.9 (10.0)	62.8 (10.0)
Mean average change from baseline from month 1 to month 12				
Average Month 1 to Month 12 mean (SD)	69.0 (12.1)	60.6 (12.5)	65.3 (12.8)	60.3 (18.0)
Average change from baseline mean (SD)	9.0 (5.2)	7.7 (6.5)	8.4 (5.7)	-2.4 (11.9)
Comparison *vs.* sham				
Difference in LS means	12.7	14.4	12.9	-
95% CI for difference	(6.3, 19.1)	(6.3, 22.4)	(7.6, 18.2)	-
p-value	0.0004	0.0011	<0.0001	-
Mean change from baseline to Month 12				
Month 12 mean (SD)	70.1 (11.6)	60.5 (12.6)	65.9 (12.8)	59.4 (23.2)
Change from baseline mean (SD)	10.1 (6.1)	7.6 (7.1)	9.0 (6.6)	-3.4 (17.6)
Comparison *vs.* sham				
Difference in LS means	13.6	11.0	12.5	-
95% CI for difference	(3.4, 23.7)	(-0.5, 22.6)	(4.7, 20.2)	-
p-value	0.0027	0.0082	0.0004	-
CRT				
Baseline mean (SD)	452.7 (108.8)	464.3 (135.6)	457.8 (118.8)	421.6 (93.7)
Month 12 mean (SD)	266.3 (68.7)	263.7 (102.5)	265.2 (83.2)	420.9 (139.2)
Change from baseline mean (SD)	-186.4 (122.7)	-200.5 (160.7)	-192.6 (137.7)	-0.8 (133.2)
Comparison *vs.* sham				
Difference in LS means	-185.7	-199.8	-191.9	-
95% CI for difference	(-280.6, -90.7)	(-314.6, -84.9)	(-278.2, -105.5)	-
p-value	<0.0001	0.0017	<0.0001	-

BCVA: best-corrected visual acuity; CRT: central retinal thickness; LS: least square

Supplementary Table 3B. Mean change in best-corrected visual acuity (BCVA, letters) and central retinal thickness (CRT, µm) from baseline to Month 12 (Group B)

Mean change	Ranibizumab 0.3 to 0.6 mg N=37	Ranibizumab 0.5 to 1.0 mg N=40	Ranibizumab Pooled N=77	Sham N=32
BCVA				
Baseline mean (SD)	58.8 (10.7)	63.4 (8.1)	61.2 (9.7)	60.2 (8.5)
Mean average change from baseline from month 1 to month 12				
Average Month 1 to Month 12 mean (SD)	68.2 (10.8)	69.4 (11.8)	68.8 (11.3)	61.4 (11.5)
Average change from baseline mean (SD)	9.4 (5.8)	6.0 (9.9)	7.6 (8.3)	1.2 (8.4)
Comparison *vs.* sham				
Difference in LS means	8.1	5.5	6.7	
95% CI for difference	(4.7, 11.5)	(1.0, 9.9)	(3.2, 10.1)	
p-value	<0.0001	0.0067	0.0002	
Mean change from baseline to Month 12				
Month 12 mean (SD)	71.2 (10.9)	72.6 (12.3)	71.9 (11.6)	59.8 (13.6)
Change from baseline mean (SD)	12.4 (6.8)	9.2 (11.9)	10.7 (9.8)	-0.4 (12.1)
Comparison *vs.* sham				
Difference in LS means	12.8	9.6	11.1	-
95% CI for difference	(8.2, 17.4)	(3.9, 15.2)	(6.7, 15.5)	-
p-value	<0.0001	0.0005	<0.0001	-
CRT				
Baseline mean (SD)	462.1 (110.6)	447.7 (117.2)	454.6 (113.5)	463.3 (105.8)
Month 12 mean (SD)	255.9 (73.2)	263.6 (90.1)	259.9 (82.0)	389.6 (140.2)
Change from baseline mean (SD)	-202.6 (20.3)	-184.1 (23.1)	-194.7 (15.4)	-73.7 (23.2)
Comparison *vs.* sham				
Difference in LS means	-132.5	-110.4	-121.0	-
95% CI for difference	(-200.5, -64.5)	(-182.3, -38.4)	(-180.4, -61.6)	-
p-value	<0.0001	0.0001	<0.0001	

BCVA: best-corrected visual acuity; CRT: central retinal thickness; LS: least square

Supplementary Table 3C. Mean change in best-corrected visual acuity (BCVA, letters) and central retinal thickness (CRT, µm) from baseline to Month 12 (Group A+B)

Mean change	Ranibizumab 0.3 to 0.6 mg N=51	Ranibizumab 0.5 to 1.0 mg N=51	Ranibizumab Pooled N=102	Sham N=49
BCVA				
Baseline mean (SD)	59.2 (10.2)	61.2 (9.5)	60.2 (9.9)	61.1 (9.0)
Mean average change from baseline from month 1 to month 12				
Average Month 1 to Month 12 mean (SD)	68.4 (11.1)	67.5 (12.4)	68.0 (11.7)	61.0 (13.9)
Average change from baseline mean (SD)	9.2 (5.6)	6.4 (9.2)	7.8 (7.7)	-0.1 (9.8)
Comparison *vs.* sham				
Difference in LS means	9.4	6.7	7.9	-
95% CI for difference	(6.2, 12.6)	(3.0, 10.5)	(5.0, 10.9)	-
p-value	<0.0001	0.0004	<0.0001	-
Mean change from baseline to Month 12				
Month 12 mean (SD)	70.9 (11.0)	70.0 (13.2)	70.5 (12.1)	59.7 (17.3)
Change from baseline mean (SD)	11.8 (6.6)	8.8 (11.0)	10.3 (9.1)	-1.4 (14.2)
Comparison *vs.* sham				
Difference in LS means	13.4	10.6	11.9	-
95% CI for difference	(9.0, 17.8)	(5.6, 15.7)	(8.1, 15.7)	-
p-value	<0.0001	<0.0001	<0.0001	-
CRT				
Baseline mean (SD)	459.5 (109.1)	451.3 (120.1)	455.4 (114.2)	448.9 (102.8)
Month 12 mean (SD)	258.8 (71.5)	263.6 (91.9)	261.2 (81.9)	400.5 (139.2)
Change from baseline mean (SD)	-200.7 (122.2)	-187.6 (147.8)	-194.2 (135.1)	-48.4 (153.4)
Comparison *vs.* sham				
Difference in LS means	-157.3	-152.7	-155.0	-
95% CI for difference	(-202.4. -112.1)	(-205.4, -100.0)	(-195.4, -114.6)	-
p-value	<0.0001	<0.0001	<0.0001	-

BCVA: best-corrected visual acuity; CRT: central retinal thickness; LS: least square

Supplementary Table 4A. Best-corrected visual acuity (BCVA, letters) of the study eye (letters): categorized change from baseline at month 12 (Group A)

Number of letters change from baseline	Ranibizumab 0.3 to 0.6 mg N=14 n (%)	Ranibizumab 0.5 to 1.0 mg N=11 n (%)	Ranibizumab Pooled N=25 n (%)	Sham N=17 n (%)
Gain of ≥ 1 letters	13 (92.9)	9 (81.8)	22 (88.0)	9 (52.9)
p-vale (ranibizumab *vs.* sham)	0.0393	0.2201	0.0403	-
≥10 letters				
Gain	10 (71.4)	4 (36.4)	14 (56.0)	3 (17.6)
Loss	0	0	0	4 (23.5)
p- value (ranibizumab *vs.* sham)	0.0039	0.1576	0.0061	-
≥15 letters				
Gain	3 (21.4)	2 (18.2)	5 (20.0)	2 (11.8)
Loss	0	0	0	3 (17.6)
p-value (ranibizumab *vs.* sham)	0.3535	0.2606	0.2191	-

p-value calculated by: Cochran-Mantel-Haenszel (CMH) test is on rank scores. Stratified analysis includes baseline visual acuity (≤60, >60 letters) and baseline central retinal thickness (≤400, >400 μm).BCVA: best-corrected visual acuity

Supplementary Table 4B. Best-corrected visual acuity (BCVA, letters) of the study eye (letters): categorized change from baseline at month 12 (Group B)

Number of letters change from baseline	Ranibizumab 0.3 to 0.6 mg N=37 n (%)	Ranibizumab 0.5 to 1.0 mg N=40 n (%)	Ranibizumab Pooled N=77 n (%)	Sham N=32 n (%)
Gain of ≥ 1 letters	36 (97.3)	34 (85.0)	70 (90.9)	18 (56.3)
p-value (ranibizumab *vs.* sham)	<0.0001	0.0067	<0.0001	-
≥10 letters				
Gain	27 (73.0)	21 (52.5)	48 (62.3)	6 (18.8)
Loss	0	5 (12.5)	5 (6.5)	8 (25.0)
p-value (ranibizumab *vs.* sham)	<0.0001	0.0039	<0.0001	-
≥15 letters				
Gain	15 (40.5)	13 (32.5)	28 (36.4)	3 (9.4)
Loss	0	3 (7.5)	3 (3.9)	7 (21.9)
p-value (ranibizumab *vs.* sham)	0.0003	0.0057	0.0002	-

p-value calculated by: Cochran-Mantel-Haenszel (CMH) test is on rank scores. Stratified analysis includes baseline visual acuity (≤60, >60 letters) and baseline central retinal thickness (≤400, >400 μm).BCVA: best-corrected visual acuity

Supplementary Table 4C. Best-corrected visual acuity (BCVA, letters) of the study eye (letters): categorized change from baseline at month 12 (Group A+B)

Number of letters change from baseline	Ranibizumab 0.3 to 0.6 mg N=51 n (%)	Ranibizumab 0.5 to 1.0 mg N=51 n (%)	Ranibizumab Pooled N=102 n (%)	Sham N=49 n (%)
Gain of ≥ 1 letters	49 (96.1)	43 (84.3)	92 (90.2)	27 (55.1)
p-value (ranibizumab *vs.* sham)	<0.0001	0.0013	<0.0001	-
≥10 letters				
Gain	37 (72.5)	25 (49.0)	62 (60.8)	9 (18.4)
Loss	0	5 (9.8)	5 (4.9)	12 (24.5)
p-value (ranibizumab *vs.* sham)	<0.0001	0.0010	<0.0001	-
≥15 letters				
Gain	18 (35.3)	15 (29.4)	33 (32.4)	5 (10.2)
Loss	0	3 (5.9)	3 (2.9)	10 (20.4)
p-value (ranibizumab *vs.* sham)	0.0001	0.0037	0.0001	-

p-value calculated by: Cochran-Mantel-Haenszel (CMH) test is on rank scores. Stratified analysis includes baseline visual acuity (≤60, >60 letters) and baseline central retinal thickness (≤400, >400 μm).BCVA: best-corrected visual acuity

Supplementary Table 5A. Most frequent serious adverse events over 12 months, Group (A+B)

Serious adverse events n (%)	Ranibizumab 0.3 to 0.6 mg N=51	Ranibizumab 0.5 to 1.0 mg N=51	Ranibizumab Pooled N=102	Sham N=49
Ocular				
Total	1 (2.0)	3 (5.9)	4 (3.9)	1 (2.0)
Vitreous haemorrhage*	1 (2.0)	0	1 (1.0)	0
Retinal ischemia	0	1 (2.0)	1 (1.0)	0
Retinal artery occlusion*	0	1 (2.0)	1 (1.0)	0
Endophthalmitis*	1 (2.0)	1 (2.0)	2 (2.0)	0
Retinal detachment	0	0	0	1 (2.0)
Non-ocular				
Total	8 (15.7)	6 (11.8)	14 (13.7)	8 (16.3)
Metabolism and nutrition disorders	2 (3.9)	1 (2.0)	3 (2.9)	1 (2.0)
Infections and infestations	1 (2.0)	1 (2.0)	2 (2.0)	3 (6.1)
Urinary bladder cancer	1 (2.0)	0	1 (1.0)	0

* suspected to be related to study drug/procedure

Supplementary Table 5B. Non-ocular serious adverse events over 12 months, Group (A+B)

Serious adverse events n (%)	Ranibizumab 0.3 to 0.6 mg N=51	Ranibizumab 0.5 to 1.0 mg N=51	Ranibizumab Pooled N=102	Sham N=49
Any system organ class				
Total	8 (15.7)	6 (11.8)	14 (13.7)	8 (16.3)
Blood and lymphatic system disorders				
Total	1 (2.0)	0	1 (1.0)	0
Anaemia	1 (2.0)	0	1 (1.0)	0
Cardiac disorders				
Total	0	1 (2.0)	1 (1.0)	2 (4.1)
Myocardial infarction*	0	1 (2.0)	1 (1.0)	1 (2.0)
Angina pectoris	0	0	0	1 (2.0)
General disorders and administration site conditions				
Total	0	0	0	1 (2.0)
Pitting oedema	0	0	0	1 (2.0)
Infections and infestations				
Total	1 (2.0)	1 (2.0)	2 (2.0)	3 (6.1)
Gastroenteritis viral	1 (2.0)	0	1 (1.0)	0
Infected epidermal cyst	0	1 (2.0)	1 (1.0)	0
Cellulitis	0	0	0	1 (2.0)
Diabetic gangrene	0	0	0	1 (2.0)
Gastroenteritis	0	0	0	1 (2.0)
Injury, poisoning and procedural complications				
Total	4 (7.8)	0	4 (3.9)	0
Allergic transfusion reaction	1 (2.0)	0	1 (1.0)	0
Concussion	1 (2.0)	0	1 (1.0)	0
Radius fracture	1 (2.0)	0	1 (1.0)	0
Spinal fracture	1 (2.0)	0	1 (1.0)	0
Metabolism and nutrition disorders				
Total	2 (3.9)	1 (2.0)	3 (2.9)	1 (2.0)
Hypoglycaemia	1 (2.0)	1 (2.0)	2 (2.0)	0
Hyperglycaemia	1 (2.0)	0	1 (1.0)	0
Diabetes mellitus inadequate control	0	0	0	1 (2.0)
Musculoskeletal and connective tissue disorders				
Total	2 (3.9)	0 (0.0)	2 (2.0)	1 (2.0)
Intervertebral disc protrusion	1 (2.0)	0	1 (1.0)	0

Osteoarthritis	1 (2.0)	0	1 (1.0)	0
Back pain	0	0	0	1 (2.0)
Neoplasms benign, malignant and unspecified				
Total	2 (3.9)	0	2 (2.0)	0
Bladder cancer	1 (2.0)	0	1 (1.0)	0
Lung neoplasm malignant	1 (2.0)	0	1 (1.0)	0
Nervous system disorders				
Total	0	1 (2.0)	1 (1.0)	0
Transient ischaemic attack	0	1 (2.0)	1 (1.0)	0
Renal and urinary disorders				
Total	0	2 (3.9)	2 (2.0)	2 (4.1)
Nephrolithiasis	0	1 (2.0)	1 (1.0)	0
Renal failure chronic	0	1 (2.0)	1 (1.0)	1 (2.0)
Renal failure	0	0	0	1 (2.0)
Respiratory, thoracic and mediastinal disorders				
Total	0	0	0	1 (2.0)
Dyspnoea	0	0	0	1 (2.0)
Vascular disorders				
Total	0	0	0	1 (2.0)
Hypertension	0	0	0	1 (2.0)

* suspected to be related to study drug

Supplementary Table 6. Most frequent adverse events over 12 months, Group (A+B)

Adverse events n (%)	Ranibizumab 0.3 to 0.6 mg (N=51)	Ranibizumab 0.5 to 1.0 mg (N=51)	Ranibizumab Pooled (N=102)	Sham (N=49)
Ocular				
Total	38 (74.5)	42 (82.4)	80 (78.4)	28 (57.1)
Conjunctival haemorrhage*	10 (19.6)	13 (25.5)	23 (22.5)	7 (14.3)
Eye pain*	9 (17.6)	9 (17.6)	18 (17.6)	10** (20.4)
Intraocular pressure increased*†	6 (11.8)	15 (29.4)	21 (20.6)	1** (2.0)
Non-ocular				
Total	32 (62.7)	32 (62.7)	64 (62.7)	32 (65.3)
Nasopharyngitis	5 (9.8)	5 (9.8)	10 (9.8)	1 (2.0)
Hypertension	3 (5.9)	4 (7.8)	7 (6.9)	4 (8.2)
Potentially related to systemic VEGF inhibition				
Total	5 (9.8)	9 (17.6)	14 (13.7)	6 (12.2)
Arterial thromboembolic events‡	0	3 (5.9)	3 (2.9)	2 (4.1)
Hypertension	4 (7.8)	5 (9.8)	9 (8.8)	5 (10.2)
Non-ocular haemorrhage	1 (2.0)	1 (2.0)	2 (2.0)	0

* suspected to be related to study drug/procedure

**one event documented after start of treatment with non-study medication (marketed Lucentis)

†transient post-injection

‡ Myocardial infarction (1 sham and ranibizumab); retinal artery occlusion and transient ischemic attack (1 each in ranibizumab); angina pectoris (1 in sham)

Supplementary Table 7A Hb_{A1c} levels at baseline and at 12 months between groups

	Hb_{A1c} levels (%) at baseline (mean±SD)	**Hb_{A1c} levels (%) at 12 months (mean±SD)**
Ranibizumab pooled	7.43 (1.0) N= 102	7.60 (1.0) N= 86
Sham	7.48 (1.1) N= 49	7.46 (1.1) N= 39

Supplementary Table 7B Blood pressure levels at baseline and at 12 months between treatment groups

	Systolic blood pressure (mmHg) levels (mean±SD)		**Diastolic blood pressure (mmHg) levels (mean±SD)**	
	At baseline	**At 12 months**	**At baseline**	**At 12 months**
Ranibizumab pooled	140.1 (12.7) N= 101	141.0 (16.0) N= 88	79.9 (8.4) N= 101	77.8 (10.1) N= 88
Sham	137.7 (14.1) N= 47	139.8 (14.9) N= 38	79.6 (11.3) N= 47	76.2 (10.5) N= 38