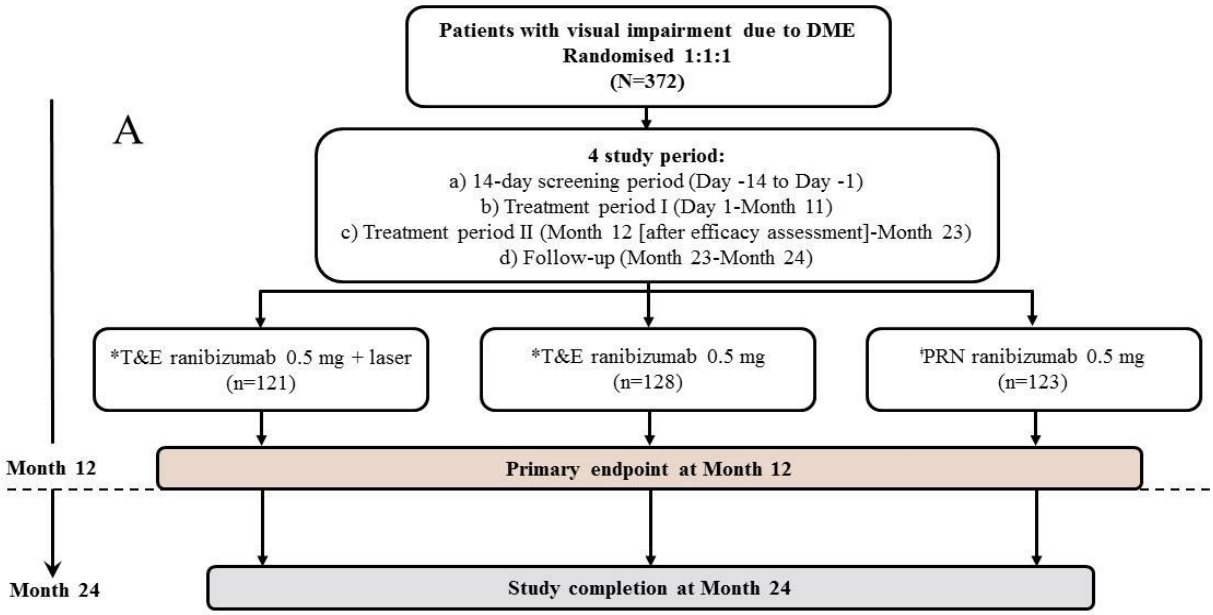
Supplementary Figure S1: RETAIN (A) study design and (B) treatment schedule



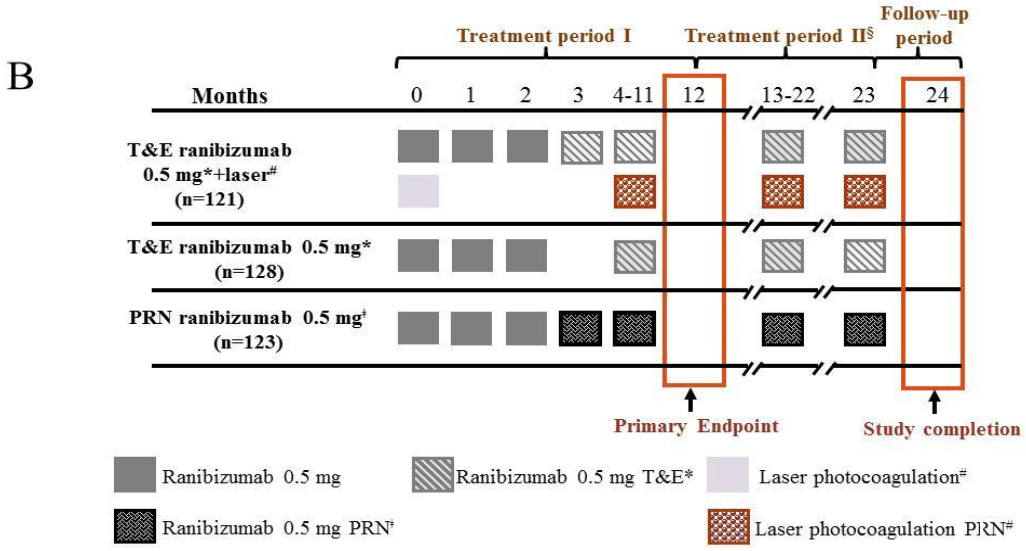
Note: Treatment was resumed if a patient's vision worsens due to their disease, as per the retreatment criterion defined in European SmPC

*Ranibizumab injection at baseline (T&E+laser: additional laser treatment at baseline and PRN subsequently according to ETDRS guidelines); monthly ranibizumab 0.5 mg treatment until BCVA stability, monthly monitoring, incremental extension in the inter-treatment interval by 1 month (maximum prolongation up to 3 months) at stable BCVA, when BCVA decreases due to DME at T&E visit resume monthly treatment until BCVA stability and re-enter the extension treatment phase

†Ranibizumab injection at baseline, monthly treatment until BCVA stability, monthly monitoring, when BCVA decreases due to DME resume monthly treatment until BCVA stability; ranibizumab given PRN

13 countries included Belgium, Czech Republic, France, Greece, Hungary, Ireland, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, and the United Kingdom

BCVA, best-corrected visual acuity; DME, diabetic macular oedema; ETDRS, early treatment diabetic retinopathy study; PRN, pro re nata; T&E, treat-and-extend



§After assessment of efficacy for BCVA stability

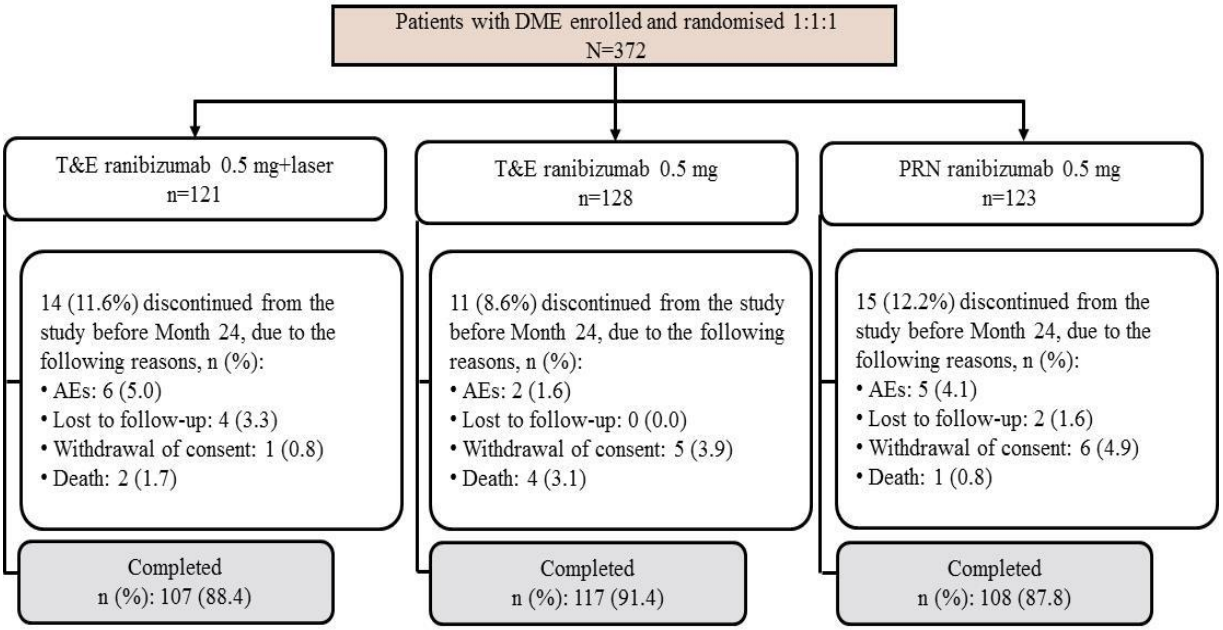
*Ranibizumab 0.5 mg T&E: monthly ranibizumab 0.5 mg administered until BCVA stability (no BCVA change for 3 consecutive monthly visits; phase-A), monthly monitoring, followed by incremental extension of treatment-free interval by 1 month, up to a maximum interval of 3 months, at stable VA (phase-B). If a decrease in VA is observed due to DME at the T&E visit, phase-A is resumed followed by phase-B

†Ranibizumab 0.5 mg PRN: monthly ranibizumab 0.5 mg administered until BCVA stability (no BCVA change for 3 consecutive monthly visits; phase-A), monthly monitoring; If BCVA decrease due to DME observed, monthly ranibizumab treatment resumed until VA stability (Phase A)

#Laser: Administered at baseline and thereafter at a minimum interval of 90 days, according to the ETDRS guidelines at investigator's discretion

BCVA, best-corrected visual acuity; DME, diabetic macular oedema; ETDRS, early treatment diabetic retinopathy study; PRN, pro re nata; T&E, treat-and-extend; VA, visual acuity

Supplementary Figure S2: Patient disposition flowchart



AE, adverse event; DME, diabetic macular oedema; PRN, pro re nata; T&E, treat-and-extend

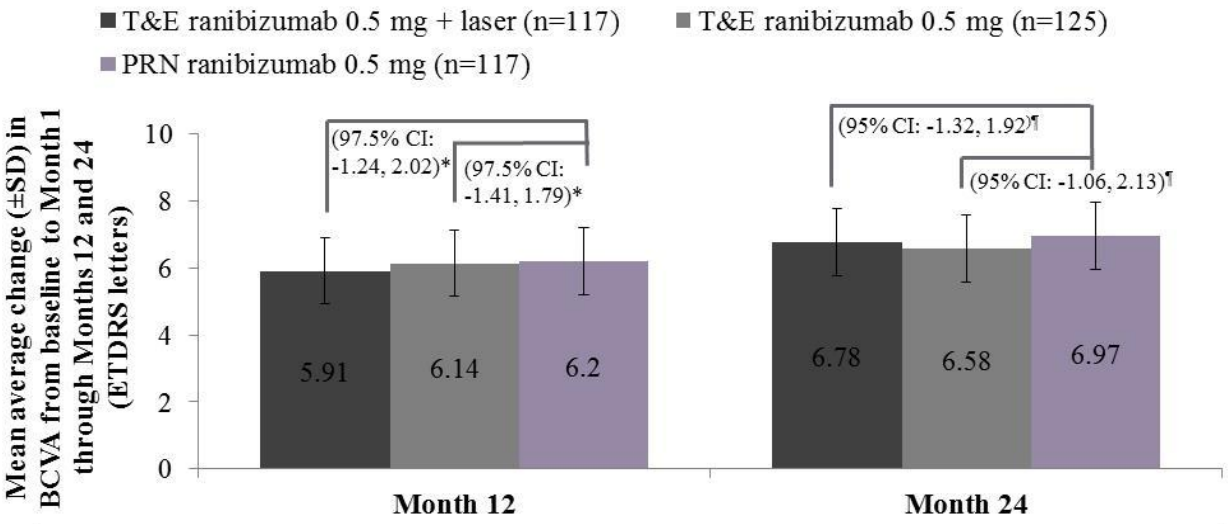
Analyses patient sets

Analysis sets	T&E ranibizumab 0.5 mg+laser n (%)	T&E ranibizumab 0.5 mg n (%)	PRN ranibizumab 0.5 mg n (%)	Total n (%)
Randomised set	121 (100)	128 (100)	123 (100)	372 (100)
Full analysis set	117 (96.7)	125 (97.7)	117 (95.1)	359 (96.5)
Safety set	126	126	118	370

Percentages are based on the total number of patients in the randomised set in the specific treatment group.
Safety set is based on actual treatment group; other populations are based on the randomised treatment group.
Number of patients in the safety set was lower than in the randomised set due to two patients who did not receive any study medication. Both patients were randomised but discontinued before any study drug was administered. There were four patients randomised to the PRN group and three patients randomised to T&E group who received laser treatment and were analysed in the safety set as part of the T&E+laser group. Also, two patients randomised to the T&E+laser group did not receive laser treatment and therefore were analysed in the safety set as part of the T&E group.
The randomised set comprised all randomised patients, i.e. those given a randomisation number.
The full analysis set consisted of all randomised patients who received at least one application of study treatment (ranibizumab or laser), and had at least one postbaseline efficacy assessment in the study eye.
The safety set consisted of all patients who received at least one administration of study treatment in the study eye and had at least one postbaseline safety assessment.
PRN, pro re nata; T&E, treat-and-extend

Note: The analyses presented in RETAIN were all performed with the FAS at Month 24. The two FAS analysed for Month 12 at the two time points (Months 12 and 24) were different due to the need to exclude 10 patients from the Month 24 analysis at a single site due to Good Clinical Practice deviations. The impact of this difference on the efficacy outcomes was negligible across groups (BCVA difference 0.03–0.1 letters, CSFT ~2%; range: 0.33–2.32). The safety data from these 10 patients were included in the analysis. The inclusion of patients in the safety set was determined by the actual treatment received, rather than the treatment group the patient was randomised to.

Supplementary Figure S3: The mean average change in best-corrected visual acuity (BCVA) from baseline to Month 1 through Months 12 (primary endpoint) and 24 (FAS–MV/LOCF)



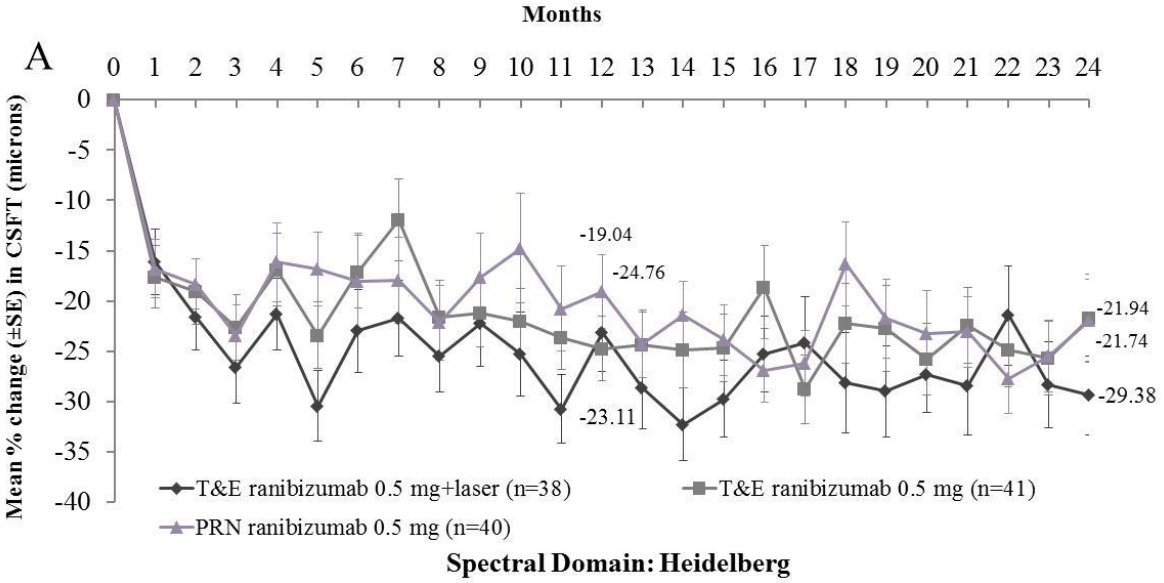
Non-inferiority of each of the T&E ranibizumab groups to the PRN ranibizumab group was established applying the CMH test with both nominal p-values <0.0001 which is less than <0.0125 as required for statistical significance at the multiple one-sided 2.5% significance level

¶Upper limits of the 97.5% CIs for the differences were <4 letters for both comparisons; subsequent assessment did not confirm the superiority of both T&E regimens over the PRN regimen. Assessments of superiority of the T&E ranibizumab groups over PRN ranibizumab group using nominal one-sided p values for untransformed CMH tests showed that the comparisons of T&E ranibizumab+laser vs PRN ranibizumab (p=0.7064) and T&E ranibizumab vs PRN ranibizumab (p=0.6052), respectively, were statistically non-significant exceeding the critical level of 0.0125 for both comparisons

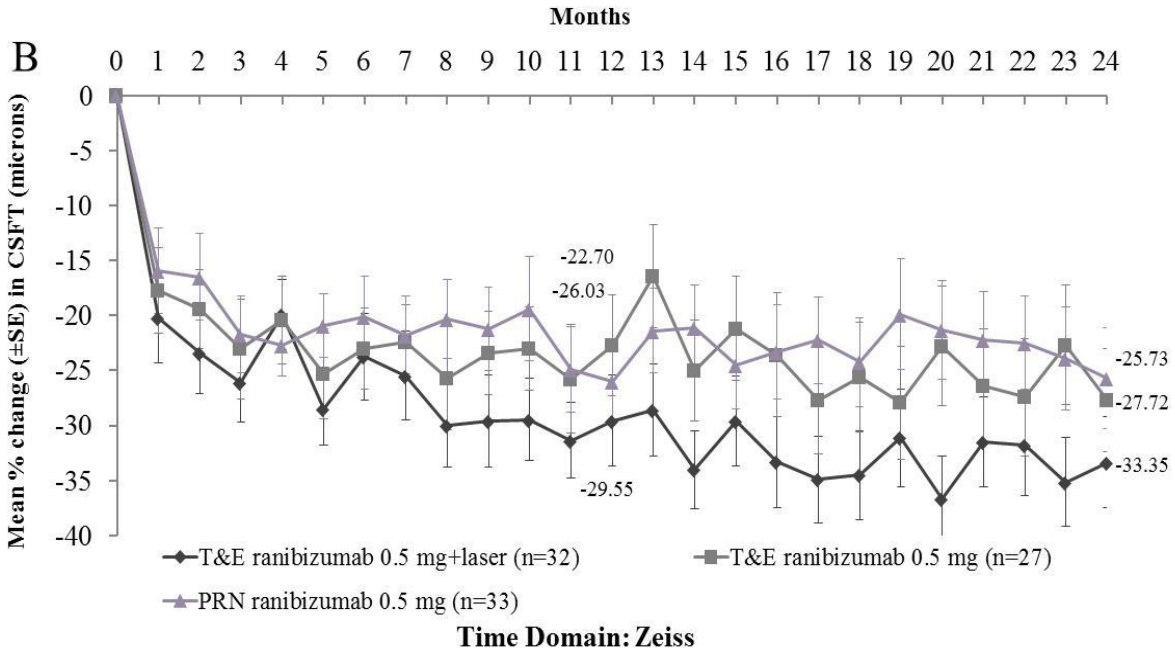
*ANOVA untransformed comparison of the LS mean changes; Full analysis set (MV/LOCF): consisted of all randomized patients who received at least one application of study treatment (ranibizumab or laser), and had at least one post baseline efficacy assessment in the study eye.); Stratified analysis includes baseline VA (≤60 letters, >60 letters and ≤73 letters, >73 letters) as factor

BCVA, best-corrected visual acuity; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ETDRS, early treatment diabetic retinopathy study; FAS, full analysis set; MV/LOCF, mean value imputation/last observation carried forward; PRN, pro re nata; SD, standard deviation; T&E, treat-and-extend; VA, visual acuity

Supplementary Figure S4: The mean percentage change in central subfield thickness (CSFT) from baseline by Optical Coherence Tomography (OCT) machine type—(A) Heidelberg and (B) Zeiss (FAS–MV/LOCF)



Full analysis set consisted of all randomized patients who received at least one application of study treatment (ranibizumab or laser), and had at least one post baseline efficacy assessment in the study eye)
CSFT, central subfield thickness; FAS, full analysis set; MV/LOCF, mean value imputation/last observation carried forward; OCT, optical coherence tomography; PRN, pro re nata; SE, standard error; T&E, treat-and-extend



Full analysis set consisted of all randomized patients who received at least one application of study treatment (ranibizumab or laser), and had at least one post baseline efficacy assessment in the study eye)
CSFT, central subfield thickness; FAS, full analysis set; MV/LOCF, mean value imputation/last observation carried forward; OCT, optical coherence tomography; PRN, pro re nata; SE, standard error; T&E, treat-and-extend