Sponsor

Novartis

Generic Drug Name

Ranibizumab

Therapeutic Area of Trial

Visual impairment due to diabetic macular edema

Approved Indication

- Approved in > 100 countries for neovascular (wet) age-related macular degeneration (AMD)
- Approved in > 80 countries for visual impairment due to diabetic macular edema (DME)
- Approved in > 80 countries for visual impairment due to macular edema secondary to retinal vein occlusion (branch and central RVO)

Study Number

CRFB002D2301 and CRFB002D2301E1

Title

An open-label, multi-center, 24-month extension study to evaluate the safety of ranibizumab as symptomatic treatment for visual impairment due to diabetic macular edema in patients who have completed the RESTORE trial

Phase of Development

IIIb

Study Start/End Dates

Core study
Study start date: 13 May 2008 (First patient first visit)
Study end date: 27 Jan 2010 (Last patient last visit)

Extension study
23-Jun-2009 (First patient first visit)
19-Jan-2012 (Last patient last visit)

Study Design/Methodology

Core study
This was a randomized, double-masked, multicenter, active control study of ranibizumab. Consenting patients participated in a screening period, lasting 3 to 14 days, to evaluate the patient eligibility. After eligibility confirmation at baseline, patients were randomized in a 1:1:1 ratio to one of the three treatment arms, i.e. to ranibizumab (0.5 mg), intravitreal in-

jections (plus sham laser), adjunctive administration of ranibizumab (0.5 mg) intravitreal injections with active laser, or laser treatment (plus sham injections) for 12 months. Only one eye was selected and treated as the study eye.

Extension study
This was a 24-month, open-label, multi-center extension study to RESTORE (RFB002D2301) in patients, who have completed 12 months of study assessments and were still eligible for treatment with ranibizumab. All patients, who entered the extension study, were entitled to receive ranibizumab (0.5 mg) intravitreal injections according to stability criteria specified in the protocol, regardless of their previous treatment in the core study. The results are reported according to the treatment assignments in the core study. The eye evaluated was the same eye that was selected as study eye in the core study.

Centres

Core Study:
73 centers in 14 countries: Australia (4), Belgium (2), Canada (7), France (4), Germany (15), Greece (5), Hungary (5), Italy (6), Netherlands (3), New Zealand (1), Spain (6), Switzerland (6), Turkey (6), United Kingdom (3).
Extension Study:
Australia (4), Belgium (2), Canada (5), France (3), Germany (11), Hungary (5), Italy (5), Netherlands (3), New Zealand (1), Spain (6), Switzerland (6), Turkey (5), United Kingdom (1)

Publication

In preparation

Objectives

Core study

Primary objective(s)

- The primary objective of this study was to demonstrate superiority of ranibizumab 0.5 mg as mono-therapy or as adjunctive to laser treatment in the mean change from base-line in best corrected visual acuity (BCVA) over a 12-month treatment period.

Secondary objective(s)

- to evaluate whether ranibizumab (0.5 mg) as mono-therapy or adjunctive to laser was superior to laser treatment
  - in the number of patients with visual acuity above 73 letters and
  - in the number of patients with improvement in BCVA
- to evaluate the time course of BCVA changes on ranibizumab (0.5 mg) mono-therapy and adjunctive therapy relative to laser treatment
- to evaluate the effects of ranibizumab (0.5 mg) mono-therapy and adjunctive therapy on central retinal thickness and other anatomical changes relative to laser treatment
- to evaluate the effects of ranibizumab (0.5 mg) mono-therapy and adjunctive therapy on patient-reported outcomes (PROs) relative to laser treatment
- to evaluate the safety of intravitreal injections of ranibizumab (0.5 mg) as mono-therapy and adjunctive therapy in patients with DME overall and relative to laser treatment

Extension study

Primary objective(s)

- The primary objective was to evaluate ocular and non-ocular adverse events during the 24-months study period in patients treated with ranibizumab (0.5 mg)

Secondary objective(s)

- To describe the ocular and non-ocular adverse events over a cumulative 36-month peri-od – including the core and the extension study – in patients treated with ranibizumab (0.5 mg)
- To evaluate the change of the BCVA over the 24-month study period in patients treated with ranibizumab (0.5 mg)
- To evaluate the change of the BCVA over the 36-month study period – including the core and the extension study in patients treated with ranibizumab (0.5 mg)

Test Product (s), Dose(s), and Mode(s) of Administration

Core and Extension studies

0.5 mg ranibizumab (labeled as RFB002 0.5mg/0.05ml), intravitreal injection. Laser photo-coagulation was allowed at any time during the extension study.

Reference Product(s), Dose(s), and Mode(s) of Administration

Core Study:

- sham injection (labeled as RFB002 0mg/0ml)
- laser photocoagulation
- sham laser

Extension Study:

This was an open-label, uncontrolled study.

Criteria for Evaluation

Core and Extension Studies:

Primary variables

- The assessments performed for activity of ranibizumab on retinal structure and visual function were best-corrected visual acuity (BCVA) with ETDRS-like chart at 4 meters, optical coherence tomography, color fundus photography, and fluorescein angiography
- Health-related quality of life was assessed using the National Eye Institute Visual Function Questionnaire – 25 (NEI-VFQ-25), Time Trade Off (TTO), and EuroQoL (EQ-5D) questionnaires

Safety and tolerability

- Safety assessments consisted of collecting all AEs, SAEs, ophthalmic examinations, intraocular pressure, vital signs, and laboratory parameters

Statistical Methods

The statistical analysis was performed by Novartis personnel according to the Statistical Analysis Plan.

Data were summarized with respect to demographic and baseline disease characteristics, efficacy, drug exposure, and safety observations and assessments.

Descriptive statistics included n (number of observations), mean, standard deviation (standard error, as needed), median and ranges for continuous variables, and frequencies and percentages for categorical variables, and were provided by treatment group defined according to actual treatment received in the core study unless otherwise specified. In the core study, estimates of treatment group differences, confidence intervals and p-values were presented where appropriate, although in the extension study, there was no intention to compare treatment groups by means of statistical hypothesis testing.

Unless otherwise specified, the following conventions were utilized throughout the analysis:

- confidence intervals were 2-sided and at a 95% level,
- hypothesis tests were evaluated at a two-sided 0.05 / one-sided 0.025 level of significance.

The last assessment collected just prior to start of treatment was considered to be the baseline value in the core study. All assessments performed after the first study treatment were considered to be post-baseline.

Two baseline values were used in the extension analysis – a baseline value at the start of the core study (core baseline) and at the start of the extension study (extension baseline).

The core baseline was considered to be the last assessment collected just prior to start of treatment in the core study (Day 1). Post-baseline always referred to assessments performed post start of treatment, i.e. after the first study treatment.

The extension baseline was considered to be the last assessment collected on the Month 12 (core) assessment. Post-baseline always referred to assessments performed post Month 12 (Visit 14).

No interim analysis was performed for the core study. In the extension study, an interim analysis was performed when all patients enrolled into the extension had either completed Visit 26 (the Month 12 Visit of the extension) or terminated the study at / prior this visit.

Study Population: Inclusion/Exclusion Criteria and Demographics

Core Study

Inclusion criteria:

- Male or female patients >18 years of age who have signed an informed consent
- Patients with Type 1 or Type 2 diabetes mellitus with HbA1c not more than 10.0% at screening (Visit 1). Patients had to be on diet, exercise, and/or pharmacological treatment for diabetes
- Patients with visual impairment due to focal or diffuse DME in at least one eye that was eligible for laser treatment. The study eye had to fulfill the following criteria at Visit 1:
  - BCVA score between 78 and 39 letters, inclusively, using ETDRS-like visual acuity testing charts at a testing distance of 4 meters (approximate Snellen equivalent of 20/32 to 20/160)
- Decrease in vision due to DME and not due to other causes.
- Medication for the management of diabetes must have been stable within 3 months prior to randomization and expected to remain stable during the course of the study

Exclusion criteria:

Ocular concomitant conditions/ diseases

- Concomitant conditions in the study eye which could, in the opinion of the investigator, prevent the improvement of visual acuity on study treatment
- Active intraocular inflammation (grade trace or above) in either eye
- Any active infection (e.g. conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) in either eye
- History of uveitis in either eye

- Structural damage within 0.5 disc diameter of the center of the macula in the study eye likely to preclude improvement in visual acuity following the resolution of macular edema
- Ocular disorders in the study eye that may confound interpretation of study results, compromise visual acuity or require medical or surgical intervention during the 12-month study period
- Uncontrolled glaucoma in either eye (e.g. intraocular pressure (IOP) > 24 mmHg on medications, or according to investigator's judgment)
- Neovascularization of the iris in either eye
- Evidence of vitreomacular traction in either eye
- Active proliferative diabetic retinopathy in the study eye
- Patients who were monocular or had a BCVA score in the non-study eye (fellow eye) ≤ 24 letters (approximate Snellen equivalent of 20/320) at Visit 1

Ocular treatments

- Panretinal laser photocoagulation in the study eye within 6 months prior to the study
- Focal/grid laser photocoagulation in the study eye within 3 months prior to study entry
- Treatment with anti-angiogenic drugs (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, etc.) in study eye within 3 months prior to randomization
- Any intraocular surgery in the study eye within 3 months prior to randomization
- History of vitrectomy in study eye
- History of intravitreal corticosteroid treatment in phakic study eye
- Intravitreal corticosteroids in post-cataract surgical study eyes (aphakic or pseudophakic without damaged posterior capsule) within 3 months prior to randomization
- Ocular conditions in the study eye that require chronic concomitant therapy with topical ocular or systemically administered corticosteroids

Systemic conditions or treatments

- History of stroke
- Renal failure requiring dialysis or renal transplant OR renal insufficiency with creatinine levels > 2.0 mg/dl
- Untreated diabetes mellitus
- Blood pressure systolic > 160 mmHg or diastolic > 100 mmHg
- Untreated hypertension or change in antihypertensive treatment within 3 months preceding baseline
- Current use of or likely need for systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Chloroquine/ hydroxychloroquine (Plaquenil), Tamoxifen, Phenothiazines and Ethambutol
- Known hypersensitivity to ranibizumab or any component of the ranibizumab formulation or to fluorescein
- Any type of advanced, severe or unstable disease or its treatment, that could interfere

with primary and/or secondary outcome evaluations including any medical condition that could be expected to progress, recur, or change to such an extent that it may bias the assessment of the clinical status of the patient to a significant degree or put the patient at special risk

Compliance/Administrative

- Previous participation in any clinical studies of investigational drugs within 1 month (or a period corresponding to 5 half-lives of the investigational drug, whichever is longer) prior to randomization
- Women of child-bearing potential, UNLESS they are using two birth control methods.
- Pregnant or nursing (lactating) women
- Inability to comply with study or follow-up procedures

Extension Study

Main Inclusion Criteria:

- Completion of the RESTORE trial assessments through Month 12
- Written informed consent before any study related activity of the extension protocol was performed.

Main Exclusion Criteria:

- Use of investigational drugs, other than those provided in RESTORE (RFB002D2301) study at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer;
- Current use or likely need of systemic medications known to be toxic to the lens, retina or optic nerve, including Deferoxamine, Choroquine/hydroxychloroquine (Plaquenil), Tamoxifen, Phenothiazines, and Ethambutol;
- History of hypersensitivity to ranibizumab or any component of the ranibizumab formulation;
- Uncontrolled glaucoma in either eye (intraocular pressure (IOP) > 24 mmHg on medication or according to investigator's judgment);
- Evidence of vitreomacular traction in either eye at Month 12;
- Active proliferative diabetic retinopathy in the study eye at Month 12.

Number of Subjects

Core Study

Patient disposition (Randomized set)

Disposition/Reason	Ranibizumab 0.5mg N=116 n (%)	Ranibizumab 0.5mg + Laser N=118 n (%)	Laser N=111 n (%)
Completed	102 (87.9)	103 (87.3)	98 (88.3)
Discontinued	14 (12.1)	15 (12.7)	13 (11.7)
Adverse Event(s)	5 (4.3)	3 (2.5)	3 (2.7)
Abnormal laboratory value(s)	1 (0.9)	0 (0.0)	0 (0.0)
Unsatisfactory therapeutic effect	1 (0.9)	1 (0.8)	1 (0.9)
Subject withdrew consent	4 (3.4)	7 (5.9)	7 (6.3)
Lost to follow-up	0 (0.0)	1 (0.8)	0 (0.0)
Death	2 (1.7)	2 (1.7)	2 (1.8)
Protocol deviation	1 (0.9)	1 (0.8)	0 (0.0)

Percentages are based on the total number of patients in the Randomized set.

Extension Study

Patient disposition in extension (Safety set)

Disposition Reason	Ranibizumab 0.5 mg N = 83 n (%)	Ranibizumab 0.5 mg + Laser N = 83 n (%)	Pooled Ranibizumab N = 166 n (%)	Laser with Ranibizumab in extension N = 59 n (%)	Laser without Ranibizumab in extension N =15 n (%)	Laser N = 74 n (%)	Total N = 240 n (%)
Completed extension	73(88.0)	72(86.7)	145(87.3)	49(83.1)	14(93.3)	63(85.1)	208(86.7)
Discontinued in extension	10(12.0)	11(13.3)	21(12.7)	10(16.9)	1(6.7)	11(14.9)	32(13.3)
Adverse Event(s)	2(2.4)	2(2.4)	4(2.4)	2(3.4)	0(0.0)	2(2.7)	6(2.5)
Subject withdrew consent	3(3.6)	4(4.8)	7(4.2)	3(5.1)	1(6.7)	4(5.4)	11(4.6)
Lost to follow-up	2(2.4)	1(1.2)	3(1.8)	2(3.4)	0(0.0)	2(2.7)	5(2.1)
Administrative problems	1(1.2)	1(1.2)	2(1.2)	0(0.0)	0(0.0)	0(0.0)	2(0.8)
Death	2(2.4)	3(3.6)	5(3.0)	3(5.1)	0(0.0)	3(4.1)	8(3.3)

Percentages are based on the total number of patients in the Safety set.

Demographic and Background Characteristics

Core Study

Demographic summary by treatment group (Randomized set)

Demographic Variable	Ranibizumab 0.5mg N=116	Ranibizumab 0.5mg + Laser N=118	Laser N=111
Age (Year)			
N	116	118	111
Mean	62.9	64.0	63.5
SD	9.29	8.15	8.81
Median	62.5	65.0	63.0
Min	38	42	37
Max	83	87	84
Age group (years) - n (%)			
<55	24 (20.7%)	14 (11.9%)	13 (11.7%)
55 - <65	41 (35.3%)	42 (35.6%)	53 (47.7%)
65 - <75	40 (34.5%)	53 (44.9%)	31 (27.9%)
≥75	11 (9.5%)	9 (7.6%)	14 (12.6%)
Sex - n (%)			
Male	73 (62.9%)	70 (59.3%)	58 (52.3%)
Female	43 (37.1%)	48 (40.7%)	53 (47.7%)
Predominant Race – n (%)			
Caucasian	109 (94.0%)	111 (94.1%)	106 (95.5%)
Black	1 (0.9%)	1 (0.8%)	0 (0.0%)
Asian	2 (1 7%)	0 (0.0%)	1 (0.9%)
Pacific islander	1 (0.9%)	0 (0.0%)	1 (0.9%)
Other	2 (1.7%)	6 (5.1%)	3 (2.7%)
Missing	1 (0.9%)	0 (0.0%)	0 (0.0%)

Percentages are based on the total number of patients in the Randomized set.

Extension study

Demographics at core baseline (Safety set)

Demo-graphic Variable	Ran 0.5 mg N = 83	Ran 0.5 mg + Laser N = 83	Pooled Ran N = 166	Laser with Ran in exten-sion N = 59	Laser without Ran in extension N = 15	Laser N = 74	Total N = 240
Age (years)							
n	83	83	166	59	15	74	240
Mean	61.7	63.8	62.8	63.1	59.6	62.4	62.6
SD	9.17	8.32	8.79	8.27	10.85	8.89	8.80
Median	61.0	65.0	63.0	63.0	61.0	62.0	63.0

Min	38	42	38	37	41	37	37
Max	83	87	87	81	80	81	87
Age group (years) - n (%)							
< 55	20(24.1%)	11(13.3%)	31(18.7%)	7(11.9%)	5(33.3%)	12(16.2%)	43(17.9%)
55 - < 65	31(37.3%)	30(36.1%)	61(36.7%)	29(49.2%)	5(33.3%)	34(45.9%)	95(39.6%)
55 - < 75	27(32.5%)	35(42.2%)	62(37.3%)	17(28.8%)	3(20.0%)	20(27.0%)	82(34.2%)
≥ 75	5(6.0%)	7(8.4%)	12(7.2%)	6(10.2%)	2(13.3%)	8(10.8%)	20(8.3%)
Sex- n (%)							
Male	52(62.7%)	50(60.2%)	102 (61.4%)	31(52.5%)	9(60.0%)	40(54.1%)	142 (59.2%)
Female	31(37.3%)	33(39.8%)	64(38.6%)	28(47.5%)	6(40.0%)	34(45.9%)	98(40.8%)
Predominant race – n (%)							
Caucasian	76(91.6%)	79(95.2%)	155 (93.4%)	58(98.3%)	14(93.3%)	72(97.3%)	227 (94.6%)
Black	1(1.2%)	0(0.0%)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)
Asian	2(2.4%)	0(0.0%)	2(1.2%)	0(0.0%)	1(6.7%)	1(1.4%)	3(1.3%)
Pacific Is-lander	1(1.2%)	0(0.0%)	1(0.6%)	1(1.7%)	0(0.0%)	1(1.4%)	2(0.8%)
Other	2(2.4%)	4(4.8%)	6(3.6%)	0(0.0%)	0(0.0%)	0(0.0%)	6(2.5%)
Missing	1(1.2%)	0(0.0%)	1(0.6%)	0(0.0%)	0(0.0%)	0(0.0%)	1(0.4%)

Percentages are based on the total number of patients in the Safety set.

Efficacy Result(s)

Core Study

Visual acuity of the study eye (letters): Mean average change from Month 1 to Month 12 compared to baseline (Full analysis set / LOCF)

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	115	118	110
	Mean (SD)	64.7 (10.07)	63.4 (9.99)	62.6 (11.01)
	Median	68.0	65.0	65.0
	Min - Max	38.0 - 81.0	38.0 - 79.0	36.0 - 78.0
Average Month 1 to Month 12	n	115	118	110
	Mean (SD)	70.8 (10.53)	69.2 (11.44)	63.4 (12.26)
	Median	73.7	71.5	66.2
	Min - Max	38.6 - 88.7	28.5 - 93.3	32.0 - 84.2
Average change from baseline	n	115	118	110
	Mean (SD)	6.1 (6.43)	5.9 (7.92)	0.8 (8.56)
	Median	6.1	6.0	1.3
	Min - Max	-10.9 - 25.2	-26.7 - 27.6	-37.8 - 26.8

	95% CI for mean (1)	(4.9, 7.3)	(4.4, 7.3)	(-0.8, 2.4)
Comparison vs. Laser	Difference in LS means (2)	5.4	4.9	
	95% CI for difference (2)	(3.5, 7.4)	(2.8, 7.0)	
	p-value (3)	<.0001	<.0001	

- n is the number of patients with a value for both baseline and average Month 1 to Month 12.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- (1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- (2) Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score

Visual acuity of the study eye (letters): Mean change from baseline at Month 12 (Full analysis set / LOCF)

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	115	118	110
	Mean (SD)	64.7 (10.07)	63.4 (9.99)	62.6 (11.01)
	Median	68.0	65.0	65.0
	Min - Max	38.0 - 81.0	38.0 - 79.0	36.0 - 78.0
Value at Month 12	n	115	118	110
	Mean (SD)	71.5 (11.79)	69.7 (14.23)	63.4 (14.00)
	Median	75.0	72.0	66.5
	Min - Max	38.0 - 93.0	6.0 - 93.0	14.0 - 85.0
Change from baseline	n	115	118	110
	Mean (SD)	6.8 (8.25)	6.4 (11.77)	0.9 (11.44)
	Median	7.0	7.0	1.5
	Min - Max	-18.0 - 26.0	-60.0 - 31.0	-60.0 - 30.0
	95% CI for mean (1)	(5.3, 8.3)	(4.2, 8.5)	(-1.3, 3.0)
Comparison vs. Laser	Difference in LS means (2)	6.2	5.4	
	95% CI for difference (2)	(3.6, 8.7)	(2.4, 8.4)	
	p-value (3)	<.0001	0.0004	

- n is the number of patients with a value at both baseline and the Month 12 visit.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- (1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- (2) Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

Extension Study

Visual acuity of study eye (letters): Mean change from extension baseline at Month 36 – LOCF (Safety set)

Parameter	Statistic	Ranibizumab 0.5 mg N = 83	Ranibizumab 0.5mg + Laser N = 83	Ranibizumab Pooled N = 166	Laser N = 74
Extension baseline	n	83	80	163	74
	Mean (SD)	74.1 (9.46)	71.3 (10.50)	72.7 (10.05)	65.2 (11.86)
	Median	76.0	72.0	73.0	68.0
	Min - Max	40 - 93	39 - 90	39 - 93	34 - 85
Month 36	n	83	80	163	74
	Mean (SD)	74.1 (12.08)	70.8 (11.74)	72.5 (11.99)	68.9 (11.85)
	Median	78.0	72.0	75.0	70.5
	Min - Max	13 - 94	36 - 90	13 - 94	35 - 95
Change from	n	83	80	163	74
extension baseline	Mean (SD)	0.1 (9.10)	-0.5 (9.19)	-0.2 (9.12)	3.7 (6.88)
	Median	0.0	0.0	0.0	3.0
	Min - Max	-45 - 28	-39 - 22	-45 - 28	-11 - 29

n is the number of patients with a value at both extension baseline and the Month 36 visit.

Visual acuity of the study eye (letters): Mean average change from core baseline from Month 1 to Month 36 – subgroup analysis – LOCF (Safety set)

Subgroup by	Ranibizumab 0.5 mg			Ranibizumab 0.5 mg + laser			Ranibizumab pooled			Laser		
DME type	Focal n = 47		Diffuse n = 32	Focal n = 47		Diffuse n = 34	Focal n = 94		Diffuse n = 66	Focal n = 34		Diffuse n = 36
	8.6		7.3	6.5		6.5	7.6		6.9	4.7		2.6
Baseline visual acuity (letters)	≤60 n = 23	61-73 n= 43	>73 n = 17	≤60 n = 28	61-73 n = 40	>73 n = 15	≤60 n = 51	61-73 n = 83	>73 n = 32	≤60 n = 27	61-73 n = 35	>73 n = 12
	10.7	8.0	3.6	8.4	7.0	2.2	9.4	7.5	3.0	6.5	3.0	0.8
Diabetes mellitus type	Type I n = 9		Type II n = 74	Type I n =12		Type II n =70	Type I n =21		Type II n =144	Type I n = 10		Type II n = 63
	6.7		8.0	7.6		6.4	7.2		7.2	5.8		3.7
Prior focal and/or grid laser treatment	Yes n = 46		No n = 37	Yes n = 40		No n = 43	Yes n = 86		No n = 80	Yes n = 33		No n = 41
	8.1		7.5	6.6		6.6	7.4		7.0	3.6		4.1
Baseline CRST (µm)	< 300 n = 12	300-400 n = 24	> 400 n = 47	< 300 n = 14	300-400 n = 25	> 400 n = 42	< 300 n = 26	300-400 n = 49	> 400 n = 89	< 300 n = 13	300-400 n = 26	> 400 n = 34
	6.2	6.4	9.0	4.8	6.6	7.0	5.5	6.5	8.1	5.5	5.3	2.2
Duration of DME at baseline (months)	≤3 n = 20	>3-≤12 n = 21	>12 n = 42	≤3 n = 21	>3-≤12 n = 20	>12 n = 42	≤3 n = 41	>3-≤12 n = 41	>12 n = 84	≤3 n = 16	>3-≤12 n = 17	>12 n = 41
	10.4	7.8	6.7	9.2	5.2	5.9	9.8	6.6	6.3	4.0	3.4	4.1

Baseline visual acuity and central retinal subfield thickness	< 300	≥ 300	< 300	≥ 300	< 300	≥ 300	< 300	≥ 300
≤ 73 letters	8.8 (n = 7)	8.9 (n = 59)	7.5 (n=11)	7.5 (n = 55)	8.0 (n = 18)	8.2 (n = 114)	6.6 (n = 10)	4.1 (n = 51)
> 73 letters	2.6 (n = 5)	4.1 (n = 12)	-5.1 (n =3)	4.0 (n = 12)	-0.3 (n = 8)	4.1 (n = 24)	1.9 (n = 3)	0.4 (n = 9)
Baseline ischemia	Yes n = 26	No n = 26	Yes n = 22	No n = 29	Yes n = 48	No n = 55	Yes n = 13	No n = 35
	7.4	10.0	5.0	7.5	6.3	8.7	2.7	3.7

Baseline triglycerides (mmol/L)	<1.5 n = 33	≥1.5-<3 n = 43	≥3 n = 7	<1.5 n = 35	≥1.5-<3 n = 37	≥3 n = 11	<1.5 n = 68	≥1.5-<3 n = 80	≥3 n = 18	<1.5 n = 33	≥1.5-<3 n = 33	≥3 n = 8
	7.5	7.8	10.0	8.0	5.7	4.7	7.8	6.9	6.8	2.6	4.7	6.1
Baseline cholesterol (mmol/L)	<4 n = 14	≥4-<6 n = 55	≥6 n = 14	<4 n = 21	≥4-<6 n = 49	≥6 n = 13	<4 n = 35	≥4-<6 n = 104	≥6 n = 27	<4 n = 9	≥4-<6 n = 49	≥6 n = 16
	6.6	7.4	10.9	5.7	7.0	6.4	6.1	7.2	8.7	1.8	4.8	2.2

Core Study

Visual acuity of the study eye (letters): Mean average change from baseline by baseline characteristics – subgroup analysis (FAS / LOCF)

Subgroup by	Ranibizumab 0.5 mg			Ranibizumab 0.5 mg + Laser			Laser		
DME type	Focal (N=63)	Diffuse (N=45)		Focal (N=68)	Diffuse (N=46)		Focal (N=52)	Diffuse (N=52)	
	6.2	6.4		6.2	4.8		1.1	-0.2	
Baseline Visual Acuity Letters	≤60 (N=38)	61 – 73 (N=55)	> 73 (N=22)	≤60 (N=44)	61 – 73 (N=55)	> 73 (N=19)	≤60 (N=40)	61 – 73 (N=53)	> 73 (N=17)
	8.2	6.2	2.2	7.4	6.2	1.4	3.3	0.1	-2.9
Diabetes Mellitus type	Type I (N=13)	Type II (N=102)		Type I (N=15)	Type II (N=102)		Type I (N=13)	Type II (N=96)	
	6.5	6.0		7.1	5.7		2.3	0.6	
Prior focal and/or grid laser treatment	Yes (N=60)	No (N=55)		Yes (N=55)	No (N=63)		Yes (N=47)	No (N=63)	
	6.4	5.7		4.7	6.9		0.7	0.9	
Baseline CRT (µm)	<300 (N=19)	300-400 (N=32)	>400 (N=62)	<300 (N=20)	300-400 (N=37)	>400 (N=59)	<300 (N=21)	300-400 (N=34)	>400 (N=53)

	3.0	5.7	7.3	3.0	6.6	6.1	1.7	3.0	-0.9
Gender	Male (N=72)		Female (N=43)	Male (N=70)		Female (N=48)	Male (N=57)		Female (N=53)
	6.3		5.8	5.5		6.4	1.2		0.3
Age (years)	<65 (N=65)		≥65 (N=50)	<65 (N=56)		≥65 (N=62)	<65 (N=66)		≥65 (N=44)
	7.4		4.4	6.5		5.2	0.0		2.0
Duration of Diabetes at baseline (years)	<10 (N=34)		≥10 (N=80)	<10 (N=38)		≥10 (N=85)	<10 (N=40)		≥10 (N=70)
	7.6		5.5	7.2		5.2	0.9		0.7
Duration of DME at baseline (Months)	≤3 (N=27)	>3 - ≤12 (N=30)	>12 (N=57)	≤3 (N=33)	>3 - ≤12 (N=26)	>12 (N=59)	≤3 (N=29)	>3 - ≤12 (N=24)	>12 (N=57)
	7.5	7.4	4.8	8.3	4.5	5.0	-1.1	1.2	1.6
DME type and baseline visual acuity	Focal		Diffuse	Focal		Diffuse	Focal		Diffuse
≤60	8.0 (N=18)		8.4 (N=20)	7.9 (N=22)		6.9 (N=22)	3.8 (N=15)		3.0 (N=25)
61 - 73	6.5 (N=32)		5.7 (N=23)	6.2 (N=34)		6.2 (N=21)	1.2 (N=24)		-0.8 (N=29)
> 73	2.7 (N=13)		1.4 (N=9)	3.3 (N=12)		-1.9 (N=7)	-2.4 (N=13)		-4.7 (N=4)
Baseline ETDRS (diabetic retinopathy severity) score	10-35 (N=31)	43 or 47 (N=40)	53-85 (N=11)	10-35 (N=31)	43 or 47 (N=38)	53-85 (N=10)	10-35 (N=34)	43 or 47 (N=40)	53-85 (N=4)
	5.9	7.3	4.8	5.1	6.6	9.6	2.1	2.0	-0.2
Baseline visual acuity and central retinal subfield thickness (um)	< 300		≥ 300	< 300		≥ 300	< 300		≥ 300
≤73 letters	4.9 (N=11)		7.4 (N=80)	3.6 (N=16)		7.2 (N=81)	2.2 (N=16)		1.4 (N=75)
> 73 letters	0.3 (N=8)		3.3 (N=14)	0.7 (N=4)		1.6 (N=15)	0.3 (N=5)		-4.3 (N=12)
Baseline HbA1C (%)	<8 (N=83)		≥8 (N=30)	<8 (N=85)		≥8 (N=32)	<8 (N=79)		≥8 (N=28)
	6.5		5.2	6.6		3.8	0.6		1.1
Baseline SBP/DBP (mmHg)	≥140/90 (N=66)		<140/90 (N=47)	≥140/90 (N=71)		<140/90 (N=47)	≥140/90 (N=70)		<140/90 (N=40)
	5.3		7.1	5.8		5.9	0.8		0.8
Baseline presence of retinal ischemia	Yes (N=34)		No (N=35)	Yes (N=34)		No(N=41)	Yes(N=29)		No (N=42)
	6.3		7.2	6.3		5.9	0.9		1.6

Baseline Triglycer-ides(mmol/L)	< 1.5 (N=46)	1.5 - < 3 (N=59)	≥ 3 (N=10)	< 1.5 (N=47)	1.5 - < 3 (N=54)	≥ 3 (N=17)	< 1.5 (N=52)	1.5 - < 3 (N=47)	≥ 3 (N=9)
	6.1	5.9	7.3	6.1	6.5	3.2	0.9	0.6	0.9
Baseline Total cholester-ol (mmol/L)	< 4 (N=19)	4 - < 6 (N=75)	≥ 6 (N=21)	< 4 (N=28)	4 - < 6 (N=69)	≥ 6 (N=21)	< 4 (N=18)	4 - < 6 (N=70)	≥ 6 (N=20)
	6.3	6.0	6.2	4.5	7.0	4.0	0.7	1.2	-0.4

Extension Study

Visual acuity of the study eye (letters): Mean average change from core baseline from Month 1 to Month 36 – subgroup analysis – LOCF (Safety set)

Subgroup by	Ranibizumab 0.5 mg			Ranibizumab 0.5 mg + laser			Ranibizumab pooled			Laser		
DME type	Focal n = 47		Diffuse n = 32	Focal n = 47		Diffuse n = 34	Focal n = 94		Diffuse n = 66	Focal n = 34		Diffuse n = 36
	8.6		7.3	6.5		6.5	7.6		6.9	4.7		2.6
Baseline visual acuity (letters)	≤60 n = 23	61-73 n= 43	>73 n = 17	≤60 n = 28	61-73 n = 40	>73 n = 15	≤60 n = 51	61-73 n = 83	>73 n = 32	≤60 n = 27	61-73 n = 35	>73 n = 12
	10.7	8.0	3.6	8.4	7.0	2.2	9.4	7.5	3.0	6.5	3.0	0.8
Diabetes melli-tus type	Type I n = 9		Type II n = 74	Type I n =12		Type II n =70	Type I n =21		Type II n =144	Type I n = 10		Type II n = 63
	6.7		8.0	7.6		6.4	7.2		7.2	5.8		3.7
Prior focal and/or grid laser treatment	Yes n = 46		No n = 37	Yes n = 40		No n = 43	Yes n = 86		No n = 80	Yes n = 33		No n = 41
	8.1		7.5	6.6		6.6	7.4		7.0	3.6		4.1
Baseline CRST (µm)	< 300 n = 12	300-400 n = 24	> 400 n = 47	< 300 n = 14	300-400 n = 25	> 400 n = 42	< 300 n = 26	300-400 n = 49	> 400 n = 89	< 300 n = 13	300-400 n = 26	> 400 n = 34
	6.2	6.4	9.0	4.8	6.6	7.0	5.5	6.5	8.1	5.5	5.3	2.2
Duration of DME at base-line (months)	≤3 n = 20	>3-≤12 n = 21	>12 n = 42	≤3 n = 21	>3-≤12 n = 20	>12 n = 42	≤3 n = 41	>3-≤12 n = 41	>12 n = 84	≤3 n = 16	>3-≤12 n = 17	>12 n = 41
	10.4	7.8	6.7	9.2	5.2	5.9	9.8	6.6	6.3	4.0	3.4	4.1
Baseline visual acuity and cen-tral retinal sub-field thickness	< 300		≥ 300	< 300		≥ 300	< 300		≥ 300	< 300		≥ 300
≤ 73 letters	8.8 (n = 7)		8.9 (n = 59)	7.5 (n=11)		7.5 (n = 55)	8.0 (n = 18)		8.2 (n = 114)	6.6 (n = 10)		4.1 (n = 51)
> 73 letters	2.6 (n = 5)		4.1 (n = 12)	-5.1 (n =3)		4.0 (n = 12)	-0.3 (n = 8)		4.1 (n = 24)	1.9 (n = 3)		0.4 (n = 9)
Baseline ische-mia	Yes n = 26		No n = 26	Yes n = 22		No n = 29	Yes n = 48		No n = 55	Yes n = 13		No n = 35
	7.4		10.0	5.0		7.5	6.3		8.7	2.7		3.7

Baseline tri-glycerides (mmol/L)	<1.5 n = 33	≥1.5-<3 n = 43	≥3 n = 7	<1.5 n = 35	≥1.5-<3 n = 37	≥3 n = 11	<1.5 n = 68	≥1.5-<3 n = 80	≥3 n = 18	<1.5 n = 33	≥1.5-<3 n = 33	≥3 n = 8
	7.5	7.8	10.0	8.0	5.7	4.7	7.8	6.9	6.8	2.6	4.7	6.1
Baseline choles-terol (mmol/L)	<4 n = 14	≥4-<6 n = 55	≥6 n = 14	<4 n = 21	≥4-<6 n = 49	≥6 n = 13	<4 n = 35	≥4-<6 n = 104	≥6 n = 27	<4 n = 9	≥4-<6 n = 49	≥6 n = 16
	6.6	7.4	10.9	5.7	7.0	6.4	6.1	7.2	8.7	1.8	4.8	2.2

Core Study:

Visual acuity of the study eye (letters): Categorized change from baseline at Month 12 (FAS / LOCF)

Categorized change from baseline	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
N	115	118	110
Gain of ≥ 10 letters [1]	43 (37.4)	51 (43.2)	17 (15.5)
Loss of ≥ 10 letters	4 (3.5)	5 (4.2)	14 (12.7)
Gain of ≥ 15 letters [1]	26 (22.6)	27 (22.9)	9 (8.2)
Loss of ≥ 15 letters	1 (0.9)	4 (3.4)	9 (8.2)

- N is the number of patients with a value at both baseline and the Month 12 visit.
- [1] specified gain, or BCVA of 84 letters or more

Extension Study:

Visual acuity of the study eye (letters): Categorized change from extension baseline at Month 36 – LOCF (Safety set)

Categorized change from baseline	Ranibizumab 0.5 mg N = 83	Ranibizumab 0.5 mg + Laser N = 83	Ranibizumab Pooled N = 166	Laser N = 74
N	83	80	163	74
Gain of >= 1 letter	39 (47.0)	36 (45.0)	75 (46.0)	53 (71.6)
Gain of >= 10 letters [1]	16 (19.3)	14 (17.5)	30 (18.4)	15 (20.3)
Loss of >= 10 letters	9 (10.8)	11 (13.8)	20 (12.3)	2 (2.7)
Gain of >= 15 letters [1]	15 (18.1)	9 (11.3)	24 (14.7)	9 (12.2)
Loss of >= 15 letters	2 (2.4)	4 (5.0)	6 (3.7)	0 (0.0)

The row N is the number of patients with a value at both extension baseline and the specific post-baseline visit.
[1] Specified gain, or BCVA of 84 letters or more.

Core Study:

Central retinal subfield thickness of the study eye (µm): Mean change from baseline at Month 12 (FAS / LOCF)

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	113	116	108
	Mean (SD)	427.1 (118.42)	416.4 (119.91)	412.4 (124.53)
	Median	416.0	403.5	394.5
	Min - Max	153 - 747	200 - 741	184 - 748
Value at Month 12	n	113	116	108
	Mean (SD)	308.4 (112.26)	288.2 (90.11)	351.1 (139.91)
	Median	280.0	266.5	302.0
	Min - Max	138 - 696	156 - 675	150 - 717
Change from baseline	n	113	116	108
	Mean (SD)	-118.7 (115.07)	-128.3 (114.34)	-61.3 (132.29)
	Median	-103.0	-116.5	-60.0
	Min - Max	-514 - 120	-487 - 103	-451 - 329
	95% CI for mean (1)	(-140.1, -97.3)	(-149.3, -107.3)	(-86.5, -36.1)
Comparison vs. Laser	Difference in LS means (2)	-61.5	-70.6	
	95% CI for difference (2)	(-93.8, -29.2)	(-102.1, -39.0)	
	p-value (3)	0.0002	<0.0001	

- n is the number of patients with a value at both baseline and the Month 12 visit.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
(1) Two-sided 95% confidence intervals (CI) are based on t-distribution.
(2) Differences in LS means and the two-sided 95% CIs are estimated from pair wise ANOVA (stratified) model.
(3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

Extension Study:

Central retinal subfield thickness of the study eye (µm): Mean change from extension baseline at Month 36 – LOCF (Safety set)

Parameter	Statistic	Ranibizumab 0.5 mg N = 83	Ranibizumab 0.5mg + Laser N = 83	Ranibizumab Pooled N = 166	Laser N = 74
Extension baseline	n	80	79	159	72
	Mean (SD)	304.9 (107.82)	285.7 (94.20)	295.4 (101.42)	336.6 (120.66)
	Median	277.5	257.0	264.0	302.0
	Min - Max	154 - 692	156 - 675	154 - 692	150 - 635
Month 36	n	80	79	159	72

	Mean (SD)	290.3 (103.26)	278.8 (100.74)	284.6 (101.86)	256.0 (83.91)
	Median	251.5	254.0	252.0	240.5
	Min - Max	162 - 661	151 - 866	151 - 866	137 - 493
Change from	n	80	79	159	72
extension baseline	Mean (SD)	-14.6 (118.29)	-6.9 (87.17)	-10.8 (103.74)	-80.6 (107.86)
	Median	-7.5	-9.0	-8.0	-55.5
	Min - Max	-458 - 313	-280 - 357	-458 - 357	-398 - 175

n is the number of patients with a value at both extension baseline and the Month 36 visit.

Health-Related Quality of Life: Core Study

Visual functioning questionnaire (VFQ-25): Mean change from baseline at Month 12 (FAS / LOCF) – VFQ-25 Composite score

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	114	116	108
	Mean (SD)	72.8 (16.91)	74.1 (18.06)	73.5 (18.18)
	Median	77.3	77.7	78.0
	Min - Max	27.3 - 96.5	13.6 - 97.4	21.3 - 95.3
Month 12	Mean (SD)	77.8 (19.19)	79.5 (17.29)	74.1 (18.80)
	Median	86.0	85.0	80.0
	Min - Max	16.3 - 100	23.1 - 100	22.0 - 98.0
Change from baseline	Mean (SD)	5.0 (12.97)	5.4 (11.14)	0.6 (12.56)
	Median	4.6	3.9	0.1
	Min - Max	-27.7 - 46.1	-21.4 - 42.5	-33.2 - 34.8
	95% CI for mean (1)	(2.6, 7.4)	(3.3, 7.4)	(-1.8, 3.0)
Comparison vs Laser	Difference in LS means (2)	4.1	4.7	
	95% CI for difference (2)	(0.8, 7.4)	(1.7, 7.6)	
	p-value (3)	0.0137	0.0041	

- n is the number of patients with a value at both baseline and the Month 12 visit.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- (1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- (2) Differences in LS means and the two-sided 95% CIs are estimated from pairwise ANCOVA (stratified) model.
- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

Visual Functioning Questionnaire (VFQ-25): Mean change from baseline at Month 12 (FAS / LOCF) - General Vision

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	114	115	107
	Mean (SD)	58.8 (14.40)	59.5 (15.32)	58.9 (15.00)
	Median	60.0	60.0	60.0
	Min - Max	20.0 - 80.0	20.0 - 100	20.0 - 80.0
Month 12	Mean (SD)	67.7 (15.86)	67.5 (16.85)	60.0 (15.05)
	Median	60.0	60.0	60.0
	Min - Max	20.0 - 100	20.0 - 100	20.0 - 80.0
Change from baseline	Mean (SD)	8.9 (16.42)	8.0 (15.63)	1.1 (15.00)
	Median	0.0	0.0	0.0
	Min - Max	-20.0 - 60.0	-40.0 - 40.0	-40.0 - 40.0
	95% CI for mean (1)	(5.9, 12.0)	(5.1, 10.9)	(-1.8, 4.0)
Comparison vs Laser	Difference in LS means (2)	7.4	6.8	
	95% CI for difference (2)	(3.8, 11.0)	(3.2, 10.4)	
	p-value (3)	0.0005	0.0014	

- n is the number of patients with a value at both baseline and the Month 12 visit.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- (1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- (2) Differences in LS means and the two-sided 95% CIs are estimated from pairwise ANCOVA (stratified) model.
- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

Visual functioning questionnaire (VFQ-25): Mean change from baseline at Month 12 (FAS / LOCF) – Near activities

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	114	116	108
	Mean (SD)	60.5 (23.18)	63.9 (23.00)	64.8 (25.89)
	Median	58.3	66.7	66.7
	Min - Max	8.3 - 100	16.7 - 100	8.3 - 100
Month 12	Mean (SD)	69.5 (23.33)	73.0 (21.72)	65.9 (24.97)
	Median	75.0	83.3	75.0
	Min - Max	8.3 - 100	16.7 - 100	0.0 - 100
Change from baseline	Mean (SD)	9.0 (21.42)	9.1 (18.91)	1.1 (21.56)
	Median	8.3	8.3	0.0
	Min - Max	-50.0 - 66.7	-33.3 - 50.0	-66.7 - 41.7
	95% CI for mean (1)	(5.0, 13.0)	(5.6, 12.6)	(-3.0, 5.2)
Comparison vs Laser	Difference in LS means (2)	5.6	7.2	
	95% CI for difference (2)	(0.5, 10.7)	(2.5, 11.9)	
	p-value (3)	0.0113	0.0059	

- n is the number of patients with a value at both baseline and the Month 12 visit.
- Stratified analysis includes DME type (focal, diffuse/other) and baseline visual acuity (<=60, 61-73, >73 letters).
- (1) Two-sided 95% confidence intervals (CI) are based on the t-distribution.
- (2) Differences in LS means and the two-sided 95% CIs are estimated from pairwise ANCOVA (stratified) model.
- (3) p-values for treatment difference are from the two-sided stratified Cochran-Mantel-Haenszel test using the row means score statistics.

Visual functioning questionnaire (VFQ-25): Mean change from baseline at Month 12 (FAS / LOCF) – Distance activities

Parameter	Statistic	Ranibizumab 0.5 mg N = 115	Ranibizumab 0.5mg + Laser N = 118	Laser N = 110
Baseline	n	114	116	108
	Mean (SD)	72.1 (22.42)	72.2 (24.46)	71.5 (22.80)
	Median	75.0	75.0	75.0
	Min - Max	16.7 - 100	0.0 - 100	8.3 - 100
Month 12	Mean (SD)	77.5 (22.01)	77.8 (22.71)	71.9 (25.33)
	Median	83.3	83.3	75.0
	Min - Max	16.7 - 100	16.7 - 100	8.3 - 100
Change from baseline	Mean (SD)	5.3 (19.16)	5.6 (18.11)	0.4 (18.05)
	Median	0.0	0.0	0.0
	Min - Max	-50.0 - 83.3	-50.0 - 54.2	-66.7 - 50.0
	95% CI for mean (1)	(1.8, 8.9)	(2.3, 9.0)	(-3.1, 3.8)
Comparison vs Laser	Difference in LS means (2)	4.9	5.3	
	95% CI for difference (2)	(0.3, 9.6)	(0.8, 9.8)	
	p-value (3)	0.0446	0.0329	

Health-Related Quality of Life: Extension Study

Visual Functioning Questionnaire (VFQ-25): Mean change from extension baseline at Month 36 – LOCF (Safety set) – VFQ-25 Composite score

Parameter	Statistic	Ranibizumab 0.5 mg N = 83	Ranibizumab 0.5 mg + Laser N = 83	Ranibizumab Pooled N = 166	Laser N = 74
Extension baseline	n	79	78	157	70
	Mean (SD)	81.5 (18.01)	80.1 (15.68)	80.8 (16.85)	76.6 (17.21)
	Median	88.8	84.4	86.5	82.6
	Min - Max	16 - 100	34 - 100	16 - 100	30 - 98
Month 36	Mean (SD)	80.0 (19.03)	79.4 (17.26)	79.7 (18.11)	78.3 (16.72)
	Median	85.1	84.3	84.9	83.4
	Min - Max	19 - 98	15 - 100	15 - 100	38 - 98
Change from extension	Mean (SD)	-1.6 (12.34)	-0.7 (12.26)	-1.1 (12.27)	1.7 (10.67)
baseline	Median	0.0	0.0	0.0	1.2

	Min - Max	-41 - 38	-37 - 30	-41 - 38	-30 - 27

n is the number of patients with a value at both baseline and the specific post-baseline visit.

Visual Functioning Questionnaire (VFQ-25): Mean change from extension baseline at Month 36 – LOCF (Safety set) – General vision

Parameter	Statistic	Ranibizumab 0.5 mg N = 83	Ranibizumab 0.5 mg + Laser N = 83	Ranibizumab Pooled N = 166	Laser N = 74
Extension baseline	n	79	78	157	70
	Mean (SD)	69.9 (16.29)	68.2 (15.27)	69.0 (15.76)	61.4 (15.35)
	Median	80.0	60.0	80.0	60.0
	Min - Max	20 - 100	20 - 100	20 - 100	20 - 80
Month 36	Mean (SD)	67.1 (15.37)	66.9 (15.40)	67.0 (15.34)	68.3 (15.03)
	Median	60.0	60.0	60.0	80.0
	Min - Max	20 - 100	20 - 100	20 - 100	20 - 100
Change from extension	Mean (SD)	-2.8 (17.46)	-1.3 (15.90)	-2.0 (16.67)	6.9 (15.18)
baseline	Median	0.0	0.0	0.0	0.0
	Min - Max	-40 - 60	-40 - 60	-40 - 60	-20 - 60

n is the number of patients with a value at both baseline and the specific post-baseline visit.

Visual Functioning Questionnaire (VFQ-25): Mean change from extension baseline at Month 36 – LOCF (Safety set) – Near activities

Parameter	Statistic	Ranibizumab 0.5 mg N = 83	Ranibizumab 0.5 mg + Laser N = 83	Ranibizumab Pooled N = 166	Laser N = 74
Extension baseline	n	79	78	157	70
	Mean (SD)	74.2 (22.90)	74.3 (20.27)	74.2 (21.57)	68.0 (23.68)
	Median	75.0	83.3	83.3	75.0
	Min - Max	8 - 100	25 - 100	8 - 100	25 - 100
Month 36	Mean (SD)	75.7 (25.43)	72.7 (22.68)	74.2 (24.07)	74.9 (22.18)
	Median	83.3	75.0	75.0	79.2
	Min - Max	0 - 100	8 - 100	0 - 100	17 - 100
Change from extension	Mean (SD)	1.6 (18.25)	-1.6 (17.45)	0.0 (17.87)	6.9 (17.66)
baseline	Median	0.0	0.0	0.0	8.3
	Min - Max	-58 - 42	-67 - 42	-67 - 42	-42 - 58

n is the number of patients with a value at both baseline and the specific post-baseline visit.

Visual Functioning Questionnaire (VFQ-25): Mean change from extension baseline at Month 36 – LOCF (Safety set) – Distance activities

Parameter	Statistic	Ranibizumab 0.5 mg N = 83	Ranibizumab 0.5 mg + Laser N = 83	Ranibizumab Pooled N = 166	Laser N = 74
Extension baseline	n	79	78	157	70
	Mean (SD)	81.1 (20.76)	78.8 (21.36)	79.9 (21.02)	74.7 (23.53)
	Median	87.5	83.3	83.3	83.3
	Min - Max	17 - 100	25 - 100	17 - 100	8 - 100
Month 36	Mean (SD)	77.1 (24.04)	78.4 (21.90)	77.7 (22.94)	76.5 (20.77)
	Median	83.3	83.3	83.3	79.2
	Min - Max	0 - 100	8 - 100	0 - 100	17 - 100
Change from extension	Mean (SD)	-4.0 (17.85)	-0.4 (16.65)	-2.2 (17.30)	1.8 (18.82)
baseline	Median	0.0	0.0	0.0	0.0
	Min - Max	-63 - 33	-50 - 50	-63 - 50	-50 - 58

n is the number of patients with a value at both baseline and the specific post-baseline visit.

Safety Results

Core Study:

Number (%) of patients with serious adverse events, by system organ class (Safety set)

Preferred term	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
Total	**26 (22.6)**	**20 (16.7)**	**17 (15.5)**
Ocular SAE of study eye	**0 (0.0)**	**2 (1.7)**	**2 (1.8)**
Eye disorders	0 (0.0)	2 (1.7)	2 (1.8)
Ocular SAE of fellow eye	**3 (2.6)**	**1 (0.8)**	**2 (1.8)**
Eye disorders	3 (2.6)	1 (0.8)	2 (1.8)
Non-ocular SAE	**23 (20.0)**	**17 (14.2)**	**15 (13.6)**
Blood and lymphatic system disorders	1 (0.9)	0 (0.0)	1 (0.9)
Cardiac disorders	8 (7.0)	4 (3.3)	4 (3.6)
Congenital, familial and genetic disorders	0 (0.0)	1 (0.8)	0 (0.0)
Ear and labyrinth disorders	1 (0.9)	0 (0.0)	1 (0.9)
Gastrointestinal disorders	3 (2.6)	3 (2.5)	2 (1.8)
Hepatobiliary disorders	1 (0.9)	1 (0.8)	0 (0.0)
Infections and infestations	6 (5.2)	3 (2.5)	3 (2.7)
Injury, poisoning and procedural complications	2 (1.7)	0 (0.0)	0 (0.0)
Investigations	1 (0.9)	1 (0.8)	0 (0.0)
Metabolism and nutrition disorders	4 (3.5)	2 (1.7)	3 (2.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	2 (1.7)	0 (0.0)
Nervous system disorders	5 (4.3)	1 (0.8)	2 (1.8)
Renal and urinary disorders	0 (0.0)	1 (0.8)	1 (0.9)
Reproductive system and breast disorders	0 (0.0)	1 (0.8)	0. (0.0)
Respiratory, thoracic and mediastinal disorders	4 (3.5)	2 (1.7)	2 (1.8)
Vascular disorders	4 (3.5)	2 (1.7)	3 (2.7)

- Primary system organ classes are presented alphabetically.

Extension Study:

Number (%) of patients with SAEs from Month 12 to Month 36, by system organ class (Safety set)

rimary system organ class	Ranibizumab 0.5mg N=83 n (%)	Ranibizumab 0.5mg + Laser N=83 n (%)	Pooled Ranibizumab N=166 n (%)	Laser with Ranibizumab in extension N=59 n (%)	Laser without Ranibizumab in extension N=15 n (%)
Total	27 (32.5)	27 (32.5)	54 (32.5)	25 (42.4)	2 (13.3)
Ocular SAE of study eye	2 (2.4)	1 (1.2)	3 (1.8)	1 (1.7)	0 (0.0)
Eye disorders	2 (2.4)	1 (1.2)	3 (1.8)	1 (1.7)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Ocular SAE of fellow eye	4 (4.8)	1 (1.2)	5 (3.0)	2 (3.4)	0 (0.0)
Eye disorders	3 (3.6)	1 (1.2)	4 (2.4)	2 (3.4)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Non-ocular SAE	23 (27.7)	25 (30.1)	48 (28.9)	22 (37.3)	2 (13.3)
Injury, poisoning and procedural complications	7 (8.4)	5 (6.0)	12 (7.2)	1 (1.7)	0 (0.0)
Cardiac disorders	5 (6.0)	5 (6.0)	10 (6.0)	7 (11.9)	0 (0.0)
Nervous system disorders	5 (6.0)	2 (2.4)	7 (4.2)	3 (5.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (4.8)	3 (3.6)	7 (4.2)	3 (5.1)	0 (0.0)
Gastrointestinal disorders	2 (2.4)	4 (4.8)	6 (3.6)	3 (5.1)	0 (0.0)
Infections and infestations	2 (2.4)	4 (4.8)	6 (3.6)	6 (10.2)	0 (0.0)
Metabolism and nutrition disorders	2 (2.4)	3 (3.6)	5 (3.0)	3 (5.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (2.4)	3 (3.6)	5 (3.0)	1 (1.7)	0 (0.0)
Renal and urinary disorders	2 (2.4)	2 (2.4)	4 (2.4)	4 (6.8)	1 (6.7)

Blood and lymphatic system disorders	1 (1.2)	3 (3.6)	4 (2.4)	2 (3.4)	0 (0.0)
General disorders and administration site conditions	1 (1.2)	4 (4.8)	5 (3.0)	1 (1.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	2 (2.4)	3 (1.8)	0 (0.0)	1 (6.7)
Skin and subcutaneous tissue disorders	1 (1.2)	2 (2.4)	3 (1.8)	1 (1.7)	0 (0.0)
Vascular disorders	1 (1.2)	1 (1.2)	2 (1.2)	2 (3.4)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	3 (3.6)	3 (1.8)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	1 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)

Organ systems are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column

Core Study:

10 Most Frequently Reported AEs Overall by Preferred Term n (%)

Preferred term	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
Eye pain	13(11.3)	10(8.3)	12(10.9)
Nasopharyngitis	11 (9.6)	12 (10.0)	16 (14.5)
Hypertension	9 (7.8)	6 (5.0)	8 (7.3)
Conjunctival hemorrhage	9 (7.8)	11(9.2)	1(0.9)
Conjunctival hyperemia	9(7.8)	6(5.0)	6(5.5)
Influenza	6 (5.2)	2 (1.7)	6 (5.5)
Back pain	5 (4.3)	3 (2.5)	5 (4.5)
Foreign body sensation in eyes	5(4.3)	8(6.7)	3(2.7)
Bronchitis	4 (3.5)	3 (2.5)	2 (1.8)
Nausea	4 (3.5)	3 (2.5)	4 (3.6)

- Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Core Study:

Number (%) of patients who died, had serious adverse events or adverse events leading to discontinuation of study drug (Safety set)

	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
Total	28 (24.3)	22 (18.3)	20 (18.2)
Death	2 (1.7)	2 (1.7)	2 (1.8)
SAE	26 (22.6)	20 (16.7)	17 (15.5)
Ocular SAE of study eye	0 (0.0)	2 (1.7)	2 (1.8)
Ocular SAE of fellow eye	3 (2.6)	1 (0.8)	2 (1.8)
Non-ocular SAE	23 (20.0)	17 (14.2)	15 (13.6)
SAE leading to discontinuation from study drug	5 (4.3)	2 (1.7)	3 (2.7)
Ocular SAE of study eye	0 (0.0)	0 (0.0)	0 (0.0)
Ocular SAE of fellow eye	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular SAE	5 (4.3)	2 (1.7)	3 (2.7)
AE leading to discontinuation from study drug	7 (6.1)	5 (4.2)	6 (5.5)
Ocular AE of study eye	0 (0.0)	2 (1.7)	3 (2.7)
Ocular AE of fellow eye	0 (0.0)	0 (0.0)	0 (0.0)
Non-ocular AE	7 (6.1)	3 (2.5)	3 (2.7)

Extension study:

Number (%) of patients with SAEs from Month 12 to Month 36, by system organ class (Safety set)

Primary system organ class	Ranibizumab 0.5mg N=83 n (%)	Ranibizumab 0.5mg + Laser N=83 n (%)	Pooled Ranibizumab N=166 n (%)	Laser with Ranibizumab in extension N=59 n (%)	Laser without Ranibizumab in extension N=15 n (%)
Total	**27 (32.5)**	**27 (32.5)**	**54 (32.5)**	**25 (42.4)**	**2 (13.3)**
Ocular SAE of study eye	**2 (2.4)**	**1 (1.2)**	**3 (1.8)**	**1 (1.7)**	**0 (0.0)**
Eye disorders	2 (2.4)	1 (1.2)	3 (1.8)	1 (1.7)	0 (0.0)
Injury, poisoning and procedural complications	1 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Ocular SAE of fellow eye	**4 (4.8)**	**1 (1.2)**	**5 (3.0)**	**2 (3.4)**	**0 (0.0)**
Eye disorders	3 (3.6)	1 (1.2)	4 (2.4)	2 (3.4)	0 (0.0)

Injury, poisoning and procedural complications	1 (1.2)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)
Non-ocular SAE	**23 (27.7)**	**25 (30.1)**	**48 (28.9)**	**22 (37.3)**	**2 (13.3)**
Injury, poisoning and procedural complications	7 (8.4)	5 (6.0)	12 (7.2)	1 (1.7)	0 (0.0)
Cardiac disorders	5 (6.0)	5 (6.0)	10 (6.0)	7 (11.9)	0 (0.0)
Nervous system disorders	5 (6.0)	2 (2.4)	7 (4.2)	3 (5.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (4.8)	3 (3.6)	7 (4.2)	3 (5.1)	0 (0.0)
Gastrointestinal disorders	2 (2.4)	4 (4.8)	6 (3.6)	3 (5.1)	0 (0.0)
Infections and infestations	2 (2.4)	4 (4.8)	6 (3.6)	6 (10.2)	0 (0.0)
Metabolism and nutrition disorders	2 (2.4)	3 (3.6)	5 (3.0)	3 (5.1)	0 (0.0)
Musculoskeletal and connective tissue disorders	2 (2.4)	3 (3.6)	5 (3.0)	1 (1.7)	0 (0.0)
Renal and urinary disorders	2 (2.4)	2 (2.4)	4 (2.4)	4 (6.8)	1 (6.7)
Blood and lymphatic system disorders	1 (1.2)	3 (3.6)	4 (2.4)	2 (3.4)	0 (0.0)
General disorders and administration site conditions	1 (1.2)	4 (4.8)	5 (3.0)	1 (1.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.2)	2 (2.4)	3 (1.8)	0 (0.0)	1 (6.7)
Skin and subcutaneous tissue disorders	1 (1.2)	2 (2.4)	3 (1.8)	1 (1.7)	0 (0.0)
Vascular disorders	1 (1.2)	1 (1.2)	2 (1.2)	2 (3.4)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)
Hepatobiliary disorders	0 (0.0)	3 (3.6)	3 (1.8)	0 (0.0)	0 (0.0)
Investigations	0 (0.0)	1 (1.2)	1 (0.6)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)

Organ systems are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column

Other Relevant Findings

Core Study:

Number (%) of patients with ocular adverse events of the study eye (at least 3% in any group), by preferred term (Safety set)

Preferred term	Ranibizumab 0.5mg N=115 n(%)	Ranibizumab 0.5mg + Laser N=120 n(%)	Laser N=110 n(%)
Total	49(42.6)	51(42.5)	43(39.1)
Eye pain	13(11.3)	10(8.3)	12(10.9)
Conjunctival hyperaemia	9(7.8)	6(5.0)	6(5.5)
Conjunctival haemorrhage	8(7.0)	10(8.3)	0(0.0)
Foreign body sensation in eyes	5(4.3)	8(6.7)	2(1.8)
Diabetic retinal oedema	4(3.5)	3(2.5)	4(3.6)
Visual impairment	4(3.5)	2(1.7)	1(0.9)
Eye discharge	3(2.6)	4(3.3)	1(0.9)
Cataract	2(1.7)	6(5.0)	7(6.4)
Conjunctivitis	2(1.7)	5(4.2)	3(2.7)
Eye pruritus	2(1.7)	2(1.7)	5(4.5)
Lacrimation increased	2(1.7)	4(3.3)	1(0.9)
Vision blurred	2(1.7)	3(2.5)	5(4.5)
Diabetic retinopathy	1(0.9)	6(5.0)	3(2.7)
Visual acuity reduced	0(0.0)	1(0.8)	4(3.6)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column

Number (%) of patients with non-ocular adverse events (at least 3% in any group), by preferred term (Safety set)

Preferred term	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
Total	67 (58.3)	55 (45.8)	68 (61.8)
Nasopharyngitis	11 (9.6)	12 (10.0)	16 (14.5)
Hypertension	9 (7.8)	6 (5.0)	8 (7.3)
Influenza	6 (5.2)	2 (1.7)	6 (5.5)
Back pain	5 (4.3)	3 (2.5)	5 (4.5)
Bronchitis	4 (3.5)	3 (2.5)	2 (1.8)
Nausea	4 (3.5)	3 (2.5)	4 (3.6)
Urinary tract infection	4 (3.5)	1 (0.8)	0 (0.0)
Headache	3 (2.6)	2 (1.7)	4 (3.6)
Hypoglycemia	2 (1.7)	3 (2.5)	4 (3.6)

Cardiac failure	1 (0.9)	0 (0.0)	4 (3.6)
Constipation	1 (0.9)	4 (3.3)	1 (0.9)
Vomiting	1 (0.9)	1 (0.8)	4 (3.6)
Pneumonia	0 (0.0)	0 (0.0)	4 (3.6)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Extension study:

Number (%) of patients with ocular AEs of the study eye (at least 5% in the Pooled Ranibizumab treatment group) from Month 12 to Month 36, by preferred term

Preferred term	Ranibizumab 0.5mg N=83 n(%)	Ranibizumab 0.5mg + Laser N=83 n(%)	Pooled Ranibizumab N=166 n(%)	Laser with Ranibizumab in extension N=59 n(%)	Laser without Ranibizumab in extension N=15 n(%)
Total	47(56.6)	47(56.6)	94(56.6)	31(52.5)	6(40.0)
Eye pain	9(10.8)	6(7.2)	15(9.0)	8(13.6)	1(6.7)
Cataract	7(8.4)	12(14.5)	19(11.4)	6(10.2)	2(13.3)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Number (%) of patients with ocular AEs of the study eye (at least 5% in the Pooled Ranibizumab treatment group) from Day 1 to Month 36, by preferred term (Safety set)

Preferred term	Ranibizumab 0.5mg N=83 n(%)	Ranibizumab 0.5mg + Laser N=83 n(%)	Pooled Ranibizumab N=166 n(%)	Laser with Ranibizumab in extension N=59 n(%)	Laser without Ranibizumab in extension N=15 n(%)
Total	55(66.3)	56(67.5)	111(66.9)	38(64.4)	7(46.7)
Eye pain	14(16.9)	9(10.8)	23(13.9)	13(22.0)	1(6.7)
Cataract	9(10.8)	17(20.5)	26(15.7)	11(18.6)	2(13.3)
Conjunctival haemorrhage	9(10.8)	9(10.8)	18(10.8)	0(0.0)	0(0.0)
Conjunctival hyperaemia	8(9.6)	7(8.4)	15(9.0)	5(8.5)	1(6.7)
Conjunctivitis	5(6.0)	4(4.8)	9(5.4)	2(3.4)	0(0.0)
Diabetic retinal oedema	5(6.0)	5(6.0)	10(6.0)	3(5.1)	0(0.0)
Foreign body sensation in eyes	5(6.0)	7(8.4)	12(7.2)	2(3.4)	0(0.0)
Intraocular pressure increased	5(6.0)	4(4.8)	9(5.4)	0(0.0)	0(0.0)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Number (%) of patients with non-ocular AEs (at least 5% in the Pooled Ranibizumab treatment group) from Month 12 to Month 36, by preferred term

Preferred term	Ranibizumab 0.5mg N=83 n(%)	Ranibizumab 0.5mg + Laser N=83 n(%)	Pooled Ranibi-zumab N=166 n(%)	Laser with Ranibizumab in extension N=59 n(%)	Laser without Ranibizumab in extension N=15 n(%)
Total	61(73.5)	61(73.5)	122(73.5)	42(71.2)	11(73.3)
Nasopharyngitis	12(14.5)	12(14.5)	24(14.5)	10(16.9)	5(33.3)
Hypertension	7(8.4)	7(8.4)	14(8.4)	4(6.8)	1(6.7)
Influenza	7(8.4)	6(7.2)	13(7.8)	4(6.8)	3(20.0)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Number (%) of patients with non-ocular AEs (at least 5% in the Pooled Ranibizumab treatment group) from Day 1 to Month 36, by preferred term (Safety set)

Preferred term	Ranibizumab 0.5mg N=83 n(%)	Ranibizumab 0.5mg + Laser N=83 n(%)	Pooled Ranibi-zumab N=166 n(%)	Laser with Ranibizumab in extension N=59 n(%)	Laser without Ranibizumab in extension N=15 n(%)
Total	69(83.1)	68(81.9)	137(82.5)	50(84.7)	11(73.3)
Nasopharyngitis	17(20.5)	18(21.7)	35(21.1)	15(25.4)	6(40.0)
Hypertension	12(14.5)	11(13.3)	23(13.9)	7(11.9)	2(13.3)
Influenza	9(10.8)	6(7.2)	15(9.0)	8(13.6)	5(33.3)
Fall	7(8.4)	5(6.0)	12(7.2)	4(6.8)	1(6.7)
Back pain	6(7.2)	5(6.0)	11(6.6)	8(13.6)	1(6.7)

Preferred terms are sorted in descending frquency, as reported in the Ranibizumab 0.5 mg column.

Core Study:

Number (%) of patients with ocular adverse events of the study eye, suspected to be related to study drug and/or ocular injection, by preferred term (Safety set)

Preferred term	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
Total	28(24.3)	27(22.5)	20(18.2)
Eye pain	12(10.4)	10(8.3)	11(10.0)
Conjunctival hemorrhage	8(7.0)	9(7.5)	0(0.0)
Conjunctival hyperemia	8(7.0)	4(3.3)	6(5.5)
Foreign body sensation in eyes	4(3.5)	7(5.8)	2(1.8)
Eye discharge	3(2.6)	3(2.5)	1(0.9)

Visual impairment	3(2.6)	2(1.7)	0(0.0)
Eye irritation	2(1.7)	0(0.0)	2(1.8)
Eyelid oedema	2(1.7)	3(2.5)	1(0.9)
Lacrimation increased	2(1.7)	3(2.5)	1(0.9)
Vision blurred	2(1.7)	1(0.8)	2(1.8)
Corneal erosion	1(0.9)	1(0.8)	0(0.0)
Eye pruritus	1(0.9)	1(0.8)	2(1.8)
Intraocular pressure increased	1(0.9)	1(0.8)	0(0.0)
Ocular hyperaemia	1(0.9)	1(0.8)	0(0.0)
Photophobia	1(0.9)	1(0.8)	0(0.0)
Ocular discomfort	0(0.0)	1(0.8)	2(1.8)

- Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Extension study:

Number (%) of patients with ocular AEs of the study eye from Month 12 to Month 36, suspected to be related to study drug and/or ocular injection, by preferred term

Preferred term	Ranibizumab 0.5mg N=83 n (%)	Ranibizumab 0.5mg + Laser N=83 n (%)	Pooled Ranibizumab N=166 n (%)	Laser with Ranibizumab in extension N=59 n (%)
Total	11(13.3)	17(20.5)	28(16.9)	11(18.6)
Eye pain	8(9.6)	5(6.0)	13(7.8)	7(11.9)
Conjunctival haemorrhage	2(2.4)	4(4.8)	6(3.6)	0(0.0)
Dry eye	1(1.2)	0(0.0)	1(0.6)	0(0.0)
Eye discharge	1(1.2)	2(2.4)	3(1.8)	1(1.7)
Eyelid pain	1(1.2)	0(0.0)	1(0.6)	0(0.0)
Lacrimation increased	1(1.2)	2(2.4)	3(1.8)	3(5.1)
Ocular discomfort	1(1.2)	0(0.0)	1(0.6)	1(1.7)
Punctate keratitis	1(1.2)	1(1.2)	2(1.2)	0(0.0)
Vitreous floaters	1(1.2)	1(1.2)	2(1.2)	1(1.7)
Application site dryness	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Application site erythema	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Cataract	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Conjunctival hyperaemia	0(0.0)	2(2.4)	2(1.2)	1(1.7)
Eye inflammation	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Eye irritation	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Eye pruritus	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Eye swelling	0(0.0)	0(0.0)	0(0.0)	1(1.7)

Foreign body in eye	0(0.0)	2(2.4)	2(1.2)	1(1.7)
Foreign body sensation in eyes	0(0.0)	2(2.4)	2(1.2)	0(0.0)
Hyphaema	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Intraocular pressure increased	0(0.0)	3(3.6)	3(1.8)	0(0.0)
Ocular hyperaemia	0(0.0)	0(0.0)	0(0.0)	2(3.4)
Ocular hypertension	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Visual impairment	0(0.0)	0(0.0)	0(0.0)	1(1.7)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Core Study:

Number (%) of patients with non-ocular AEs, suspected to be related to study drug and/or ocular injection, by preferred term (Safety set)

Preferred term	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
Total	9 (7.8)	3 (2.5)	2 (1.8)
Pulmonary embolism	2 (1.7)	0 (0.0)	0 (0.0)
Arterial thrombosis limb	1 (0.9)	0 (0.0)	0 (0.0)
Arthralgia	1 (0.9)	0 (0.0)	0 (0.0)
Back pain	1 (0.9)	0 (0.0)	0 (0.0)
Dyspnoea	1 (0.9)	0 (0.0)	0 (0.0)
Hypertension	1 (0.9)	0 (0.0)	1 (0.9)
Hypoglycaemia	1 (0.9)	0 (0.0)	0 (0.0)
Influenza	1 (0.9)	0 (0.0)	0 (0.0)
Influenza like illness	1 (0.9)	0 (0.0)	0 (0.0)
Intestinal obstruction	1 (0.9)	0 (0.0)	0 (0.0)
Nausea	1 (0.9)	0 (0.0)	0 (0.0)
Rhinorrhoea	1 (0.9)	0 (0.0)	0 (0.0)
Urticaria	1 (0.9)	0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	1 (0.8)	0 (0.0)
Coronary artery occlusion	0 (0.0)	1 (0.8)	0 (0.0)
Dizziness	0 (0.0)	1 (0.8)	0 (0.0)
Hypertensive crisis	0 (0.0)	0 (0.0)	1 (0.9)

-Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Extension Study

Number (%) of patients with non-ocular AEs from Month 12 to Month 36, suspected to be related to study drug and/or ocular injection, by preferred term

Preferred term	Ranibizumab 0.5mg N=83 n (%)	Ranibizumab 0.5mg + Laser N=83 n (%)	Pooled Ranibizumab N=166 n (%)	Laser with Ranibizumab in extension N=59 n (%)
Total	3(3.6)	5(6.0)	8(4.8)	3(5.1)
Coronary artery disease	1(1.2)	0(0.0)	1(0.6)	1(1.7)
Subarachnoid haemorrhage	1(1.2)	0(0.0)	1(0.6)	0(0.0)
Syncope	1(1.2)	0(0.0)	1(0.6)	0(0.0)
Acute febrile neutrophilic dermatosis	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Cerebrovascular accident	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Cerebrovascular disorder	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Headache	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Myocardial infarction	0(0.0)	2(2.4)	2(1.2)	1(1.7)
Normochromic normocytic anaemia	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Peripheral arterial occlusive disease	0(0.0)	0(0.0)	0(0.0)	1(1.7)
Sepsis	0(0.0)	1(1.2)	1(0.6)	0(0.0)
Transient ischaemic attack	0(0.0)	0(0.0)	0(0.0)	1(1.7)

Preferred terms are sorted in descending frequency, as reported in the Ranibizumab 0.5 mg column.

Core Study:

Number (%) of patients with adverse events potentially related to systemic VEGF inhibition by category and preferred term (Safety set)

Preferred term	Ranibizumab 0.5 mg N=115 n (%)	Ranibizumab 0.5 mg + Laser N=120 n (%)	Laser N=110 n (%)
Total	14 (12.2)	7 (5.8)	11 (10.0)
Arterial thromboembolic events	6 (5.2)	1 (0.8)	1 (0.9)
Angina pectoris	2 (1.7)	0 (0.0)	0 (0.0)
Pulmonary embolism	2 (1.7)	0 (0.0)	1 (0.9)
Cerebrovascular accident	1 (0.9)	0 (0.0)	0 (0.0)
Myocardial infarction	1 (0.9)	1 (0.8)	0 (0.0)
Hypertension	9 (7.8)	6 (5.0)	9 (8.2)
Non-ocular haemorrhage	1 (0.9)	0 (0.0)	1 (0.9)

Epistaxis	1 (0.9)	0 (0.0)	1 (0.9)
Proteinuria	1 (0.9)	1 (0.8)	0 (0.0)

Adverse events related to safety concerns from Month 12 to Month 36 (Safety set)

Preferred term	Ranibizumab 0.5mg N=83 n (%)	Ranibizumab 0.5mg + Laser N=83 n (%)	Pooled Ranibizumab N=166 n (%)	Laser with Ranibizumab in extension N=59 n (%)
Hypersensitivity	6(7.2)	11(13.3)	17(10.2)	5(8.5)
Hypertension	7(8.4)	8(9.6)	15(9.0)	5(8.5)
Non-ocular hemorrhage	8(9.6)	2(2.4)	10(6.0)	3(5.1)
Proteinuria	1(1.2)	0(0.0)	1(0.6)	0(0.0)
Myocardial infarction	1(1.2)	5(6.0)	6(3.6)	5(8.5)
Other arterial thromboembolic events	4(4.8)	3(3.6)	7(4.2)	3(5.1)
Venous thromboembolic events	0(0.0)	1(1.2)	1(0.6)	0(0.0)

Core Study:

Number (%) of patients with critical laboratory values post-baseline (Safety set)

Parameter	Criterion	Ranibizumab 0.5 mg N=115 n/N (%)	Ranibizumab 0.5 mg + Laser N=120 n/N (%)	Laser N=110 n/N (%)
Hematology				
Hemoglobin	< 80 g/L	0/113 (0.0)	0/119 (0.0)	1/105 (0.9)
Biochemistry				
Blood urea nitrogen (BUN)	> 17.5 mmol/L	7/112 (6.3)	2/116 (1.7)	2/105 (1.9)
Creatinine	> 168 mmol/L	4/113 (3.5)	3/115 (2.6)	3/106 (2.8)
Potassium	> 6.3 mmol/L	0/113 (0.0)	1/114 (0.9)	1/106 (0.9)
Glycosylated hemoglobin (HbA1c)	> 12%	0/113 (0.0)	1/119 (0.8)	0/106 (0.0)
AST	> 66 U/L	1/113 (0.9)	1/116 (0.9)	0/106 (0.0)
ALT	> 75 U/L	0/113 (0.0)	1/117 (0.9)	2/106 (1.9)

-n is the number of patients with critical laboratory values at any time post-baseline, and a baseline value that is normal or missing (i.e. critical values in patients with missing baseline values are included).
- N is the number of patients with at least one post-baseline value for the specific laboratory test and a baseline value that is normal or missing. It is used as denominator in calculating the percentages.

Extension Study

Number (%) of patients with critical laboratory values post-extension baseline from Month 12 to Month 36

Parameter Criterion	Ran 0.5 mg N = 83	Ran 0.5 mg + Laser N = 83	Pooled Ran N = 166	Laser with Ran in extension N = 59	Laser without Ran in extension N = 15
Biochemistry	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**	**n/N (%)**
Alkaline phosphatase, serum > 145 U/L	3/81 (3.7)	5/75 (6.7)	8/156 (5.1)	3/57 (5.3)	0/15 (0.0)
Blood Urea Nitrogen (BUN) > 17.5 mmol/L	6/80 (7.5)	4/78 (5.1)	10/158 (6.3)	4/56 (7.1)	0/14 (0.0)
Creatinine > 168 µmol/L	4/80 (5.0)	4/77 (5.2)	8/157 (5.1)	9/57 (15.8)	1/15 (6.7)
Glycosylated hemoglobin (HbA1c) > 12%	3/80 (3.8)	0/77 (0.0)	3/157 (1.9)	0/57 (0.0)	0/15 (0.0)
Potassium > 6.3 mmol/L	2/81 (2.5)	0/78 (0.0)	2/159 (1.3)	1/57 (1.8)	0/15 (0.0)
SGOT (AST) > 66 U/L	1/81 (1.2)	2/78 (2.6)	3/159 (1.9)	1/57 (1.8)	0/15 (0.0)
SGPT (ALT) > 75 U/L	1/81 (1.2)	0/77 (0.0)	1/158 (0.6)	0/56 (0.0)	0/14 (0.0)
Bilirubin (total) > 42 µmol/L	1/81 (1.2)	0/78 (0.0)	1/159 (0.6)	0/57 (0.0)	0/15 (0.0)

n is the number of patients with critical laboratory values at any time post extension baseline, and an extension baseline value that is normal or missing (i.e. critical values in patients with missing extension baseline values are included).
N is the number of patients with at least one post extension baseline value for the specific laboratory test and an extension baseline value that is normal or missing. It is used as denominator in calculating the percentages.

Details of patients who died in the core study

Treatment Group Age, Gender, Race Treatment duration	Cause of death System organ class preferred term	Comments	Investigator attributed relationship to study drug
Ranibizumab 0.5 mg 54 year old Caucasian male Died Day 141/last injection received Day 85 of study treatment;	Cardiac disorders Cardiopulmonary failure	The patient was noted with edema in inferior limbs, resulting in hospitalization. Diagnosis was moderate right cardiac failure (right ventricular failure) and	Not suspected

last sham laser on Day 1		moderate hypertension. Worsening of diabetes was noted, too. Right ventricular failure resolved and patient was discharged on Day 106. The patient died before study completion.	
Ranibizumab 0.5 mg 72 year old Caucasian female Died Day 360/last injection received Day 217 of study treatment; last sham laser on Day 1	Nervous system disorders cerebrovascular accident	Her medical history included cataract operation and aortic valve replacement, mitral valve repair, and coronary artery bypass. The patient developed moderate hypertension and epistaxis, which both resolved on Day 210.	Not suspected
Ranibizumab 0.5 mg + laser 70 year old Caucasian male Died Day 313/last injection received Day 295 of study treatment; last laser on Day 1	Cardiac disorders Myocardial infarction	No past medical history was reported for this patient. The patient had severe hyperuricemia, increased blood glucose and worsening of hypertension leading to hospitalization, but resolved. On Day 313, the patient had chest pain (angina pectoris) and died on the same day.	Not suspected
Ranibizumab 0.5 mg + laser 68 year old Caucasian female Died Day 374/last injection received Day 274 of study treatment; last laser on Day 1	Renal and urinary disorders Renal failure	The patient suffered from the medical conditions hypertension, chronic bronchitis, hypercholeresterolemia and hypothyroidism. The patient was hospitalized due to diarrhea and renal failure on Day 357 and died no Day 374.	Not suspected
Laser 66 year old Caucasian male Died Day 189/last sham injection received Day 64 of study treatment; last laser on Day 1	Cardiac disorders Cardiac failure	The patient had a medical history of hypertension and no past ocular medical history. The patient had a severe gastric ulcer leading to gastric hemorrhage and was hospitalized.	Not suspected
Laser 73 year old Caucasian female	Cardiac disorders cardiac disorder	The patient suffered from hypertension. On Day 155, the patient informed the investigator about a heart problem requiring catheterization. There was no further contact with this patient. Date and cause of death was not communicated by the patient's family, but it was reported as cardiac disorder	Not suspected
Laser 71 year old Caucasian male Last treatment on Day 130. Died 7-Sep-2009, 136 days after last dose of study medication and 13 days after the last visit	Diabetic foot	The patient had a medical history of colon cancer, intestinal resection and colostomy. The patient developed diabetes related leg ulcer which resulted in hospitalization on Day 215 (18-Jul-2009). On the same day the patient also experienced acute coronary syndrome and pneumonia. In Aug 2009 the patient had deteriorating renal function, axillary vein thrombosis and septicemia. The patient experienced severe left ventricular heart failure, severe pulmonary embolus, severe pneumonia, and atrial fibrillation. The patient died on 7-Sep-2009, 136 days after the last dose of study medication.	Not suspected

Details of patients who died in the extension study

Treatment Group Age, Gender, Race Treatment duration	Cause of death System organ class preferred term	Comments	Investigator attributed relationship to study drug*
Ranibizumab 0.5 mg + laser 69 year old Caucasian male Died Day 8 of the extension/Day 366 overall Last dose of study treatment received Day 58	Respiratory, thoracic and mediastinal disorders Pulmonary embolism	Medical condition of hypertension and type 2 diabetes mellitus	Not suspected
Ranibizumab 0.5 mg + laser 72 year old Caucasian male Died Day 94 of extension/Day456 overall Last dose of study treatment received Day 334	Respiratory, thoracic and mediastinal disorders Respiratory arrest Renal and urinary disorders Chronic renal failure	Medical condition of angina pectoris, hypertension, type 2 diabetes mellitus and diabetic nephropathy, renal failure, chest pain	Not suspected
Laser with ranibizumab in extension 48 year old Caucasian male Died Day 78 of the extension/Day 445 overall Last dose of study treatment received Day 399/32	Cardiac disorders Cardiac failure	Medical condition of type 1 diabetes mellitus, diabetic retinopathy and cataract (both eyes), retinal detachment and vitrectomy (fellow eye)	Not suspected
Laser with ranibizumab in extension 56 year old Caucasian female Died Day 38 of the extension/Day 404 overall Last dose of study treatment received Day 398/32	Cardiac disorders Acute myocardial infarction	Medical condition of cardiac failure, type 2 diabetes mellitus, hypertension, and hypothyroidism	Not suspected
Ranibizumab 0.5 mg 65 year old Caucasian male Died Day 616 of the extension/Day 980 overall Last dose of study treatment received Day 428/64	Cardiac disorders Cardiogenic shock	Medical condition of diabetic polyneuropathy, type 2 diabetes mellitus, coronary heart disease, chronic venous insufficiency, dermatosis, diabetic foot, depression, hypercholesterolemia	Not suspected
Ranibizumab 0.5 mg 66 year old Caucasian female Died Day 426 of the extension/Day 788 overall Last dose of study treatment received Day 783/421	Multi-organ failure Infections and infestations Sepsis General disorders and administration site conditions	Medical condition of coronary heart disease, hypertension, hypercholesterolemia, and type 2 diabetes mellitus	Not suspected
Ranibizumab 0.5 mg + laser 79 year old Caucasian male Died Day 397 of the extension/Day 757 overall Last dose of study treatment received Day 599/239	General disorders and administration site conditions Malaise, anemia, liver disorder	Medical condition of high eye pressure, type 2 diabetes mellitus, hypercholesterolemia, cataract	Not suspected

Laser with ranibizumab in extension 57 year old Caucasian male Died Day 498 of the extension/Day 861 overall Last dose of study treatment received Day 428/65	Neoplasms benign, malignant and unspecified Gastric cancer	Medical condition of diabetic retinopathy, type 2 diabetes mellitus, dislipidemia	Not suspected

* Relationship to study drug and/or to ocular injection

Date of Clinical Trial Report

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CRFB002D2301E1 30 Aug 2012

Date Inclusion on Novartis Clinical Trial Results Database

25 Jan 2011- core study
17 Jan 2013- extension study

Date of Latest Update

17 Jan 2013