Full Novartis CTRD Template

Sponsor

Novartis Pharmaceuticals UK Ltd

Generic Drug Name

Ranibizumab

Therapeutic Area of Trial

Diabetic Macular Oedema.

Approved Indication

Ranibizumab is indicated in adults for the treatment of visual impairment due to diabetic macular oedema

Protocol Number

CRFB002DGB14

Title

RELIGHT - Ranibizumab treatment of diabetic macular oEdema with bimonthLy monItorinG after a pHase of initial Treatment. A UK, 18-month, prospective, open-label, multicentre, single-arm Phase IIIb study, with 12-month primary endpoint, assessing the efficacy and safety of Ranibizumab in patients with visual impairment

Study Phase

Phase IIIb

Study Start/End Dates

13-Jan-2011to 14-Apr-2013

Study Design/Methodology

The study was an 18-month, prospective, open-label, multicentre, single-arm study, with 12-month primary endpoint. A screening period (days -14 to -3) was used to assess eligibility. During Treatment period 1 (days 1 to 60), three consecutive ranibizumab treatments were given to all subjects at the first three monthly visits. Treatment period 2 (days 61 to 150) consisted of monthly follow-up with pro re nata treatment based on retreatment criteria. During Treatment period 3 (days 151 to 360) consisted of bimonthly follow-up with pro re nata treatment based on retreatment criteria. Laser treatment was allowed from day 180 onwards. Lastly, Treatment period 4 (Days 361 to 540) consisted of bimonthly follow-up with pro re nata treatment based on retreatment criteria. An analysis for the primary endpoint was performed at 12 months, but no changes in the study conduct were planned based on the results of this analysis.

Centers

15 centres in the UK

Publication

Full manuscript under development

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

Ranibizumb 0.5 mg in 0.05 ml solution administered intravitreally.

Statistical Methods

The primary variable, the difference from baseline to Month 12 in the level of BCVA, was tested to determine if the mean improvement was ≥5 by a paired t-test using the Last Observation Carried Forward (LOCF) method. The primary analysis was based on the Full Analysis set, consisting of all patients who received at least one application of study treatment and had at least one post-baseline assessment for BCVA. For sensitivity purposes, the primary analysis was repeated using the Per Protocol set, consisting of all patients in the Full Analysis set who completed the treatment phase of the trial without clinically significant protocol deviations. Secondary efficacy variables were analyzed in the Full Analysis set and are presented descriptively. Patient-reported outcomes are presented descriptively. Safety variables are presented descriptively based on the Safety set, consisting of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Male or female patients ≥18 years of age who gave written informed consent.
- Patients with Type 1 or Type 2 DM.
- Patients with visual impairment due to focal or diffuse DMO, and no other causes, in at least one eye who were eligible for laser treatment in the opinion of the

investigator. If both eyes were eligible, the one with the worse VA, as assessed at Visit 1, was selected for study treatment unless, based on medical reasons, the investigator deemed the other eye to be the more appropriate candidate for study treatment.

- BCVA between 78 and 24 in the study eye using Early Treatment Diabetic Retinopathy Study (ETDRS)-like VA testing charts after adjustment for the testing distance of 4 meters (approximate Snellen equivalent of 6/9 to 6/96) at screening.
- Increased CRT which, in the opinion of the investigator, was due to DMO.

Exclusion criteria

- Previous participation in any clinical studies of investigational drugs (excluding vitamins and minerals) within 1 month (or a period corresponding to 5 half-lives of the investigational drug, whatever is longer) prior to first study drug treatment.
- Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, including women whose career, lifestyle, or sexual orientation precludes intercourse with a male partner and women whose partners have been sterilized by vasectomy or other means, UNLESS they were using two birth control methods. The two methods could be a double barrier method or a barrier method plus a hormonal method. Adequate barrier methods of contraception included: diaphragm, condom (by the partner), intrauterine device (copper or hormonal), sponge or spermicide. Hormonal contraceptives included any marketed contraceptive agent that includes an estrogen and/or a progestational agent.
- Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive serum pregnancy test (human chorionic gonadotrophin [hCG] >5 mIU/ml).
- Inability to comply with study procedures.
- Concomitant conditions in the study eye which could, in the opinion of the investigator, prevent the improvement of VA on study treatment (e.g. cataract, retinal vascular occlusion, retinal detachment, macular hole, vitreomacular traction, or choroidal neovascularization of any cause e.g. AMD, ocular histoplasmosis, or pathologic myopia).
- Active intraocular inflammation (grade trace or above) or infection (e.g. conjunctivitis, keratitis, scleritis, endophthalmitis) in either eye at enrollment.
- History of uveitis in either eye at any time.
- Structural damage within 0.5 disc diameter of the center of the macular in the study eye likely to preclude improvement in VA following the resolution of macular edema, including atrophy of the retinal pigment epithelium, subretinal fibrosis, laser scar(s), epiretinal membrane involving fovea or organized hard exudate plaques.
- Planned medical or surgical intervention during the 18-month study period.
- Uncontrolled glaucoma in either eye at screening (intraocular pressure [IOP] >24 mmHg on medication or according to investigator's judgment).
- Neovascularization of the iris in either eye.
- Active proliferative diabetic retinopathy in the study eye.
- Panretinal or focal/grid laser photocoagulation in the study eye within 3 months prior to Visit 2.
- Treatment with anti-angiogenic drugs and corticosteroids in the study eye (pegaptanib sodium, anecortave acetate, bevacizumab, ranibizumab, VEGF-Trap, etc.) within 3 months prior to Visit 2.
- Any intraocular surgery in the study eye within 3 months prior to Visit 2.
- History of vitrectomy in study eye.

- Ocular conditions in the study eye that required chronic concomitant therapy with topical ocular or systemically administered corticosteroids.
- History of acute thromboembolic event within 4 months of screening.
- Renal failure requiring dialysis or renal transplant OR renal insufficiency with e-GFR <30 levels at screening.
- Untreated DM.
- Blood pressure systolic >160 mmHg or diastolic >100 mmHg at screening and Visit 2.
- 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.
- Current use of, or likely need for, glitazones.
- Known hypersensitivity to ranibizumab or any component thereof or drugs of similar chemical classes.
- Any type of advanced, severe or unstable disease or its treatment, that could interfere with primary and/or secondary variable evaluations including any medical condition that could be expected to progress, recur, or change to such an extent that it may have biased the assessment of the clinical status of the patient to a significant degree or put the patient at special risk.

Participant Flow

Patient disposition - n (%) of patients (Enrolled set)

Disposition	Reason	Ranibizumab N=109 n (%)
Did subject complete the study?	No	10 (9.2)
	Yes	99 (90.8)
Primary reason for discontinuation?	Adverse event(s)	4 (3.7)
	Subject withdrew consent	2 (1.8)
	Lost to follow-up	2 (1.8)
	Death	1 (0.9)
	Protocol violation	1 (0.9)

Baseline Characteristics

Demographic characteristics at baseline (Enrolled set)

Demographic variable	Category/statistic	Ranibizumab N=109
Age (years)	N	109
	Mean (SD)	63.7 (9.69)

	Median	63.5
	Range	38 - 87
Age group (years) - n (%)	<50	8 (7.3)
	50 - <65	51 (46.8)
	65 - <75	38 (34.9)
	75 - <85	10 (9.2)
	≥85	2 (1.8)
Sex - n (%)	Male	77 (70.6)
	Female	32 (29.4)
Predominant race - n (%)	Caucasian	93 (85.3)
	Black	2 (1.8)
	Asian	6 (5.5)
	Other	8 (7.3)
Ethnicity - n (%)	Hispanic/Latino	1 (0.9)
	Indian (Indian subcontinent)	6 (5.5)
	Mixed ethnicity	1 (0.9)
	Other	100 (91.7)
	Unknown	1 (0.9)
Study eye iris color - n (%)	Black	2 (1.8)
	Brown	22 (20.2)
	Hazel	13 (11.9)
	Green	4 (3.7)
	Blue	47 (43.1)
	Grey	21 (19.3)
Height (cm)	N	109
	Mean (SD)	168.9 (9.08)
	Median	170.0
	Range	152 - 192
Weight (kg)	N	109
	Mean (SD)	90.23 (19.110)
	Median	88.00
	Range	49.4 - 145.0
Body Mass Index (kg/m^2)	N	109
	Mean (SD)	31.62 (6.439)
	Median	30.88
	Range	19.4 - 56.6

Diabetes characteristics at baseline (Enrolled set)

Characteristic	Category/statistic	Ranibizumab N=109
Diabetes mellitus (DM) present - n (%)	Type 1	17 (15.6)
	Type 2	92 (84.4)
Time since first diagnosis of DM (years)	N	109
	Mean (SD)	15.35 (9.905)
	Median	14.62
	Range	0.2 - 46.7
Time since first diagnosis of DM (categorized) (years)	<2	8 (7.3)
	2 - <10	25 (22.9)
	10 - <15	23 (21.1)
	15 - <20	19 (17.4)
	≥20	34 (31.2)
HbA1c (percent)	N	108
	Mean (SD)	7.90 (1.441)
	Median	7.70
	Range	5.4 - 12.2
HbA1c group (percent) categorized	<7	32 (29.4)
	7 - <8	30 (27.5)
	8 - <10	35 (32.1)
	10 - 12	10 (9.2)
	>12	1 (0.9)
	Missing	1 (0.9)
HbA1c (mmol/mol)	N	108
	Mean (SD)	62.89 (15.754)
	Median	60.66
	Range	35.5 - 109.8
HbA1c group (mmol/mol) categorized	≤ 50	22 (20.2)
	>50 - 60	30 (27.5)
	>60 - 70	24 (22.0)
	>70 - 80	18 (16.5)
	>80 - 90	7 (6.4)
	>90 - 100	2 (1.8)
	>100 - 110	5 (4.6)

Characteristic	Category/statistic	Ranibizumab N=109
Diabetes mellitus (DM) present - n (%)	Type 1	17 (15.6)
	Type 2	92 (84.4)
	Missing	1 (0.9)

Diabetic Macula (O)Edema (DMO) history at baseline (Enrolled set)

Characteristic	Category/statistic	Ranibizumab N=109
DMO present in study eye - n (%)	Yes	109 (100.0)
Duration of DMO in study eye (years)	n	108
	Mean (SD)	3.37 (3.706)
	Median	2.02
	Range	0.0 - 26.5
Duration of DMO in study eye (categorized) (years) (1)	≤0.25	8 (7.3)
	>0.25 - <1.0	20 (18.3)
	≥1.0	80 (73.4)
	Missing	1 (0.9)
DMO present in fellow eye - n (%)	Yes	76 (69.7)
	No	33 (30.3)
Duration of DMO in fellow eye (years)	n	75
	Mean (SD)	3.71 (4.288)
	Median	2.33
	Range	0.0 - 26.5
Duration of DMO in fellow eye (categorized) (years) (1)	≤0.25	6 (7.9)
	>0.25 - <1.0	12 (15.8)
	≥1.0	57 (75.0)
	Missing	1 (1.3)

Outcome Measures

Summary of Efficacy

Primary Outcome Result(s)

Mean visual acuity (letters) of study eye by visit (Full analysis set)

Visual acuity (letters) of the study eye: summary statistics of absolute value and change from baseline by visit (Full analysis set [LOCF])

		Baseline	Ranibizumab N=109	
Time point	Statistic		Post-baseline	Change
Baseline (Visit 2)	N	109		
	Mean	62.9		
	SD	11.39		
	Median	64.0		
	Min	24		
	Max	84		
Month 1 (Visit 3)	N	108	108	108
	Mean	62.8	65.8	3.00
	SD	11.38	9.13	7.201
	Median	64.0	67.0	1.00
	Min	24	37	-14.0
	Max	84	82	35.0
	SEM			0.693
	p-value			<0.001
	95% CI			(1.63, 4.37)
Month 2 (Visit 4)	N	108	108	108
	Mean	62.8	67.5	4.64
	SD	11.38	9.70	7.621
	Median	64.0	69.0	2.00
	Min	24	37	-9.0
	Max	84	84	29.0
	SEM			0.733
	p-value			<0.001
	95% CI			(3.19, 6.09)
Month 3 (Visit 5)	N	103	103	103
	Mean	62.8	68.3	5.49
	SD	11.59	10.32	7.979
	Median	64.0	69.0	4.00
	Min	24	35	-8.0
	Max	84	88	38.0
	SEM			0.786

Time point	Statistic	Baseline	Ranibizumab N=109 Post-baseline	Change
	p-value			<0.001
	95% CI			(3.93, 7.04)
Month 4 (Visit 6)	n	105	105	105
	Mean	62.8	68.8	6.02
	SD	11.50	9.71	8.753
	Median	64.0	70.0	5.00
	Min	24	38	-8.0
	Max	84	87	42.0
	SEM			0.854
	p-value			<0.001
	95% CI			(4.33, 7.71)
Month 5 (Visit 7)	n	105	105	105
	Mean	62.8	68.8	6.05
	SD	11.53	10.17	8.215
	Median	64.0	70.0	6.00
	Min	24	33	-10.0
	Max	84	84	33.0
	SEM			0.802
	p-value			<0.001
	95% CI			(4.46, 7.64)
Month 6 (Visit 8)	n	102	102	102
	Mean	62.5	69.0	6.56
	SD	11.48	9.88	8.591
	Median	64.0	71.0	5.50
	Min	24	32	-10.0
	Max	84	84	43.0
	SEM			0.851
	p-value			<0.001
	95% CI			(4.87, 8.25)
Month 7 (Visit 9)	n	100	100	100
	Mean	62.7	67.4	4.64
	SD	11.51	11.12	8.820
	Median	64.0	69.0	5.00
	Min	24	33	-20.0

		Baseline	Ranibizumab N=109	
Time point	Statistic		Post-baseline	Change
	Max	84	93	26.0
	SEM			0.882
	p-value			<0.001
	95% CI			(2.89, 6.39)
Month 9 (Visit 10)	n	100	100	100
	Mean	62.9	68.1	5.18
	SD	11.62	10.52	7.735
	Median	64.5	70.0	4.00
	Min	24	32	-10.0
	Max	84	83	33.0
	SEM			0.773
	p-value			<0.001
	95% CI			(3.65, 6.71)
Month 11 (Visit 11)	n	99	99	99
	Mean	63.1	68.9	5.82
	SD	11.44	10.89	9.418
	Median	65.0	71.0	5.00
	Min	24	34	-20.0
	Max	84	85	42.0
	SEM			0.947
	p-value			<0.001
	95% CI			(3.94, 7.70)
Month 12 (Visit 12)	n	100	100	100
	Mean	63.2	68.1	4.91
	SD	11.49	12.51	10.319
	Median	65.0	70.5	5.00
	Min	24	3	-51.0
	Max	84	85	28.0
	SEM			1.032
	p-value			<0.001
	95% CI			(2.86, 6.96)
LOCF (Month 12)	n	109	109	109
	Mean	62.9	67.8	4.81
	SD	11.39	12.53	10.142

Time point	Statistic	Baseline	Ranibizumab N=109 Post-baseline	Change
	Median	64.0	70.0	5.00
	Min	24	3	-51.0
	Max	84	85	28.0
	SEM			0.971
	p-value			<0.001
	95% CI			(2.88, 6.73)
Month 13 (Visit 13)	n	99	99	99
	Mean	63.3	68.5	5.29
	SD	11.54	12.15	9.103
	Median	65.0	71.0	5.00
	Min	24	13	-23.0
	Max	84	84	29.0
	SEM			0.915
	p-value			<0.001
	95% CI			(3.48, 7.11)
Month 15 (Visit 14)	n	100	100	100
	Mean	63.2	68.5	5.32
	SD	11.49	12.07	10.215
	Median	65.0	71.0	5.00
	Min	24	10	-44.0
	Max	84	85	33.0
	SEM			1.021
	p-value			<0.001
	95% CI			(3.29, 7.35)
Month 17 (Visit 15)	n	99	99	99
	Mean	63.2	68.4	5.22
	SD	11.55	12.23	11.134
	Median	65.0	70.0	5.00
	Min	24	4	-50.0
	Max	84	85	39.0
	SEM			1.119
	p-value			<0.001
	95% CI			(3.00, 7.44)
Month 18 (Visit 16)	n	104	104	104

Time point	Statistic	Baseline	Ranibizumab N=109 Post-baseline	Change
	Mean	63.1	69.6	6.50
	SD	11.55	12.72	11.635
	Median			6.00
	Min			-50.0
	Max			30.0
	SEM			1.141
	p-value			<0.001
	95% CI			(4.24, 8.76)

Change = Post-baseline – baseline
n = the number of subjects with evaluable measurements at both baseline and the post-baseline visit.
Two-sided 95% confidence intervals (CI) are from a t-distribution.
p-values are from a paired t-test.

Secondary Outcome Result(s)

Optical coherence tomography: Central retinal thickness of the study eye (µm): Summary statistics of absolute value and change from baseline, by visit (Full analysis set)

Time point	Statistic	Baseline	Ranibizumab N=109 Post-baseline	Change
Baseline (V2)	n	102		
	Mean	418.1		
	SD	159.20		
	Median	380.0		
	Min	191		
	Max	797		
Mth1 (v3)	n	99	99	99
	Mean	423.1	331.3	-91.85
	SD	158.89	128.09	137.697
	Median	393.0	282.0	-40.00
	Min	191	134	-526.0
	Max	797	750	204.0
	SEM			13.839
	p-value			<0.001

			Ranibizumab N=109	
Time point	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	95% CI			(-119.31, -64.39)
Mth2 (v4)	n	101	101	101
	Mean	419.8	303.6	-116.18
	SD	159.06	109.41	141.663
	Median	391.0	271.0	-61.00
	Min	191	126	-534.0
	Max	797	616	156.0
	SEM			14.096
	p-value			<0.001
	95% CI			(-144.14, -88.21)
Mth3 (v5)	n	96	96	96
	Mean	423.2	298.2	-125.00
	SD	159.77	100.55	148.162
	Median	396.5	273.5	-66.00
	Min	191	126	-534.0
	Max	797	587	118.0
	SEM			15.122
	p-value			<0.001
	95% CI			(-155.02, -94.98)
Mth4 (v6)	n	95	95	95
	Mean	423.4	307.1	-116.24
	SD	160.49	114.28	141.226
	Median	393.0	274.0	-66.00
	Min	191	112	-534.0
	Max	797	681	89.0
	SEM			14.489
	p-value			<0.001
	95% CI			(-145.01, -87.47)
Mth5 (v7)	n	98	98	98
	Mean	418.0	305.0	-112.94
	SD	159.04	113.53	167.044
	Median	380.0	266.5	-70.00
	Min	191	119	-541.0
	Max	797	660	316.0

		Ranibizumab N=109		
Time point	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	SEM			16.874
	p-value			<0.001
	95% CI			(-146.43, -79.45)
Mth6 (v8)	n	97	97	97
	Mean	421.9	289.3	-132.66
	SD	159.43	106.29	160.415
	Median	393.0	259.0	-75.00
	Min	191	127	-533.0
	Max	797	669	150.0
	SEM			16.288
	p-value			<0.001
	95% CI			(-164.99,-100.33)
Mth7 (v9)	n	94	94	94
	Mean	418.6	325.2	-93.35
	SD	158.09	137.34	146.667
	Median	392.0	271.5	-55.50
	Min	191	133	-527.0
	Max	797	801	197.0
	SEM			15.128
	p-value			<0.001
	95% CI			(-123.39, -63.31)
Mth9 (v10)	n	95	95	95
	Mean	413.8	324.5	-89.38
	SD	157.97	135.24	149.295
	Median	369.0	270.0	-63.00
	Min	191	139	-520.0
	Max	797	800	326.0
	SEM			15.317
	p-value			<0.001
	95% CI			(-119.79, -58.97)
Mth11 (v11)	n	92	92	92
	Mean	418.6	311.7	-106.84
	SD	157.12	143.77	155.095
	Median	380.0	259.5	-68.00

			Ranibizumab N=109	
Time point	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	Min	191	140	-499.0
	Max	797	770	294.0
	SEM			16.170
	p-value			<0.001
	95% CI			(-138.96, -74.72)
Mth12 (v12)	n	94	94	94
	Mean	414.0	286.9	-127.09
	SD	158.37	107.82	158.457
	Median	365.5	258.0	-92.00
	Min	191	133	-527.0
	Max	797	681	251.0
	SEM			16.344
	p-value			<0.001
	95% CI			(-159.54, -94.63)
Mth13 (v13)	n	93	93	93
	Mean	415.7	320.6	-95.10
	SD	158.36	143.68	157.490
	Median	369.0	264.0	-51.00
	Min	191	139	-495.0
	Max	797	762	247.0
	SEM			16.331
	p-value			<0.001
	95% CI			(-127.54, -62.67)
Mth15 (v14)	n	92	92	92
	Mean	416.1	306.3	-109.76
	SD	158.83	122.22	147.474
	Median	365.5	266.3	-71.50
	Min	191	120	-537.0
	Max	797	769	310.0
	SEM			15.375
	p-value			<0.001
	95% CI			(-140.30, -79.22)
Mth17 (v15)	n	94	94	94
	Mean	412.1	307.5	-104.59

			Ranibizumab N=109	
Time point	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	SD	158.68	121.22	165.028
	Median	362.0	262.5	-66.00
	Min	191	127	-533.0
	Max	797	634	268.0
	SEM			17.021
	p-value			<0.001
	95% CI			(-138.39, -70.78)
Mth18 (v16)	n	95	95	95
	Mean	420.3	270.0	-150.23
	SD	157.13	90.49	168.267
	Median	391.0	252.0	-119.00
	Min	196	135	-534.0
	Max	797	607	233.0
	SEM			17.264
	p-value			<0.001
	95% CI			(-184.51,-115.95)

Change = Post baseline – baseline.
n = the number of subjects with evaluable measurements at both baseline and the post-baseline visit.
Two-sided 95% confidence intervals (CI) are from a t-distribution.
p-values are from a paired t-test.

Visual acuity (letters) of the study eye: proportion of gains/losses from baseline to month 12 (Full analysis set)

	Ranibizumab N= 109
Loss of 15 or more letters - n(%)	
N/A	9 (8.3)
No	99 (90.8)
Yes	1 (0.9)
Loss of 10 or more letters - n(%)	
N/A	9 (8.3)
No	92 (84.4)
Yes	8 (7.3)
Loss of 5 or more letters - n(%)	
N/A	9 (8.3)
No	88 (80.7)
Yes	12 (11.0)
No change - n(%)	
N/A	9 (8.3)
No	95 (87.2)
Yes	5 (4.6)
Gain of 5 or more letters - n(%)	
N/A	9 (8.3)
No	47 (43.1)
Yes	53 (48.6)
Gain of 10 or more letters - n(%)	
N/A	9 (8.3)
No	73 (67.0)
Yes	27 (24.8)

Fundus photography: diabetic retinopathy disease severity scale: Shift table by visit (Full analysis set)

		Extreme value n(%)						
Visit	Baseline	No	Mild	Mod	Sev	Pro	N/A	Total N= 109
Month 12	No	0 (0.0)	2 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.8)
	Mild	1 (0.9)	21 (19.3)	5 (4.6)	0 (0.0)	0 (0.0)	2 (1.8)	29 (26.6)
	Mod	0 (0.0)	12 (11.0)	20 (18.3)	1 (0.9)	1 (0.9)	7 (6.4)	41 (37.6)
	Sev	1 (0.9)	3 (2.8)	15 (13.8)	6 (5.5)	1 (0.9)	1 (0.9)	27 (24.8)
	Pro	0 (0.0)	2 (1.8)	0 (0.0)	2 (1.8)	4 (3.7)	1 (0.9)	9 (8.3)
	N/A	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
	Total	2 (1.8)	41 (37.6)	40 (36.7)	9 (8.3)	6 (5.5)	11 (10.1)	109 (100.0)
Month 18	No	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)	1 (0.9)	0 (0.0)	2 (1.8)
	Mild	0 (0.0)	15 (13.8)	10 (9.2)	0 (0.0)	2 (1.8)	2 (1.8)	29 (26.6)
	Mod	0 (0.0)	7 (6.4)	24 (22.0)	2 (1.8)	4 (3.7)	4 (3.7)	41 (37.6)
	Sev	0 (0.0)	2 (1.8)	11 (10.1)	9 (8.3)	5 (4.6)	0 (0.0)	27 (24.8)
	Pro	0 (0.0)	2 (1.8)	0 (0.0)	1 (0.9)	6 (5.5)	0 (0.0)	9 (8.3)
	N/A	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)
	Total	0 (0.0)	27 (24.8)	46 (42.2)	12 (11.0)	18 (16.5)	6 (5.5)	109 (100.0)

Laser photocoagulation rescue treatment of the study eye (Full analysis set)

	Ranibizumab N= 109 n (%)
Any treatment - n(%)	
No	93 (85.3)
Yes	16 (14.7)
Number of treatments - n(%)	
0	93 (85.3)
1	11 (10.1)
2	5 (4.6)
Time of first treatment (days) - n(%)	
>30 - 60	1 (6.3)
>180 - 210	5 (31.3)
>210 - 240	1 (6.3)
>240 - 270	1 (6.3)
>330 - 360	1 (6.3)
>360 - 390	3 (18.8)
>390 - 420	1 (6.3)
>450 - 480	1 (6.3)
>480 - 510	1 (6.3)
>510 - 540	1 (6.3)

Summary of Safety Results

Number (%) of patients with ocular adverse events of the study eye (at least 2%), by preferred term (Safety set)

Preferred term	Ranibizumab N=109 n (%)
Total subjects with AEs	63 (57.8%)
Conjunctival hemorrhage	7 (6.4%)
Macular edema	7 (6.4%)
Foreign body sensation in eyes	5 (4.6%)
Cataract	4 (3.7%)
Dry eye	4 (3.7%)
Vision blurred	4 (3.7%)
Corneal abrasion	3 (2.8%)
Cystoid macular edema	3 (2.8%)
Diabetic retinal edema	3 (2.8%)
Diabetic retinopathy	3 (2.8%)
Eye pain	3 (2.8%)
Eye pruritus	3 (2.8%)
Vitreous hemorrhage	3 (2.8%)

Preferred terms are sorted in descending frequency.
A subject with multiple occurrences of an AE is counted only once in the AE category.

Number (%) of patients with non-ocular adverse events (at least 2%) by preferred term (Safety set)

Preferred term	Ranibizumab N=109 n (%)
Total subjects with AEs	83 (76.1%)
Lower respiratory tract infection	12 (11.0%)
Nasopharyngitis	10 (9.2%)
Localized infection	8 (7.3%)
Cough	7 (6.4%)
Rash	5 (4.6%)
Urinary tract infection	5 (4.6%)
Blood pressure increased	4 (3.7%)
Fall	4 (3.7%)
Headache	4 (3.7%)
Sinusitis	4 (3.7%)
Upper respiratory tract infection	4 (3.7%)
Anemia	3 (2.8%)
Contusion	3 (2.8%)
Hypertension	3 (2.8%)
Respiratory tract infection	3 (2.8%)
Skin ulcer	3 (2.8%)
Toothache	3 (2.8%)
Vertigo	3 (2.8%)
Viral infection	3 (2.8%)

Preferred terms are sorted in descending frequency.
A subject with multiple occurrences of an AE is counted only once in the AE category.

Number (%) of patients with serious adverse events, by preferred term (Safety set)

Category	Preferred term	Ranibizumab N=109 n (%)
Ocular SAE of study eye	Total	3 (2.8%)
	Visual acuity reduced	2 (1.8%)
	Vitreous hemorrhage	1 (0.9%)
Ocular SAE of fellow eye	Total	3 (2.8%)

Category	Preferred term	Ranibizumab N=109 n (%)
	Cataract operation	1 (0.9%)
	Retinal hemorrhage	1 (0.9%)
	Visual acuity reduced	1 (0.9%)
Non-ocular SAE	Total	21 (19.3%)
	Hypoglycemia	2 (1.8%)
	Transient ischemic attack	2 (1.8%)
	Abdominal abscess	1 (0.9%)
	Anemia	1 (0.9%)
	Benign tumor excision	1 (0.9%)
	Blood glucose fluctuation	1 (0.9%)
	Cardiac failure	1 (0.9%)
	Cerebral infarction	1 (0.9%)
	Chest pain	1 (0.9%)
	Demyelination	1 (0.9%)
	Dizziness	1 (0.9%)
	Dyspnea	1 (0.9%)
	Foot fracture	1 (0.9%)
	Gastroesophageal reflux disease	1 (0.9%)
	Hepatic cancer	1 (0.9%)
	Hip fracture	1 (0.9%)
	Ischemia	1 (0.9%)
	Labyrinthitis	1 (0.9%)
	Leg amputation	1 (0.9%)
	Localized infection	1 (0.9%)
	Lower respiratory tract infection	1 (0.9%)
	Myelodysplastic syndrome	1 (0.9%)
	Myocardial infarction	1 (0.9%)
	Nephropathy	1 (0.9%)
	Ovarian cancer	1 (0.9%)
	Overdose	1 (0.9%)
	Paraplegia	1 (0.9%)
	Serum ferritin decreased	1 (0.9%)
	Squamous cell carcinoma of lung	1 (0.9%)
	Toe amputation	1 (0.9%)

Category	Preferred term	Ranibizumab N=109 n (%)
	Urinary retention	1 (0.9%)
	Urinary tract infection	1 (0.9%)

Preferred terms are sorted in descending frequency and then alphabetically.
A subject with multiple occurrences of an AE is counted only once in the AE category

Date of Clinical Trial Report

5 March 2014

Date Inclusion on Novartis Clinical Trial Results Database

14 April 2014

Date of Latest Update