NOVARTIS

Sponsor

Novartis Pharmaceuticals UK Ltd.

Generic Drug Name

Ranibizumab

Therapeutic Area of Trial

Choroidal Neovascularization (CNV) secondary to pathological myopia (PM)

Approved Indication

Lucentis is indicated in adults for:

- The treatment of neovascular (wet) age-related macular degeneration (AMD)
- The treatment of visual impairment due to diabetic macular oedema (DME)
- The treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO)

Protocol Number

CRFB002AGB10

Title

A phase II, open-label, multicenter, 12-month study to evaluate the efficacy and safety of ranibizumab (0.5 mg) in patients with choroidal neovascularization (CNV) secondary to pathological myopia (PM).

Study Phase

Phase II

Study Start/End Dates

15 Jan 2010 to 20 April 2012

Study Design/Methodology

The study used a 12-month, prospective, observational, open-label, single-arm, multicenter design. A screening period of 11 days (Days -14 to -3) was used to assess eligibility. At baseline, all eligible patients received one initial injection of ranibizumab followed by repeated monthly administration as needed for up to a further 11 months based on pre-specified criteria. Visits to assess efficacy and safety were scheduled at one-monthly intervals during the treatment period.

Centers

12 centers in the UK.

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

Ranibizumb 0.5 mg in 0.05 ml solution administered intravitreally.

Statistical Methods

Data analysis

Data were analyzed for this clinical study report when all patients had completed the 12-month study period and the database was cleaned and locked.

Analysis sets

The **Full Analysis set** consisted of all patients who received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned. No data were excluded from the Full Analysis set analyses because of protocol deviations.

The **Per Protocol set** consisted of all patients in the Full Analysis set who completed the treatment phase of the trial without clinically significant protocol deviations. Clinically significant protocol deviations were defined in the Statistical Analysis Plan. If deviations occurred, then the data from specific patients, visits, or evaluations could be excluded from the Per Protocol set. The criteria and determination of clinically relevant protocol deviations and patient specific identification of data to be excluded from the Per Protocol set were databased and finalized prior to database lock.

The **Safety set** consisted of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Patients were analyzed

according to treatment received. The statement that a patient had no AEs also constituted a safety assessment.

Analysis of the primary variable(s)

Variable
The primary variable was the difference from baseline to Month 12 in the level of BCVA (letters).

Statistical hypothesis, model, and method of analysis
Currently the only approved treatment for subfoveal CNV secondary to PM is vPDT. However vPDT has only been demonstrated to stabilize vision compared to placebo. Case series published to date of the effect of ranibizumab in CNV secondary to PM suggest the treatment will improve vision over 12 months. Although the present study was non-comparative, if it could be demonstrated that ranibizumab improved vision at 12 months then this would provide the first substantive evidence for the efficacy of ranibizumab in CNV secondary to PM. A clinically important improvement in VA is considered to be 10 letters. The null hypothesis to be tested was expressed as:

$H0: \theta = 0$ versus $H1: \theta \neq 0$

where θ was the mean change from baseline to 12 months in BCVA.

The null hypothesis was tested by a paired t-test. The mean change from baseline to 12 months in BCVA is presented together with 95% confidence interval.

The primary analysis was performed on the Full Analysis set.

Handling of missing values/censoring/discontinuations
For the Full Analysis set, the analysis followed a last observation carried forward (LOCF) approach. In the event that a subject received rescue medication and continued in the study, the last observed value prior to receipt of rescue medication was used in the LOCF procedure.

Supportive analyses
For sensitivity purposes, the primary analysis was repeated using the Per Protocol set. For the Per Protocol set, it was assumed that a complete set of valid observations for the efficacy endpoints would be available. Therefore, no general rules for handling of missing values were specified. In case missing values occurred, details regarding their handling were to be described in a Statistical Analysis Plan.

Analysis of secondary variable(s)

Efficacy
Secondary variables were:
From visual acuity: Mean change in BCVA from baseline to Month 6, percentage of patients gaining $\geq$ 15 letters, and percentage of patients losing $\geq$ 15 letters.
From Optical Coherence Tomography: Mean change in CRT in µm from baseline to Months 6 and 12, and presence or absence of intraretinal cysts and subretinal fluid.
From color fundus photography and fluorescein angiography: Mean change in lesion area in mm2 from screening (pre-treatment) to Months 6 and 12, change in fluorescein

leakage from screening (pre-treatment) to Months 6 and 12, and presence or absence of subretinal/intraretinal hemorrhage or any other disease.

The analysis of the secondary efficacy objectives focused on the Full Analysis set. At all timepoints assessed, each efficacy variable is presented graphically.

Hypothesis tests carried out at timepoints other than 6 and 12 months are considered exploratory

Safety

Safety parameters were AEs, ophthalmic examinations, IOP and vital signs. All safety analyses were performed using the Safety set.

Adverse Events
AEs were deemed treatment emergent if the onset date was on or after the date of first study treatment. Any AEs recorded prior to the start of study treatment were listed as prior medical conditions. Only treatment-emergent AEs are summarized.

AEs are summarized by presenting the number and percentage of patients having any AE, having an eye-related AE, having an AE in each primary system organ class and having each individual AE based on the preferred term. Patients who experienced multiple AEs for a preferred term were counted once, as were patients with multiple AEs per system organ class.

All other information collected (e.g., severity or relationship to study treatment) was tabulated and listed as appropriate. Summary tables are also presented for the subset of AEs suspected to be treatment related.

Deaths, SAEs and AEs leading to discontinuation of study treatment are listed separately and, if appropriate, summarized by primary system organ class and preferred term.
No laboratory data were collected in this study.

Vital signs are summarized by presenting shift tables using extended normal ranges with thresholds representing clinical relevant abnormality and by presenting descriptive statistics of raw data and change from baseline. Values outside the extended normal range are listed by patient and treatment arm and flagged in data listings.

No abnormal ranges were specified in the protocol. The Medical Advisor required the following abnormal ranges to be used:

Variable	**Criterion value**	**Change Relative to Baseline**
Heart rate/ pulse	High Low	Either ≥120 with an increase from baseline ≥25, or >130 absolute Either ≤50 with a decrease from baseline ≥30, or <40 absolute
Systolic blood pressure	High Low	Either ≥180 with an increase from baseline ≥30, or >200 absolute Either ≤ 90 with a decrease from baseline ≥30, or <75 absolute

Variable	Criterion value	Change Relative to Baseline
Diastolic blood pressure	High Low	Either ≥ 105 with an increase from baseline ≥20, or >115 absolute Either ≤ 50 with a decrease from baseline ≥20, or <40 absolute

The ophthalmic slit-lamp examination, IOP and ophthalmoscopy are presented descriptively (absolute values and changes). Continuous variables are summarized by the statistics n, mean, standard deviation, median, minimum and maximum; categorical variables are summarized by frequency distribution (n and %).

Sample size calculation

For the primary efficacy variable (change in BCVA from baseline to 12 months), a sample size of 58 was estimated to have 90% power to detect a difference in mean BCVA of 10, assuming a standard deviation of differences of 23, using a paired t-test with a 0.05 two-sided significance level.

In order to inform the sample size calculations, information was obtained from Monés et al 2009, who reported data on visual acuity changes at 12 months in patients with CNV secondary to PM treated with intravitreal ranibizumab (Monés et al 2009). The baseline mean (SD) visual acuity was 53.04 (16.65) which increased to 62.57 (19.27) at 12 months. In the present study, an improvement of 10 letters in BCVA was considered clinically important. A conservative estimate for the standard deviation of differences of 23 was derived from Monés et al 2009. In order to allow for non-completing patients a total of 64 patients was targeted (one eye per patient). Sample size calculations were done using nQuery Advisor v6.01.

Power for analysis of key secondary variables

Not applicable.

Interim analysis

An interim analysis was performed when 75% of patients (48) had been followed up for six months, to provide data on the short-term efficacy/safety benefit of ranibizumab treatment in CNV due to PM, increase the experience with guided individualized ranibizumab treatment on an ongoing basis and allow a decision to be made whether to continue the study.

Factors which would lead to early termination of the study at this point were:
1) Evidence of a mean deterioration in VA
2) Significant safety concerns

As the study was open-label with a single treatment group and the primary efficacy variable was not to be examined at the time of the interim analysis, no adjustments for multiple testing were required. Results of the interim analysis did not show any evidence of a mean deterioration in VA or safety concerns, and did not result in early termination of the study.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Male or female outpatients of any race, aged 18 years or older
- Diagnosis of active primary or recurrent subfoveal or juxtafoveal CNV secondary to PM
- Diagnosis of high myopia of at least -6 dioptres in the study eye spherical equivalent. For subjects who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye must have been at least -6 dioptres
- Patients who have a BCVA score between 78 and 24 letters in the study eye using Early Treatment Diabetic Retinopathy Study (ETDRS)-like grading charts (approximately 6/9 - 6/96 Snellen equivalent)
- Patients must give fully informed consent and be willing and able to comply with all study procedures

Exclusion Criteria:

- History of any surgical intervention in the study eye within two months preceding screening
- Previous macular laser photocoagulation, treatment with intravitreal steroids, verteporfin with photodynamic therapy (Visudyne®) or anti-VEGF agents ranibizumab, bevacizumab or pegaptanib sodium (Macugen®) in the study eye
- Previous treatment with intravenously administered bevacizumab (Avastin®)
- Prior treatment in the study eye with external-beam radiation therapy, vitrectomy, or transpupillary thermotherapy
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
- History of allergic reaction to fluorescein
- Concurrent use of systemic anti-VEGF agents

Other protocol-defined inclusion/exclusion criteria applied

Participant Flow

In total, 84 patients were screened. Of these, 19 did not fulfill entry criteria and were not enrolled into the study. The most frequent reasons for non-enrollment were not meeting diagnostic/severity criteria (n=7), unacceptable test procedure result (n=3) and unacceptable past medical history/concomitant diagnosis (n=2)

The remaining 65 patients entered the study. Three patients did not complete the study

	Ranibizumab N=65 n(%)
Did subject complete the study?	
No	3 (4.6)
Yes	62 (95.4)
Primary reason for discontinuation?[a]	

	Ranibizumab N=65 n(%)
Did subject complete the study?	
No	3 (4.6)
Yes	62 (95.4)
Unsatisfactory therapeutic effect	1 (1.5)
Protocol violation	1 (1.5)
Lost to follow-up	1 (1.5)

[a] The primary reason for discontinuation as given by the investigator on the study completion paper CRF

Baseline Characteristics

Demographic variable	Ranibizumab N=65
Age (years)	
N	65
Mean	55.5
SD	14.97
Median	55.9
Minimum	21
Maximum	92
Age group - n (%)	
<50	21 (32.3)
50 - < 65	29 (44.6)
65 - < 75	10 (15.4)
75 - < 85	3 (4.6)
≥85	2 (3.1)
Sex - n (%)	
Male	19 (29.2)
Female	46 (70.8)
Predominant race - n (%)	
Caucasian	59 (90.8)
Black	1 (1.5)
Oriental	2 (3.1)
Other	3 (4.6)
Ethnicity - n (%)	
Other	56 (86.2)
Unknown	1 (1.5)
Hispanic/Latino	2 (3.1)
Chinese	2 (3.1)
Indian (Indian subcontinent)	3 (4.6)
Mixed ethnicity	1 (1.5)

Study eye iris color - n (%)	
Black	3 (4.6)
Brown	8 (12.3)
Hazel	15 (23.1)
Green	8 (12.3)
Blue	25 (38.5)
Grey	6 (9.2)
Height (cm)	
n	64
Mean	165.6
SD	10.13
Median	164.0
Minimum	145
Maximum	192
Weight (kg)	
n	64
Mean	76.79
SD	17.998
Median	74.65
Minimum	47.2
Maximum	124.0

SD, standard deviation

Outcome Measures

Primary Outcome Result

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

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
Baseline (V2)	N	65		
	Mean	59.5		
	SD	13.59		
	Median	60.0		
	Min	26		
	Max	85		
Month 1 (V3)	N	63	63	63
	Mean	59.8	68.5	8.71
	SD	13.73	13.56	12.676
	Median	60.0	73.0	7.00
	Min	26	38	-42.0
	Max	85	85	44.0

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	SEM			1.597
	p-value			<0.001
	95% CI			(5.52, 11.91)
Month 2 (V4)	N	63	63	63
	Mean	59.9	70.3	10.43
	SD	13.66	12.95	12.644
	Median	60.0	73.0	7.00
	Min	26	27	-23.0
	Max	85	90	47.0
	SEM			1.593
	p-value			<0.001
	95% CI			(7.24, 13.61)
Month 3 (V5)	n	63	63	63
	Mean	59.4	69.3	9.92
	SD	13.51	13.18	13.234
	Median	60.0	72.0	8.00
	Min	26	35	-29.0
	Max	85	92	47.0
	SEM			1.667
	p-value			<0.001
	95% CI			(6.59, 13.25)
Month 4 (V6)	n	63	63	63
	Mean	59.4	71.0	11.60
	SD	13.51	13.72	13.863
	Median	60.0	73.0	10.00
	Min	26	37	-19.0
	Max	85	89	46.0
	SEM			1.747
	p-value			<0.001
	95% CI			(8.11, 15.09)
Month 5 (V7)	n	62	62	62
	Mean	59.9	69.6	9.68
	SD	12.92	14.30	14.409
	Median	60.0	74.0	9.00
	Min	34	37	-29.0
	Max	85	90	46.0
	SEM			1.830

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	p-value			<0.001
	95% CI			(6.02, 13.34)
Month 6 (V8)	n	61	61	61
	Mean	59.6	70.7	11.13
	SD	13.30	15.45	15.414
	Median	60.0	74.0	8.00
	Min	26	19	-28.0
	Max	85	93	48.0
	SEM			1.974
	p-value			<0.001
	95% CI			(7.18, 15.08)
Month 7 (V9)	n	61	61	61
	Mean	59.1	71.4	12.38
	SD	13.60	14.40	14.590
	Median	59.0	74.0	10.00
	Min	26	22	-24.0
	Max	85	93	47.0
	SEM			1.868
	p-value			<0.001
	95% CI			(8.64, 16.11)
Month 8 (V10)	n	60	60	60
	Mean	59.6	72.2	12.62
	SD	12.96	13.89	12.344
	Median	59.5	77.0	11.50
	Min	34	25	-21.0
	Max	85	92	49.0
	SEM			1.594
	p-value			<0.001
	95% CI			(9.43, 15.81)
Month 9 (V11)	n	61	61	61
	Mean	59.3	72.8	13.49
	SD	13.62	14.42	14.302
	Median	60.0	76.0	13.00
	Min	26	17	-29.0
	Max	85	89	51.0
	SEM			1.831
	p-value			<0.001

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	95% CI			(9.83, 17.15)
Month 10 (V12)	n	60	60	60
	Mean	59.4	73.5	14.15
	SD	13.31	13.29	13.519
	Median	59.5	77.0	13.00
	Min	26	28	-18.0
	Max	85	94	51.0
	SEM			1.745
	p-value			<0.001
	95% CI			(10.66, 17.64)
Month 11 (V13)	n	59	59	59
	Mean	58.8	72.6	13.80
	SD	13.60	14.79	14.706
	Median	59.0	77.0	12.00
	Min	26	13	-33.0
	Max	85	93	51.0
	SEM			1.915
	p-value			<0.001
	95% CI			(9.96, 17.63)
Month 12 (V14)	n	63	63	63
	Mean	59.3	73.0	13.76
	SD	13.58	13.29	14.018
	Median	60.0	75.0	10.00
	Min	26	27	-19.0
	Max	85	94	49.0
	SEM			1.766
	p-value			<0.001
	95% CI			(10.23, 17.29)
LOCF	n	65	65	65
	Mean	59.5	73.1	13.60
	SD	13.59	13.13	13.862
	Median	60.0	75.0	10.00
	Min	26	27	-19.0
	Max	85	94	49.0
	SEM			1.719
	p-value			<0.001

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	95% CI			(10.17, 17.03)

Change = Post-baseline – baseline.
n = the number of patients 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.
SEM, standard error of mean; SD, standard deviation; LOCF, last observation carried forward

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)

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
Baseline (V2)	N	62		
	Mean	384.66		
	SD	130.884		
	Median	390.00		
	Min	108.0		
	Max	812.0		
Month 1 (V3)	N	60	60	60
	Mean	389.67	280.55	-109.12
	SD	127.980	89.705	127.353
	Median	393.00	264.00	-111.00
	Min	116.0	160.0	-610.0
	Max	812.0	572.0	221.0
Month 2 (V4)	N	60	60	60
	Mean	385.22	277.10	-108.12
	SD	133.041	87.237	125.988
	Median	393.00	263.50	-120.50
	Min	108.0	121.0	-633.0
	Max	812.0	618.0	104.0
Month 3 (V5)	N	60	62	60
	Mean	386.98	269.16	-114.77
	SD	132.172	80.621	124.371
	Median	393.00	253.50	-101.00
	Min	108.0	140.0	-646.0
	Max	812.0	510.0	121.0

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
Month 4 (V6)	N	60	63	60
	Mean	386.98	252.32	-130.23
	SD	132.172	77.277	129.904
	Median	393.00	233.00	-136.00
	Min	108.0	134.0	-652.0
	Max	812.0	502.0	105.0
Month 5 (V7)	N	60	62	60
	Mean	386.98	257.19	-126.65
	SD	132.172	76.495	127.646
	Median	393.00	239.50	-127.00
	Min	108.0	119.0	-633.0
	Max	812.0	487.0	154.0
Month 6 (V8)	N	59	61	59
	Mean	387.53	256.72	-128.76
	SD	133.240	82.714	127.840
	Median	394.00	235.00	-119.00
	Min	108.0	112.0	-633.0
	Max	812.0	486.0	91.0
	SEM			16.643
	p-value			<0.001
	95% CI			(-162, -95.4)
Month 7 (V9)	N	58	58	58
	Mean	388.57	262.19	-126.38
	SD	134.160	87.695	137.481
	Median	394.50	235.00	-112.00
	Min	108.0	107.0	-633.0
	Max	812.0	532.0	186.0
	SEM			18.052
	p-value			<0.001
	95% CI			(-163, -90.2)
Month 8 (V10)	N	58	58	58
	Mean	385.60	253.60	-132.00
	SD	133.576	83.757	133.839
	Median	393.00	232.50	-110.50
	Min	108.0	112.0	-633.0
	Max	812.0	515.0	97.0
	SEM			17.574

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	p-value			<0.001
	95% CI			(-167, -96.8)
Month 9 (V11)	N	58	58	58
	Mean	392.17	256.50	-135.67
	SD	129.491	85.250	131.823
	Median	394.50	237.50	-124.00
	Min	108.0	132.0	-639.0
	Max	812.0	561.0	143.0
	SEM			17.309
	p-value			<0.001
	95% CI			(-170, -101)
Month 10 (V12)	N	58	58	58
	Mean	389.84	249.79	-140.05
	SD	133.196	79.485	131.586
	Median	394.50	232.50	-125.00
	Min	108.0	119.0	-640.0
	Max	812.0	502.0	101.0
	SEM			17.278
	p-value			<0.001
	95% CI			(-175, -105)
Month 11 (V13)	N	55	55	55
	Mean	393.78	248.71	-145.07
	SD	131.840	80.771	139.904
	Median	395.00	224.00	-141.00
	Min	116.0	88.0	-637.0
	Max	812.0	496.0	128.0
	SEM			18.865
	p-value			<0.001
	95% CI			(-183, -107)
Month 12 (V14)	N	61	61	61
	Mean	386.56	251.39	-135.16
	SD	131.108	78.060	134.117
	Median	392.00	231.00	-104.00
	Min	108.0	88.0	-639.0
	Max	812.0	513.0	121.0
	SEM			17.172
	p-value			<0.001

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	95% CI			(-170, -101)

Change = Post-baseline – baseline.
n = the number of patients 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.
SEM, standard error of mean; SD, standard deviation

Visual acuity (letters) of the study eye: proportion of gains/losses from baseline to Month 12 by visit (Full Analysis set)

	Ranibizumab N=65
Loss of 15 or more letters - n(%)	
N/A	2 (3.1)
No	62 (95.4)
Yes	1 (1.5)
Loss of 8 or more letters - n(%)	
N/A	2 (3.1)
No	62 (95.4)
Yes	1 (1.5)
Gain of 5 or more letters - n(%)	
N/A	2 (3.1)
No	14 (21.5)
Yes	49 (75.4)
Gain of 10 or more letters - n(%)	
N/A	2 (3.1)
No	30 (46.2)
Yes	33 (50.8)
Gain of 15 or more letters - n(%)	
N/A	2 (3.1)
No	39 (60.0)
Yes	24 (36.9)

N/A, not available

Fluorescein angiogram and fundus photography (study eye): area of lesion (mm^2) summary statistics of absolute value and change from baseline by visit (Full Analysis set)

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
Baseline (V2)	n	65		

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	Mean	1.46		
	SD	1.351		
	Median	1.01		
	Min	0.1		
	Max	6.6		
Month 1 (V3)	n	50	50	50
	Mean	1.58	1.22	-0.36
	SD	1.454	1.501	0.787
	Median	1.15	0.74	-0.23
	Min	0.1	0.0	-3.7
	Max	6.6	7.5	2.2
	SEM			0.111
	p-value			0.0021
	95% CI			(-0.6, -0.1)
Month 2 (V4)	n	2	2	2
	Mean	0.97	0.35	-0.63
	SD	0.382	0.092	0.474
	Median	0.97	0.35	-0.63
	Min	0.7	0.3	-1.0
	Max	1.2	0.4	-0.3
	SEM			0.335
	p-value			0.3132
	95% CI			(-4.9, 3.6)
Month 3 (V5)	n	4	4	4
	Mean	0.56	0.57	0.01
	SD	0.146	0.144	0.157
	Median	0.57	0.56	0.01
	Min	0.4	0.4	-0.2
	Max	0.7	0.8	0.2
	SEM			0.078
	p-value			0.9532
	95% CI			(-0.2, 0.3)
Month 4 (V6)	n	2	2	2
	Mean	0.67	0.45	-0.22
	SD	0.157	0.016	0.173
	Median	0.67	0.45	-0.22
	Min	0.6	0.4	-0.3

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	Max	0.8	0.5	-0.1
	SEM			0.123
	p-value			0.3204
	95% CI			(-1.8, 1.3)
Month 5 (V7)	n	2	2	2
	Mean	0.70	0.22	-0.47
	SD	0.434	0.053	0.487
	Median	0.70	0.22	-0.47
	Min	0.4	0.2	-0.8
	Max	1.0	0.3	-0.1
	SEM			0.345
	p-value			0.3998
	95% CI			(-4.9, 3.9)
Month 6 (V8)	n	48	48	48
	Mean	1.61	1.10	-0.51
	SD	1.482	1.425	0.994
	Median	1.15	0.53	-0.52
	Min	0.1	0.0	-3.7
	Max	6.6	7.5	2.3
	SEM			0.144
	p-value			0.0008
	95% CI			(-0.8, -0.2)
Month 7 (V9)	n	4	4	4
	Mean	1.44	0.80	-0.64
	SD	1.265	0.974	0.339
	Median	0.94	0.36	-0.62
	Min	0.6	0.2	-1.1
	Max	3.3	2.3	-0.2
	SEM			0.170
	p-value			0.0330
	95% CI			(-1.2, -0.1)
Month 8 (V10)	n		0	0
	Mean			
	SD			
	Median			
	Min			
	Max			

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	SEM			
	p-value			
	95% CI			(,)
Month 9 (V11)	n	1	1	1
	Mean	4.46	5.66	1.20
	SD			
	Median	4.46	5.66	1.20
	Min	4.5	5.7	1.2
	Max	4.5	5.7	1.2
	SEM			
	p-value			
	95% CI			(,)
Month 10 (V12)	n	1	1	1
	Mean	2.48	2.29	-0.19
	SD			
	Median	2.48	2.29	-0.19
	Min	2.5	2.3	-0.2
	Max	2.5	2.3	-0.2
	SEM			
	p-value			
	95% CI			(,)
Month 11 (V13)	n	1	1	1
	Mean	0.56	0.72	0.16
	SD			
	Median	0.56	0.72	0.16
	Min	0.6	0.7	0.2
	Max	0.6	0.7	0.2
	SEM			
	p-value			
	95% CI			(,)
Month 12 (V14)	n	50	50	50
	Mean	1.73	1.36	-0.37
	SD	1.428	1.782	1.161
	Median	1.29	0.66	-0.39
	Min	0.1	0.0	-3.7
	Max	6.6	8.1	3.6
	SEM			0.164

Visit	Statistic	Baseline	Ranibizumab N=65 Post-baseline	Change
	p-value			0.0287
	95% CI			(-0.7, -0.0)

Change = Post-baseline – baseline.
n = the number of patients 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.
SEM, standard error of mean; SD, standard deviation

Baseline fluorescein angiography and fundus photography characteristics of the study eye (Safety set)

Parameter/statistics	Ranibizumab N= 65
Fluorescein angiogram performed – n (%)	
Yes	65 (100.0)
Evidence of CNV – n (%)	
Yes	65 (100.0)
CNV location in relation to the fovea – n (%)	
Subfoveal	43 (66.2)
Juxtafoveal	17 (26.2)
Probably subfoveal/ juxtafoveal	5 (7.7)
Area of Lesion (mm^2)	
n	65
Mean	1.463
SD	1.3511
Median	1.010
Minimum	0.12
Maximum	6.56
Subretinal/intraretinal hemorrhage - n(%)	
Yes	41 (63.1)
No	24 (36.9)
Other disease - n(%)	
Yes	5 (7.7)
No	58 (89.2)
N/A	1 (1.5)
Questionable	1 (1.5)

Fluoroscein angiogram and fundus photography (study eye): leakage, subretinal/intraretinal haemorrhage and other disease. Summary by visit (Full analysis set)

Parameter	Visit		Ranibizumab N= 65 n (%)
Leakage	Mth1 (v3)	Complete absence of fluoroscein leakage	34 (53.1)
		Leakage within original leakage area	20 (31.3)
		N/A	9 (14.1)
		Progression compared to original lesion area	1 (1.6)
	Mth 2 (v4)	Complete absence of fluoroscein leakage	1 (1.6)
		Leakage within original leakage area	1 (1.6)
		N/A	60 (96.8)
	Mth 3 (v5)	Complete absence of fluoroscein leakage	3 (4.8)
		Leakage within original leakage area	1 (1.6)
		N/A	59 (93.7)
	Mth 4 (v6)	Complete absence of fluoroscein leakage	2 (3.1)
		N/A	62 (96.9)
	Mth 5 (v7)	Complete absence of fluoroscein leakage	2 (3.2)
		N/A	61 (96.8)
	Mth 6 (v8)	Complete absence of fluoroscein leakage	45 (72.6)
		Leakage within original leakage area	9 (14.5)
		N/A	7 (11.3)
		Progression compared to original lesion area	1 (1.6)
	Mth 7 (v9)	Complete absence of fluorescein leakage	3 (4.8)
		Leakage within original leakage area	1 (1.6)
		N/A	58 (93.5)

	Mth 8 (v10)	N/A	61 (100.0)
	Mth 9 (v11)	Complete absence of fluorescein leakage	1 (1.6)
		N/A	60 (98.4)
	Mth 10 (v12)	Leakage within original leakage area	1 (1.7)
		N/A	59 (98.3)
	Mth 11 (v13)	Complete absence of fluorescein leakage	2 (3.2)
		N/A	60 (96.8)
	Mth 12 (v14)	Can't grade	1 (1.6)
		Complete absence of fluorescein leakage	54 (84.4)
		Leakage within original leakage area	4 (6.3)
		N/A	5 (7.8)
Subretinal/intraretinal Haemorrhage	Mth1 (v3)	N/A	10 (15.6)
		No	43 (67.2)
		Yes	11 (17.2)
	Mth 2 (v4)	N/A	59 (95.2)
		No	3 (4.8)
	Mth 3 (v5)	N/A	59 (93.7)
		No	4 (6.3)
	Mth4 (v6)	N/A	62 (96.9)
		No	2 (3.1)
	Mth 5 (v7)	N/A	60 (95.2)
		No	3 (4.8)
	Mth 6 (v8)	N/A	6 (9.7)
		No	52 (83.9)
		Yes	4 (6.5)
	Mth 7 (v9)	N/A	57 (91.9)
		No	4 (6.5)
		Yes	1 (1.6)
	Mth 8 (v10)	N/A	61 (100.0)
	Mth 9 (v11)	N/A	59 (96.7)
		No	1 (1.6)
		Yes	1 (1.6)
	Mth 10 (v12)	N/A	59 (98.3)
		No	1 (1.7)
	Mth 11 (v13)	N/A	60 (96.8)
		No	2 (3.2)
	Mth 12 (v14)	N/A	5 (7.8)
		No	58 (90.6)
		Yes	1 (1.6)
Other disease	Mth1 (v3)	N/A	10 (15.6)
		No	51 (79.7)
		Questionable	1 (1.6)
		Yes	2 (3.1)
	Mth 2 (v4)	N/A	59 (95.2)
		No	3 (4.8)
	Mth 3 (v5)	N/A	59 (93.7)
		No	4 (6.3)

Mth 4 (v6)	N/A	62 (96.9)
	No	2 (3.1)
Mth 5 (v7)	N/A	60 (95.2)
	No	2 (3.2)
	Yes	1 (1.6)
Mth 6 (v8)	N/A	6 (9.7)
	No	51 (82.3)
	Questionable	1 (1.6)
	Yes	4 (6.5)
Mth 7 (v9)	N/A	58 (93.5)
	No	3 (4.8)
	Yes	1 (1.6)
Mth 8 (v10)	N/A	61 (100.0)
Mth 9 (v11)	N/A	59 (96.7)
	No	2 (3.3)
Mth 10 (v12)	N/A	59 (98.3)
	No	1 (1.7)
Mth 11 (v13)	N/A	60 (96.8)
	No	2 (3.2)
Mth 12 (v14)	N/A	5 (7.8)
	No	59 (92.2)

- Excludes data at unscheduled visits

Time to first retreatment following the month 1 treatment (months) – Kaplan–Meier estimates (Full analysis set)

		Point estimate Ranibizumab N= 65	95% CI
Time to first retreatment following the month 1 treatment (months)	25th percentile	1.07	(0.95, 1.22)
	Median	2.00	(1.25, 3.42)
	75th percentile	6.24	(3.71,)

- Time to first re-treatment is calculated as time difference in months starting from the date of the first treatment until the date of first re-treatment
- Median, 25%, 75% percentiles are based on Kaplan-Meier estimates of survival function
- 95% CI based on Kaplan-Meier methods

Number of retreatments following the baseline treatment: Summary statistics (Full Analysis set)

	Ranibizumab N=65
Patients with at least one retreatment - n(%)	
No	14 (21.5)
Yes	51 (78.5)
Total number of treatments	
N	65
Mean	3.6
SD	2.57
Median	3.0
Minimum	1
Maximum	12
Total number of retreatments	
N	65
Mean	2.6
SD	2.57
Median	2.0
Minimum	0
Maximum	11
Frequency of retreatments - n(%)	
0	14 (21.5)
1	12 (18.5)
2	11 (16.9)
3	10 (15.4)
4	6 (9.2)
5	4 (6.2)
6	4 (6.2)
8	1 (1.5)
9	1 (1.5)
11	2 (3.1)

SD, standard deviation

Safety Results

Number (%) of patients with AEs by primary system organ class (Safety set)

Primary system organ class	Preferred term	Ranibizumab N=65 n(%)
Any primary system organ class	-Total	46 (70.8%)
Blood and lymphatic system disorders	-Total	1 (1.5%)
	Anemia	1 (1.5%)
Cardiac disorders	-Total	1 (1.5%)
	Angina pectoris	1 (1.5%)
Eye disorders	-Total	24 (36.9%)
	Anterior chamber inflammation	1 (1.5%)
	Blepharitis	1 (1.5%)
	Blindness	1 (1.5%)
	Choroidal neovascularization	1 (1.5%)
	Conjunctival hemorrhage	4 (6.2%)
	Conjunctival hyperemia	1 (1.5%)
	Conjunctivitis	1 (1.5%)
	Eye discharge	1 (1.5%)
	Eye inflammation	1 (1.5%)
	Eye pain	7 (10.8%)
	Eyelid pain	1 (1.5%)
	Foreign body sensation in eyes	3 (4.6%)
	Glaucoma	1 (1.5%)
	Hyphema	1 (1.5%)
	Metamorphopsia	2 (3.1%)
	Normal tension glaucoma	1 (1.5%)
	Ocular discomfort	1 (1.5%)
	Photophobia	1 (1.5%)
	Punctate keratitis	1 (1.5%)
	Retinal detachment	1 (1.5%)
	Retinal tear	1 (1.5%)
	Ulcerative keratitis	1 (1.5%)
	Vision blurred	2 (3.1%)
	Visual acuity reduced	2 (3.1%)
	Visual impairment	1 (1.5%)
	Vitreous detachment	1 (1.5%)
	Vitreous floaters	4 (6.2%)
Gastrointestinal disorders	-Total	4 (6.2%)

Primary system organ class	Preferred term	Ranibizumab N=65 n(%)
	Diarrhea	1 (1.5%)
	Hiatus hernia	1 (1.5%)
	Irritable bowel syndrome	1 (1.5%)
	Vomiting	1 (1.5%)
General disorders and administration site conditions	-Total	4 (6.2%)
	Extravasation	1 (1.5%)
	Mass	1 (1.5%)
	Non-cardiac chest pain	1 (1.5%)
	Tenderness	1 (1.5%)
Hepatobiliary disorders	-Total	1 (1.5%)
	Cholelithiasis	1 (1.5%)
Immune system disorders	-Total	1 (1.5%)
	Seasonal allergy	1 (1.5%)
Infections and infestations	-Total	19 (29.2%)
	Candidiasis	1 (1.5%)
	Endophthalmitis	1 (1.5%)
	Fungal infection	1 (1.5%)
	Gastroenteritis viral	1 (1.5%)
	Hordeolum	1 (1.5%)
	Infected dermal cyst	1 (1.5%)
	Influenza	2 (3.1%)
	Localized infection	1 (1.5%)
	Lower respiratory tract infection	5 (7.7%)
	Nasopharyngitis	6 (9.2%)
	Sinusitis	2 (3.1%)
	Tonsillitis	1 (1.5%)
	Upper respiratory tract infection	2 (3.1%)
Injury, poisoning and procedural complications	-Total	11 (16.9%)
	Corneal abrasion	1 (1.5%)
	Exposure via father	1 (1.5%)
	Fall	4 (6.2%)
	Head injury	1 (1.5%)
	Joint dislocation	1 (1.5%)
	Procedural complication	1 (1.5%)
	Procedural nausea	2 (3.1%)
	Procedural pain	1 (1.5%)

Primary system organ class	Preferred term	Ranibizumab N=65 n(%)
	Procedural site reaction	1 (1.5%)
	Rib fracture	1 (1.5%)
	Wrist fracture	1 (1.5%)
Investigations	-Total	6 (9.2%)
	Blood cholesterol increased	1 (1.5%)
	Blood pressure increased	1 (1.5%)
	Colonoscopy	1 (1.5%)
	Endoscopy	1 (1.5%)
	Intraocular pressure increased	2 (3.1%)
	Urine analysis abnormal	1 (1.5%)
Metabolism and nutrition disorders	-Total	4 (6.2%)
	Gout	2 (3.1%)
	Hypercholesterolemia	1 (1.5%)
	Type 2 diabetes mellitus	1 (1.5%)
Musculoskeletal and connective tissue disorders	-Total	8 (12.3%)
	Arthralgia	2 (3.1%)
	Back pain	4 (6.2%)
	Muscle spasms	1 (1.5%)
	Musculoskeletal pain	2 (3.1%)
	Osteoarthritis	1 (1.5%)
	Rheumatoid arthritis	1 (1.5%)
	Tendonitis	1 (1.5%)
Nervous system disorders	-Total	6 (9.2%)
	Dizziness	2 (3.1%)
	Headache	4 (6.2%)
	Migraine	2 (3.1%)
	Syncope	1 (1.5%)
Psychiatric disorders	-Total	3 (4.6%)
	Anxiety	1 (1.5%)
	Depression	1 (1.5%)
	Panic attack	1 (1.5%)
Reproductive system and breast disorders	-Total	1 (1.5%)
	Breast mass	1 (1.5%)
Respiratory, thoracic and mediastinal disorders	-Total	9 (13.8%)
	Asthma	1 (1.5%)

Primary system organ class	Preferred term	Ranibizumab N=65 n(%)
	Chronic obstructive pulmonary disease	1 (1.5%)
	Cough	4 (6.2%)
	Nasal polyps	1 (1.5%)
	Oropharyngeal pain	1 (1.5%)
	Rhinitis allergic	1 (1.5%)
Skin and subcutaneous tissue disorders	-Total	2 (3.1%)
	Rash	1 (1.5%)
	Scab	1 (1.5%)
	Skin reaction	1 (1.5%)
Surgical and medical procedures	-Total	4 (6.2%)
	Fracture treatment	1 (1.5%)
	Tooth extraction	2 (3.1%)
	Trabeculectomy	1 (1.5%)
Vascular disorders	-Total	3 (4.6%)
	Hypertension	3 (4.6%)

Primary system organ classes are presented alphabetically
A patient with multiple occurrences of an AE is counted only once in the AE category.
A patient with multiple AEs within a primary system organ class is counted only once in the total row.

Number (%) of patients with AEs by preferred term (at least 2% incidence) (Safety set)

Preferred term	Ranibizumab N=65 n(%)
Any adverse event	46 (70.8%)
Eye pain	7 (10.8%)
Nasopharyngitis	6 (9.2%)
Lower respiratory tract infection	5 (7.7%)
Back pain	4 (6.2%)
Conjunctival hemorrhage	4 (6.2%)
Cough	4 (6.2%)
Fall	4 (6.2%)
Headache	4 (6.2%)
Vitreous floaters	4 (6.2%)
Foreign body sensation in eyes	3 (4.6%)
Hypertension	3 (4.6%)
Arthralgia	2 (3.1%)
Dizziness	2 (3.1%)

Preferred term	Ranibizumab N=65 n(%)
Gout	2 (3.1%)
Influenza	2 (3.1%)
Intraocular pressure increased	2 (3.1%)
Metamorphopsia	2 (3.1%)
Migraine	2 (3.1%)
Musculoskeletal pain	2 (3.1%)
Procedural nausea	2 (3.1%)
Sinusitis	2 (3.1%)
Tooth extraction	2 (3.1%)
Upper respiratory tract infection	2 (3.1%)
Vision blurred	2 (3.1%)
Visual acuity reduced	2 (3.1%)

Preferred terms are presented alphabetically;
A patient with multiple occurrences of an AE is counted only once in the AE category.

Number (%) of patients who died or experienced other serious or clinically significant adverse events (Safety set)

	Ranibizumab N=65 n(%)
Death	0
Serious adverse event(s)	3 (4.6%)
Discontinued due to AEs	0
Discontinued due to SAE	0
Discontinued due to non-serious AE	0
Drug-related AE discontinuation	0
AE requiring dose adjustment or interruption	1 (1.5%)

AE, adverse event; SAE, serious adverse event

Other Relevant Findings

Well-being questionnaire (W-BQ12) scores: Summary statistics and change from baseline by visit (Full Analysis set)

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
W-BQ12: Negative well-being				
Baseline (V2)	N	65		

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	Mean	2.3		
	SD	2.80		
	Median	1.0		
	Min	0		
	Max	11		
Month 1 V3)	N	59	59	59
	Mean	2.1	1.4	-0.71
	SD	2.45	1.95	1.966
	Median	1.0	0.0	0.00
	Min	0	0	-8.0
	Max	10	8	3.0
	SEM			0.256
	p-value			0.0073
	95% CI			(-1.2, -0.2)
Month 6 (V8)	n	61	61	61
	Mean	2.3	1.7	-0.59
	SD	2.86	2.47	2.741
	Median	1.0	0.0	0.00
	Min	0	0	-8.0
	Max	11	12	11.0
	SEM			0.351
	p-value			0.0978
	95% CI			(-1.3, 0.1)
Month 12 (V14)	n	61	61	61
	Mean	2.2	1.5	-0.67
	SD	2.68	2.60	2.657
	Median	1.0	0.0	0.00
	Min	0	0	-8.0
	Max	11	12	10.0
	SEM			0.340
	p-value			0.0528
	95% CI			(-1.4, 0.0)
W-BQ12: Energy				
Baseline (V2)	n	65		
	Mean	7.6		
	SD	2.54		
	Median	8.0		

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	Min	1		
	Max	12		
Month 1 (V3)	n	59	59	59
	Mean	7.7	7.6	-0.03
	SD	2.37	2.30	2.392
	Median	8.0	8.0	0.00
	Min	2	1	-6.0
	Max	12	12	8.0
	SEM			0.311
	p-value			0.9137
	95% CI			(-0.7, 0.6)
Month 6 (V8)	n	61	61	61
	Mean	7.6	8.0	0.38
	SD	2.43	2.48	2.484
	Median	8.0	8.0	0.00
	Min	1	1	-5.0
	Max	12	12	8.0
	SEM			0.318
	p-value			0.2406
	95% CI			(-0.3, 1.0)
Month 12 (V14)	n	61	61	61
	Mean	7.6	8.1	0.49
	SD	2.53	2.44	2.314
	Median	8.0	9.0	0.00
	Min	1	0	-6.0
	Max	12	12	6.0
	SEM			0.296
	p-value			0.1021
	95% CI			(-0.1, 1.1)
W-BQ12: Positive well-being				
Baseline (V2)	n	65		
	Mean	8.3		
	SD	2.74		
	Median	8.0		
	Min	0		
	Max	12		

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
Month 1 (V3)	n	59	59	59
	Mean	8.2	8.6	0.32
	SD	2.62	2.59	3.093
	Median	8.0	9.0	0.00
	Min	0	0	-10.0
	Max	12	12	12.0
	SEM			0.403
	p-value			0.4271
	95% CI			(-0.5, 1.1)
Month 6 (V8)	n	61	61	61
	Mean	8.2	8.9	0.70
	SD	2.78	2.61	2.917
	Median	8.0	9.0	1.00
	Min	0	0	-6.0
	Max	12	12	12.0
	SEM			0.374
	p-value			0.0640
	95% CI			(-0.0, 1.5)
Month 12 (V14)	n	61	61	61
	Mean	8.2	8.7	0.49
	SD	2.78	2.66	2.637
	Median	8.0	9.0	0.00
	Min	0	0	-5.0
	Max	12	12	11.0
	SEM			0.338
	p-value			0.1504
	95% CI			(-0.2, 1.2)
W-BQ12: General Well-being				
Baseline (V2)	n	65		
	Mean	25.6		
	SD	6.96		
	Median	27.0		
	Min	3		
	Max	36		
Month 1 (V3)	n	59	59	59
	Mean	25.8	26.8	1.00
	SD	6.38	5.03	6.206

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	Median	27.0	28.0	0.00
	Min	8	15	-10.0
	Max	36	35	27.0
	SEM			0.808
	p-value			0.2208
	95% CI			(-0.6, 2.6)
Month 6 (V8)	n	61	61	61
	Mean	25.5	27.2	1.67
	SD	6.98	6.08	6.752
	Median	27.0	28.0	1.00
	Min	3	9	-14.0
	Max	36	36	28.0
	SEM			0.865
	p-value			0.0578
	95% CI			(-0.1, 3.4)
Month 12 (V14)	n	61	61	61
	Mean	25.6	27.3	1.66
	SD	7.00	6.35	5.831
	Median	27.0	29.0	2.00
	Min	3	0	-10.0
	Max	36	36	25.0
	SEM			0.747
	p-value			0.0304
	95% CI			(0.2, 3.1)

Change = Post-baseline – baseline.
n = the number of patients 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.
SEM, standard error of mean; SD, standard deviation

Macular Disease Treatment Satisfaction Questionnaire (MacTSQ) scores: Summary statistics and change from baseline by visit (Full Analysis set)

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
MacTSQ: Information provision and convenience				
Month 1 (V3)	N	62		
	Mean	28.7		

			Ranibizumab N=65	
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	SD	10.85		
	Median	33.5		
	Min	4		
	Max	36		
Month 6 (V8)	N	59	59	59
	Mean	28.6	29.2	0.59
	SD	11.05	9.73	7.598
	Median	34.0	33.0	0.00
	Min	4	4	-18.0
	Max	36	36	30.0
	SEM			0.989
	p-value			0.5510
	95% CI			(-1.39, 2.57)
Month 12 (V14)	N	61	61	61
	Mean	28.8	32.9	4.07
	SD	10.92	6.03	12.564
	Median	34.0	35.0	0.00
	Min	4	6	-29.0
	Max	36	36	31.0
	SEM			1.609
	p-value			0.0141
	95% CI			(0.85, 7.28)
MacTSQ: Impact of treatment				
Month 1 (V3)	N	62		
	Mean	26.2		
	SD	7.87		
	Median	28.0		
	Min	6		
	Max	36		
Month 6 (V8)	N	59	59	59
	Mean	26.0	29.6	3.61
	SD	7.97	7.31	5.126
	Median	28.0	33.0	3.00
	Min	6	7	-5.0
	Max	36	36	22.0
	SEM			0.667
	p-value			<0.001

		Ranibizumab N=65		
Visit	**Statistic**	**Baseline**	**Post-baseline**	**Change**
	95% CI			(2.27, 4.95)
Month 12 (V14)	N	61	61	61
	Mean	26.2	32.0	5.80
	SD	7.93	4.88	7.225
	Median	28.0	34.0	5.00
	Min	6	17	-13.0
	Max	36	36	30.0
	SEM			0.925
	p-value			<0.001
	95% CI			(3.95, 7.65)
MacTSQ: MacTSQ				
Month 1 (V3)	N	62		
	Mean	55.0		
	SD	17.88		
	Median	62.0		
	Min	10		
	Max	72		
Month 6 (V8)	N	59	59	59
	Mean	54.6	58.8	4.20
	SD	18.17	16.21	11.115
	Median	62.0	65.0	3.00
	Min	10	13	-19.0
	Max	72	72	52.0
	SEM			1.447
	p-value			0.0052
	95% CI			(1.31, 7.10)
Month 12 (V14)	N	61	61	61
	Mean	55.0	64.9	9.87
	SD	18.01	9.23	18.644
	Median	62.0	68.0	5.00
	Min	10	24	-40.0
	Max	72	72	58.0
	SEM			2.387
	p-value			0.0001
	95% CI			(5.09, 14.64)

Change = Post-baseline – baseline.

n = the number of patients 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. SEM, standard error of mean

Date of Clinical Trial Report

31 December 2012

Date Inclusion on Novartis Clinical Trial Results Database

05 March 2013

Date of Latest Update