Sponsor

Novartis

Generic Drug Name

Ranibizumab

Therapeutic Area of Trial

Subfoveal choroidal neovascularization secondary to age-related macular degeneration

Approved Indication

Age-related macular degeneration

Study Number

CRFB002A2402

Title

A phase IV, long-term, open-label, multicenter extension study to evaluate the safety and tolerability of ranibizumab in patients with subfoveal choroidal neovascularization (CNV) secondary to age-related macular degeneration (AMD).

Phase of Development

Phase IV

Study Start/End Dates

30-Jul-2007 to 28-Jan-2010

Study Design/Methodology

This was a long-term, open-label, single arm, multicenter extension study to evaluate the safety and tolerability of ranibizumab in patients with subfoveal CNV secondary to AMD who had been previously treated in either of the two ranibizumab studies CRFB002A2302 (EXCITE) or CRFB002A2303 (SUSTAIN). This 24-month study CRFB002A2402 (SECURE) consisted of a 23-month treatment phase and a 1-month follow-up phase. Patients received open-label intravitreal injections of 0.5 mg ranibizumab no more frequently than every 30 days for 24 months.

Centres

41 study centers in 10 countries: Australia (1), Belgium (3), Germany (13), Hungary (3), Israel (3), Netherlands (2), Portugal (2), Spain (8), Turkey (2), and United Kingdom (4).

Publication

None

Objectives

Primary objective(s)

- To assess the ocular and non-ocular safety of ranibizumab by the incidence and severity of ocular and non-ocular adverse events during the 24-month study period.

Secondary objective(s)

- To assess the mean change from baseline in best-corrected visual acuity (BCVA) at Months 6, 12, 18, and 24.
- To assess the number of injections with ranibizumab.

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

Ranibizumab 0.5 mg was administered as an intravitreal injection in accordance with the EU Prescribing Information. Patients were not required to undergo the loading phase of 3 consecutive monthly doses. Patient's visual acuity was monitored on a monthly basis. Ranibizumab should be administered to the patients who experienced a loss in visual acuity (Early Treatment for Diabetic Retinopathy Study; ETDRS), of greater than 5 letters.

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

Not applicable

Criteria for Evaluation

Primary variables

- Incidence and severity of treatment emergent ocular and non-ocular adverse events.

Secondary variables

- Change in BCVA of the study eye from the baseline of the previous study at months 12 and 24 of SECURE, by historical treatment group.
- Categorized change in BCVA of the study eye from the baseline of the previous study at months 12 and 24 of SECURE, by historical treatment group.
- Change in BCVA of the study eye from baseline of the SECURE study at months 6, 12, 18, and 24, by historical treatment group.
- Number of injections with ranibizumab, by historical treatment group.

Safety and tolerability

Safety was assessed by standard ophthalmic examinations, including tonometry, visual acuity, incidence of ocular and systemic adverse events and vital signs.

The tolerability of ranibizumab was assessed by examination of the relationship of AEs/SAEs (ocular and non-ocular) to study drug and ocular injection procedure, and by examination of the documented reasons for premature discontinuation from study drug.

Pharmacology

Not applicable

Other

Not applicable

Statistical Methods

The primary objective of this study was to assess the incidence and severity of treatment emergent ocular and non-ocular adverse events, classified by system organ class and preferred term, during the 24-month study period. Incidence rates together with exact 95% binomial (Clopper-Pearson) confidence intervals (CI) for the incidences rates were calculated. Other safety assessments were summarized descriptively.

The efficacy variable was the change in BCVA. It was analyzed for the change in BCVA of the study eye from the baseline (both from previous study and Day 1 of the SECURE study) by visit. Descriptive statistics for the change from baseline to each scheduled monthly visits in BCVA were presented along with the corresponding 2-sided 95% CI for mean of change from baseline (based on a t-distribution). The BCVA of the study eye was summarized according to proportion of patients who gained $\geq$ 0 / 5 / 10 / 15 letters and lost < 15 / 30 letters from baseline by visit. Missing values for BCVA at scheduled visits were handled using the last observation carried forward (LOCF) method. Only post SECURE study baseline missing values were imputed.

There was no statistical hypothesis testing intended.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male or female patients who completed the 12-month treatment period of study CRFB002A2302 (EXCITE) or CRFB002A2303 (SUSTAIN).
2. Male or female patients who provided written informed consent.

Exclusion criteria

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer.

Number of Subjects

Patient disposition (All enrolled patients)

Disposition	Ranibizumab 0.5 mg Total n (%)
Enrolled set	234
Treated patients	205 (87.6)
Study completion status	
Completed	210 (89.7)
Discontinued	24 (10.3)
Reason for discontinuation	
Adverse event(s)	8 (3.4)
Abnormal laboratory value(s)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)
Unsatisfactory therapeutic effect	1 (0.4)
Subject's condition no longer requires study drug	0 (0.0)
Subject withdrew consent	8 (3.4)
Lost to follow-up	2 (0.9)
Administrative problems	0 (0.0)
Death	5 (2.1)
Protocol deviation	0 (0.0)

Percentage is based on the number of enrolled patients as denominator

Demographic and Background Characteristics

Demographic characteristics at baseline (Safety set)

Characteristic	Ranibizumab 0.5 mg Total N = 234
Previous study treatment – n (%)	
CRFB002A2302 (EXCITE)	134 (57.3)
0.3 mg quarterly	47 (20.1)
0.5 mg quarterly	44 (18.8)
0.3 mg monthly	43 (18.4)
CRFB002A2303 (SUSTAIN)	100 (42.7)
Gender – n (%)	
Male	101 (43.2)
Female	133 (56.8)
Age (years)	
n	234
Mean (SD)	75.5 (7.62)
Median	76.0
Range	54, 95
Age group (years) – n (%)	

50 to < 65	19 (8.1)
65 to < 75	80 (34.2)
75 to < 85	107 (45.7)
≥ 85	28 (12.0)
Race – n (%)	
Caucasian	234 (100.0)
Ethnicity – n (%)	
Hispanic / Latino	22 (9.4)
Other	212 (90.6)

Ocular characteristics of the study eye at baseline (Safety set)

Characteristic	Ranibizumab 0.5 mg Total N = 234
Study eye - n (%)	
Left	117 (50.0)
Right	117 (50.0)
Best-corrected visual acuity (letters)	
n	231
Mean (SD)	60.7 (16.14)
Median	62.0
Range	7, 88
Best-corrected visual acuity (letters) - n (%)	
≤ 52	59 (25.2)
> 52	172 (73.5)
Missing	3 (1.3)

Primary Objective Result(s)

Number (%) of patients with ocular SAEs of the study eye, by preferred term (Safety set)

Preferred term	Ranibizumab 0.5 mg Total N = 234
Total	11 (4.7)
Cataract	6 (2.6)
Endophthalmitis	2 (0.9)
Corneal edema	1 (0.4)
Hyphaema	1 (0.4)
Intraocular lens dislocation	1 (0.4)
Intraocular pressure increased	1 (0.4)
Maculopathy	1 (0.4)
Retinal detachment	1 (0.4)

Number (%) of patients with non-ocular SAEs, by preferred term (Safety set)

Preferred term	Ranibizumab 0.5 mg Total N = 234
Total	62 (26.5)
Cerebrovascular accident	5 (2.1)
Osteoarthritis	3 (1.3)
Angina pectoris	2 (0.9)
Atrial fibrillation	2 (0.9)
Cholelithiasis	2 (0.9)
Colon cancer	2 (0.9)
Hip fracture	2 (0.9)
Myocardial infarction	2 (0.9)
Tachycardia	2 (0.9)
Urinary tract infection	2 (0.9)
Abdominal pain	1 (0.4)
Acute myocardial infarction	1 (0.4)
Angina unstable	1 (0.4)
Ankle fracture	1 (0.4)
Arthralgia	1 (0.4)
Arthritis infective	1 (0.4)
Atrioventricular block	1 (0.4)
Basal ganglia infarction	1 (0.4)
Benign pancreatic neoplasm	1 (0.4)
Benign prostatic hyperplasia	1 (0.4)
Bile duct stone	1 (0.4)
Breast cancer	1 (0.4)
Bronchiectasis	1 (0.4)
Bronchitis	1 (0.4)
Bundle branch block left	1 (0.4)
Cardiac arrest	1 (0.4)
Cellulitis	1 (0.4)
Cerebral ischemia	1 (0.4)
Colon neoplasm	1 (0.4)
Convulsion	1 (0.4)
Coronary artery disease	1 (0.4)
Cough	1 (0.4)
Depression	1 (0.4)
Enteritis	1 (0.4)
Enteritis necroticans	1 (0.4)
Facial bones fracture	1 (0.4)
Fall	1 (0.4)
Fibula fracture	1 (0.4)
Gastrointestinal neoplasm	1 (0.4)
Gastrointestinal obstruction	1 (0.4)

Hepatic vein occlusion	1 (0.4)
Hyperglycemia	1 (0.4)
Inguinal hernia	1 (0.4)
Ischemic stroke	1 (0.4)
Large intestine perforation	1 (0.4)
Liver function test abnormal	1 (0.4)
Lower limb fracture	1 (0.4)
Mediastinitis	1 (0.4)
Myocarditis	1 (0.4)
Nerve root compression	1 (0.4)
Patella fracture	1 (0.4)
Peritoneal abscess	1 (0.4)
Peritonitis	1 (0.4)
Pneumonia	1 (0.4)
Post procedural fistula	1 (0.4)
Postoperative fever	1 (0.4)
Postoperative wound infection	1 (0.4)
Prostate cancer	1 (0.4)
Pulmonary edema	1 (0.4)
Pyelonephritis	1 (0.4)
Pyrexia	1 (0.4)
Rectal hemorrhage	1 (0.4)
Rectocele	1 (0.4)
Renal failure	1 (0.4)
Respiratory distress	1 (0.4)
Salivary gland edema	1 (0.4)
Sick sinus syndrome	1 (0.4)
Stress urinary incontinence	1 (0.4)
Syncope	1 (0.4)
Ulna fracture	1 (0.4)
Umbilical hernia	1 (0.4)
Vaginal prolapse	1 (0.4)
Viral infection	1 (0.4)
Vomiting	1 (0.4)

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

Preferred term	Ranibizumab 0.5 mg Total N = 234
Total	126 (53.8)
Retinal hemorrhage	30 (12.8)
Cataract	27 (11.5)
Intraocular pressure increased	15 (6.4)
Visual acuity reduced	14 (6.0)
Eye pain	13 (5.6)
Choroidal neovascularization	12 (5.1)
Macular edema	7 (3.0)
Retinal edema	7 (3.0)
Blepharitis	6 (2.6)
Conjunctivitis	6 (2.6)
Conjunctival hemorrhage	5 (2.1)
Lacrimation increased	5 (2.1)
Macular degeneration	5 (2.1)

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

Preferred term	Ranibizumab 0.5 mg Total N = 234
Total	160 (68.4)
Hypertension	21 (9.0)
Nasopharyngitis	21 (9.0)
Fall	17 (7.3)
Upper respiratory tract infection	11 (4.7)
Urinary tract infection	11 (4.7)
Depression	8 (3.4)
Influenza	8 (3.4)
Abdominal pain upper	7 (3.0)
Arthralgia	7 (3.0)
Bronchitis	7 (3.0)
Nausea	7 (3.0)
Osteoporosis	7 (3.0)
Anxiety	6 (2.6)
Back pain	6 (2.6)
Cough	6 (2.6)
Diarrhea	6 (2.6)
Vomiting	6 (2.6)
Arrhythmia	5 (2.1)
Asthma	5 (2.1)
Cerebrovascular accident	5 (2.1)
Constipation	5 (2.1)
Dyspepsia	5 (2.1)
Insomnia	5 (2.1)
Musculoskeletal pain	5 (2.1)

Secondary Objective Result(s)

Absolute value and change from previous baseline of BCVA of the study eye at months 12 and 24 of SECURE, by treatment history (Full analysis set, LOCF)

	Ranibizumab 0.5 mg				
	EXCITE (1)				
Best-corrected visual acuity	0.3 mg quarterly N = 47	0.5 mg quarterly N = 44	0.3 mg monthly N = 99	SUSTAIN(2) N = 99	Total N = 233
Previous baseline					
n	47	44	43	99	233
Mean (SD)	55.2 (12.88)	56.0 (13.54)	55.6 (13.41)	55.7 (11.51)	55.6 (12.47)
Median	56.0	60.0	56.0	56.0	57.0
Range	26, 78	20, 73	27, 73	25, 80	20, 80
Value at Month 12					
n	47	44	43	99	233
Mean (SD)	57.8 (17.79)	61.8 (15.81)	58.8 (20.40)	57.2 (18.61)	58.5 (18.27)
Median	62.0	64.0	62.0	60.0	62.0
Range	10, 88	28, 85	0, 90	6, 90	0, 90
Change from previous baseline at Month 12					
n	47	44	43	99	233
Mean (SD)	2.6 (17.57)	5.8 (14.46)	3.2 (18.89)	1.5 (16.33)	2.8 (16.73)
Median	4.0	7.0	5.0	4.0	5.0
Range	-60, 33	-29, 32	-48, 43	-54, 32	-60, 43
95% CI for Mean	(-2.6, 7.8)	(1.4, 10.2)	(-2.6, 9.0)	(-1.8, 4.7)	(0.7, 5.0)
Value at Month 24					
n	47	44	43	99	233
Mean (SD)	56.3 (19.49)	56.7 (17.79)	57.1 (19.82)	55.2 (20.49)	56.1 (19.57)
Median	59.0	58.0	60.0	58.0	58.0
Range	11, 88	15, 85	8, 90	0, 90	0, 90
Change from previous baseline at Month 24					
n	47	44	43	99	233
Mean (SD)	1.1 (18.12)	0.7 (18.21)	1.5 (19.84)	-0.5 (18.18)	0.4 (18.39)
Median	3.0	6.0	0.0	4.0	3.0
Range	-51, 33	-49, 31	-46, 44	-55, 33	-55, 44
95% CI for Mean	(-4.2, 6.4)	(-4.9, 6.2)	(-4.6, 7.6)	(-4.1, 3.2)	(-1.9, 2.8)

Patients previously treated in study (1) CRFB002A2302 (EXCITE); (2) CRFB002A2303 (SUSTAIN)
Previous baseline is defined as the Day 1 value of the previous studies.
Two-sided 95% confidence intervals (CI) for means are from a t-distribution.

Categorized change in BCVA of the study eye from the previous baseline at months 12 and 24 of SECURE, by treatment history (Full analysis set, LOCF)

	Ranibizumab 0.5 mg				
	EXCITE (1)				
Visit BCVA letters from previous baseline	0.3 mg quarterly N = 47	0.5 mg quarterly N = 44	0.3 mg monthly N = 43	SUSTAIN (2) N = 99 n (%)	Total N = 233 n (%)

	n (%)	n (%)	n (%)		
Month 12					
Loss of < 30	43 (91.5)	44 (100.0)	40 (93.0)	92 (92.9)	219 (94.0)
Loss of < 15	41 (87.2)	38 (86.4)	36 (83.7)	87 (87.9)	202 (86.7)
Gain of ≥ 0	33 (70.2)	33 (75.0)	26 (60.5)	60 (60.6)	152 (65.2)
Gain of ≥ 5	22 (46.8)	28 (63.6)	22 (51.2)	47 (47.5)	119 (51.1)
Gain of ≥ 10	16 (34.0)	18 (40.9)	18 (41.9)	34 (34.3)	86 (36.9)
Gain of ≥ 15	9 (19.1)	13 (29.5)	15 (34.9)	24 (24.2)	61 (26.2)
Month 24					
Loss of < 30	44 (93.6)	40 (90.9)	41 (95.3)	90 (90.9)	215 (92.3)
Loss of < 15	39 (83.0)	37 (84.1)	33 (76.7)	80 (80.8)	189 (81.1)
Gain of ≥ 0	29 (61.7)	30 (68.2)	23 (53.5)	55 (55.6)	137 (58.8)
Gain of ≥ 5	0 (42.6)	25 (56.8)	18 (41.9)	46 (46.5)	109 (46.8)
Gain of ≥ 10	16 (34.0)	15 (34.1)	15 (34.9)	34 (34.3)	80 (34.3)
Gain of ≥ 15	11 (23.4)	10 (22.7)	14 (32.6)	0 (20.2)	55 (23.6)

Patients previously treated in study (1) CRFB002A2302 (EXCITE); (2) CRFB002A2303 (SUSTAIN)
Previous baseline is defined as the Day 1 value of the previous studies.
% is based on full analysis set and it is calculated as n/N*100.

Absolute value and change from SECURE baseline of BCVA of the study eye at months 6, 12, 18, and 24, by treatment history (Full analysis set, LOCF)

	Ranibizumab 0.5 mg				
	EXCITE (1)				
Best-corrected visual acuity	**0.3 mg quarterly N = 47**	**0.5 mg quarterly N = 44**	**0.3 mg monthly N = 43**	**SUSTAIN (2) N = 99**	**Total N = 233**
Baseline					
n	47	43	42	98	230
Mean (SD)	59.9 (15.36)	62.5 (15.58)	62.7 (17.22)	59.3 (16.37)	60.6 (16.15)
Median	62.0	62.0	62.0	59.5	61.5
Range	11, 85	22, 88	7, 88	14, 87	7, 88
Value at month 6					
n	47	43	42	98	230
Mean (SD)	58.1 (18.15)	61.9 (16.47)	60.6 (18.49)	57.8 (17.88)	59.1 (17.76)
Median	62.0	65.0	61.5	59.0	61.0
Range	9, 88	11, 86	9, 87	14, 95	9, 95
Change from baseline at month 6					
n	47	43	42	98	230
Mean (SD)	-1.8 (9.42)	-0.6 (6.35)	-2.2 (11.03)	-1.5 (8.68)	-1.5 (8.90)
Median	0.0	0.0	0.0	-1.0	-1.0
Range	-38, 10	-15, 18	-63, 13	-30, 34	-63, 34
95% CI for Mean	(-4.6, 1.0)	(-2.5, 1.4)	(-5.6, 1.3)	(-3.2, 0.3)	(-2.7, -0.3)
Value at month 12					
n	47	43	42	98	230
Mean (SD)	57.8 (17.79)	61.7 (15.98)	58.5 (20.57)	57.7 (18.05)	58.6 (18.07)

Median	62.0	64.0	61.5	60.0	62.0
Range	10, 88	28, 85	0, 90	6, 90	0, 90
Change from baseline at month 12					
n	47	43	42	98	230
Mean (SD)	-2.1 (8.67)	-0.8 (7.11)	-4.2 (14.43)	-1.6 (10.44)	-2.0 (10.44)
Median	0.0	0.0	-2.0	0.0	0.0
Range	-37, 13	-22, 18	-77, 15	-36, 30	-77, 30
95% CI for Mean	(-4.6, 0.5)	(-3.0, 1.4)	(-8.7, 0.3)	(-3.7, 0.5)	(-3.4, -0.7)
Value at month 18					
n	47	43	42	98	230
Mean (SD)	56.9 (18.18)	59.2 (17.17)	57.8 (18.71)	56.3 (20.17)	57.2 (18.89)
Median	62.0	64.0	59.5	60.0	61.0
Range	11, 88	17, 84	15, 91	0, 86	0, 91
Change from baseline at month 18					
n	47	43	42	98	230
Mean (SD)	-2.9 (10.93)	-3.3 (11.26)	-5.0 (12.52)	-3.0 (12.18)	-3.4 (11.78)
Median	-1.0	0.0	-3.0	0.0	-1.0
Range	-42, 18	-42, 17	-42, 16	-47, 31	-47, 31
95% CI for Mean	(-6.1, 0.3)	(-6.8, 0.1)	(-8.9, -1.1)	(-5.5, -0.6)	(-4.9, -1.9)
Value at month 24					
n	47	43	42	98	230
Mean (SD)	56.3 (19.49)	57.0 (17.91)	56.9 (20.02)	55.7 (20.03)	56.3 (19.42)
Median	59.0	58.0	58.5	58.5	58.5
Range	11, 88	15, 85	8, 90	0, 90	0, 90
Change from baseline at month 24					
n	47	43	42	98	230
Mean (SD)	-3.6 (11.89)	-5.5 (11.94)	-5.9 (15.61)	-3.6 (12.94)	-4.3 (13.04)
Median	-1.0	-3.0	-2.0	-1.0	-2.0
Range	-42, 14	-44, 10	-69, 19	-47, 30	-69, 30
95% CI for Mean	(-7.0, -0.1)	(-9.2, -1.8)	(-10.7, -1.0)	(-6.2, -1.0)	(-6.0, -2.6)

Patients previously treated in study (1) CRFB002A2302 (EXCITE); (2) CRFB002A2303 (SUSTAIN).
Baseline is defined as the Day 1 of the SECURE study.
Two-sided 95% confidence intervals (CI) for means are from a t-distribution.

Total number of injections received, by treatment history (Safety set)

	Ranibizumab 0.5 mg				
	EXCITE (1)				
	0.3 mg quarterly N = 47	**0.5 mg quarterly N = 44**	**0.3 mg monthly N = 43**	**SUSTAIN (2) N = 100**	**Total N = 234**
Number of injections					
n	47	44	43	100	234
Mean (SD)	6.6 (6.04)	6.5 (4.19)	6.9 (5.80)	5.4 (6.00)	6.1 (5.67)
Median	5.0	6.0	6.0	3.0	4.0

Range	0, 21	0, 16	0, 19	0, 24	0, 24
Number of injections* - n (%)					
0	6 (12.8)	2 (4.5)	3 (7.0)	18 (18.0)	29 (12.4)
1	5 (10.6)	4 (9.1)	6 (14.0)	16 (16.0)	31 (13.2)
2	2 (4.3)	2 (4.5)	5 (11.6)	11 (11.0)	20 (8.5)
3	7 (14.9)	6 (13.6)	3 (7.0)	8 (8.0)	24 (10.3)
4	2 (4.3)	4 (9.1)	1 (2.3)	7 (7.0)	14 (6.0)
5	2 (4.3)	2 (4.5)	2 (4.7)	3 (3.0)	9 (3.8)
6	4 (8.5)	3 (6.8)	4 (9.3)	2 (2.0)	13 (5.6)
7	2 (4.3)	2 (4.5)	2 (4.7)	8 (8.0)	14 (6.0)
8	5 (10.6)	3 (6.8)	4 (9.3)	2 (2.0)	14 (6.0)
9	0 (0.0)	4 (9.1)	0 (0.0)	6 (6.0)	10 (4.3)
10	2 (4.3)	5 (11.4)	1 (2.3)	2 (2.0)	10 (4.3)
11	1 (2.1)	1 (2.3)	1 (2.3)	2 (2.0)	5 (2.1)
12	1 (2.1)	2 (4.5)	3 (7.0)	2 (2.0)	8 (3.4)
13	2 (4.3)	2 (4.5)	0 (0.0)	1 (1.0)	5 (2.1)
14	0 (0.0)	1 (2.3)	2 (4.7)	3 (3.0)	6 (2.6)
15	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.4)
16	0 (0.0)	1 (2.3)	3 (7.0)	1 (1.0)	5 (2.1)
17	2 (4.3)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.9)
18	1 (2.1)	0 (0.0)	1 (2.3)	1 (1.0)	3 (1.3)
19	0 (0.0)	0 (0.0)	2 (4.7)	0 (0.0)	2 (0.9)
20	1 (2.1)	0 (0.0)	0 (0.0)	1 (1.0)	2 (0.9)
21	2 (4.3)	0 (0.0)	0 (0.0)	2 (2.0)	4 (1.7)
22	0 (0.0)	0 (0.0)	0 (0.0)	2 (2.0)	2 (0.9)
23	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
24	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (0.4)

Patients previously treated in study (1) CRFB002A2302 (EXCITE); (2) CRFB002A2303 (SUSTAIN).
The number of injections is the total number of injections received since the start of the study.
*Distribution of patients according to number of injections received during the study.

Safety Results

Number (%) of patients with ocular AEs of the study eye suspected to be related to study drug or treatment procedure, by preferred term (Safety set)

Preferred term	Ranibizumab 0.5 mg Total N = 234
Related to study drug	
Total	6 (2.6)
Endophthalmitis	1 (0.4)
Intraocular pressure increased	1 (0.4)
Lacrimation increased	1 (0.4)
Retinal artery occlusion	1 (0.4)
Retinal hemorrhage	1 (0.4)
Retinal pigment epitheliopathy	1 (0.4)
Subretinal fibrosis	1 (0.4)
Related to treatment procedure	
Total	34 (14.5)
Eye pain	12 (5.1)
Intraocular pressure increased	10 (4.3)
Conjunctival hemorrhage	5 (2.1)
Punctate keratitis	4 (1.7)
Conjunctival hyperemia	2 (0.9)
Corneal erosion	2 (0.9)
Endophthalmitis	2 (0.9)
Eye irritation	2 (0.9)
Lacrimation increased	2 (0.9)
Myodesopsia	2 (0.9)
Procedural pain	2 (0.9)
Blepharitis allergic	1 (0.4)
Cataract	1 (0.4)
Corneal abrasion	1 (0.4)
Dark circles under eyes	1 (0.4)
Eye swelling	1 (0.4)
Retinal artery occlusion	1 (0.4)
Retinal hemorrhage	1 (0.4)
Retinal scar	1 (0.4)
Scar	1 (0.4)
Scleral hyperemia	1 (0.4)
Vitritis	1 (0.4)

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

Preferred term	Ranibizumab 0.5 mg Total N = 234
Related to study drug	
Total	3 (1.3)
Cerebrovascular accident	1 (0.4)
Heart rate irregular	1 (0.4)

Nausea	1 (0.4)
Related to treatment procedure	
Total	4 (1.7)
Cerebrovascular accident	1 (0.4)
Heart rate irregular	1 (0.4)
Nausea	1 (0.4)
Rhinorrhea	1 (0.4)

Patients discontinued study drug (All enrolled patients)

Disposition	Ranibizumab 0.5 mg Total N = 234 n (%)
Study drug discontinued	24 (10.3)
Completed the study	2 (0.9)
Discontinued study	22 (9.4)
Reason for discontinued study drug	
Adverse event(s)	9 (3.8)
Abnormal laboratory value(s)	0 (0.0)
Abnormal test procedure result(s)	0 (0.0)
Unsatisfactory therapeutic effect	2 (0.9)
Subject's condition no longer requires study drug	0 (0.0)
Subject withdrew consent	6 (2.6)
Lost to follow-up	1 (0.4)
Administrative problems	0 (0.0)
Death	5 (2.1)
Protocol deviation	1 (0.4)

Percentage is based on the number of enrolled patients as denominator

10 most frequently reported AEs overall by preferred term n (%)

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

Preferred term	Ranibizumab 0.5 mg Total N = 234
Retinal hemorrhage	30 (12.8)
Cataract	27 (11.5)
Intraocular pressure increased	15 (6.4)
Visual acuity reduced	14 (6.0)
Eye pain	13 (5.6)
Choroidal neovascularization	12 (5.1)
Macular edema	7 (3.0)
Retinal edema	7 (3.0)
Blepharitis	6 (2.6)
Conjunctivitis	6 (2.6)

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

Preferred term	Ranibizumab 0.5 mg Total N = 234
Hypertension	21 (9.0)
Nasopharyngitis	21 (9.0)
Fall	17 (7.3)
Upper respiratory tract infection	11 (4.7)
Urinary tract infection	11 (4.7)
Depression	8 (3.4)
Influenza	8 (3.4)
Abdominal pain upper	7 (3.0)
Arthralgia	7 (3.0)
Bronchitis	7 (3.0)

Serious Adverse Events and Deaths

Number (%) of patients with deaths, serious adverse events (SAEs), and study drug discontinuation due to AEs (Safety set)

	Ranibizumab 0.5 mg Total N = 234
Total (1)	73 (31.2)
Deaths	5 (2.1)
SAEs	69 (29.5)
Ocular SAE of study eye	11 (4.7)
Ocular SAE of fellow eye	2 (0.9)
Non-ocular SAE	62 (26.5)
SAEs causing discontinuation of study drug	12 (5.1)
Ocular SAE of study eye	2 (0.9)
Ocular SAE of fellow eye	0 (0.0)
Non-ocular SAE	10 (4.3)
AEs causing discontinuation of study drug	16 (6.8)
Ocular AE of study eye*	5 (2.1)
Ocular AE of fellow eye**	1 (0.4)
Non-ocular AE	10 (4.3)

* For one patient, assessment of discontinuation of study drug was done at Month 23 visit and had no impact on further study medication.

** Not corrected by error in the database

(1) The total number of patients with at least one of the events mentioned in this table.

A patient with multiple occurrences of a SAE/AE under a given category is counted only once.

Patients with “SAEs causing discontinuation of study drug” were also counted under the categories “AEs causing discontinuation” and “SAEs”.

Other Relevant Findings

Not applicable

Date of Clinical Trial Report

31-Aug-2010

Date Inclusion on Novartis Clinical Trial Results Database

25-Jan-2011

Date of Latest Update

16-Jan-2011