Clinical Trial Results Database (CTRD)

Sponsor

Novartis

Generic Drug Name

Ranibizumab

Therapeutic Area of Trial

Ophthalmology

Approved Indication

DME

Protocol Number

CRFB002DFR08

Title

Open-label, multicenter, study of the efficacy and safety of Lucentis® (ranibizumab 0.5 mg) in Diabetic patients presenting a visual impairment due to diabetic macular edema in Current medical practice (LUDIC).

Phase of Development

Phase IV

Study Start/End Dates

28-Fev-2011 (FPFV) to 10-Sep-2012 (LPLV)

Study Design/Methodology

This phase IV study was conducted according to an open-label design to reflect daily practice as closely as possible and to confirm the real life benefits for patients. The aim of the study was to confirm the proportion of patients with a 10 letters gain or more on BCVA (Best Corrected Visual Activity) after 6 months in current medical practice. The 6 months' timeframe allowed the clinical response to be assessed effectively in terms of visual acuity. In fact, a rapid improvement in BCVA has been observed up to Month 3 in development studies (RESTORE study) followed by stabilization up to Month 12. This 6-month study (CRFB002DFR08) has therefore allowed the clinical response to treatment to be observed in current practice.

The patient cohort enrolled in this study took into account the indication obtained during the approval of the CHMP granted on 21 October 2010. In fact, no reference to first or second line treatment was made for Lucentis® as its MA is extensive and not restricted in this indication (visual impairment due to DME - degenerative macular edema).

The purpose of including patients who may or may not have benefited from a "standard of care" in this disease was to confirm the efficacy of the product in current medical practice.

Centres

46 centers in 1 country : France

Publication

NA

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

Intra-vitreal injection (IVT) of Ranibizumab (Lucentis®), 0.5 mg (0.05 mL).

Patients received a monthly IVT of Lucentis® and this treatment was continued until maximum visual acuity was obtained, as confirmed by stable visual acuity during three consecutive monthly assessments carried out during treatment with ranibizumab.

The patients had to be subsequently followed up on a monthly basis in terms of visual acuity. If a reduction in visual acuity due to DME was once again observed during a check-up, monthly injections had to be reinstated until visual acuity was once again stable for three consecutive monthly assessments.

A minimum interval of 4 weeks should be left between two doses.

Statistical Methods

Statistical analysis plans

Patient data were described in terms of demographic and characteristic parameters on inclusion, efficacy parameters and tolerability and safety parameters. The data from all centers that participated in the study were pooled.

Descriptive statistics including the mean, standard deviation, minimum, maximum and median for quantitative variables and frequency tables for qualitative variables were presented per visit.

The statistical tests were performed bilaterally with a 0.05 level of significance.

The statistical analyses were carried out using SAS®software, v8.2.

Efficacy evaluation

Primary efficacy endpoint

The primary objective was to evaluate the proportion of patients with a gain equal to or more than 10 letters on BCVA (Best Corrected Visual Activity) after 6 months in current medical practice.

BCVA was measured according to the ETDRS scale at a testing distance of 4 meters. The variation in BCVA was determined on the basis of values collected during the baseline visit (or otherwise during the screening visit) and the visit in Month 6. The main analysis focused solely on patients with values recorded at both these visits. The proportion of patients with a gain ≥ 10 letters was described together with its 95% bilateral confidence interval.

A sensitivity analysis was carried out by recording during Month 6 the last BCVA measured in the event of a missing value in Month 6 ("last observation carried forward" method [LOCF]). Furthermore, an analysis was carried out as a function of the absolute variation in HbA1c from baseline to Month 6: < 0.5% versus ≥ 0.5%.

Sample size determination

The primary objective was to evaluate the proportion of patients with a gain equal to or more than 10 letters on BCVA after 6 months in the eye under study, in current medical practice.

In the RESTORE study, 35.5% of patients gained ≥ 10 letters in their BCVA score after 6 months. The number of patients was therefore calculated on the basis of a hypothetical success rate of 35%.

To guarantee adequate total precision (half length of the 95% confidence interval), set at ± 5% of the estimate of this proportion of patients, 350 patients had to be evaluated (nQuery Advisor® version 6.01).

Approximately 30% of patients were estimated to be non-eligible in terms of primary endpoint assessment: untreated patients or those with no BCVA score at 6 months. Overall, 500 patients ought therefore to have been enrolled in the study. Nevertheless, despite extending the enrollment period by 3 months, only 393 subjects were actually enrolled.

Study Population: Inclusion/Exclusion Criteria and Demographics

Study population in the interventional treatment phase (study per se)

The study population comprised 350 type I or II diabetics with visual impairment due to DME.

Population participating in the optional phase and given treatment on compassionate grounds

This population comprised 20 patients either participating or who participated in the initial interventional study and for whom both the physician and patient clearly expressed the desire to continue treatment.

These patients were able to receive Lucentis® free of charge until reimbursement was introduced in this indication if the eye under study still warranted IVT therapy (i.e. up until 22 June 2012).

Inclusion criteria

Patients were included in the study if they presented with the following inclusion criteria:

For the interventional treatment phase (study per se):

- *Male or female patients over 18 years of age who had signed an informed consent form.*
- *Patients with type I or type II diabetes (according to American Diabetes Association [ADA] and World Health Organization [WHO] guidelines) with glycosylated hemoglobin (HbA1c) ≤ 10% at screening (Visit 1). The patients had to be on a diet, exercise and/or receive appropriate pharmacological treatment for diabetes.*
- *Central retinal thickness on OCT ≥ 350 µm or clearly increased by 2 standard deviations or more in relation to the standard value on the measuring device used (always the same) in the center, during the baseline visit.*
- *BCVA score ≥ 39 and≤ 73 letters in the eye under study using the Early Treatment Diabetic Retinopathy Study (ETDRS) scale at a testing distance of 4 meters (equivalent to values ranging from approximately 20/32 to 20/160 on the Snellen scale) during the baseline visit at Visit 2.*
- *The decrease in vision was due to DME and not to other causes, in the investigator's opinion.*
- *Medication for the management of diabetes must have been stable for at least 3 months and was expected to remain unchanged during the course of the study.*
- *Patients had to be members of a French national health insurance scheme or covered by such a scheme.*
- *The patients could already have been treated for DME over the last 12 months, by laser, intra-vitreal corticotherapy or anti-VEGF.*

For the optional compassionate phase:

- *To have been eligible and included in the study per se (main study).*
- *Having completed the main study.*
- *A desire on the part of the physician and patient to participate in this optional phase and have access to the treatment.*
- *For group 1 patients: patients who completed the main study within the last month and warranting continued IVT, stable visual acuity still not being obtained during treatment over 3 consecutive visits.*
- *For group 2 patients: patients who completed the main study more than one month ago and warranting the resumption of IVT due to a recurrent decrease in visual acuity since leaving the main study.*
- *Having signed an addendum to the informed consent form.*

Exclusion criteria

These patients were included in the study if they did not present with any of the following exclusion criteria:

Criteria relating to eye diseases

- *Concomitant lesion(s) in the study eye which could, in the investigator's opinion, prevent*

the improvement of visual acuity on study treatment.

- *Active intraocular inflammation (trace grade or above) in either eye, at the time of enrollment.*
- *Any active or suspected infection (e.g. conjunctivitis, keratitis, scleritis, uveitis, endophthalmitis) in either eye, at the time of enrollment.*
- *History of uveitis in either eye, at any time.*

Criteria relating to concomitant eye diseases or treatments

- *Active systemic infection.*
- *History of stroke within 3 months prior to recruitment.*
- *Renal failure requiring dialysis or renal transplant or renal insufficiency with creatinine levels > 2.0 mg/dL at screening.*
- *Untreated diabetes.*
- *Systolic blood pressure (SBP) > 160 mmHg or diastolic blood pressure (DBP) > 100 mmHg at baseline.*
- *Untreated arterial hypertension.*
- *Known hypersensitivity to ranibizumab or any component of the ranibizumab formulation.*

Others

- *Women of childbearing potential, defined as any woman physiologically likely to become pregnant UNLESS a contraceptive method was used. This could a barrier or hormonal method. Adequate barrier methods of contraception include the coil, condom (for the partner), intrauterine device (copper or hormonal), foam or spermicide. Hormonal contraceptives include all contraceptive pills on the market containing oœstrogen and/or progesterone.*
- *Pregnant women (who have had a pregnancy test) or those who are breastfeeding.*
- *Patient participating in another clinical study or who has participated in a study with an investigational study drug 30 days or 5 half-lives before enrolling in the study.*

Participant Flow

Recruitment of patients (1)
Screened population

	Total
Date of FPFV	*28/02/2011*
Date of LPFV	*30/12/2011*
Duration of inclusions (months)	*10*
Date of LPLV (visit 2)	*09/01/2012*
Date of LPLV (month 6)	*27/07/2012*
Duration of study until month 6 (months)	*16.9*
Number of screened patients	*393*

Number of active centers (1)	*N*	*46*
Number of screened patients by active center (1)	*N*	*46*
	Mean	*8.5*
	SD	*5.30*
	Minimum	*1.0*
	Median	*7.5*
	Maximum	*30.0*
Number of screened patients by active center (N(%)) (1)	*N*	*46*
	1	*1 (2.2 %)*
	2	*1 (2.2 %)*
	3	*2 (4.3 %)*
	4	*5 (10.9 %)*
	5	*5 (10.9 %)*
	6	*2 (4.3 %)*
	7	*7 (15.2 %)*
	8	*2 (4.3 %)*
	9	*4 (8.7 %)*
	10	*8 (17.4 %)*
	11	*3 (6.5 %)*
	12	*1 (2.2 %)*
	13	*1 (2.2 %)*
	15	*1 (2.2 %)*
	21	*1 (2.2 %)*
	22	*1 (2.2 %)*
	30	*1 (2.2 %)*

Recruitment of patients (2)
Included population

		Total
Number of treated patients		*350*
Number of active centers (1)		*46*
Number of treated patients by active center (1)	*N*	*46*
	Mean	*7.6*
	SD	*4.86*
	Minimum	*1.0*
	Median	*7.0*
	Maximum	*28.0*
Number of treated patients by active center (N(%)) (1)	*N*	*46*
	1	*1 (2.2 %)*
	2	*2 (4.3 %)*
	3	*3 (6.5 %)*
	4	*6 (13.0 %)*
	5	*5 (10.9 %)*
	6	*4 (8.7 %)*
	7	*5 (10.9 %)*

	8	*5 (10.9 %)*
	9	*4 (8.7 %)*
	10	*4 (8.7 %)*
	11	*2 (4.3 %)*
	12	*2 (4.3 %)*
	18	*1 (2.2 %)*
	20	*1 (2.2 %)*
	28	*1 (2.2 %)*

(1) Active centers are those with at least one included patient
The percentages are calculated to the number of active centers
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Premature study discontinuations
Not included population

		Total (N = 43)
Primary reason of discontinuation	*N*	*43*
	Do not respond to study selection criteria	*31 (72.1 %)*
	Adverse event(s)	*1 (2.3 %)*
	Abnormal laboratory value(s)	*0 (0.0 %)*
	Abnormal test procedure result(s)	*0 (0.0 %)*
	Unsatisfactory therapeutic effect	*0 (0.0 %)*
	Protocol violation	*2 (4.7 %)*
	Subject withdrew consent	*7 (16.3 %)*
	Lost to follow-up	*1 (2.3 %)*
	Administrative problems	*1 (2.3 %)*
	Death	*0 (0.0 %)*

The percentages are calculated to the available answers
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Premature study discontinuations until month 6
Included population

		Total (N = 350)
Premature study discontinuation	*N*	*350*
	No	*322 (92.0 %)*
	Yes	*28 (8.0 %)*
Primary reason of discontinuation	*N*	*28*
	Do not respond to study selection criteria	*0 (0.0 %)*
	Adverse event(s)	*11 (39.3 %)*
	Abnormal laboratory value(s)	*0 (0.0 %)*
	Abnormal test procedure result(s)	*0 (0.0 %)*
	Unsatisfactory therapeutic effect	*6 (21.4 %)*
	Protocol violation	*2 (7.1 %)*
	Subject withdrew consent	*3 (10.7 %)*
	Lost to follow-up	*5 (17.9 %)*
	Administrative problems	*1 (3.6 %)*
	Death	*0 (0.0 %)*
Time to last visit (months)	*N*	*28*
	Mean	*3.2*
	SD	*1.48*
	Minimum	*0.2*
	Median	*3.2*
	Maximum	*5.5*

Number of injections	*N*	*28*
	Mean	*3.3*
	SD	*1.36*
	Minimum	*1.0*
	Median	*3.0*
	Maximum	*6.0*

Time to last visit (from date of first injection) and number of injections are only displayed for patients who prematurely discontinued study
The percentages are calculated to the available answers
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Recruitment of patients in optional follow-up beyond month 6
Included population

(1) Active centers are those with at least one patient in follow-up
The percentages are calculated to the number of active centers
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		Total (N = 20)
Duration of follow-up (months)	*N*	*20*
	Mean	*1.4*
	SD	*0.66*
	Minimum	*0.5*
	Median	*1.2*
	Maximum	*3.3*
Number of visits during follow-up	*N*	*20*
	2	*14 (70.0 %)*
	3	*6 (30.0 %)*

		Total
Date of FPFV		*10/05/2012*
Date of LPFV		*21/06/2012*
Duration of inclusions in follow-up (months)		*1.4*
Date of LPLV		*10/09/2012*
Duration of follow-up (months)		*4*
Number of patients in follow-up		*20*
Number of active centers (1)	*N*	*11*
Number of patients in follow-up by active center (1)	*N*	*11*
	Mean	*1.8*
	SD	*1.25*
	Minimum	*1.0*
	Median	*1.0*
	Maximum	*4.0*

Number of patients in follow-up by active center (N(%)) (1)	*N*	*11*
	1	*7 (63.6 %)*
	2	*1 (9.1 %)*
	3	*1 (9.1 %)*
	4	*2 (18.2 %)*

Duration and number of visits during optional follow-up beyond month 6
Included population

		Total (N = 20)
Duration of follow-up (months)	*N*	*20*
	Mean	*1.4*
	SD	*0.66*
	Minimum	*0.5*
	Median	*1.2*
	Maximum	*3.3*
Number of visits during follow-up	*N*	*20*
	2	*14 (70.0 %)*
	3	*6 (30.0 %)*

The percentages are calculated to the size (N=) of the column (number of patients in follow-up)
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Premature study discontinuations of optional follow-up beyond month 6
Included population

		Total (N = 20)
Premature discontinuation	*N*	*20*
	No	*20 (100.0 %)*
Primary reason of discontinuation	*N*	*0*

Analysis populations
Screened population

	Total (N = 393)
Included	*350 (89.1 %)*
Safety	*350 (89.1 %)*
ITT	*335 (85.2 %)*
Per Protocol M6	*261 (66.4 %)*
Per Protocol	*261 (66.4 %)*

The percentages are calculated to the size (N=) of the column
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Reasons for exclusion from the analysis populations
Screened population

		Total (N = 393)
Included	Included	350 (89.1 %)
	Excluded	43 (10.9 %)
	-->Not treated	43 (10.9 %)
Safety	Included	350 (89.1 %)
	Excluded	43 (10.9 %)
	-->Not treated	43 (10.9 %)
	-->No safety data	43 (10.9 %)
ITT	Included	335 (85.2 %)
	Excluded	58 (14.8 %)
	-->Not treated	43 (10.9 %)
	-->No efficacy data	50 (12.7 %)
	-->Deviation excluding from all efficacy analyses	10 (2.5 %)
Per Protocol M6	Included	261 (66.4 %)
	Excluded	132 (33.6 %)
	-->Not treated	43 (10.9 %)
	-->No efficacy data	50 (12.7 %)
	-->Deviation excluding from all efficacy analyses	10 (2.5 %)
	-->Deviation excluding from the PPM6 population	81 (20.6 %)
Per Protocol	Included	261 (66.4 %)
	Excluded	132 (33.6 %)
	-->Not treated	43 (10.9 %)
	-->No efficacy data	50 (12.7 %)
	-->Deviation excluding from all efficacy analyses	10 (2.5 %)
	-->Deviation excluding from the PP population	81 (20.6 %)

Baseline Characteristics

Demography ITT population

		Total (N = 335)
Sex	N	335
	Male	205 (61.2 %)
	Female	130 (38.8 %)
Age (years)	N	335
	Mean	63.7
	SD	11.19
	Minimum	25.8
	Median	64.5
	Maximum	90.5
Age (N(%))	N	335
	<55 years	61 (18.2 %)
	55-65 years	117 (34.9 %)
	65-75 years	105 (31.3 %)
	>=75 years	52 (15.5 %)

Weight (kg)	*N*	*327*
	Mean	*82.4*
	SD	*16.40*
	Minimum	*45.0*
	Median	*81.0*
	Maximum	*145.0*
Height (cm)	*N*	*326*
	Mean	*167.4*
	SD	*8.67*
	Minimum	*140.0*
	Median	*168.0*
	Maximum	*188.0*
BMI (kg/m²)	*N*	*321*
	Mean	*29.3*
	SD	*5.18*
	Minimum	*18.2*
	Median	*28.6*
	Maximum	*53.3*
BMI (N(%))	*N*	*321*
	<25 kg/m²	*66 (20.6 %)*
	25-30 kg/m²	*129 (40.2 %)*
	>=30 kg/m²	*126 (39.3 %)*
	Missing	*14*

		Total (N = 335)
DME presence	*N*	*335*
	Study eye only	*74 (22.1 %)*
	Study eye + fellow eye	*261 (77.9 %)*
Time since diagnosis of DME in the study eye (years)	*N*	*332*
	Mean	*2.2*
	SD	*2.31*
	Minimum	*0.0*
	Median	*1.7*
	Maximum	*25.8*
Time since diagnosis of DME in the study eye (N(%))	*N*	*332*
	<= 0.25 year	*42 (12.7 %)*
	0.25 - 1 year	*68 (20.5 %)*
	>= 1 year	*222 (66.9 %)*
	Missing	*3*
Time since diagnosis of DME in the fellow eye (years)	*N*	*257*
	Mean	*2.3*

	SD	*2.08*
	Minimum	*0.0*
	Median	*1.9*
	Maximum	*12.9*
Time since diagnosis of DME in the fellow eye (N(%))	*N*	*257*
	<= 0.25 year	*33 (12.8 %)*
	0.25 - 1 year	*48 (18.7 %)*
	>= 1 year	*176 (68.5 %)*
	Missing	*4*
Time between diagnosis of DME in the study eye and fellow eye (months) (1)	*N*	*257*
	Mean	*0.3*
	SD	*11.87*
	Minimum	*-60.9*
	Median	*0.0*
	Maximum	*120.8*
Time between diagnosis of DME in the study eye and fellow eye (months)(2)	*N*	*257*
	Mean	*3.0*
	SD	*11.49*
	Minimum	*0.0*
	Median	*0.0*
	Maximum	*120.8*

		Novartis drug N=163	***Pbo N=160***	***Total N=323***
Age (years)	*n*	*163*	*160*	*323*
	Mean	*64.0*	*64.1*	*64.0*
	SD	*8.29*	*9.43*	*8.86*
	Median	*64.0*	*64.0*	*64.0*
	Min - Max	*44 - 85*	*40 - 90*	*40 - 90*
Age group – n (%)	*19–39 years*	*0 (0.0)*	*0 (0.0)*	*0 (0.0)*
	40–64 years	*85 (52.1)*	*84 (52.5)*	*169 52.3)*
	≥ 65 years	*78 (47.9)*	*76 (47.5)*	*154 47.7)*
Sex – (%)	*Male*	*89 (54.6)*	*87 (54.4)*	*176 (54.5)*
	Female	*74 (45.4)*	*73 (45.6)*	*147 (45.5)*
Race – n (%)	*Caucasian*	*14 (89.0)*	*146 (9 .3)*	*291 (90.1)*
	Black	*10 (6.1)*	*10 (6.3)*	*20 (6.2)*
	Asian	*5 (3.1)*	*3 (1.9)*	*8 (2.5)*
	Other	*3 (1.8)*	*1 (0.6)*	*4 (1.2)*

Outcome Measures

Primary Outcome Results

Frequency of patients with gain in visual acuity of >= 10 letters at month 6
ITT population

		Total (N = 335)
Gain of >=10 letters	N	308
	No	185 (60.1 %)
		[54.60; 65.53]
	Yes	123 (39.9 %)
		[34.47; 45.40]
	Missing	27

Baseline is value at inclusion, or at selection if missing. Final value is value at month 6 visit.
Elements in square brackets are 95% confidence intervals
The percentages are calculated to the available answers
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Secondary Outcome Result(s)

Gain in VA at month 6

	Value at the visit						Difference to the baseline visit							
	N	Mean	SD	Median	Min	Max	N	Mean	CI95%	SD	Median	Min	Max	P-value (1)
Baseline	335	57.0	10.25	58.0	24.0	81.0								
V3 - M1	334	60.8	11.43	62.0	16.0	92.0	334	3.8	[3.0;4.6]	7.42	3.0	-23.0	35.0	< 0.001
V4 - M2	330	62.3	12.63	64.0	5.0	88.0	330	5.4	[4.3;6.4]	9.68	5.0	-65.0	35.0	< 0.001
V5 - M3	325	63.5	11.69	65.0	23.0	91.0	325	6.4	[5.5;7.4]	8.67	6.0	-33.0	36.0	< 0.001
V6 - M4	315	63.8	12.72	65.0	0.0	90.0	315	6.7	[5.5;7.8]	10.51	7.0	-69.0	39.0	< 0.001
V7 - M5	311	63.7	12.85	65.0	0.0	88.0	311	6.5	[5.3;7.7]	10.75	7.0	-69.0	40.0	< 0.001
V8 - M6	308	64.3	12.32	65.0	25.0	85.0	308	7.1	[5.9;8.2]	10.17	7.0	-29.0	40.0	< 0.001
M6 - LOCF	335	63.7	12.68	65.0	13.0	85.0	335	6.7	[5.6;7.8]	10.38	7.0	-29.0	40.0	< 0.001

(1) Comparison to baseline value by a Wilcoxon signed rank test.
Baseline is visit 2, or visit 1 in case value is missing at visit 2. Difference is visit - baseline.
Elements in square brackets are 95% confidence intervals
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Number of injections needed to obtain a gain >=10 letters; and number of injection needed to obtain a stable gain, (ITT population)

		Total (N = 335)
Number of injections needed to get a gain of >=10	N	190

letters		
	Mean	*2.3*
	SD	*1.32*
	Minimum	*1.0*
	Median	*2.0*
	Maximum	*6.0*
Response to treatment (3 letters)	*N*	*335*
	Yes	*290 (86.6 %)*
	>> Stable VA at 3 consecutive visits	*127 (43.8 %)*
	>> No stable VA at 3 consecutive visits	*163 (56.2 %)*
	No	*45 (13.4 %)*
	>> Delta CRT >=50 µm	*16 (35.6 %)*
	>> Delta CRT <50 µm	*29 (64.4 %)*
	>> Delta CRT >=100 µm	*10 (22.2 %)*
	>> Delta CRT <100 µm	*35 (77.8 %)*
Number of injections needed to get a stable (<3 letters) visual acuity at 3 consecutive visits	*N*	*127*
	Mean	*3.9*
	SD	*1.04*
	Minimum	*2.0*
	Median	*4.0*
	Maximum	*6.0*
Response to treatment (5 letters)	*N*	*335*
	Yes	*269 (80.3 %)*
	>> Stable VA at 3 consecutive visits	*187 (69.5 %)*
	>> No stable VA at 3 consecutive visits	*82 (30.5 %)*
	No	*66 (19.7 %)*
	>> Delta CRT >=50 µm	*22 (33.3 %)*
	>> Delta CRT <50 µm	*44 (66.7 %)*
	>> Delta CRT >=100 µm	*12 (18.2 %)*
	>> Delta CRT <100 µm	*54 (81.8 %)*
Number of injections needed to get a stable (<5 letters) visual acuity at 3 consecutive visits	*N*	*187*
	Mean	*3.8*
	SD	*1.00*
	Minimum	*2.0*
	Median	*4.0*
	Maximum	*6.0*

Response to treatment: at least one visual acuity >= baseline visual acuity + 3 letters (first definition), or >= baseline visual acuity + 5 letters (second definition)
Numbers of injections needed to get a stable visual acuity are calculated only among responders to treatment
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Correlation between the gain in VA after 3 IVT and the gain in VA at 6 months

	Value at the visit						Difference to the baseline visit							
	N	*Mean*	*SD*	*Median*	*Min*	*Max*	*N*	*Mean*	*SD*	*Median*	*Min*	*Max*	*P-value (1)*	*Correlation coefficient (2)*
Baseline	*300*	*57.2*	*10.20*	*58.5*	*24.0*	*78.0*								
After 3 injections (3)	*300*	*63.7*	*11.54*	*65.0*	*23.0*	*91.0*	*300*	*6.5*	*8.60*	*6.0*	*-33.0*	*36.0*	*< 0.001*	
V8 - M6	*300*	*64.3*	*12.22*	*65.0*	*25.0*	*85.0*	*300*	*7.1*	*9.96*	*7.0*	*-29.0*	*37.0*	*< 0.001*	*0.6678 - <.0001*

(1) Comparison to baseline value by a Wilcoxon signed rank test.
(2) Pearson correlation coefficient and associated p-value between differences from baseline to after 3 injections and from baseline to month 6
(3) First value measured after 3 injections
Baseline is visit 2, or visit 1 in case value is missing at visit 2. Difference is visit - baseline.
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Safety Results

Adverse events until month 6 (Safety population)

		Total (N = 350)
Patients with at least one AE	*N*	*174 (49.7 %)*
Number of AE per patient	*N*	*174*
	Mean	*2*
	SD	*1.40*
	Minimum	*1*
	Median	*2*
	Maximum	*11*
Total number of AE	*N*	*339*
Site (1)	*Both eyes*	*12 (3.5 %)*
	Study eye	*85 (25.1 %)*
	Fellow eye	*27 (8.0 %)*
	Non ocular event	*215 (63.4 %)*
Severity (1)	*Mild*	*165 (48.7 %)*
	Moderate	*134 (39.5 %)*
	Severe	*40 (11.8 %)*
Patients with at least one AE whose relationship to injection technics is suspected	*N*	*30 (8.6 %)*
Total number of AE whose relationship to injection technics is suspected	*N*	*43*
Patients with at least one AE whose relationship to Lucentis is suspected	*N*	*11 (3.1 %)*
Total number of AE whose relationship to Lucentis is suspected	*N*	*16*
Patients with at least one SAE	*N*	*27 (7.7 %)*

Total number of SAE	*N*	*45*
Patients with at least one SAE whose relationship to injection technics is suspected	*N*	*2 (0.6 %)*
Total number of SAE whose relationship to injection technics is suspected	*N*	*3*
Patients with at least one SAE whose relationship to Lucentis is suspected	*N*	*2 (0.6 %)*
Total number of SAE whose relationship to Lucentis is suspected	*N*	*3*
Patients with at least one AE cause of premature discontinuation	*N*	*12 (3.4 %)*
Total number of AE cause of premature discontinuation	*N*	*15*
Patients with at least one AE whose relationship to injection technics is suspected and cause of premature discontinuation	*N*	*1 (0.3 %)*
Total number of AE whose relationship to injection technics is suspected and cause of premature discontinuation	*N*	*1*
Patients with at least one AE whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0 (0.0 %)*
Total number of AE whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0*
Patients with at least one ocular AE whose relationship to injection technics is suspected and cause of premature discontinuation	*N*	*1 (0.3 %)*
Total number of ocular AE whose relationship to injection technics is suspected and cause of premature discontinuation	*N*	*1*
Patients with at least one ocular AE whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0 (0.0 %)*
Total number of ocular AE whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0*
Patients with at least one non ocular AE whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0 (0.0 %)*
Total number of non ocular AE whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0*
Patients with at least one AE in study eye whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0 (0.0 %)*
Total number of AE in study eye whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0*
Patients with at least one AE in fellow eye whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0 (0.0 %)*
Total number of AE in fellow eye whose relationship to Lucentis is suspected and cause of premature discontinuation	*N*	*0*

Only AE after first injection of Lucentis are displayed
(1) The percentages are calculated to the total number of AE.
Start day of event is set at 15th in case missing to assign it before or after any injection, and before or after month 6
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Adverse events until month 6, by organ system and preferred term, according to relationship to injection technics and Lucentis (Safety population)

		Total (N= 350)				
			Relationship to injection technics		Relationship to Lucentis	
		Total	Suspected	Not suspected	Suspected	Not suspected
Any adverse event		*174 (49.7%)*	*30 (8.6%)*	*144 (41.1%)*	*11 (3.1%)*	*163 (46.6%)*
Cardiac disorders	*Total*	*7 (2.0%)*	*0 (0.0%)*	*7 (2.0%)*	*1 (0.3%)*	*6 (1.7%)*
	Angina pectoris	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Atrial fibrillation	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Atrial tachycardia	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Atrioventricular block second degree	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Bundle branch block left	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Bundle branch block right	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Cardiac arrest	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Cardiac failure	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Myocardial infarction	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*
	Myocardial ischaemia	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Palpitations	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Congenital, familial and genetic disorders	*Total*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Malformation venous	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Ear and labyrinth disorders	*Total*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Meniere's disease	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Eye disorders	*Total*	*83 (23.7%)*	*22 (6.3%)*	*61 (17.4%)*	*5 (1.4%)*	*78 (22.3%)*
	Anterior chamber disorder	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
	Blepharitis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Cataract	*9 (2.6%)*	*3 (0.9%)*	*6 (1.7%)*	*0 (0.0%)*	*9 (2.6%)*
	Cataract cortical	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
	Cataract nuclear	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Conjunctival haemorrhage	*7 (2.0%)*	*5 (1.4%)*	*2 (0.6%)*	*2 (0.6%)*	*5 (1.4%)*
	Conjunctival hyperaemia	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Conjunctivitis	*6 (1.7%)*	*2 (0.6%)*	*4 (1.1%)*	*0 (0.0%)*	*6 (1.7%)*
	Diabetic retinal oedema	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*	*1 (0.3%)*	*4 (1.1%)*
	Dry eye	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Eye allergy	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Eye disorder	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Eye haemorrhage	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Eye inflammation	*2 (0.6%)*	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*2 (0.6%)*
	Eye irritation	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Eye pain	*7 (2.0%)*	*4 (1.1%)*	*3 (0.9%)*	*0 (0.0%)*	*7 (2.0%)*
	Eye pruritus	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
	Eyelid oedema	*2 (0.6%)*	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*2 (0.6%)*
	Eyelid ptosis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Keratitis	*3 (0.9%)*	*1 (0.3%)*	*2 (0.6%)*	*0 (0.0%)*	*3 (0.9%)*
	Lacrimation increased	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
	Macular fibrosis	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Macular oedema	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*

	Ocular discomfort	*2 (0.6%)*	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*2 (0.6%)*
	Ocular hypertension	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*
	Punctate keratitis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Retinal aneurysm	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Retinal detachment	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Retinal disorder	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Retinal exudates	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Retinal haemorrhage	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Retinopathy	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Ulcerative keratitis	*5 (1.4%)*	*3 (0.9%)*	*2 (0.6%)*	*0 (0.0%)*	*5 (1.4%)*
	Uveitis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Vision blurred	*5 (1.4%)*	*1 (0.3%)*	*4 (1.1%)*	*0 (0.0%)*	*5 (1.4%)*
	Visual acuity reduced	*7 (2.0%)*	*0 (0.0%)*	*7 (2.0%)*	*1 (0.3%)*	*6 (1.7%)*
	Vitreous floaters	*2 (0.6%)*	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*2 (0.6%)*
	Vitreous haemorrhage	*3 (0.9%)*	*1 (0.3%)*	*2 (0.6%)*	*1 (0.3%)*	*2 (0.6%)*
Gastrointestinal disorders	*Total*	*7 (2.0%)*	*2 (0.6%)*	*5 (1.4%)*	*2 (0.6%)*	*5 (1.4%)*
	Diarrhoea	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Dyspepsia	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Nausea	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*
	Rectal haemorrhage	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Vomiting	*3 (0.9%)*	*2 (0.6%)*	*1 (0.3%)*	*2 (0.6%)*	*1 (0.3%)*
General disorders and administration site conditions	*Total*	*18 (5.1%)*	*2 (0.6%)*	*16 (4.6%)*	*1 (0.3%)*	*17 (4.9%)*
	Asthenia	*6 (1.7%)*	*0 (0.0%)*	*6 (1.7%)*	*0 (0.0%)*	*6 (1.7%)*
	Chest pain	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Fatigue	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*
	General physical health deterioration	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Influenza like illness	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*	*1 (0.3%)*	*4 (1.1%)*
	Injection site pain	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
	Malaise	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Pain	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
Hepatobiliary disorders	*Total*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Cytolytic hepatitis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Immune system disorders	*Total*	*4 (1.1%)*	*1 (0.3%)*	*3 (0.9%)*	*0 (0.0%)*	*4 (1.1%)*
	Drug hypersensitivity	*3 (0.9%)*	*1 (0.3%)*	*2 (0.6%)*	*0 (0.0%)*	*3 (0.9%)*
	Hypersensitivity	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Infections and infestations	*Total*	*32 (9.1%)*	*1 (0.3%)*	*31 (8.9%)*	*2 (0.6%)*	*30 (8.6%)*
	Bronchitis	*8 (2.3%)*	*0 (0.0%)*	*8 (2.3%)*	*0 (0.0%)*	*8 (2.3%)*
	Erysipelas	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
	Furuncle	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Gastroenteritis	*3 (0.9%)*	*1 (0.3%)*	*2 (0.6%)*	*1 (0.3%)*	*2 (0.6%)*
	Influenza	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
	Localised infection	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Lung infection	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Nasopharyngitis	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*
	Rhinitis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Sepsis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Sinusitis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Skin infection	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Tonsillitis	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Tooth abscess	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Urinary tract infection	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*1 (0.3%)*	*2 (0.6%)*

Injury, poisoning and procedural complications	*Total*	*9 (2.6%)*	*2 (0.6%)*	*7 (2.0%)*	*0 (0.0%)*	*9 (2.6%)*
	Eye burns	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
	Eye injury	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Femur fracture	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Foreign body in eye	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
	Head injury	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Muscle strain	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Open wound	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Overdose	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Radiation retinopathy	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Investigations	*Total*	*9 (2.6%)*	*0 (0.0%)*	*9 (2.6%)*	*0 (0.0%)*	*9 (2.6%)*
	Blood creatine phosphokinase increased	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Blood culture positive	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Blood pressure increased	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Blood pressure systolic increased	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Glycosylated haemoglobin increased	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Intraocular pressure increased	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Liver function test abnormal	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Weight increased	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Metabolism and nutrition disorders	*Total*	*10 (2.9%)*	*0 (0.0%)*	*10 (2.9%)*	*0 (0.0%)*	*10 (2.9%)*
	Diabetes mellitus inadequate control	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*	*0 (0.0%)*	*5 (1.4%)*
	Hyperglycaemia	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Hypoglycaemia	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*
Musculoskeletal and connective tissue disorders	*Total*	*9 (2.6%)*	*0 (0.0%)*	*9 (2.6%)*	*0 (0.0%)*	*9 (2.6%)*
	Arthralgia	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Back pain	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*
	Muscle spasms	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Osteoarthritis	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	*Total*	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*	*0 (0.0%)*	*4 (1.1%)*
	Brain neoplasm	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Oesophageal adenocarcinoma	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Prostate cancer recurrent	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Renal cancer	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Nervous system disorders	*Total*	*14 (4.0%)*	*1 (0.3%)*	*13 (3.7%)*	*1 (0.3%)*	*13 (3.7%)*
	Balance disorder	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Carpal tunnel syndrome	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Cerebrovascular accident	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Cognitive disorder	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Convulsion	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Diabetic neuropathy	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Dizziness	*4 (1.1%)*	*1 (0.3%)*	*3 (0.9%)*	*1 (0.3%)*	*3 (0.9%)*
	Headache	*2 (0.6%)*	*1 (0.3%)*	*1 (0.3%)*	*1 (0.3%)*	*1 (0.3%)*
	Hypoxic-ischaemic encephalopathy	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*

	Neuropathy peripheral	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Paraesthesia	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Sciatica	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Transient ischaemic attack	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Psychiatric disorders	*Total*	*5 (1.4%)*	*1 (0.3%)*	*4 (1.1%)*	*0 (0.0%)*	*5 (1.4%)*
	Anxiety	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
	Depression	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Hallucinations, mixed	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Insomnia	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Stress	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Renal and urinary disorders	*Total*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Nephrolithiasis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Renal failure acute	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
Respiratory, thoracic and mediastinal disorders	*Total*	*10 (2.9%)*	*0 (0.0%)*	*10 (2.9%)*	*0 (0.0%)*	*10 (2.9%)*
	Allergic bronchitis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Bronchospasm	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Cough	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Dyspnoea	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Epistaxis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Respiratory acidosis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Rhinitis allergic	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Sleep apnoea syndrome	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
Skin and subcutaneous tissue disorders	*Total*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
	Angioedema	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Skin ulcer	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
Surgical and medical procedures	*Total*	*7 (2.0%)*	*1 (0.3%)*	*6 (1.7%)*	*1 (0.3%)*	*6 (1.7%)*
	Aortic aneurysm repair	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Cataract operation	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*	*0 (0.0%)*	*3 (0.9%)*
	Medical device removal	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Tooth extraction	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Vitrectomy	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*
Vascular disorders	*Total*	*45 (12.9%)*	*3 (0.9%)*	*42 (12.0%)*	*1 (0.3%)*	*44 (12.6%)*
	Aortic aneurysm	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Arterial spasm	*1 (0.3%)*	*1 (0.3%)*	*0 (0.0%)*	*0 (0.0%)*	*1 (0.3%)*
	Extremity necrosis	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Haemorrhage	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*	*0 (0.0%)*	*2 (0.6%)*
	Hypertension	*38 (10.9%)*	*2 (0.6%)*	*36 (10.3%)*	*1 (0.3%)*	*37 (10.6%)*
	Hypotension	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Shock haemorrhagic	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*
	Varicose ulceration	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*	*0 (0.0%)*	*1 (0.3%)*

Only AE after first injection of Lucentis are displayed
A patient contributing to one of the categories defined by table rows is taken into account only once in this category whatever the number of events reported.
He(she) contributes to the column corresponding to the maximum imputability of events reported in the category, so that the column 'Total'
is the sum of columns 'suspected' and 'not suspected', plus events of undefined imputability, if there are some.
The percentages are calculated to the size (N=) of the column.
Start day of event is set at 15th in case missing to assign it before or after any injection, and before or after month 6
G:\BusUnits\PH-DEV\MIPS\Bmo\CLIMSAS\LUDIC\stat\pgm\s_aev2.sas 01OCT12 14:54 Datasets Date : 28SEP12

Adverse Events by System Organ Class

	Novartis product N (%)	*Comparator N (%)*
Patients studied		
Randomized patients	*471*	*415*
Patients with drug-related AE	*21 (4.5)*	*50 (10.8)*
Drug-related AEs by primary system organ class		
Respiratory, thoracic and mediastinal disorders	*5 (1.1)*	*37 (8.0)*
Nervous system disorders	*0 (0.0)*	*7 (1.5)*
Gastrointestinal disorders	*6 (1.3)*	*2 (0.4)*
General disorders	*2 (0.4)*	*3 (0.6)*
Cardiac disorders	*2 (0.4)*	*2 (0.4)*
Vascular disorders	*1 (0.2)*	*3 (0.6)*
Skin and subcutaneous tissue disorders	*3 (0.6)*	*0 (0.0)*
Ear and labyrinth disorders	*2 (0.4)*	*0 (0.0)*
Reproductive system and breast disorders	*0 (0.0)*	*2 (0.4)*
Renal and urinary disorders	*0 (0.0)*	*1 (0.2)*
Infections and infestations	*0 (0.0)*	*0 (0.0)*
Psychiatric disorders	*0 (0.0)*	*0 (0.0)*
Immune system disorders	*1 (0.2)*	*0 (0.2)*

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

	Novartis product	*Comparator*
Nasopharyngitis	*7 (1.1)*	*6 (0.9)*
Headache	*4 (0.6)*	*4 (0.6)*
Influenza	*4 (0.6)*	*4 (0.6)*
Diarrhea	*4 (0.6)*	*4 (0.6)*
Depression	*3 (0.5)*	*2 (0.3)*
Sinusitis	*2 (0.3)*	*2 (0.3)*
Bronchitis	*2 (0.3)*	*2 (0.3)*
Hypotension	*2 (0.3)*	*2 (0.3)*
Palpitations	*2 (0.3)*	*2 (0.3)*
Vertigo	*2 (0.3)*	*2 (0.3)*

Serious Adverse Events and Deaths

	Novartis product	*Comparator*
No. (%) of subjects studied	*836*	*832*
No. (%) of subjects with AE(s)	*337 (40.3)*	*356 (42.8)*
Number (%) of subjects with serious or other significant events	*n (%)*	*n (%)*
Death	*1 (0.1)*	*0 (0.0)*
SAE(s)	*14 (1.7)*	*21 (2.5)*
Discontinued due to SAE(s)	*2 (0.2)*	*8 (1.0)*

Other Relevant Findings

NA

Date Inclusion on Novartis Clinical Trial Results Database

07 SEP 2013

Date of Clinical Trial Report

11-Jul-2013