



Clinical trial results:

Multicenter randomized open-label three-arms controlled 12 months clinical proof of concept study to evaluate efficacy and safety of Ranibizumab alone or in combination with laser photocoagulation vs. laser photocoagulation alone in Proliferative Diabetic Retinopathy

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Summary

EudraCT number	2011-005542-35
Trial protocol	DE
Global end of trial date	05 December 2017

Results information

Result version number	v1 (current)
This version publication date	16 December 2018
First version publication date	16 December 2018

Trial information

Trial identification

Sponsor protocol code	CRFB002DDE21
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01594281
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	05 December 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	05 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study was to assess the efficacy and safety of the anti-Vascular Endothelial Growth Factor (VEGF) agent ranibizumab (0.5 mg) with or without Panretinal laser photocoagulation (PRP) compared to PRP alone in patients with Proliferative Diabetic Retinopathy (PDR).

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 December 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 106
Worldwide total number of subjects	106
EEA total number of subjects	106

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	86

From 65 to 84 years	20
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in Germany.

Pre-assignment

Screening details:

Patients were screened for eligibility at 23 German study sites and randomized at 22 of the 23 sites.

Period 1

Period 1 title	Interventional Core Phase
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

An open-label design had been chosen in which the evaluation of the primary objective was performed by a reading center. The reading center that was evaluating the primary and several secondary and exploratory objectives was blinded to randomization and therefore assessed these objectives uninfluenced by treatment information. However, laser burns were visible on the images, and no full blinding regarding PRP was possible for the reading center.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranibizumab mono

Arm description:

One intravitreal injection of ranibizumab 0.5 mg to the study eye monthly until stability regarding morphological parameters is confirmed (ie, no further improvement of morphology or no worsening of morphology for 3 consecutive months)

Arm type	Experimental
Investigational medicinal product name	ranibizumab 0.5 mg
Investigational medicinal product code	
Other name	Lucentis RFB002
Pharmaceutical forms	Solution for injection in pre-filled syringe, Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

One intravitreal injection of ranibizumab 0.5 mg to the study eye monthly until stability regarding morphological parameters is confirmed (ie, no further improvement of morphology or no worsening of morphology for 3 consecutive months)

Arm title	PRP mono
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Arm description:

Panretinal laser photocoagulation (PRP) treatment administered to the study eye in accordance with the modified diabetic retinopathy study (DRS) guidelines for panretinal laser photocoagulation procedures. If stability of morphological parameters could not be confirmed after 3 months, additional laser treatment was initiated.

Arm type	Panretinal laser photocoagulation
No investigational medicinal product assigned in this arm	
Arm title	Ranibizumab+PRP

Arm description:

Ranibizumab 0.5 mg as described for the ranibizumab mono arm and PRP treatment as described for the PRP mono arm until stability regarding morphological parameters is confirmed

Arm type	Experimental
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Investigational medicinal product name	ranibizumab 0.5 mg
Investigational medicinal product code	
Other name	Lucentis RFB002
Pharmaceutical forms	Solution for injection, Solution for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

One intravitreal injection of ranibizumab 0.5 mg to the study eye monthly until stability regarding morphological parameters is confirmed (ie, no further improvement of morphology or no worsening of morphology for 3 consecutive months)

Number of subjects in period 1	Ranibizumab mono	PRP mono	Ranibizumab+PRP
Started	35	35	36
Completed	29	26	28
Not completed	6	9	8
Adverse Event	4	4	4
Subject Withdrew Consent	-	1	1
Protocol Deviation	1	-	-
Death	1	1	2
Lost to follow-up	-	3	1

Period 2

Period 2 title	Non-Interventional Follow Up Phase
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

An open-label design had been chosen in which the evaluation of the primary objective was performed by a reading center. The reading center that was evaluating the primary and several secondary and exploratory objectives was blinded to randomization and therefore assessed these objectives uninfluenced by treatment information. However, laser burns were visible on the images, and no full blinding regarding PRP was possible for the reading center.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ranibizumab mono

Arm description:

Treatment per physician's routine standard of care until Month 24.

Arm type	Experimental
Investigational medicinal product name	ranibizumab 0.5 mg
Investigational medicinal product code	
Other name	RFB002
Pharmaceutical forms	Solution for injection, Solution for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

Treatment per physician's routine standard of care until Month 24.

Arm title	PRP mono
Arm description: Treatment per physician's routine standard of care until Month 24.	
Arm type	Panretinal laser photocoagulation
No investigational medicinal product assigned in this arm	
Arm title	Ranibizumab+PRP
Arm description: Treatment per physician's routine standard of care until Month 24.	
Arm type	Experimental
Investigational medicinal product name	ranibizumab 0.5 mg
Investigational medicinal product code	
Other name	RFB002
Pharmaceutical forms	Solution for injection, Solution for injection in pre-filled syringe
Routes of administration	Intravitreal use

Dosage and administration details:

Treatment per physician's routine standard of care until Month 24.

Number of subjects in period 2^[1]	Ranibizumab mono	PRP mono	Ranibizumab+PRP
Started	28	21	25
Follow Up Set (FUS)	28	20	25
Completed	25	19	23
Not completed	3	2	2
Subject Withdrew Consent	1	-	1
Administrative Problems	-	-	1
Lost to follow-up	2	2	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patients were invited to enter a twelve month Follow Up phase after completion of the core phase. A separate informed consent was signed for the Follow Up phase.

Baseline characteristics

Reporting groups

Reporting group title	Ranibizumab mono
Reporting group description: One intravitreal injection of ranibizumab 0.5 mg to the study eye monthly until stability regarding morphological parameters is confirmed (ie, no further improvement of morphology or no worsening of morphology for 3 consecutive months)	
Reporting group title	PRP mono
Reporting group description: Panretinal laser photocoagulation (PRP) treatment administered to the study eye in accordance with the modified diabetic retinopathy study (DRS) guidelines for panretinal laser photocoagulation procedures. If stability of morphological parameters could not be confirmed after 3 months, additional laser treatment was initiated.	
Reporting group title	Ranibizumab+PRP
Reporting group description: Ranibizumab 0.5 mg as described for the ranibizumab mono arm and PRP treatment as described for the PRP mono arm until stability regarding morphological parameters is confirmed	

Reporting group values	Ranibizumab mono	PRP mono	Ranibizumab+PRP
Number of subjects	35	35	36
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	30	26
From 65-84 years	5	5	10
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	52.5	53.0	55.0
standard deviation	± 11.0	± 12.1	± 13.4
Sex: Female, Male Units: Subjects			
Female	14	11	8
Male	21	24	28

Reporting group values	Total		
Number of subjects	106		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		

Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	86		
From 65-84 years	20		
85 years and over	0		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	33		
Male	73		

End points

End points reporting groups

Reporting group title	Ranibizumab mono
Reporting group description: One intravitreal injection of ranibizumab 0.5 mg to the study eye monthly until stability regarding morphological parameters is confirmed (ie, no further improvement of morphology or no worsening of morphology for 3 consecutive months)	
Reporting group title	PRP mono
Reporting group description: Panretinal laser photocoagulation (PRP) treatment administered to the study eye in accordance with the modified diabetic retinopathy study (DRS) guidelines for panretinal laser photocoagulation procedures. If stability of morphological parameters could not be confirmed after 3 months, additional laser treatment was initiated.	
Reporting group title	Ranibizumab+PRP
Reporting group description: Ranibizumab 0.5 mg as described for the ranibizumab mono arm and PRP treatment as described for the PRP mono arm until stability regarding morphological parameters is confirmed	
Reporting group title	Ranibizumab mono
Reporting group description: Treatment per physician's routine standard of care until Month 24.	
Reporting group title	PRP mono
Reporting group description: Treatment per physician's routine standard of care until Month 24.	
Reporting group title	Ranibizumab+PRP
Reporting group description: Treatment per physician's routine standard of care until Month 24.	
Subject analysis set title	Ranibizumab mono
Subject analysis set type	Full analysis
Subject analysis set description: Interventional Core Phase: All randomized patients with at least one study treatment and one post-baseline assessment.	
Subject analysis set title	PRP mono
Subject analysis set type	Full analysis
Subject analysis set description: Interventional Core Phase: All randomized patients with at least one study treatment and one post-baseline assessment.	
Subject analysis set title	Ranibizumab+PRP
Subject analysis set type	Full analysis
Subject analysis set description: Interventional Core Phase: All randomized patients with at least one study treatment and one post-baseline assessment.	
Primary: Change from baseline in area of neovascularizations (NVs) at End of Core Study (EOCS)	
End point title	Change from baseline in area of neovascularizations (NVs) at End of Core Study (EOCS)
End point description: The area of neovascularizations (NV) was assessed by a central reading center via fluorescein angiography (FA) images. The area of NV was calculated as the sum of area of neovascularization of the disc (NVD) and neovascularization elsewhere (NVE) and was recorded in square millimeters. A higher positive change value may indicate a greater formation of new, abnormal blood vessels and thus disease progression. One eye (study eye) contributed to the analysis.	
End point type	Primary

End point timeframe:

Baseline, EOCS

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	33	33	
Units: square millimeters				
arithmetic mean (standard deviation)	-4.6 (\pm 11.3)	-0.9 (\pm 3.9)	-1.7 (\pm 3.0)	

Statistical analyses

Statistical analysis title	Change from BL in area of NV at EOCS
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0344
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.4
upper limit	-0.2

Statistical analysis title	Change from BL in area of NV at EOCS
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3809
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.8
upper limit	1.5

Statistical analysis title	Change from BL in area of NV at EOCS
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2113
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	4.3

Secondary: Change from baseline in area of neovascularizations (NVs) at Month 3

End point title	Change from baseline in area of neovascularizations (NVs) at Month 3
End point description:	
The area of neovascularizations (NV) was assessed by a central reading center via fluorescein angiography (FA) images. The area of NV was calculated as the sum of area of neovascularization of the disc (NVD) and neovascularization elsewhere (NVE) and was recorded in square millimeters. A higher positive change value may indicate a greater formation of new, abnormal blood vessels and thus disease progression. One eye (study eye) contributed to the analysis.	
End point type	Secondary
End point timeframe:	
Baseline, Month 3	

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	33	32	33	
Units: square millimeters				
arithmetic mean (standard deviation)	-5.9 (± 12.7)	-0.7 (± 2.8)	-2.7 (± 3.9)	

Statistical analyses

Statistical analysis title	Change from BL in area of NV at Month 3
Comparison groups	Ranibizumab mono v PRP mono

Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0081
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	-0.6

Statistical analysis title	Change from BL in area of NV at Month 3
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7494
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	1.5

Statistical analysis title	Change from BL in area of NV at Month 3
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	65
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0175
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	2.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	3.9

Secondary: Best Corrected Visual Acuity (BCVA) (ETDRS letters) at EOCS

End point title	Best Corrected Visual Acuity (BCVA) (ETDRS letters) at EOCS
End point description:	BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts at a testing distance of 4 meters. A higher number of ETDRS letters may indicate better visual acuity. One eye (study eye) contributed to the analysis.
End point type	Secondary
End point timeframe:	EOCS

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	36	
Units: letters				
arithmetic mean (standard deviation)	84.4 (± 8.6)	76.8 (± 17.0)	78.9 (± 12.2)	

Statistical analyses

Statistical analysis title	BCVA (ETDRS letters) at EOCS
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0495
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	5.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	11

Statistical analysis title	BCVA (ETDRS letters) at EOCS
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2767
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	8.5

Statistical analysis title	BCVA (ETDRS letters) at EOCS
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3641
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.9
upper limit	2.9

Secondary: Percentage of patients with change from baseline in BCVA (ETDRS letters) at EOCS

End point title	Percentage of patients with change from baseline in BCVA (ETDRS letters) at EOCS
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End point description:

BCVA was assessed using Early Treatment Diabetic Retinopathy Study (ETDRS)-like charts at a testing distance of 4 meters. No clinically relevant change was defined as <5 letters gain or loss. A higher positive change value may indicate a greater improvement in visual acuity. One eye (study eye) contributed to the analysis.

End point type	Secondary
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End point timeframe:

Baseline, EOCS

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	36	
Units: percentage of participants				
number (not applicable)				
≥15 letters gain from Baseline at EOCS	0.0	2.9	0.0	
≥10 letters gain from Baseline at EOCS	5.7	11.4	8.3	
≥5 letters gain from Baseline at EOCS	31.4	20.0	13.9	
No clinically relevant change from Baseline	51.4	42.9	61.1	
≥5 letters loss from Baseline at EOCS	17.1	37.1	25.0	

≥10 letters loss from Baseline at EOCS	11.4	11.4	8.3	
≥15 letters loss from Baseline at EOCS	2.9	8.6	2.8	

Statistical analyses

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥10 letters gain	
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4019
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.47
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.08
upper limit	2.749

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥5 letters gain	
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2772
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.833
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.614
upper limit	5.471

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
No clinically relevant change	
Comparison groups	Ranibizumab mono v PRP mono

Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4731
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.412
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.55
upper limit	3.622

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description: ≥5 letters loss	
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.065
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.155
upper limit	1.068

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description: ≥10 letters loss	
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.229
upper limit	4.361

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥15 letters loss	
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	70
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3261
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.314
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.031
upper limit	3.173

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥10 letters gain	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.668
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.667
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.104
upper limit	4.253

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥5 letters gain	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0838
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	2.842
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	9.283

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
No clinically relevant change	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4116
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.674
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.263
upper limit	1.729

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥5 letters loss	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4197
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.621
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.195
upper limit	1.977

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description: ≥10 letters loss	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6632
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.419
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.294
upper limit	6.856

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description: ≥15 letters loss	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9839
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.029
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.062
upper limit	17.127

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description: ≥10 letters gain	
Comparison groups	PRP mono v Ranibizumab+PRP

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.663
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.419
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.294
upper limit	6.858

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥5 letters gain	
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4941 ^[1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.55
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.441
upper limit	5.444

Notes:

[1] - P-value was calculated as a point estimate.

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
No clinically relevant change	
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1259
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.477
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.185
upper limit	1.231

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥5 letters loss	
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.271
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.773
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	4.913

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥10 letters loss	
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.6632
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.419
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.294
upper limit	6.856

Statistical analysis title	Change from BL in BCVA (ETDRS letters) at EOCS
Statistical analysis description:	
≥15 letters loss	
Comparison groups	PRP mono v Ranibizumab+PRP

Number of subjects included in analysis	71
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.314
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	3.282
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.325
upper limit	33.171

Secondary: Number of patients with change from baseline in ETDRS severity grade of diabetic retinopathy (DR) at EOCS

End point title	Number of patients with change from baseline in ETDRS severity grade of diabetic retinopathy (DR) at EOCS
End point description:	
<p>The severity level of diabetic retinopathy was determined using the ETDRS severity scale. However, in contrast to the original ETDRS severity scale, wide field fluorescein angiography images were used in addition to color fundus photography for identification of NVs and prior PRP treatment was not considered for determining the severity level. Eyes could be graded in the following classes: "DR absent" (10), "questionable DR" (14,15), "NPDR" (20-53), "mild PDR" (60-61), "moderate PDR" (65), "high risk PDR" (71-75), "advanced PDR" (81-85) and "cannot grade" (90). One eye (study eye) contributed to the analysis. No statistical analysis was conducted for ≥ 1 class deterioration or ≥ 2 class deterioration from Baseline at EOCS because ratios could not be calculated in case of zero frequencies in at least one of the three treatment groups.</p>	
End point type	Secondary
End point timeframe:	
Baseline, EOCS	

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	29	26	28	
Units: participants				
≥ 1 class improvement from Baseline at EOCS	10	9	13	
≥ 2 class improvement from Baseline at EOCS	2	2	5	
≥ 1 class deterioration from Baseline at EOCS	2	0	1	
≥ 2 class deterioration from Baseline at EOCS	0	0	0	

Statistical analyses

Statistical analysis title	Change from BL in DR severity grade at EOCS
Statistical analysis description:	
≥ 1 class improvement from Baseline at EOCS	
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9918
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.994
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.327
upper limit	3.026

Statistical analysis title	Change from BL in DR severity grade at EOCS
Statistical analysis description:	
≥ 1 class improvement from Baseline at EOCS	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3595
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.607
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.209
upper limit	1.765

Statistical analysis title	Change from BL in DR severity grade at EOCS
Statistical analysis description:	
≥ 1 class improvement from Baseline at EOCS	
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3787
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.611

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.204
upper limit	1.83

Statistical analysis title	Change from BL in DR severity grade at EOCS
Statistical analysis description:	
≥ 2 class improvement from Baseline at EOCS	
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	55
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9097
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.889
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.116
upper limit	6.806

Statistical analysis title	Change from BL in DR severity grade at EOCS
Statistical analysis description:	
≥ 2 class improvement from Baseline at EOCS	
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	57
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.223
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.341
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.06
upper limit	1.925

Statistical analysis title	Change from BL in DR severity grade at EOCS
Statistical analysis description:	
≥ 2 class improvement from Baseline at EOCS	
Comparison groups	PRP mono v Ranibizumab+PRP

Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2792
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.383
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.068
upper limit	2.177

Secondary: Change from baseline in central subfield thickness at EOCS

End point title	Change from baseline in central subfield thickness at EOCS
End point description:	Central subfield retinal thickness (CST) was assessed by a central reading center using Optical Coherence Tomography images. A positive change value may indicate disease progression. One eye (study eye) contributed to the analysis.
End point type	Secondary
End point timeframe:	
Baseline, EOCS	

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	31	31	
Units: micrometer				
arithmetic mean (standard deviation)	-6.0 (± 15.1)	36.2 (± 55.9)	17.6 (± 46.7)	

Statistical analyses

Statistical analysis title	Change from BL in CST at EOCS
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0003
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-40.7

Confidence interval	
level	95 %
sides	2-sided
lower limit	-62.1
upper limit	-19.3

Statistical analysis title	Change from BL in CST at EOCS
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0357
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-22.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-44.2
upper limit	-1.6

Statistical analysis title	Change from BL in CST at EOCS
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1034
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	17.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	39.3

Secondary: Change from baseline in foveal center point retinal thickness at EOCS

End point title	Change from baseline in foveal center point retinal thickness at EOCS
End point description:	
Foveal center point retinal thickness (FCPT) was assessed by a central reading center using Optical Coherence Tomography images. A positive change value may indicate disease progression. One eye (study eye) contributed to the analysis.	
End point type	Secondary

End point timeframe:

Baseline, EOCS

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	32	31	31	
Units: micrometer				
arithmetic mean (standard deviation)	-4.7 (\pm 21.2)	48.1 (\pm 83.7)	25.5 (\pm 53.5)	

Statistical analyses

Statistical analysis title	Change from BL in FCPT at EOCS
Comparison groups	Ranibizumab mono v PRP mono
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0007
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-51.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-81.1
upper limit	-22.3

Statistical analysis title	Change from BL in FCPT at EOCS
Comparison groups	Ranibizumab mono v Ranibizumab+PRP
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0542
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-28.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-58.4
upper limit	0.5

Statistical analysis title	Change from BL in FCPT at EOCS
Comparison groups	PRP mono v Ranibizumab+PRP
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1288
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	22.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.7
upper limit	52.3

Secondary: Number of ranibizumab injections until EOCS

End point title	Number of ranibizumab injections until EOCS
End point description:	
The total number of ranibizumab injections until EOCS was calculated. One eye (study eye) contributed to the analysis. No statistical analysis was conducted.	
End point type	Secondary
End point timeframe:	
Baseline to EOCS	

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	36	
Units: injections				
arithmetic mean (standard deviation)	5.2 (± 2.3)	999 (± 999)	5.0 (± 2.2)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of PRP laser spots until EOCS

End point title	Number of PRP laser spots until EOCS
End point description:	
The total number of PRP laser spots from baseline until EOCS was calculated. One eye (study eye) contributed to the analysis. No statistical analysis was conducted.	
End point type	Secondary
End point timeframe:	
Baseline to EOCS	

End point values	Ranibizumab mono	PRP mono	Ranibizumab+PRP	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	35	35	36	
Units: PRP laser spots				
arithmetic mean (standard deviation)	999 (± 999)	1919.4 (± 673.1)	1670.0 (± 568.4)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Baseline to Month 12 phase Ranibizumab
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Reporting group description:

Baseline to Month 12 phase Ranibizumab

Reporting group title	Baseline to Month 12 phase Panretinal laser
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Reporting group description:

Baseline to Month 12 phase Panretinal laser

Reporting group title	Baseline to Month 12 phase Combination
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Reporting group description:

Baseline to Month 12 phase Combination

Reporting group title	Follow-up phase Ranibizumab
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Reporting group description:

Follow-up phase Ranibizumab

Reporting group title	Follow-up phase Panretinal laser
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Reporting group description:

Follow-up phase Panretinal laser

Reporting group title	Follow-up phase Combination
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Reporting group description:

Follow-up phase Combination

Serious adverse events	Baseline to Month 12 phase Ranibizumab	Baseline to Month 12 phase Panretinal laser	Baseline to Month 12 phase Combination
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 35 (22.86%)	11 / 35 (31.43%)	16 / 36 (44.44%)
number of deaths (all causes)	1	1	2
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CHRONIC LYMPHOCYTIC LEUKAEMIA (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

GASTRIC CANCER (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
DIABETIC MICROANGIOPATHY (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY OCCLUSION (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL VENOUS DISEASE (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
PREGNANCY (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

CHEST PAIN (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL SWELLING (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
COUGH (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
PSYCHIATRIC DECOMPENSATION (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BLOOD GLUCOSE FLUCTUATION (Non-ocular)			

subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FRACTURED COCCYX (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPHAEMA (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KIDNEY CONTUSION (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENISCUS INJURY (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIB FRACTURE (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
SPINAL FRACTURE (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE (Non-ocular)			

subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONGESTIVE CARDIOMYOPATHY (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEART VALVE STENOSIS (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIZZINESS (Non-ocular)			

subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
SUDDEN HEARING LOSS (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
ANTERIOR CHAMBER DISORDER (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATARACT (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATARACT (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINAL OEDEMA (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINAL OEDEMA (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINOPATHY (Left eye)			

subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINOPATHY (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GLAUCOMA (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MACULAR FIBROSIS (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MACULAR FIBROSIS (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MACULAR OEDEMA (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OPEN ANGLE GLAUCOMA (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL DETACHMENT (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL HAEMORRHAGE (Both eyes)			

subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL HAEMORRHAGE (Right eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL NEOVASCULARISATION (Right eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VISUAL ACUITY REDUCED (Left eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITREOUS ADHESIONS (Right eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITREOUS HAEMORRHAGE (Left eye)			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITREOUS HAEMORRHAGE (Right eye)			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
ABDOMINAL PAIN (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC GASTRITIS (Non-ocular)			

subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DENTAL CYST (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UMBILICAL HERNIA (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
COLD SWEAT (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC FOOT (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	3 / 36 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
CHRONIC KIDNEY DISEASE (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION (Non-ocular)			

subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEITIS (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
GASTROENTERITIS (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTED SKIN ULCER (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOCALISED INFECTION (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS CHRONIC (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION (Non-ocular)			

subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OBESITY (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Follow-up phase Ranibizumab	Follow-up phase Panretinal laser	Follow-up phase Combination
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 28 (17.86%)	5 / 20 (25.00%)	11 / 25 (44.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
CHRONIC LYMPHOCYTIC LEUKAEMIA (Non-ocular)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GASTRIC CANCER (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
DIABETIC MICROANGIOPATHY (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERTENSION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERIAL OCCLUSIVE DISEASE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL ARTERY OCCLUSION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL VENOUS DISEASE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
PREGNANCY (Non-ocular)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
CHEST PAIN (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GENERAL PHYSICAL HEALTH DETERIORATION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
NON-CARDIAC CHEST PAIN (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
PERIPHERAL SWELLING (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
COUGH (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DYSPNOEA (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
PSYCHIATRIC DECOMPENSATION (Non-ocular)			

subjects affected / exposed	0 / 28 (0.00%)	1 / 20 (5.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
BLOOD GLUCOSE FLUCTUATION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	1 / 20 (5.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
FRACTURED COCCYX (Non-ocular)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HUMERUS FRACTURE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPHAEMA (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
KIDNEY CONTUSION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENISCUS INJURY (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RIB FRACTURE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

SPINAL FRACTURE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
TENDON RUPTURE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	1 / 20 (5.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
ACUTE MYOCARDIAL INFARCTION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ATRIAL FIBRILLATION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CONGESTIVE CARDIOMYOPATHY (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CORONARY ARTERY DISEASE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HEART VALVE STENOSIS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	1 / 20 (5.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
CEREBROVASCULAR ACCIDENT (Non-ocular)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIZZINESS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
SUDDEN HEARING LOSS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
ANTERIOR CHAMBER DISORDER (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATARACT (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CATARACT (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINAL OEDEMA (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINAL OEDEMA (Right eye)			

subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINOPATHY (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	2 / 20 (10.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC RETINOPATHY (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	1 / 20 (5.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
GLAUCOMA (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MACULAR FIBROSIS (Left eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MACULAR FIBROSIS (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MACULAR OEDEMA (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OPEN ANGLE GLAUCOMA (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL DETACHMENT (Left eye)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL HAEMORRHAGE (Both eyes)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL HAEMORRHAGE (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
RETINAL NEOVASCULARISATION (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VISUAL ACUITY REDUCED (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITREOUS ADHESIONS (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITREOUS HAEMORRHAGE (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
VITREOUS HAEMORRHAGE (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	2 / 25 (8.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

ABDOMINAL PAIN (Non-ocular)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
CHRONIC GASTRITIS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DENTAL CYST (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIARRHOEA (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
UMBILICAL HERNIA (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
COLD SWEAT (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETIC FOOT (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
CHRONIC KIDNEY DISEASE (Non-ocular)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Musculoskeletal and connective tissue disorders			
INTERVERTEBRAL DISC PROTRUSION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEITIS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
GASTROENTERITIS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
INFECTED SKIN ULCER (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
LOCALISED INFECTION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
MENINGITIS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OSTEOMYELITIS CHRONIC (Non-ocular)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
POSTOPERATIVE WOUND INFECTION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
DEHYDRATION (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
DIABETES MELLITUS (Non-ocular)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPERGLYCAEMIA (Non-ocular)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HYPOGLYCAEMIA (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
OBESITY (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Baseline to Month 12 phase Ranibizumab	Baseline to Month 12 phase Panretinal laser	Baseline to Month 12 phase Combination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	34 / 35 (97.14%)	29 / 35 (82.86%)	34 / 36 (94.44%)
Investigations			
BLOOD CHOLESTEROL INCREASED (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences (all)	0	0	1
BLOOD PRESSURE INCREASED (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences (all)	0	1	0
BLOOD TRIGLYCERIDES INCREASED (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	1	0	0
GLYCOSYLATED HAEMOGLOBIN INCREASED (Non-ocular)			
subjects affected / exposed	4 / 35 (11.43%)	0 / 35 (0.00%)	6 / 36 (16.67%)
occurrences (all)	5	0	6
INTRAOCULAR PRESSURE INCREASED (Left eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	3 / 36 (8.33%)
occurrences (all)	1	0	4
INTRAOCULAR PRESSURE INCREASED (Right eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	3
Injury, poisoning and procedural complications			
CONTUSION (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
FALL (Non-ocular)			
subjects affected / exposed	1 / 35 (2.86%)	3 / 35 (8.57%)	0 / 36 (0.00%)
occurrences (all)	1	3	0
FOOT FRACTURE (Non-ocular)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
PROCEDURAL PAIN (Both eyes)			

subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 35 (0.00%) 0	3 / 36 (8.33%) 3
PROCEDURAL PAIN (Left eye) subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 35 (5.71%) 11	4 / 36 (11.11%) 11
RIB FRACTURE (Non-ocular) subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0
ROAD TRAFFIC ACCIDENT (Non-ocular) subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0
SCRATCH (Non-ocular) subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0
Vascular disorders HYPERTENSION (Non-ocular) subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	1 / 35 (2.86%) 1	0 / 36 (0.00%) 0
Nervous system disorders HEADACHE (Non-ocular) subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	4 / 35 (11.43%) 4	5 / 36 (13.89%) 6
Eye disorders ABNORMAL SENSATION IN EYE (Right eye) subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0
BLEPHARITIS (Both eyes) subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2
CATARACT (Both eyes) subjects affected / exposed occurrences (all)	3 / 35 (8.57%) 3	1 / 35 (2.86%) 1	1 / 36 (2.78%) 1
CATARACT (Right eye) subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	1 / 35 (2.86%) 1	0 / 36 (0.00%) 0
CONJUNCTIVAL HAEMORRHAGE (Left			

eye)			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	3 / 36 (8.33%)
occurrences (all)	4	0	6
CONJUNCTIVAL HAEMORRHAGE (Right eye)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	2
CONJUNCTIVITIS ALLERGIC (Both eyes)			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences (all)	3	0	1
CORNEAL EROSION (Left eye)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	6 / 36 (16.67%)
occurrences (all)	2	0	9
CORNEAL EROSION (Right eye)			
subjects affected / exposed	3 / 35 (8.57%)	5 / 35 (14.29%)	1 / 36 (2.78%)
occurrences (all)	4	6	1
CYSTOID MACULAR OEDEMA (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	0	2	3
DIABETIC RETINAL OEDEMA (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	0	1	3
DIABETIC RETINAL OEDEMA (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	6 / 36 (16.67%)
occurrences (all)	0	0	7
DIABETIC RETINOPATHY (Both eyes)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	0	1	2
DIABETIC RETINOPATHY (Left eye)			
subjects affected / exposed	7 / 35 (20.00%)	1 / 35 (2.86%)	7 / 36 (19.44%)
occurrences (all)	7	1	7
DIABETIC RETINOPATHY (Right eye)			
subjects affected / exposed	4 / 35 (11.43%)	2 / 35 (5.71%)	3 / 36 (8.33%)
occurrences (all)	4	4	3
DRY EYE (Both eyes)			

subjects affected / exposed	3 / 35 (8.57%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	3	2	2
EYE IRRITATION (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	4 / 36 (11.11%)
occurrences (all)	0	1	5
EYE IRRITATION (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	4
EYE PAIN (Left eye)			
subjects affected / exposed	2 / 35 (5.71%)	3 / 35 (8.57%)	5 / 36 (13.89%)
occurrences (all)	2	4	6
EYE PAIN (Right eye)			
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)	6 / 36 (16.67%)
occurrences (all)	3	1	7
FOREIGN BODY SENSATION IN EYES (Left eye)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	6	0	0
FOREIGN BODY SENSATION IN EYES (Right eye)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	2	0	2
GLARE (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
IRIS NEOVASCULARISATION (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
IRIS NEOVASCULARISATION (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	1 / 35 (2.86%)	3 / 36 (8.33%)
occurrences (all)	0	1	3
LACRIMATION INCREASED (Left eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	3 / 36 (8.33%)
occurrences (all)	0	0	3
LACRIMATION INCREASED (Right eye)			

subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	1	1	4
MACULAR FIBROSIS (Left eye)			
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences (all)	3	1	0
MACULAR FIBROSIS (Right eye)			
subjects affected / exposed	1 / 35 (2.86%)	2 / 35 (5.71%)	3 / 36 (8.33%)
occurrences (all)	1	2	3
MACULAR OEDEMA (Both eyes)			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	0	2	2
MACULAR OEDEMA (Left eye)			
subjects affected / exposed	5 / 35 (14.29%)	4 / 35 (11.43%)	4 / 36 (11.11%)
occurrences (all)	6	5	4
MACULAR OEDEMA (Right eye)			
subjects affected / exposed	3 / 35 (8.57%)	8 / 35 (22.86%)	4 / 36 (11.11%)
occurrences (all)	4	12	6
OCULAR DISCOMFORT (Left eye)			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	5	0	0
OCULAR HYPERAEMIA (Left eye)			
subjects affected / exposed	4 / 35 (11.43%)	0 / 35 (0.00%)	4 / 36 (11.11%)
occurrences (all)	5	0	4
OCULAR HYPERAEMIA (Right eye)			
subjects affected / exposed	3 / 35 (8.57%)	0 / 35 (0.00%)	4 / 36 (11.11%)
occurrences (all)	4	0	6
PUNCTATE KERATITIS (Both eyes)			
subjects affected / exposed	0 / 35 (0.00%)	3 / 35 (8.57%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
RETINAL CYST (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	3 / 35 (8.57%)	0 / 36 (0.00%)
occurrences (all)	0	3	0
RETINAL EXUDATES (Left eye)			
subjects affected / exposed	2 / 35 (5.71%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	2	2	0
RETINAL HAEMORRHAGE (Left eye)			

subjects affected / exposed	5 / 35 (14.29%)	0 / 35 (0.00%)	3 / 36 (8.33%)
occurrences (all)	5	0	3
RETINAL HAEMORRHAGE (Right eye)			
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)	3 / 36 (8.33%)
occurrences (all)	3	1	3
RETINAL ISCHAEMIA (Left eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	4
RETINAL NEOVASCULARISATION (Both eyes)			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
RETINAL NEOVASCULARISATION (Left eye)			
subjects affected / exposed	5 / 35 (14.29%)	4 / 35 (11.43%)	9 / 36 (25.00%)
occurrences (all)	6	4	10
RETINAL NEOVASCULARISATION (Right eye)			
subjects affected / exposed	12 / 35 (34.29%)	3 / 35 (8.57%)	10 / 36 (27.78%)
occurrences (all)	13	4	11
VISION BLURRED (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	4 / 36 (11.11%)
occurrences (all)	0	2	4
VISUAL ACUITY REDUCED (Both eyes)			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	2	1	2
VISUAL ACUITY REDUCED (Left eye)			
subjects affected / exposed	5 / 35 (14.29%)	3 / 35 (8.57%)	12 / 36 (33.33%)
occurrences (all)	5	3	16
VISUAL ACUITY REDUCED (Right eye)			
subjects affected / exposed	7 / 35 (20.00%)	9 / 35 (25.71%)	5 / 36 (13.89%)
occurrences (all)	9	13	7
VISUAL IMPAIRMENT (Left eye)			
subjects affected / exposed	1 / 35 (2.86%)	1 / 35 (2.86%)	2 / 36 (5.56%)
occurrences (all)	1	1	2
VITREOUS ADHESIONS (Right eye)			

subjects affected / exposed	2 / 35 (5.71%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	2	3	0
VITREOUS DETACHMENT (Both eyes)			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	0 / 36 (0.00%)
occurrences (all)	0	2	0
VITREOUS FLOATERS (Left eye)			
subjects affected / exposed	3 / 35 (8.57%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences (all)	3	1	0
VITREOUS FLOATERS (Right eye)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
VITREOUS HAEMORRHAGE (Left eye)			
subjects affected / exposed	6 / 35 (17.14%)	6 / 35 (17.14%)	5 / 36 (13.89%)
occurrences (all)	6	8	7
VITREOUS HAEMORRHAGE (Right eye)			
subjects affected / exposed	4 / 35 (11.43%)	7 / 35 (20.00%)	5 / 36 (13.89%)
occurrences (all)	4	10	6
RETINAL ISCHAEMIA (Right eye)			
subjects affected / exposed	1 / 35 (2.86%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	1	0	2
Gastrointestinal disorders			
DIARRHOEA (Non-ocular)			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	1 / 36 (2.78%)
occurrences (all)	2	1	1
NAUSEA (Non-ocular)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0
TOOTHACHE (Non-ocular)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	1 / 36 (2.78%)
occurrences (all)	2	0	1
VOMITING (Non-ocular)			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	0 / 36 (0.00%)
occurrences (all)	2	1	0
Respiratory, thoracic and mediastinal disorders			

COUGH (Non-ocular) subjects affected / exposed occurrences (all)	4 / 35 (11.43%) 4	1 / 35 (2.86%) 2	3 / 36 (8.33%) 3
Skin and subcutaneous tissue disorders DIABETIC FOOT (Non-ocular) subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2
Endocrine disorders HYPOTHYROIDISM (Non-ocular) subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0
Musculoskeletal and connective tissue disorders ARTHRITIS (Non-ocular) subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 35 (0.00%) 0	2 / 36 (5.56%) 2
PAIN IN EXTREMITY (Non-ocular) subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 35 (0.00%) 0	3 / 36 (8.33%) 3
BACK PAIN (Non-ocular) subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0
Infections and infestations BRONCHITIS (Non-ocular) subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 35 (0.00%) 0	0 / 36 (0.00%) 0
GASTROENTERITIS (Non-ocular) subjects affected / exposed occurrences (all)	1 / 35 (2.86%) 1	0 / 35 (0.00%) 0	4 / 36 (11.11%) 5
HORDEOLUM (Left eye) subjects affected / exposed occurrences (all)	2 / 35 (5.71%) 2	2 / 35 (5.71%) 2	0 / 36 (0.00%) 0
INFLUENZA (Non-ocular) subjects affected / exposed occurrences (all)	0 / 35 (0.00%) 0	2 / 35 (5.71%) 4	2 / 36 (5.56%) 3
NASOPHARYNGITIS (Non-ocular)			

subjects affected / exposed	7 / 35 (20.00%)	12 / 35 (34.29%)	9 / 36 (25.00%)
occurrences (all)	10	15	13
RHINITIS (Non-ocular)			
subjects affected / exposed	2 / 35 (5.71%)	1 / 35 (2.86%)	1 / 36 (2.78%)
occurrences (all)	2	2	1
SINUSITIS (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	2 / 35 (5.71%)	2 / 36 (5.56%)
occurrences (all)	0	2	2
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA (Non-ocular)			
subjects affected / exposed	0 / 35 (0.00%)	0 / 35 (0.00%)	2 / 36 (5.56%)
occurrences (all)	0	0	2
VITAMIN D DEFICIENCY (Non-ocular)			
subjects affected / exposed	2 / 35 (5.71%)	0 / 35 (0.00%)	0 / 36 (0.00%)
occurrences (all)	2	0	0

Non-serious adverse events	Follow-up phase Ranibizumab	Follow-up phase Panretinal laser	Follow-up phase Combination
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 28 (75.00%)	12 / 20 (60.00%)	21 / 25 (84.00%)
Investigations			
BLOOD CHOLESTEROL INCREASED (Non-ocular)			
subjects affected / exposed	3 / 28 (10.71%)	1 / 20 (5.00%)	0 / 25 (0.00%)
occurrences (all)	3	1	0
BLOOD PRESSURE INCREASED (Non-ocular)			
subjects affected / exposed	2 / 28 (7.14%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
BLOOD TRIGLYCERIDES INCREASED (Non-ocular)			
subjects affected / exposed	2 / 28 (7.14%)	2 / 20 (10.00%)	1 / 25 (4.00%)
occurrences (all)	2	2	1
GLYCOSYLATED HAEMOGLOBIN INCREASED (Non-ocular)			
subjects affected / exposed	3 / 28 (10.71%)	2 / 20 (10.00%)	1 / 25 (4.00%)
occurrences (all)	3	2	1
INTRAOCULAR PRESSURE INCREASED (Left eye)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
INTRAOCULAR PRESSURE INCREASED (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
CONTUSION (Non-ocular)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
FALL (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
FOOT FRACTURE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
PROCEDURAL PAIN (Both eyes)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
PROCEDURAL PAIN (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
RIB FRACTURE (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
ROAD TRAFFIC ACCIDENT (Non- ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	2 / 25 (8.00%)
occurrences (all)	0	0	2
SCRATCH (Non-ocular)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
Vascular disorders			
HYPERTENSION (Non-ocular)			
subjects affected / exposed	1 / 28 (3.57%)	1 / 20 (5.00%)	1 / 25 (4.00%)
occurrences (all)	1	1	1
Nervous system disorders			

HEADACHE (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
Eye disorders			
ABNORMAL SENSATION IN EYE (Right eye) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
BLEPHARITIS (Both eyes) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
CATARACT (Both eyes) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
CATARACT (Right eye) subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 2	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
CONJUNCTIVAL HAEMORRHAGE (Left eye) subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
CONJUNCTIVAL HAEMORRHAGE (Right eye) subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	1 / 20 (5.00%) 1	0 / 25 (0.00%) 0
CONJUNCTIVITIS ALLERGIC (Both eyes) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
CORNEAL EROSION (Left eye) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
CORNEAL EROSION (Right eye) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
CYSTOID MACULAR OEDEMA (Right eye) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0

DIABETIC RETINAL OEDEMA (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
DIABETIC RETINAL OEDEMA (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
DIABETIC RETINOPATHY (Both eyes)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
DIABETIC RETINOPATHY (Left eye)			
subjects affected / exposed	2 / 28 (7.14%)	0 / 20 (0.00%)	4 / 25 (16.00%)
occurrences (all)	2	0	4
DIABETIC RETINOPATHY (Right eye)			
subjects affected / exposed	2 / 28 (7.14%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	2	0	0
DRY EYE (Both eyes)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
EYE IRRITATION (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
EYE IRRITATION (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
EYE PAIN (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
EYE PAIN (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	3	0	0
FOREIGN BODY SENSATION IN EYES (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
FOREIGN BODY SENSATION IN EYES (Right eye)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
GLARE (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
IRIS NEOVASCULARISATION (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
IRIS NEOVASCULARISATION (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
LACRIMATION INCREASED (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	1 / 20 (5.00%)	0 / 25 (0.00%)
occurrences (all)	0	1	0
LACRIMATION INCREASED (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
MACULAR FIBROSIS (Left eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
MACULAR FIBROSIS (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
MACULAR OEDEMA (Both eyes)			
subjects affected / exposed	2 / 28 (7.14%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	2	0	1
MACULAR OEDEMA (Left eye)			
subjects affected / exposed	2 / 28 (7.14%)	4 / 20 (20.00%)	3 / 25 (12.00%)
occurrences (all)	2	4	3
MACULAR OEDEMA (Right eye)			
subjects affected / exposed	5 / 28 (17.86%)	1 / 20 (5.00%)	4 / 25 (16.00%)
occurrences (all)	8	1	6
OCULAR DISCOMFORT (Left eye)			

subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
OCULAR HYPERAEMIA (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
OCULAR HYPERAEMIA (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
PUNCTATE KERATITIS (Both eyes)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
RETINAL CYST (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
RETINAL EXUDATES (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
RETINAL HAEMORRHAGE (Left eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
RETINAL HAEMORRHAGE (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	2 / 25 (8.00%)
occurrences (all)	1	0	2
RETINAL ISCHAEMIA (Left eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
RETINAL NEOVASCULARISATION (Both eyes)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	5 / 25 (20.00%)
occurrences (all)	0	0	5
RETINAL NEOVASCULARISATION (Left eye)			
subjects affected / exposed	8 / 28 (28.57%)	0 / 20 (0.00%)	4 / 25 (16.00%)
occurrences (all)	9	0	4
RETINAL NEOVASCULARISATION (Right eye)			

subjects affected / exposed	5 / 28 (17.86%)	2 / 20 (10.00%)	4 / 25 (16.00%)
occurrences (all)	5	2	4
VISION BLURRED (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
VISUAL ACUITY REDUCED (Both eyes)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
VISUAL ACUITY REDUCED (Left eye)			
subjects affected / exposed	2 / 28 (7.14%)	1 / 20 (5.00%)	1 / 25 (4.00%)
occurrences (all)	2	1	1
VISUAL ACUITY REDUCED (Right eye)			
subjects affected / exposed	3 / 28 (10.71%)	3 / 20 (15.00%)	1 / 25 (4.00%)
occurrences (all)	3	3	1
VISUAL IMPAIRMENT (Left eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	1	0	1
VITREOUS ADHESIONS (Right eye)			
subjects affected / exposed	1 / 28 (3.57%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	1	0	0
VITREOUS DETACHMENT (Both eyes)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
VITREOUS FLOATERS (Left eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	1 / 25 (4.00%)
occurrences (all)	0	0	1
VITREOUS FLOATERS (Right eye)			
subjects affected / exposed	0 / 28 (0.00%)	0 / 20 (0.00%)	0 / 25 (0.00%)
occurrences (all)	0	0	0
VITREOUS HAEMORRHAGE (Left eye)			
subjects affected / exposed	4 / 28 (14.29%)	2 / 20 (10.00%)	4 / 25 (16.00%)
occurrences (all)	5	2	6
VITREOUS HAEMORRHAGE (Right eye)			

subjects affected / exposed occurrences (all)	3 / 28 (10.71%) 3	1 / 20 (5.00%) 2	7 / 25 (28.00%) 9
RETINAL ISCHAEMIA (Right eye) subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
Gastrointestinal disorders DIARRHOEA (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
NAUSEA (Non-ocular) subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 2	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
TOOTHACHE (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
VOMITING (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
Respiratory, thoracic and mediastinal disorders COUGH (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
Skin and subcutaneous tissue disorders DIABETIC FOOT (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
Endocrine disorders HYPOTHYROIDISM (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	2 / 20 (10.00%) 2	0 / 25 (0.00%) 0
Musculoskeletal and connective tissue disorders ARTHRITIS (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
PAIN IN EXTREMITY (Non-ocular)			

subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 20 (0.00%) 0	2 / 25 (8.00%) 2
BACK PAIN (Non-ocular) subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
Infections and infestations			
BRONCHITIS (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	2 / 25 (8.00%) 2
GASTROENTERITIS (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
HORDEOLUM (Left eye) subjects affected / exposed occurrences (all)	1 / 28 (3.57%) 1	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
INFLUENZA (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
NASOPHARYNGITIS (Non-ocular) subjects affected / exposed occurrences (all)	2 / 28 (7.14%) 3	2 / 20 (10.00%) 2	3 / 25 (12.00%) 3
RHINITIS (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0
SINUSITIS (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	2 / 25 (8.00%) 2
Metabolism and nutrition disorders			
HYPERCHOLESTEROLAEMIA (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	1 / 25 (4.00%) 1
VITAMIN D DEFICIENCY (Non-ocular) subjects affected / exposed occurrences (all)	0 / 28 (0.00%) 0	0 / 20 (0.00%) 0	0 / 25 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2012	<p>Amendment 1 was issued before inclusion of the first patient and introduced the following changes:</p> <ul style="list-style-type: none">• Exploratory objectives were added. Serum biomarker samples were planned to be taken therefore.• The screening period was extended to 28 days to allow for sufficient time to obtain grade-able FA/FP images (Visit 1.1 was added).• Exclusion criteria were stated more precisely, i.e. if these were related to the study eye or either eye.• Specification of exclusion criteria #15 (previous treatment with PRP)• Specification of exclusion criteria #30 (permit for re-randomization/rescreening)• A paragraph was added clarifying rescreening conditions (5.2. Rescreening of patients).• Specification of the randomization process (eCRF)• More detailed definition of treatment/re-treatment.• Imaging procedures were clarified.• Visit 14.1 was added in order to obtain FA/FP images that can be graded by Central reading center at end of study.• OCT image of Visit 1 was to be checked by Reading Center for CSME.• The number of blood samples was increased (HbA1c, Serum Lipids, Biomarkers).• Gonioscopy was added for V1 and V14 (exclusion of Rubeosis iridis).• Visit schedule was updated.• Appendix 2 of the protocol was updated.
11 April 2014	<p>Amendment 2 was issued when 73 patients were screened, 48 were randomized, and 8 completed core study and introduced the following changes:</p> <ul style="list-style-type: none">• 2 observational Follow-Up Visits were added (6 and 12 months after Month 12 visit). As a consequence exploratory objectives, study design, schedules etc. were updated. It was clarified that in the Follow-Up phase randomization and forbidden treatments were no longer to be followed, no study medication was to be dispensed and treatment was to be done as in physician's routine.• Exclusion criteria regarding size of neovascularization, vitreous hemorrhage, history of vitrectomy for study and fellow eye and pretreatment with steroid implants were defined more precisely.• Recommendations for use of PRP therapy were moved to Appendix 3 Section 5 and updated to give more precise guidance on treatment and retreatment. Furthermore, it was clarified that if investigator center was of the opinion that PRP treatment was insufficient, PRP treatment should start immediately independent of 3 months interval to last laser treatment.• Minor updates and precisions were made in several chapters.• Use of study bulk ware in chapter 6.6.1. was deleted.• Kryocoagulation therapy as rescue therapy was added in section 6.6.4.• Use of antimicrobials before and after injection were deleted/updated to "at investigator's discretion" to align protocol with current summary of product characteristic of ranibizumab and guidance from scientific societies.• Use of concomitant anti-VEGF agents for systemic use, study and fellow eye and use of steroids (esp. when applied long term in study eye/systemically) were defined more precisely. Newly started fingolimod during core study was now prohibited. A course of action was added to give guidance if vitrectomy could not be delayed.• Specific biomarkers were added. It was clarified that if further biomarkers were of interest, they had to be defined during/at end of study with amendments.

12 November 2015	<p>Amendment 3 was issued when 148 patients were screened and 101 patients were randomized and introduced the following changes:</p> <ul style="list-style-type: none"> • Purpose to terminate the enrolment to the trial. • Sample size calculation was adapted to show reduced recruitment and site numbers. • Clarification that the primary outcome and further objectives was to be evaluated as soon as respective timepoints were completed.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: