Clinical trial results:
Clinical Efficacy and Mechanistic Evaluation of Aflibercept for Proliferative Diabetic Retinopathy

Summary

EudraCT number	2013-003272-12
Trial protocol	GB
Global end of trial date	21 December 2016

Results information

Result version number	v1 (current)
This version publication date	23 May 2019
First version publication date	23 May 2019
Summary attachment (see zip file)	End of Study Summary Report (Abstract FINAL.pdf)

Trial information

Trial identification

Sponsor protocol code	SIVS1012

Additional study identifiers

ISRCTN number	ISRCTN32207582
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Moorfields Eye Hospital
Sponsor organisation address	162 City Road, London, United Kingdom, EC1V 2PD
Public contact	Tania West, Moorfields Eye Hospital, 0044 020 7253 3411 x2937 , tania.west2@nhs.net
Scientific contact	Tania West, Moorfields Eye Hospital, 0044 020 7253 3411 x2937 , tania.west2@nhs.net

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	17 March 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	21 December 2016
Global end of trial reached?	Yes
Global end of trial date	21 December 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether mean change in best corrected visual acuity following intravitreal aflibercept therapy is non-inferior to panretinal photocoagulation (PRP) in eyes with proliferative diabetic retinopathy (PDR) at 52 weeks as measured by ETDRS letters.

Protection of trial subjects:

Laser arm (comparator arm) is the standard of care for the last 40 years. Aflibercept (intervention arm) is licensed for other intraocular conditions.
We sent the development safety update report (DSUR) annually to MHRA, ethics committee, sponsor and Bayer
Patient and public involvement (PPI) were involved in the development of patient information sheet (PIS)

Background therapy:

None for this trial

Evidence for comparator:

Laser photocoagulation has been the mainstay of treatment for diabetic macular oedema and proliferative diabetic retinopathy for over 40 years based on robust evidence base. For proliferative diabetic retinopathy, the laser treatment (panretinal photocoagulation) is applied to the peripheral retinal tissue to destroy the peripheral photoreceptors and retinal pigment epithelium to reduce retinal oxygen consumption. This reduction in hypoxic drive results in decreased growth factor production especially VEGF, which in turn causes retinal new vessel regression. Response to laser varies, while it is most desirable to see a regression of new vessels, partial regression with no further growth may also result. Although timely laser treatment is very effective in reducing visual loss compared to no treatment, laser treatments a destructive procedure with well-documented side effects. Approximately 13% develop visual loss due to development or worsening of pre-existing macular oedema. In addition, it may lead to transient or permanent loss of visual function, including peripheral visual field defects, night vision loss, loss of contrast sensitivity, and progression of visual loss in nearly 5% of individuals despite appropriate treatment.

Actual start date of recruitment	22 August 2014
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	United Kingdom: 232
Worldwide total number of subjects	232
EEA total number of subjects	232

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)	188
From 65 to 84 years	44
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at the following 22 National Health Service clinical sites. We recruited 232 participants (116 per group) between Aug 22, 2014 and Nov 30, 2015.

Pre-assignment

Screening details:

Patients were identified from medical retina clinics and laser databases and contacted using an invitation letter with a pre-screening visit if required. 290 patients were assessed for eligibility. 58 excluded of which 51 eligibility criteria not met, 4 withdrawal of consent, 1 unable to come to study visits, 1 patient non compliant, 1 other

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

Research optometrists are the primary outcome assessors and were masked to treatment allocation. Visual fields and OCT technicians were also masked. Independent reading centre graders were masked to allocation of treatment. Investigators and patients were not masked

Arms

Are arms mutually exclusive?	Yes
Arm title	Panretinal photocoagulation arm

Arm description:

PRP is the current standard of care and was delivered as per routine clinical practice. Naïve PDR patients requiring PRP treatment were for the first time initiated on it and completed in fractionated 2 weekly sessions up to and may include week 4 and then reviewed at week 12.
Participants with persistent active new vessels that had PRP previously and were randomized to the PRP arm received fill-in PRP in 1-2 two-weekly sessions.
From week 12, all patients in the PRP arm were assessed for treatment response every 8 weeks and categorised exactly as the aflibercept arm
Retreatment was based on regression pattern of the new vessels

Arm type	PRP

No investigational medicinal product assigned in this arm

Arm title	Aflibercept arm

Arm description:

All study eyes randomised to receive aflibercept received an intravitreal injection of aflibercept 2 mg/0.05ml at baseline, 4 and 8 weeks. Regression patterns of retinal neovascularisation were assessed using 4-field or wide angle fundus photography. Further treatment at week 12 was determined by the degree of regression of neovascularisation of disc and elsewhere on clinical examination with adequate visualisation of entire retina and compared to 7-field colour or wide-field photographs at screening. The patients were categorised according to treatment response into three groups: (1) No regression (2) Partial regression and (3) Total regression

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

2 mg in 0.05 ml intravitreal administration

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Only the optometrists, technicians and reading centre graders were blinded for treatment allocation while doing assessments of outcomes

Number of subjects in period 1	Panretinal photocoagulation arm	Aflibercept arm
Started	116	116
Completed	104	107
Not completed	12	9
Adverse event, serious fatal	1	2
Consent withdrawn by subject	5	5
Lost to follow-up	4	2
Protocol deviation	2	-

Baseline characteristics

Reporting groups

Reporting group title	Panretinal photocoagulation arm

Reporting group description:

PRP is the current standard of care and was delivered as per routine clinical practice. Naïve PDR patients requiring PRP treatment were for the first time initiated on it and completed in fractionated 2 weekly sessions up to and may include week 4 and then reviewed at week 12.
Participants with persistent active new vessels that had PRP previously and were randomized to the PRP arm received fill-in PRP in 1-2 two-weekly sessions.
From week 12, all patients in the PRP arm were assessed for treatment response every 8 weeks and categorised exactly as the aflibercept arm
Retreatment was based on regression pattern of the new vessels

Reporting group title	Aflibercept arm

Reporting group description:

All study eyes randomised to receive aflibercept received an intravitreal injection of aflibercept 2 mg/0.05ml at baseline, 4 and 8 weeks. Regression patterns of retinal neovascularisation were assessed using 4-field or wide angle fundus photography. Further treatment at week 12 was determined by the degree of regression of neovascularisation of disc and elsewhere on clinical examination with adequate visualisation of entire retina and compared to 7-field colour or wide-field photographs at screening. The patients were categorised according to treatment response into three groups: (1) No regression (2) Partial regression and (3) Total regression

Reporting group values	Panretinal photocoagulation arm	Aflibercept arm	Total
Number of subjects	116	116	232
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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	50.8	51.5	
standard deviation	± 13.2	± 14.6	-
Gender categorical Units: Subjects			
Female	44	33	77
Male	72	83	155
Best corrected visual acuity Units: Subjects			
54 - 69	11	10	21
>= 70	105	106	211
Macular Oedema			

Units: Subjects			
No macular oedema	87	87	174
Non-central macular oedema	28	28	56
Central macular oedema	1	1	2
Central subfield thickness			
Units: microns			
arithmetic mean	271.6	275.3	
standard deviation	± 28.1	± 30.9	-

End points

End points reporting groups

Reporting group title	Panretinal photocoagulation arm

Reporting group description:

PRP is the current standard of care and was delivered as per routine clinical practice. Naïve PDR patients requiring PRP treatment were for the first time initiated on it and completed in fractionated 2 weekly sessions up to and may include week 4 and then reviewed at week 12.
Participants with persistent active new vessels that had PRP previously and were randomized to the PRP arm received fill-in PRP in 1-2 two-weekly sessions.
From week 12, all patients in the PRP arm were assessed for treatment response every 8 weeks and categorised exactly as the aflibercept arm
Retreatment was based on regression pattern of the new vessels

Reporting group title	Aflibercept arm

Reporting group description:

All study eyes randomised to receive aflibercept received an intravitreal injection of aflibercept 2 mg/0.05ml at baseline, 4 and 8 weeks. Regression patterns of retinal neovascularisation were assessed using 4-field or wide angle fundus photography. Further treatment at week 12 was determined by the degree of regression of neovascularisation of disc and elsewhere on clinical examination with adequate visualisation of entire retina and compared to 7-field colour or wide-field photographs at screening. The patients were categorised according to treatment response into three groups: (1) No regression (2) Partial regression and (3) Total regression

Primary: Change in best corrected visual acuity ITT analysis

End point title	Change in best corrected visual acuity ITT analysis[1]

End point description:

End point type	Primary

End point timeframe:

52 weeks

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: It was an intention to treat analysis using linear mixed model

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	105		
Units: ETDRS Letters				
arithmetic mean (standard error)	-3.0 (± 0.7)	1.1 (± 0.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in uniocular Esterman visual fields defects

End point title	Change in uniocular Esterman visual fields defects

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	99		
Units: ETDRS letters				
arithmetic mean (standard error)	3.9 (± 0.9)	1.9 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in binocular Esterman visual fields defects

End point title	Change in binocular Esterman visual fields defects

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	102		
Units: ETDRS letters				
arithmetic mean (standard error)	3.2 (± 0.8)	0.2 (± 0.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in binocular visual acuity

End point title	Change in binocular visual acuity

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	106		
Units: ETDRS letters				
arithmetic mean (standard error)	-1.8 (± 0.6)	0.5 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in low luminance visual acuity

End point title	Change in low luminance visual acuity

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	107		
Units: ETDRS Letters				
arithmetic mean (standard error)	-3.4 (± 1.0)	-1.5 (± 1.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in contrast sensitivity

End point title	Change in contrast sensitivity

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	107		
Units: ETDRS letters				
arithmetic mean (standard error)	-1.0 (± 0.5)	-0.5 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in VFQ 25 composite score

End point title	Change in VFQ 25 composite score

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	104		
Units: score				
arithmetic mean (standard error)	-1.8 (± 1.3)	-0.1 (± 1.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in RetDQoL impact score

End point title	Change in RetDQoL impact score

End point description:

End point type	Secondary

End point timeframe:
52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	103		
Units: score				
arithmetic mean (standard error)	0.2 (± 0.2)	0.0 (± 0.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in RetTSQ total score

End point title	Change in RetTSQ total score

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	100	103		
Units: score				
arithmetic mean (standard error)	1.8 (± 1.0)	5.5 (± 1.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in central subfield thickness

End point title	Change in central subfield thickness

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	103	106		
Units: microns				
arithmetic mean (standard error)	24.0 (± 5.5)	-8.9 (± 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Regression pattern

End point title	Regression pattern

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	105	110		
Units: Subjects				
Total regression	25	81		
Partial regression	58	28		
No regression	22	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Regression pattern

End point title	Regression pattern

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	107		
Units: Subjects				
Total regression	35	68		
Partial regression	46	18		
No regression	7	2		
Reactivation	16	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in diabetic retinopathy score levels

End point title	Change in diabetic retinopathy score levels

End point description:

End point type	Secondary

End point timeframe:

12 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	97		
Units: Subjects				
Worse than or = Level 61	86	69		
Improved to Level 53 or better	13	28		
Improved to Level 47 or better	6	17		
Improved to Level 43 or better	6	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in diabetic retinopathy score levels

End point title	Change in diabetic retinopathy score levels

End point description:

End point type	Secondary

End point timeframe:

52 weeks

End point values	Panretinal photocoagulation arm	Aflibercept arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	102	104		
Units: Subjects				
Worse than or = Level 61	92	81		
Improved to Level 53 or better	10	23		
Improved to Level 47 or better	2	6		
Improved to Level 43 or better	2	6		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

August 2014 to December 2016

Assessment type	Non-systematic

Dictionary used

Dictionary name	no dictionary used
Dictionary version	0.0

Reporting groups

Reporting group title	Panretinal photocoagulation arm

Reporting group description:

PRP is the current standard of care and was delivered as per routine clinical practice. Naïve PDR patients requiring PRP treatment were for the first time initiated on it and completed in fractionated 2 weekly sessions up to and may include week 4 and then reviewed at week 12.
Participants with persistent active new vessels that had PRP previously and were randomized to the PRP arm received fill-in PRP in 1-2 two-weekly sessions.
From week 12, all patients in the PRP arm were assessed for treatment response every 8 weeks and categorised exactly as the aflibercept arm
Retreatment was based on regression pattern of the new vessels

Reporting group title	Aflibercept arm

Reporting group description:

All study eyes randomised to receive aflibercept received an intravitreal injection of aflibercept 2 mg/0.05ml at baseline, 4 and 8 weeks. Regression patterns of retinal neovascularisation were assessed using 4-field or wide angle fundus photography. Further treatment at week 12 was determined by the degree of regression of neovascularisation of disc and elsewhere on clinical examination with adequate visualisation of entire retina and compared to 7-field colour or wide-field photographs at screening. The patients were categorised according to treatment response into three groups: (1) No regression (2) Partial regression and (3) Total regression

Serious adverse events	Panretinal photocoagulation arm	Aflibercept arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	30 / 116 (25.86%)	30 / 116 (25.86%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	1	2	
General disorders and administration site conditions			
Other	Additional description: viral infection, pregnant lady - IUGR taken for caesarean		
subjects affected / exposed	1 / 116 (0.86%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory	Additional description: Chest infection, shortness of breath, left lower lobe pneumonia, viral pneumonia, bronchopneumonia, pulmonary embolism, pneumonia		

subjects affected / exposed	5 / 116 (4.31%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychiatric	Additional description: excess alcohol intake, overdose of citalopram, overdose of insulin, cocaine, zopliclone, temazepam		
subjects affected / exposed	0 / 116 (0.00%)	2 / 116 (1.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiovascular	Additional description: Chest pain, stroke, acute cardiac failure, heart failure, pulmonary oedema, shortness of breath, non ST elevation MI, possible TIA, coronary artery disease, unstable angina, myocardial infarction		
subjects affected / exposed	4 / 116 (3.45%)	7 / 116 (6.03%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 1	0 / 2	
Nervous system disorders			
Neurological	Additional description: fall, unresponsive		
subjects affected / exposed	1 / 116 (0.86%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Haematological	Additional description: Chronic myeloid leukaemia. multiple myeloma		
subjects affected / exposed	1 / 116 (0.86%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
New or increase in severity of vitreous haemorrhage			
subjects affected / exposed	9 / 116 (7.76%)	4 / 116 (3.45%)	
occurrences causally related to treatment / all	1 / 10	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 116 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal ulcer			

subjects affected / exposed	1 / 116 (0.86%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrovascular proliferation			
subjects affected / exposed	0 / 116 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
reduced blurred vision			
subjects affected / exposed	0 / 116 (0.00%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastro-intestinal	Additional description: abdominal pain, perforated stomach ulcer, vomiting, diarrhoea, constipation, nausea, pain, gastroenteritis, exacerbation of gastroparesis		
subjects affected / exposed	2 / 116 (1.72%)	6 / 116 (5.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Transaminitis			
subjects affected / exposed	1 / 116 (0.86%)	0 / 116 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatological	Additional description: gout, wide excision of squamous cell carcinoma, cellulitis, open wound on knee		
subjects affected / exposed	2 / 116 (1.72%)	1 / 116 (0.86%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Genitourinary	Additional description: renal biopsy, pre-malignant endometrial lesion, acute renal failure, frequency of micturition, loin pain, acute pyelonephritis, urinary tract infection		
subjects affected / exposed	3 / 116 (2.59%)	4 / 116 (3.45%)	
occurrences causally related to treatment / all	0 / 5	0 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Endocrine disorder	Additional description: hyperglycaemia, diabetic ketoacidosis, low glucose level, uncontrolled diabetes, kidney and pancreas transplant, hypoglycaemic attack		

subjects affected / exposed	3 / 116 (2.59%)	5 / 116 (4.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal			
subjects affected / exposed	5 / 116 (4.31%)	6 / 116 (5.17%)	
occurrences causally related to treatment / all	0 / 6	0 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Panretinal photocoagulation arm	Aflibercept arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	72 / 116 (62.07%)	83 / 116 (71.55%)	
General disorders and administration site conditions			
Allergies	Additional description: Hayfever, allergic reaction to fluorescein		
subjects affected / exposed	3 / 116 (2.59%)	4 / 116 (3.45%)	
occurrences (all)	3	4	
Other	Additional description: Flu, raised creatinine, fatigue, dental abscess, cold, blunt trauma, cut over eyebrow, infection foot, generalised weakness, viral cold, fall		
subjects affected / exposed	8 / 116 (6.90%)	9 / 116 (7.76%)	
occurrences (all)	10	12	
Immune system disorders			
Rheumatoid arthritis	Additional description: both hands		
subjects affected / exposed	0 / 116 (0.00%)	1 / 116 (0.86%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Respiratory	Additional description: cough, runny nose, flu, chest infection , URTI, common cold, shortness of breath, dyspnoea, sore throat, pleural effusion		
subjects affected / exposed	15 / 116 (12.93%)	20 / 116 (17.24%)	
occurrences (all)	16	23	
Psychiatric disorders			
Psychiatric	Additional description: anxiety, depression, self harm		
subjects affected / exposed	2 / 116 (1.72%)	2 / 116 (1.72%)	
occurrences (all)	2	2	
Cardiac disorders			

Cardiovascular events	Additional description: TIA, non ST MI, chest pain, hypertension, hypotension, left ventricular hypertrophy, dizziness,		
subjects affected / exposed	5 / 116 (4.31%)	9 / 116 (7.76%)	
occurrences (all)	6	10	
Nervous system disorders			
Neurological	Additional description: migraine, epilepsy, vertigo, memory loss, restless leg, headache, blurred vision, carpal tunnel syndrome		
subjects affected / exposed	4 / 116 (3.45%)	6 / 116 (5.17%)	
occurrences (all)	4	8	
Blood and lymphatic system disorders			
Haematological	Additional description: anaemia, hyperkalaemia, low Hb levels, gum bleeding		
subjects affected / exposed	2 / 116 (1.72%)	4 / 116 (3.45%)	
occurrences (all)	2	4	
Ear and labyrinth disorders			
Ear Nose and Throat	Additional description: sinusitis, ear infection, labyrinthitis, tooth cavity infection, hearing loss, flu, sore throat, laryngitis, glandular fever, tonsillitis,		
subjects affected / exposed	8 / 116 (6.90%)	8 / 116 (6.90%)	
occurrences (all)	10	9	
Eye disorders			
Cataract progression			
subjects affected / exposed	1 / 116 (0.86%)	2 / 116 (1.72%)	
occurrences (all)	2	2	
New or progressing tractional RD			
subjects affected / exposed	2 / 116 (1.72%)	1 / 116 (0.86%)	
occurrences (all)	2	1	
New or increase in severity of vitreous haemorrhage			
subjects affected / exposed	22 / 116 (18.97%)	14 / 116 (12.07%)	
occurrences (all)	27	21	
Macular Oedema			
subjects affected / exposed	2 / 116 (1.72%)	4 / 116 (3.45%)	
occurrences (all)	2	4	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 116 (0.86%)	7 / 116 (6.03%)	
occurrences (all)	1	7	
Eye pain			
subjects affected / exposed	4 / 116 (3.45%)	4 / 116 (3.45%)	
occurrences (all)	5	4	
Transient reduced visual acuity			

subjects affected / exposed	8 / 116 (6.90%)	2 / 116 (1.72%)	
occurrences (all)	9	2	
Raised intraocular pressure			
subjects affected / exposed	1 / 116 (0.86%)	2 / 116 (1.72%)	
occurrences (all)	1	2	
Other	Additional description: NVE fellow eye, floaters, blurred vision, uveitis, corneal abrasion, hordeolum, lamellar hole, ERM, inflammation of tear gland, blepharitis, herpes simplex keratitis, superficial punctate keratitis, nystagmus		
subjects affected / exposed	18 / 116 (15.52%)	24 / 116 (20.69%)	
occurrences (all)	25	37	
Gastrointestinal disorders			
GI group of disorders	Additional description: vomiting, gastric reflux, irritable bowel syndrome, sickness, gastroenteritis, diarrhoea, heart burn, faecal impaction, oesophagitis, constipation		
subjects affected / exposed	7 / 116 (6.03%)	9 / 116 (7.76%)	
occurrences (all)	7	10	
Skin and subcutaneous tissue disorders			
Dermatological	Additional description: diabetic foot ulcer, infected breast cyst, stomach abscess drained, boils, suspected skin cancer, cellulitis, itching, blister, infected sebaceous cyst		
subjects affected / exposed	5 / 116 (4.31%)	8 / 116 (6.90%)	
occurrences (all)	5	8	
Renal and urinary disorders			
Genito urinary disorders	Additional description: poor renal function, vaginal discharge, UTI, chronic renal failure, epididymo-orchitis, renal colic,		
subjects affected / exposed	5 / 116 (4.31%)	9 / 116 (7.76%)	
occurrences (all)	8	9	
Endocrine disorders			
All endocrine disorders	Additional description: hypoglycaemic episode, dehydration, unstable diabetes, Vit D deficiency		
subjects affected / exposed	6 / 116 (5.17%)	5 / 116 (4.31%)	
occurrences (all)	6	6	
Increasing severity of diabetic retinopathy			
subjects affected / exposed	1 / 116 (0.86%)	5 / 116 (4.31%)	
occurrences (all)	1	5	
Musculoskeletal and connective tissue disorders			
Musculo-skeletal	Additional description: generalised aches and pains, swollen painful foot, tendinitis, fracture toes, headache, fall, pulled muscle, ulcer toe, knee pain, trigger finger, carpal tunnel syndrome, myalgia, back pain, damaged ligaments, cellulitis, restless leg syndrome		
subjects affected / exposed	17 / 116 (14.66%)	17 / 116 (14.66%)	
occurrences (all)	24	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2014	Labelling of IMP
10 October 2014	Letter of invitation, patient consent form, patient information sheet revision and addition of 5 sites
17 September 2015	Inclusion of qualified trained nurse injectors

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.

It was a phase 2b study with follow-up for only 52 weeks. As a 5 year study, it will provide long-term outcomes of ranibizumab in PDR, information about the disease-modifying effect of anti-VEGF, and the long-term compliance of patients.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30303670

http://www.ncbi.nlm.nih.gov/pubmed/28494920