Clinical trial results:
A multi center, single arm, interventional Phase 4 study to evaluate a Treat and Extend regimen of intravitreal aflibercept for treatment of macular edema secondary to central retinal vein occlusion

Summary

EudraCT number	2014-003193-17
Trial protocol	DE GB DK FR IT
Global end of trial date	31 July 2019

Results information

Result version number	v1
This version publication date	05 July 2020
First version publication date	05 July 2020

Trial information

Trial identification

Sponsor protocol code	BAY86-5321/17514

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02800642
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser Wilhelm Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	31 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	31 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the efficacy and durability (treatment interval) of 2 mg intravitreal (IVT) aflibercept in a Treat and Extend (T&E) regimen over a treatment period of 76 weeks using protocol defined visual and anatomic criteria in subjects with macular edema secondary to CRVO

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all the subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 June 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Italy: 23
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 49
Worldwide total number of subjects	162
EEA total number of subjects	126

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)	62
From 65 to 84 years	89
85 years and over	11

Subject disposition

Recruitment

Recruitment details:

A total of 244 subjects were screened in 42 study centers in 8 countries, the first subject first visit was on 10/Jun/2016 and last subject last visit was on 31/Jun/2019

Pre-assignment

Screening details:

Of the 244 screened subjects, 162 subjects completed screening and entered the treatment period

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	IVT aflibercept

Arm description:

Subjects with macular edema secondary to CRVO were treated with 2 mg study drug intravitreal aflibercept over a treatment period of 76 weeks

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

The recommended dose for intravitreal aflibercept is 2 mg equivalent to 50 microliter. Study treatment will be administered at baseline and at monthly intervals until stabilization of disease. When stability is achieved, the treatment interval can be extended based on visual and anatomic outcomes as judged by the treating investigator

Number of subjects in period 1	IVT aflibercept
Started	162
Completed	137
Not completed	25
Consent withdrawn by subject	3
Physician decision	2
Death	3
Other	10
Adverse event	6
Lost to follow-up	1

Baseline characteristics

Reporting groups	
Reporting group title	IVT aflibercept
Reporting group description:	
Subjects with macular edema secondary to CRVO were treated with 2 mg study drug intravitreal aflibercept over a treatment period of 76 weeks	

Reporting group values	IVT aflibercept	Total	
Number of subjects	162	162	
Age categorical Units: Subjects			
18-64 years	62	62	
65-84 years	89	89	
>= 85 years	11	11	
Age continuous Units: years			
arithmetic mean	66.4		
standard deviation	± 13.3	-	
Gender categorical Units: Subjects			
Female	65	65	
Male	97	97	
Race Units: Subjects			
White	154	154	
Black	1	1	
Asian	3	3	
Not reported	4	4	
Ethnicity Units: Subjects			
Hispanic or Latino	2	2	
Not Hispanic or Latino	156	156	
Not reported	4	4	

End points

End points reporting groups

Reporting group title	IVT aflibercept
Reporting group description:	
Subjects with macular edema secondary to CRVO were treated with 2 mg study drug intravitreal aflibercept over a treatment period of 76 weeks	
Subject analysis set title	Safety analysis set
Subject analysis set type	Safety analysis
Subject analysis set description:	
The SAF included all subjects who received any study drug	
Subject analysis set title	Full analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The FAS included all enrolled subjects who received any study drug, had a baseline BCVA assessment, and had at least one post-baseline BCVA assessment. With regard to the efficacy evaluation of this study, the FAS was considered the primary analysis	

Primary: The proportion of subjects who gain ≥ 15 letters in best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy score (ETDRS) chart compared to baseline

End point title	The proportion of subjects who gain ≥ 15 letters in best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy score (ETDRS) chart compared to baseline[1]
End point description:	
Subjects who completed the study with a gain of ≥ 15 letters or dropped the study after Week 24 and having a permanent resolution of macular edema and a gain of ≥ 15 letters from baseline with regard to the latest BCVA assessment. The ETDRS chart includes 70 letters in total, more letters read correctly represents a better visual acuity	
End point type	Primary
End point timeframe:	
Baseline and Week 76	

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: The statistical analysis was provided in the Attachment

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: percent				
number (confidence interval 95%)	65.6 (57.7 to 72.9)			

Attachments (see zip file)	Statistical analysis/17514_Statisitical Analysis_Primary_BCVA

Statistical analyses

No statistical analyses for this end point

Primary: The proportion of subjects with a mean treatment interval between injections of ≥ 8 weeks

End point title	The proportion of subjects with a mean treatment interval between injections of ≥ 8 weeks[2]

End point description:

Subjects who completed the study with a mean treatment interval between injections of ≥ 8 weeks or dropped out of the study after Week 24 and having a permanent resolution of macular edema

End point type	Primary

End point timeframe:

From the last actual visit of the initiation phase to Week 76

Notes:

[2] - 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: The statistical analysis was provided in the Attachment

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: percent				
number (confidence interval 95%)	45.0 (37.1 to 53.1)			

Attachments (see zip file)	Statistical analysis/17514_Statisitical Analysis_Primary_mean

Statistical analyses

No statistical analyses for this end point

Secondary: The change in best corrected visual acuity (BCVA) as measured by the early treatment diabetic retinopathy (ETDR) letter score from baseline

End point title	The change in best corrected visual acuity (BCVA) as measured by the early treatment diabetic retinopathy (ETDR) letter score from baseline

End point description:

The ETDRS chart includes 70 letters in total and the letter score ranges from 0 to 100. More letters read correctly results in a higher letter score, which represents better visual acuity

End point type	Secondary

End point timeframe:

Baseline and Week 24, 52, and 76

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: scores				
arithmetic mean (standard deviation)				
Absolute BCVA letter score at baseline	51.9 (± 16.8)			
Absolute BCVA letter score at Week 24	72.4 (± 16.6)			
Absolute BCVA letter score at Week 52	71.8 (± 18.1)			

Absolute BCVA letter score at Week 76	72.3 (± 18.5)			
Change from baseline at Week 24	20.4 (± 17.0)			
Change from baseline at Week 52	19.9 (± 19.1)			
Change from baseline at Week 76	20.3 (± 19.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: The change in central retinal thickness (CRT) from baseline

End point title	The change in central retinal thickness (CRT) from baseline

End point description:

CRT was measured in the study eye by spectral domain optical coherence tomography (SD-OCT)

End point type	Secondary

End point timeframe:

Baseline and Week 24, 52 and 76

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	158			
Units: micrometer				
arithmetic mean (standard deviation)				
Absolute CRT at baseline	759.9 (± 246.0)			
Absolute CRT at Week 24	271.2 (± 53.1)			
Absolute CRT at Week 52	279.8 (± 106.8)			
Absolute CRT at Week 76	265.4 (± 57.9)			
Change from baseline at Week 24	-488.9 (± 254.6)			
Change from baseline at Week 52	-481.3 (± 266.5)			
Change from baseline at Week 76	-496.1 (± 252.4)			

Statistical analyses

No statistical analyses for this end point

Secondary: The number of injections per subject

End point title	The number of injections per subject

End point description:

End point type	Secondary

End point timeframe:
From baseline to Week 76

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: injections				
arithmetic mean (standard deviation)	12.2 (± 2.53)			

Statistical analyses

No statistical analyses for this end point

Secondary: The mean treatment interval between injections

End point title	The mean treatment interval between injections

End point description:

End point type	Secondary

End point timeframe:
From baseline to Week 76

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	150			
Units: weeks				
arithmetic mean (standard deviation)	6.37 (± 1.150)			

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of subjects who gain ≥ 15 letters in best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy score (ETDRS) chart compared to baseline

End point title	The proportion of subjects who gain ≥ 15 letters in best corrected visual acuity (BCVA) on the early treatment diabetic retinopathy score (ETDRS) chart compared to baseline

End point description:
The ETDRS chart includes 70 letters in total. More letters read correctly represents a better visual acuity

End point type	Secondary

End point timeframe:

Baseline and Week 24, Week 52

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: percent				
number (confidence interval 95%)				
Week 24	68.8 (61.0 to 75.8)			
Week 52	68.1 (60.3 to 75.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of subjects with change in retinal non-perfusion (FA/FP) status from baseline

End point title	The proportion of subjects with change in retinal non-perfusion (FA/FP) status from baseline

End point description:

The change in retinal non-perfusion status by fundus angiography (FA)/fundus photography (FP)-confirmed ischemic disc area. The status was categorized into: no non-perfusion, <10 ischemic disc area, >=10 ischemic disc area and missing status

End point type	Secondary

End point timeframe:

Baseline and Week 24, 52 and 76

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: percent				
number (not applicable)				
Baseline to week 24: no to <10	4.4			
Baseline to week 24: no to >=10	3.8			
Baseline to week 24: no to missing	6.3			
Baseline to week 24: <10 to no	0.6			
Baseline to week 24: <10 to >=10	0.6			
Baseline to week 24: <10 to missing	0			
Baseline to week 24: >=10 to no	1.3			
Baseline to week 24: >=10 to <10	0			
Baseline to week 24: >=10 to missing	0.6			
Baseline to week 24: missing to no	0			
Baseline to week 24: missing to <10	0.6			

Baseline to week 24: missing to >=10	0.6			
Baseline to week 24: no status change	81.9			
Baseline to week 52: no to <10	5.0			
Baseline to week 52: no to >=10	5.6			
Baseline to week 52: no to missing	10.6			
Baseline to week 52: <10 to no	1.9			
Baseline to week 52: <10 to >=10	0			
Baseline to week 52: <10 to missing	0			
Baseline to week 52: >=10 to no	1.9			
Baseline to week 52: >=10 to <10	0			
Baseline to week 52: >=10 to missing	0			
Baseline to week 52: missing to no	0			
Baseline to week 52: missing to <10	0.6			
Baseline to week 52: missing to >=10	0.6			
Baseline to week 52: no status change	73.8			
Baseline to week 76: no to <10	3.1			
Baseline to week 76: no to >=10	4.4			
Baseline to week 76: no to missing	18.1			
Baseline to week 76: <10 to no	1.3			
Baseline to week 76: <10 to >=10	0.6			
Baseline to week 76: <10 to missing	0.6			
Baseline to week 76: >=10 to no	0.3			
Baseline to week 76: >=10 to <10	0			
Baseline to week 76: missing to no	0			
Baseline to week 76: missing to <10	0.6			
Baseline to week 76: missing to >=10	0.6			
Baseline to week 76: no status change	69.4			

Statistical analyses

No statistical analyses for this end point

Secondary: The proportion of subjects with absence of subretinal fluid

End point title	The proportion of subjects with absence of subretinal fluid
End point description: n is the number of subjects analyzed for each respective endpoint	
End point type	Secondary
End point timeframe: Baseline, week 24, week 52 and week 76	

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	160			
Units: percent				
number (confidence interval 95%)				

Baseline (n=160)	25.6 (19.1 to 33.1)			
Week 24 (n=154)	98.7 (95.4 to 99.8)			
Week 52 (n=153)	95.4 (90.8 to 98.1)			
Week 76 (n=137)	97.8 (93.7 to 99.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Incidence and severity of ocular treatment-emergent adverse events

End point title	Incidence and severity of ocular treatment-emergent adverse events

End point description:

End point type	Secondary

End point timeframe:

Up to 30 days after week 76

End point values	IVT aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	162			
Units: subjects				
Any ocular TEAEs	90			
Severity: mild	39			
Severity: moderate	43			
Severity: severe	8			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Up to 30 days after week 76	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	IVT aflibercept
Reporting group description:	
Subjects with macular edema secondary to CRVO were treated with 2 mg study drug intravitrealaflibercept over a treatment period of 76 weeks.	

Serious adverse events	IVT aflibercept		
Total subjects affected by serious adverse events			
subjects affected / exposed	32 / 162 (19.75%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events	2		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to lymph nodes			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Endometriosis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Delirium			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 162 (2.47%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Atrial flutter			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Bundle branch block bilateral			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure acute			

subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mitral valve incompetence			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular tachycardia			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dementia			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Amaurosis fugax			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cataract			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Iridocyclitis				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal artery occlusion				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal degeneration				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal ischaemia				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Retinal vein occlusion				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual acuity reduced				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual impairment				
subjects affected / exposed	1 / 162 (0.62%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
Gastric ulcer				
subjects affected / exposed	2 / 162 (1.23%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				

subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic haemorrhage			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal colic			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteoarthritis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal pain			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infections and infestations			
Endocarditis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lower respiratory tract infection			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Gastroenteritis viral			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal viral infection			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urosepsis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Latent syphilis			
subjects affected / exposed	1 / 162 (0.62%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	IVT aflibercept		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	81 / 162 (50.00%)		
Investigations			
Intraocular pressure increased			
subjects affected / exposed	20 / 162 (12.35%)		
occurrences (all)	40		
Vascular disorders			
Hypertension			
subjects affected / exposed	19 / 162 (11.73%)		
occurrences (all)	25		
Eye disorders			
Macular oedema			
subjects affected / exposed	12 / 162 (7.41%)		
occurrences (all)	13		
Conjunctival haemorrhage			
subjects affected / exposed	18 / 162 (11.11%)		
occurrences (all)	23		
Retinal ischaemia			
subjects affected / exposed	13 / 162 (8.02%)		
occurrences (all)	16		
Retinal haemorrhage			
subjects affected / exposed	14 / 162 (8.64%)		
occurrences (all)	14		
Visual acuity reduced			
subjects affected / exposed	26 / 162 (16.05%)		
occurrences (all)	37		
Vitreous detachment			
subjects affected / exposed	9 / 162 (5.56%)		
occurrences (all)	11		
Foreign body sensation in eyes			
subjects affected / exposed	9 / 162 (5.56%)		
occurrences (all)	13		
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	26 / 162 (16.05%)		
occurrences (all)	40		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 April 2016	Clarification that the secondary and exploratory variables of retinal perfusion status included data from screening/baseline combined visit; Clarification on time point for follow up and the final study visit; Eligibility criteria did not need to be repeated at the baseline visit; Definition of types of age related macular degeneration (Exclusion criterion 22); Clarification on time period for stability criteria; Clarification that PRP rescue may be used per investigator discretion; Pregnancy testing was mandatory for women of childbearing potential at every treatment visit prior to injection and at end of study visit if required by local regulations.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported