Clinical trial results:
A 12-months, randomized, VA-assessor blinded, multicenter, controlled phase IV trial to investigate non inferiority of two treatment algorithms (discretion of the investigator vs. pro re nata) of 0.5 mg ranibizumab in patients with visual impairment due to diabetic macula edema

Summary

EudraCT number	2014-002854-37
Trial protocol	DE
Global end of trial date	08 June 2017

Results information

Result version number	v1 (current)
This version publication date	20 June 2018
First version publication date	20 June 2018

Trial information

Trial identification

Sponsor protocol code	CRFB002DDE26

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02366468
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	08 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that the mean average change of BCVA in patients with DME treated with ranibizumab injections at the discretion of the investigator and in accordance with disease activity criteria is non-inferior to current standard of care (PRN).

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	23 February 2015
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	Germany: 135
Worldwide total number of subjects	135
EEA total number of subjects	135

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)	59
From 65 to 84 years	76
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

a total of 135 patients were randomized and assigned in a 1:1 ratio to the treatment arms. Two patients (one patient in each treatment arm) did not have any post-baseline BCVA assessments and were not counted as "Started". Both patients were included in the safety evaluations.

Pre-assignment

Screening details:

At Screening, the eligibility criteria were performed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Discretion of the investigator (DI)

Arm description:

Investigational - ranibizumab 0.5 mg

Arm type	Experimental
Investigational medicinal product name	ranibizumab 0.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

ranibizumab 0.5 mg, after initial monthly treatment until maximum BCVA and no signs or no further change of disease activity, the investigator treated patients at their own discretion. There were no strict recommendations for retreatment or scheduling of upcoming visits.

Arm title	Pro re nata (PRN)

Arm description:

Standard of Care - ranibizumab 0.5 mg

Arm type	Active comparator
Investigational medicinal product name	ranibizumab 0.5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

ranibizumab 0.5 mg, after initial monthly therapy until maximum BCVA and no signs or no further improvement of disease activity, patients were monitored every month and retreated if any signs of disease activity occurred

Number of subjects in period 1[1]	Discretion of the investigator (DI)	Pro re nata (PRN)
Started	67	66
Full Analysis Set (FAS)	67	66
Per Protocol Set (PPS)	62	61
Completed	62	58
Not completed	5	8
Adverse event, serious fatal	-	2
Consent withdrawn by subject	1	4
Adverse event, non-fatal	2	-
Lost to follow-up	2	-
not specified	-	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Two patients (one patient in each treatment arm) did not have any post-baseline BCVA assessments and were not counted as "Started". Both patients were included in the safety evaluations.

Baseline characteristics

Reporting groups	
Reporting group title	Discretion of the investigator (DI)
Reporting group description: Investigational - ranibizumab 0.5 mg	
Reporting group title	Pro re nata (PRN)
Reporting group description: Standard of Care - ranibizumab 0.5 mg	

Reporting group values	Discretion of the investigator (DI)	Pro re nata (PRN)	Total
Number of subjects	67	66	133
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)	29	30	59
From 65-84 years	38	36	74
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	62.6	65.0	
standard deviation	± 13.73	± 10.37	-
Sex: Female, Male Units: Subjects			
Female	22	25	47
Male	45	41	86
Race/Ethnicity, Customized Units: Subjects			
Caucasian|	64	64	128
Black|	1	1	2
Asian|	0	1	1
Other|	2	0	2

End points

End points reporting groups	
Reporting group title	Discretion of the investigator (DI)
Reporting group description: Investigational - ranibizumab 0.5 mg	
Reporting group title	Pro re nata (PRN)
Reporting group description: Standard of Care - ranibizumab 0.5 mg	

Primary: Mean average change from baseline in Best Corrected Visual Acuity (BCVA) of the study eye from month 1 to study treatment completion (Month 12)	
End point title	Mean average change from baseline in Best Corrected Visual Acuity (BCVA) of the study eye from month 1 to study treatment completion (Month 12)
End point description: BCVA was assessed as letters read using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. The mean average change from baseline was defined as the difference between the average level of BCVA (ETDRS letters) over all post-baseline assessments from Month 1 to Month 12. A positive change represents an improvement in visual acuity	
End point type	Primary
End point timeframe: Baseline, Month 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 and 12	

End point values	Discretion of the investigator (DI)	Pro re nata (PRN)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: Letters				
arithmetic mean (standard deviation)				
Baseline (Day 1)|	67.4 (± 9.52)	65.1 (± 9.59)		
post baseline average over month 1 to month 12|	73.5 (± 9.50)	73.8 (± 7.75)		
Visit-averaged change from baseline|	6.1 (± 6.54)	8.6 (± 6.45)		

Statistical analyses

Statistical analysis title	Change in Best Corrected Visual Acuity
Statistical analysis description: The primary objective was to demonstrate that the mean visit-averaged change from baseline of BCVA over month 1 to treatment completion for the DI arm was non-inferior to the PRN arm.	
Comparison groups	Discretion of the investigator (DI) v Pro re nata (PRN)

Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	ANCOVA
Parameter estimate	Median difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.04
upper limit	1.27

Secondary: Number of visits

End point title	Number of visits
End point description:	
Mean number of visits during the study	
End point type	Secondary
End point timeframe:	
Baseline to Month 12	

End point values	Discretion of the investigator (DI)	Pro re nata (PRN)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: Visits				
arithmetic mean (standard deviation)	12.7 (± 1.92)	12.9 (± 2.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of injections

End point title	Number of injections
End point description:	
mean number of injections in the study eye during the study	
End point type	Secondary
End point timeframe:	
Baseline to Month 12	

End point values	Discretion of the investigator (DI)	Pro re nata (PRN)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: Injections				
arithmetic mean (standard deviation)	8.4 (± 2.98)	7.8 (± 3.25)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of treatment free intervals

End point title	Number of treatment free intervals

End point description:

A treatment-free interval is the interval between the first NO treatment given when the reason for NO treatment given is one of the three stability criteria and the first subsequent YES treatment given after that.

End point type	Secondary

End point timeframe:

Baseline to Month 12

End point values	Discretion of the investigator (DI)	Pro re nata (PRN)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: Intervals				
arithmetic mean (standard deviation)	1.6 (± 0.76)	1.7 (± 0.94)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in central subfield retinal thickness (CSRT)

End point title	Mean change in central subfield retinal thickness (CSRT)

End point description:

Evaluated by central reading center assessing OCT images

End point type	Secondary

End point timeframe:

Baseline to Month 12

End point values	Discretion of the investigator (DI)	Pro re nata (PRN)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: µm				
arithmetic mean (standard deviation)				
Baseline|	420.0 (± 114.98)	431.0 (± 128.13)		
Month 12 (LOCF)|	313.3 (± 61.21)	320.6 (± 85.27)		
Change from Baseline to Month 12 (LOCF)|	-106.7 (± 109.58)	-110.4 (± 101.97)		

Statistical analyses

Statistical analysis title	Mean change in CSRT to Month 12
Comparison groups	Discretion of the investigator (DI) v Pro re nata (PRN)
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.62
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	5.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.1
upper limit	28.56

Secondary: Mean change of foveal center point thickness

End point title	Mean change of foveal center point thickness
End point description:	
Evaluated by central reading center assessing OCT images	
End point type	Secondary
End point timeframe:	
Baseline to Month 12	

End point values	Discretion of the investigator (DI)	Pro re nata (PRN)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: µm				
arithmetic mean (standard deviation)				
Baseline|	398.8 (± 144.10)	405.0 (± 138.06)		
Month 12 - LOCF|	273.3 (± 84.85)	280.6 (± 105.44)		
Change from Baseline to Month 12 (LOCF)|	-125.6 (± 142.69)	-124.4 (± 113.29)		

Statistical analyses

Statistical analysis title	Mean change of foveal center point thickness
Comparison groups	Discretion of the investigator (DI) v Pro re nata (PRN)
Number of subjects included in analysis	133
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.925
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-33.66
upper limit	30.59

Secondary: Change in diabetic retinopathy study (DRS) retinopathy scale

End point title	Change in diabetic retinopathy study (DRS) retinopathy scale
End point description:	
Evaluated by central reading center scoring fundus photography	
End point type	Secondary
End point timeframe:	
Baseline to Month 12	

End point values	Discretion of the investigator (DI)	Pro re nata (PRN)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	67	66		
Units: Participants				
> 2 steps improvement	7	7		
2 steps improvement	3	4		
1 step improvement	6	1		
0 steps	38	34		
1 step loss	4	4		
2 steps loss	2	1		
> 2 steps loss	1	5		
Missing	6	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Ranibizumab 0.5 mg PRN
Reporting group description:	
Ranibizumab 0.5 mg PRN	
Reporting group title	Ranibizumab 0.5 mg DI
Reporting group description:	
Ranibizumab 0.5 mg DI	

Serious adverse events	Ranibizumab 0.5 mg PRN	Ranibizumab 0.5 mg DI	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 67 (32.84%)	13 / 68 (19.12%)	
number of deaths (all causes)	2	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acoustic neuroma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			

subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic myeloid leukaemia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Behcet's syndrome			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 67 (1.49%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 67 (1.49%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Disorientation			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood glucose increased			
subjects affected / exposed	2 / 67 (2.99%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary nitrogen increased			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fall			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin abrasion			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIIth nerve injury			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	2 / 67 (2.99%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	1 / 67 (1.49%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart valve incompetence			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic neuropathy			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid function disorder			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	1 / 67 (1.49%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Duodenitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	2 / 67 (2.99%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (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			
Diabetic foot			
subjects affected / exposed	1 / 67 (1.49%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 67 (0.00%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			

subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 67 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 67 (1.49%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	1 / 67 (1.49%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ranibizumab 0.5 mg PRN	Ranibizumab 0.5 mg DI	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 67 (64.18%)	44 / 68 (64.71%)	
Investigations			
Glycosylated haemoglobin increased			
subjects affected / exposed	7 / 67 (10.45%)	5 / 68 (7.35%)	
occurrences (all)	7	6	
Intraocular pressure increased			
subjects affected / exposed	6 / 67 (8.96%)	8 / 68 (11.76%)	
occurrences (all)	6	19	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 67 (0.00%)	4 / 68 (5.88%)	
occurrences (all)	0	5	
Hypertension			
subjects affected / exposed	7 / 67 (10.45%)	3 / 68 (4.41%)	
occurrences (all)	10	4	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 67 (1.49%)	4 / 68 (5.88%)	
occurrences (all)	1	8	
Eye disorders			
Cataract			
subjects affected / exposed	5 / 67 (7.46%)	2 / 68 (2.94%)	
occurrences (all)	6	4	
Conjunctival haemorrhage			
subjects affected / exposed	14 / 67 (20.90%)	13 / 68 (19.12%)	
occurrences (all)	20	21	
Corneal erosion			
subjects affected / exposed	4 / 67 (5.97%)	4 / 68 (5.88%)	
occurrences (all)	4	4	
Eye irritation			
subjects affected / exposed	5 / 67 (7.46%)	1 / 68 (1.47%)	
occurrences (all)	10	2	
Eye pain			

subjects affected / exposed	4 / 67 (5.97%)	7 / 68 (10.29%)	
occurrences (all)	4	16	
Foreign body sensation in eyes			
subjects affected / exposed	1 / 67 (1.49%)	6 / 68 (8.82%)	
occurrences (all)	1	10	
Macular oedema			
subjects affected / exposed	5 / 67 (7.46%)	5 / 68 (7.35%)	
occurrences (all)	5	10	
Ocular discomfort			
subjects affected / exposed	4 / 67 (5.97%)	4 / 68 (5.88%)	
occurrences (all)	6	15	
Visual acuity reduced			
subjects affected / exposed	8 / 67 (11.94%)	7 / 68 (10.29%)	
occurrences (all)	18	16	
Visual impairment			
subjects affected / exposed	2 / 67 (2.99%)	4 / 68 (5.88%)	
occurrences (all)	3	6	
Vitreous floaters			
subjects affected / exposed	5 / 67 (7.46%)	3 / 68 (4.41%)	
occurrences (all)	7	4	
Vitreous haemorrhage			
subjects affected / exposed	2 / 67 (2.99%)	6 / 68 (8.82%)	
occurrences (all)	3	8	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 67 (2.99%)	4 / 68 (5.88%)	
occurrences (all)	2	4	
Pain in extremity			
subjects affected / exposed	1 / 67 (1.49%)	4 / 68 (5.88%)	
occurrences (all)	1	4	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	4 / 67 (5.97%)	1 / 68 (1.47%)	
occurrences (all)	5	1	
Viral upper respiratory tract infection			

subjects affected / exposed occurrences (all)	18 / 67 (26.87%) 22	19 / 68 (27.94%) 24	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2016	This amendment was issued to stop further recruitment to the study. The reason to stop recruitment was new and relevant scientific evidence regarding treatment patterns with ranibizumab which did not justify continuing the trial with newly included patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported